

# Handbook of Topical Drug Treatment in Dermatology

Rebecca M. Law  
Howard I. Maibach  
*Editors*

 Springer

---

# Handbook of Topical Drug Treatment in Dermatology

---

Rebecca M. Law  
Howard I. Maibach  
Editors

# Handbook of Topical Drug Treatment in Dermatology

 Springer

### *Editors*

Rebecca M. Law   
School of Pharmacy and Faculty  
of Medicine (Discipline of Family  
Medicine)  
Memorial University  
of Newfoundland  
St. John's, NL, Canada

Howard I. Maibach  
Department of Dermatology  
University of California San  
Francisco (UCSF)  
San Francisco, CA, USA

ISBN 978-3-031-93615-9      ISBN 978-3-031-93616-6 (eBook)  
<https://doi.org/10.1007/978-3-031-93616-6>

© The Editor(s) (if applicable) and The Author(s), under exclusive license to Springer Nature Switzerland AG 2025

This work is subject to copyright. All rights are solely and exclusively licensed by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed.

The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

The publisher, the authors and the editors are safe to assume that the advice and information in this book are believed to be true and accurate at the date of publication. Neither the publisher nor the authors or the editors give a warranty, expressed or implied, with respect to the material contained herein or for any errors or omissions that may have been made. The publisher remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

This Springer imprint is published by the registered company Springer Nature Switzerland AG

The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

If disposing of this product, please recycle the paper.



*In Remembrance*

Aaron B. Lerner MD PhD

(September 21,  
1920–February 3, 2007)

*Dr. Lerner was the first Chair of the Department of Dermatology at Yale University. He was a renowned dermatologist, researcher, and professor. He is known for his discovery of melatonin in 1958, where he led a team of researchers to isolate and to name the hormone melatonin. He also isolated MSH (melanocyte-stimulating hormone). He was also an expert in inherited*

*diseases, in particular vitiligo, where he developed a skin transplantation therapy. Upon retirement in 1991, he was named a Professor Emeritus of Dermatology.*

Wayne P.F. Gulliver MD  
FRCP(C)

(March 4, 1958–September 5, 2025)

*Dr. Gulliver was one of the lead researchers on the team who discovered the HLA-Cw6 gene for psoriasis, and put Newfoundland and Labrador genetic research on the world map. He was a renowned dermatologist, researcher, professor, and a leader in psoriasis. He received many awards and accolades throughout his prestigious career including the Albert Neisser award, considered the “Nobel Prize” of Dermatology. Always leading by example, he embraced many leadership roles including being the first Chair of Medicine at Memorial University who was from Newfoundland and Labrador.*

---

## Preface

The concept for this book was conceived in Howard Maibach's home office during one of Rebecca Law's numerous visits. Howard has an enormous home office/library with hundreds of his treasured textbooks and publications. He has already published a systemic drug treatment in dermatology handbook with Sarah Wakelin (currently in its third edition), so clearly a topical drug treatment in dermatology handbook would make a suitable companion textbook.

Thus began the recruitment of authors with expertise in specific dermatologic conditions, and authors with expertise in one specific dermatologic category of drugs, or even in one specific drug treatment. With the intent of also providing a learning experience for students and a teaching experience for their mentors, some of our authors have involved their students, residents, and/or fellows in preparation of their chapters.

The handbook is in two sections. The first section includes foundational chapters discussing general principles such as factors affecting percutaneous absorption, extemporaneous compounding, pharmacogenomics, factors affecting topical therapy in pediatrics and geriatrics, and systemic considerations when topical drug treatments are used. The second section includes chapters of drug monographs grouped either by disease state (e.g., acne, atopic dermatitis) or drug classification (e.g., antibiotics, corticosteroids) or stand alone (e.g., sirolimus). There is cross-referencing between chapters.

The chapters have been reviewed and edited by the editors and by Springer. FDA drug monographs and LexiComp/LexiDrug drug monographs are consistent reference sources for each drug monograph chapter, in addition to specific additional references and readings for each drug treatment.

The editors' hope is to provide a handbook that will be useful to clinicians and educators. We welcome corrections or comments regarding this book.

St. John's, NL, Canada  
San Francisco, CA, USA

Rebecca M. Law  
Howard I. Maibach

---

## Acknowledgments

We thank Springer and in particular Michelle Tam, Jeffrey Taub, Marie Felina Francois, Kavitha Manikannan, Rekha Muthusamy, Shanjini Rajasekaran and Patricia Gutierrez for their involvement with the publication of the first edition of this handbook.

---

# Contents

## Part I General Principles

- 1 20 Clinically Pertinent Factors/Observations  
for Percutaneous Absorption in Humans . . . . . 1**  
Rebecca M. Law, Mai A. Ngo,  
and Howard I. Maibach
- 2 Pharmaceutical Compounding of Topical  
Dermatologic Treatments . . . . . 31**  
Maggie Shukla, Heather Warren,  
and Stephen Coombs
- 3 Pharmacogenomics . . . . . 67**  
Le Hanh Dung Do, Rebecca M. Law,  
and Howard I. Maibach
- 4 Clinical Pharmacology of Dermatology  
Products in Pediatric Drug Development . . . . . 83**  
Gilbert J. Burckart, Elimika Pfuma Fletcher,  
and Chinmay Shukla
- 5 Clinical Pharmacology of Topical Therapy  
in Pediatrics . . . . . 95**  
Chinmay Shukla, Aaron Park,  
Elimika Pfuma Fletcher, and Gilbert J. Burckart
- 6 Topical Drug Use in the Elderly. . . . . 111**  
Rebecca M. Law and Meghan T. Greene

- 7 Systemic Considerations Relating to Topical Drug Treatment. . . . . 115**  
Amanda Tzenov and Rebecca M. Law

## **Part II Drug Monographs**

- 8 Topical Drug Treatments for Acne . . . . . 129**  
Brian W. Connor, Jason Ya, and Lisa E. Maier
- 9 Rosacea and Topical Drug Treatments . . . . . 183**  
Lisa E. Maier, Brian W. Connor, and Jason Ya
- 10 Topical Drug Treatment in Actinic Keratosis. . . . . 211**  
Chavy Chiang and Anuk Burli
- 11 Topical Analgesics . . . . . 225**  
Sheeva Shahinfar, Rebecca M. Law,  
and Howard I. Maibach
- 12 Topical Antibiotics. . . . . 241**  
Taylor Skinner, Parsa Abdi, Mahan Maazi,  
and Rebecca M. Law
- 13 Topical Antifungals . . . . . 297**  
Laurie A. Temiz, Austinn C. Miller,  
Susuana Adjei, and Stephen K. Tying
- 14 Topical Antineoplastics in Dermatology . . . . . 361**  
Christina Huang, Paola A. Baker, Chavy Chiang,  
Anuk Burli, Enzo Berardesca, Bradley D. Kwinta,  
Larisa J. Geskin, and Jack L. Arbiser
- 15 Antipruritic Agents . . . . . 383**  
Nadia Kashetsky and Aileen Feschuk
- 16 Antiviral Agents . . . . . 413**  
Rebecca M. Law, Drake Carter, Sean Mangion,  
and Howard I. Maibach
- 17 Atopic Dermatitis: Topical Therapy . . . . . 439**  
Rebecca M. Law

|           |                                                                                                                        |            |
|-----------|------------------------------------------------------------------------------------------------------------------------|------------|
| <b>18</b> | <b>Topical Corticosteroids</b> . . . . .                                                                               | <b>453</b> |
|           | Kiha Kim, Taylor Skinner, and Rebecca M. Law                                                                           |            |
| <b>19</b> | <b>Ectoparasiticides</b> . . . . .                                                                                     | <b>527</b> |
|           | Dirk B. Robertson                                                                                                      |            |
| <b>20</b> | <b>Depigmenting and Pigmenting Agents</b> . . . . .                                                                    | <b>543</b> |
|           | Anuk Burli and Chavy Chiang                                                                                            |            |
| <b>21</b> | <b>Psoriasis</b> . . . . .                                                                                             | <b>559</b> |
|           | Rebecca M. Law, Erin Bartholomew,<br>Mimi Chung, Sarah J. Currie, Marwa Hakimi,<br>Samuel Yeroushalmi, and Wilson Liao |            |
| <b>22</b> | <b>Retinoids</b> . . . . .                                                                                             | <b>595</b> |
|           | Enzo Berardesca                                                                                                        |            |
| <b>23</b> | <b>Seborrheic Dermatitis</b> . . . . .                                                                                 | <b>617</b> |
|           | Aileen Feschuk and Nadia Kashetsky                                                                                     |            |
| <b>24</b> | <b>Sinecatechins</b> . . . . .                                                                                         | <b>639</b> |
|           | Victoria Nguyen, Linda B. Ou,<br>and Rebecca M. Law                                                                    |            |
| <b>25</b> | <b>Sirolimus for Facial Angiofibroma Associated<br/>with Tuberous Sclerosis Complex</b> . . . . .                      | <b>645</b> |
|           | Arian Farahani, Michael Pham,<br>Sreedevi Boggarapu, and Eric Beresford                                                |            |
| <b>26</b> | <b>Trichogenic and Antitrichogenic Agents</b> . . . . .                                                                | <b>653</b> |
|           | Sheeva Shahinfar, Rebecca M. Law,<br>and Howard I. Maibach                                                             |            |
| <b>27</b> | <b>Miscellaneous Agents</b> . . . . .                                                                                  | <b>667</b> |
|           | Rebecca M. Law, Victoria Nguyen,<br>Linda B. Ou, Sheeva Shahinfar,<br>and Howard I. Maibach                            |            |
|           | <b>Index</b> . . . . .                                                                                                 | <b>703</b> |



---

## Contributors

**Parsa Abdi** Faculty of Medicine, Memorial University of Newfoundland, St. John's, NL, Canada

**Susuana Adjei** Center for Clinical Studies, Webster, TX, USA

**Jack L. Arbiser** Department of Dermatology, Emory University School of Medicine, Winship Cancer Institute, Atlanta Veterans Administration Health Center, Atlanta, GA, USA

**Paola A. Baker** Department of Dermatology, Emory University School of Medicine, Atlanta, GA, USA

**Erin Bartholomew** Department of Dermatology, Eastern Virginia Medical School, Norfolk, VA, USA

**Enzo Berardesca** Dr. Phillip Frost Department of Dermatology and Cutaneous Surgery, Miller School of Medicine, University of Miami, Miami, FL, USA

**Eric Beresford** Formerly with Nobelpharma America, LLC, Bethesda, MD, USA

**Sreedevi Boggarapu** Formerly with Nobelpharma America, LLC, Bethesda, MD, USA

**Gilbert J. Burckart** Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, USA

**Anuk Burli** Department of Dermatology, Stanford University School of Medicine, Redwood City, CA, USA

**Drake Carter** Chicago Medical School, Rosalind Franklin University of Medicine & Science, North Chicago, IL, USA

**Chavy Chiang** Department of Dermatology, University of Rochester Medical Center, Rochester, NY, USA

**Mimi Chung** University of Alabama at Birmingham, Birmingham, AL, USA

**Brian W. Connor** Schweiger Dermatology Group, New York, NY, USA

**Stephen Coombs** School of Pharmacy, Memorial University, St. John's, NL, Canada

Faculty of Medicine, Discipline of Family Medicine, Memorial University, St. John's, NL, Canada

**Sarah J. Currie** Faculty of Medicine, Memorial University of Newfoundland, St. John's, NL, Canada

**Le Hanh Dung Do** Roger Williams Medical Center, Providence, RI, USA

**Arian Farahani** Medical Science Liaison at Nobelpharma America, LLC, Bethesda, MD, USA

**Aileen Feschuk** Faculty of Medicine, Memorial University of Newfoundland, St. John's, NL, Canada

**Elimika Pfuma Fletcher** Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, USA

**Larisa J. Geskin** Department of Dermatology at Columbia University Irving Medical Center, New York, NY, USA

**Meghan T. Greene** Faculty of Medicine, Memorial University of Newfoundland, St. John's, NL, Canada

**Marwa Hakimi** Department of Dermatology, University of California San Francisco (UCSF), San Francisco, CA, USA

**Christina Huang** Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA, USA

**Nadia Kashetsky** Department of Dermatology and Skin Science, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada

**Kiha Kim** Faculty of Medicine, Memorial University, St. John's, NL, Canada

**Bradley D. Kwinta** Department of Dermatology at Columbia University Irving Medical Center, New York, NY, USA

**Rebecca M. Law** School of Pharmacy and Faculty of Medicine (Discipline of Family Medicine), Memorial University of Newfoundland, St. John's, NL, Canada

**Wilson Liao** Department of Dermatology, University of California San Francisco (UCSF), San Francisco, CA, USA

**Mahan Maazi** Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada

**Howard I. Maibach** Department of Dermatology, University of California San Francisco (UCSF), San Francisco, CA, USA

**Lisa E. Maier** Department of Dermatology, UW Medicine, Seattle, WA, USA

**Sean Mangion** UniSA: Clinical and Health Sciences, University of South Australia, Adelaide, SA, Australia

Therapeutics Research Centre, Basil Hetzel Institute of Translational Health Research, The Queen Elizabeth Hospital, Woodville, SA, Australia

Sydney Medical School, The University of Sydney, Camperdown, NSW, Australia

**Austinn C. Miller** Center for Clinical Studies, Webster, TX, USA

**Mai A. Ngo** California Department of Toxic Substances Control, Sacramento, CA, USA

**Victoria Nguyen** School of Pharmacy, University of Waterloo, Kitchener, ON, Canada

**Linda B. Ou** Sunnybrook Health Sciences Centre, Toronto, ON, Canada

**Aaron Park** Acelyrin Inc., McLean, Virginia, USA

**Michael Pham** Sr. Director, Head of Medical Affairs at Nobelpharma America, LLC, Bethesda, MD, USA

**Dirk B. Robertson** Department of Dermatology, Emory University School of Medicine, Atlanta, GA, USA

**Sheeva Shahinfar** Texas A&M University College of Medicine, Bryan, TX, USA

**Chinmay Shukla** Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, USA

**Maggie Shukla** Compounding Wellness Sterile Lab, Mount Pearl, NL, Canada

**Taylor Skinner** Faculty of Medicine, Memorial University of Newfoundland, St. John's, NL, Canada

**Laurie A. Temiz** Department of Dermatology and Cutaneous Surgery, University of South Florida, Tampa, FL, USA  
Center for Clinical Studies, Webster, TX, USA

**Stephen K. Tyring** Center for Clinical Studies, Webster, TX, USA

Department of Dermatology, University of Texas Health Science Center, Houston, TX, USA

**Amanda Tzenov** Faculty of Medicine, Memorial University of Newfoundland, St. John's, NL, Canada

**Heather Warren** Compounding Wellness Sterile Lab, Mount Pearl, NL, Canada

**Jason Ya** Department of Dermatology, Stanford University School of Medicine, Redwood City, CA, USA

---

## Abbreviations

|                  |                                            |
|------------------|--------------------------------------------|
| ACEI             | Angiotensin-converting enzyme inhibitor    |
| ADR              | Adverse drug reaction                      |
| ALP              | Alkaline phosphatase                       |
| ALT              | Alanine aminotransferase                   |
| aPTT             | Activated partial thromboplastin time      |
| AST              | Aspartate aminotransferase                 |
| BID              | Twice daily                                |
| BP               | Blood pressure                             |
| °C               | Celsius (Centigrade)                       |
| CA               | Cancer                                     |
| Ca               | Calcium                                    |
| CDC              | Centers for Disease Control and Prevention |
| CFU              | Colony-forming unit                        |
| CK               | Creatine Kinase                            |
| Cl <sub>cr</sub> | Creatinine clearance                       |
| cm               | Centimeter (centimetre)                    |
| CNS              | Central nervous system                     |
| CO               | Cardiac output                             |
| COPD             | Chronic obstructive pulmonary disease      |
| CXR              | Chest X-ray                                |
| ECG              | Electrocardiogram                          |
| EEG              | Electroencephalogram                       |
| EENT             | Eyes, ears, nose, throat                   |
| ESR              | Erythrocyte sedimentation rate             |
| ETOH             | Ethanol                                    |
| °F               | Fahrenheit                                 |

---

|                   |                                                         |
|-------------------|---------------------------------------------------------|
| FDA               | Food and Drug Administration (United States)            |
| G6PD              | Glucose-6-phosphate dehydrogenase                       |
| GFR               | Glomerular filtration rate                              |
| GI                | Gastrointestinal                                        |
| Gtt               | Drops                                                   |
| H/A               | Headache                                                |
| Hb <sub>A1C</sub> | Hemoglobin A <sub>1C</sub>                              |
| HCTZ              | Hydrochlorothiazide                                     |
| HEENT             | Head, eyes, ears, nose, throat                          |
| IBW               | Ideal body weight                                       |
| kJ                | Kilojoule                                               |
| L                 | Liter (Litre)                                           |
| MRSA              | Methicillin-resistant <i>Staphylococcus aureus</i>      |
| MRSE              | Methicillin-resistant <i>Staphylococcus epidermidis</i> |
| MTX               | Methotrexate                                            |
| NRTI              | Nucleoside reverse transcriptase inhibitor              |
| NS                | Normal saline                                           |
| NSAID             | Nonsteroidal anti-inflammatory drug                     |
| NSCLC             | Nonsmall cell lung cancer                               |
| NTG               | Nitroglycerin                                           |
| N/V               | Nausea & vomiting                                       |
| OCT               | Optical coherence tomography                            |
| OD                | Once daily or right eye                                 |
| OS                | Left eye                                                |
| OTC               | Over-the-counter                                        |
| OU                | Each eye                                                |
| PCN               | Penicillin                                              |
| PDE               | Phosphodiesterase                                       |
| pH                | Hydrogen ion concentration                              |
| QID               | Four times daily                                        |
| RADT              | Rapid antigen detection test                            |
| RCT               | Randomized controlled trial                             |
| RNA               | Ribonucleic acid                                        |
| RSV               | Respiratory syncytial virus                             |
| RT-PCR            | Reverse transcriptase—polymerase chain reaction         |
| SC                | Subcutaneous                                            |
| SC <sub>r</sub>   | Serum creatinine                                        |
| SG                | Specific gravity                                        |

---

|                |                                                          |
|----------------|----------------------------------------------------------|
| SGOT           | Serum glutamate oxaloacetic transaminase                 |
| SGPT           | Serum glutamic pyruvic transaminase                      |
| SIADH          | Syndrome of inappropriate antidiuretic hormone secretion |
| SJS            | Stevens-Johnson syndrome                                 |
| SPF            | Sun protection factor                                    |
| TB             | Tuberculosis                                             |
| TEN            | Toxic epidermal necrolysis                               |
| TID            | Three times daily                                        |
| TMP/SMX        | Trimethoprim-sulfamethoxazole                            |
| TSH            | Thyroid-stimulating hormone                              |
| TTP            | Thrombotic thrombocytopenic purpura                      |
| T <sub>x</sub> | Treatment                                                |
| UV             | Ultraviolet                                              |

---

## Part I

# General Principles





# 20 Clinically Pertinent Factors/Observations for Percutaneous Absorption in Humans

# 1

Rebecca M. Law , Mai A. Ngo,  
and Howard I. Maibach

## Contents

|                                         |    |
|-----------------------------------------|----|
| Introduction.....                       | 4  |
| Factors in Percutaneous Absorption..... | 4  |
| Summary.....                            | 24 |
| References.....                         | 25 |

---

R. M. Law (✉)

School of Pharmacy and Faculty of Medicine (Discipline of Family  
Medicine), Memorial University of Newfoundland,  
St. John's, NL, Canada  
e-mail: [rlaw@mun.ca](mailto:rlaw@mun.ca); [rlawUCSF@gmail.com](mailto:rlawUCSF@gmail.com)

M. A. Ngo

California Department of Toxic Substances Control,  
Sacramento, CA, USA

H. I. Maibach

Department of Dermatology, University of California San Francisco  
(UCSF), San Francisco, CA, USA  
e-mail: [howard.maibach@ucsf.edu](mailto:howard.maibach@ucsf.edu)

## Introduction

Clinicians routinely use the topical route to administer medications with minimal consideration of details: If there is an approved topical formulation, then obviously absorption through the skin should work. But is percutaneous absorption that simple? What factors are involved for a medication—or for that matter, for any chemical—to be percutaneously absorbed? What can enhance or reduce topical absorption? We consider these factors when using the topical administration route as they may affect drug efficacy and/or toxicity and hence patient outcome. What follows is evidence-based; the interested reader is encouraged to access the 62 reference citations for the evidence behind this discussion of skin absorption (not mucous membranes). Furthermore, textbooks providing in-depth discussions of percutaneous absorption are available as reference sources. The reader is referred to the extensive literature on percutaneous penetration enhancers in the 5-volume series by Dragicevic N, Maibach HI. Ed. *Percutaneous Penetration Enhancers Chemical Methods in Penetration Enhancement*. Springer. ISBN 978-3-662-47039-8.

---

## Factors in Percutaneous Absorption

What questions should we ask when using a topical medication? Consider at least 20 factors. In 1983, we suggested a ten-factor guide in percutaneous absorption based on observations from in vitro and in vivo comparisons [1], which was expanded to 15 [2] in 2012, modified in 2013 [3, 4], with clinical relevance and complexities added in 2017 [5]. To aid the clinician or student, 20 factors affecting topical absorption are presented here in practical terms, including clinical implications. Questions asked are as follows:

## What Are the Relevant Physicochemical Properties of the Medication/Chemical?

**Particle Size/Molecular Weight** Smaller molecules are often more easily absorbed; most topical medications are less than or around 500 Daltons in size/molecular weight with few exceptions. Topical calcineurin inhibitors are efficacious despite larger particle sizes (tacrolimus [Protopic] at MW 822 Dalton and pimecrolimus [Elidel] at MW 810 Dalton) [3].

**Lipophilicity** The outer skin layer (stratum corneum) are corneocytes with cell membranes consisting of lipids, with proteins and water. Lipophilic drugs (and lipophilic chemicals) will be more readily absorbed than hydrophilic substances [6]. However, highly lipophilic substances may be less well absorbed than moderately lipophilic compounds.

**pH** The pH of the environment will determine the proportion of drug or chemical that is ionized versus unionized. Skin membrane proteins are basic in nature. It is the unionized form of a drug or chemical that passes through membranes. Thus, drugs and chemicals that are primarily in their unionized form in a basic pH environment will be optimally absorbed. Since basic drugs will have a greater proportion in unionized form than acidic drugs in a basic environment, therefore, basic drugs will be absorbed better than acidic drugs. Less ionization leads to increased lipid solubility and passage through membranes [7].

**pKa** pKa is a measure of a chemical's acid strength and provides details of the dissociation of an acid in aqueous solution. Since there is a specific pKa for each substance that relates to pH, knowing the pKa of a drug becomes a useful predictor of percutaneous drug absorption [7].

**Partition Coefficient (P)** The partition coefficient is the ratio of concentrations of a substance in a mixture of two immiscible phases at equilibrium. This ratio is therefore a measure of the dif-

ference in solubility of the substance in these two phases. There are two partition coefficients of relevance to percutaneous absorption: the oil-to-water partition coefficient (i.e., octanol:water  $P$ ) and the partition coefficient for cream or ointment to the stratum corneum (i.e., formulation:skin  $P$ ). Hydrophobic drugs or chemicals will have a high octanol:water  $P$  and will be mainly distributed to hydrophobic areas such as the lipid bilayers of cell membranes, whereas hydrophilic drugs or chemicals (with low octanol:water  $P$ s) will be mainly distributed to aqueous areas such as serum. The partition coefficient between a cream/ointment and the stratum corneum will depend on the product formulation. Thus, knowing the partition coefficients of a drug or chemical for various immiscible phases may be a useful predictor of percutaneous drug absorption and/or drug partitioning between biologic systems, which can include solids such as bone (i.e., blood:bone  $P$ ).

## **What Effects Do the Vehicle/Formulation of the Product Have on Drug Absorption?**

**Occlusive Vehicles** *Occlusive vehicles* often aid absorption by increasing hydration [8]. *Water-based* vehicles are nonocclusive and are less helpful for topical drug absorption, but they allow water-soluble drugs to dissolve in higher concentrations, which may offset the nonocclusive aspect.

**Oil-Based** *Oil-based vehicles* are occlusive and act as humectants to enhance drug penetration. Thus, for example, a betamethasone dipropionate 0.1% ointment will generally have greater potency than a betamethasone dipropionate 0.1% cream (note that changing salt forms may affect potency—e.g., betamethasone dipropionate 0.1% cream is more potent than betamethasone valerate 0.1% cream). Although *alcohol-based* or *acetone-based* vehicles are less occlusive and have a skin-drying effect, they may enhance solubility of some drugs and thereby augment dermal absorption.

The *pH of the vehicle* may alter the unionized:ionized drug ratio, thus affecting drug absorption, since it is the unionized form of the drug, which most efficiently crosses through the skin. Other *excipients* (i.e., inactive ingredients) in the vehicle such as surfactants may have been purposely added to enhance solubility and hence drug absorption.

### **What Effects Do the Conditions of Drug Exposure (Dose, Duration, Surface Area, and Frequency of Exposure) Have on Drug Absorption?**

Intuitively, greater *dose*, longer *treatment duration*, larger *surface area of application*, and greater *frequency of reapplication* (once up to three or four times a day) should all increase the amount of drug absorbed, and they generally do. However, (although the experimental data remains sparse), with corticosteroids, a high single exposure (hydrocortisone 40 ug/cm<sup>2</sup>) substantially increases absorption over one-third of the dose (13.3 ug/cm<sup>2</sup>) applied either once or three times in 1 day, there was no statistically significant difference seen with increasing frequency of reapplication [9]. With multiple dosing over many days, there is currently insufficient experimental data to provide a general predictive statement.

In addition, the *body surface area-to-body weight ratio (BSA:BW)* is important as this may affect drug toxicity, since drug doses are usually based on body weight (with a few exceptions such as in oncology). In particular, newborns have a BSA:BW ratio at least twice that of adults, so that topical drug doses—even when adjusted for body weight—will still cover a larger % BSA than in adults. Thus, newborns are at greater risk of systemic drug toxicity from topical application of drugs or chemicals. It is partially for this reason that sun protection in newborns less than 6 months of age does not include the use of sunscreens/sunblocks, even the physical (mineral-based) sunblocks like titanium dioxide. (Recommendations by the American Academy of Pediatrics for sun protection in this population include sun avoidance, using

a stroller cover, wearing lightweight long pants, long-sleeve shirts and hats with wide brims that shade the neck etc.)

Also, note the following: (a) There may be residual drug remaining on and in the skin even if the dose is wiped off—that is treatment duration may be unknowingly extended; (b) repeated exposure over time may lead to chronic toxicity manifestations, such as corticosteroid-induced skin atrophy; (c) inadvertent chemical/drug exposure may occur via transfer from one person to another, for example, a mother wearing sunscreen and holding her infant with bare arms (further discussed in section “[Can medications or chemicals be transferred from one person to another through skin contact, clothing, or contact with an inanimate surface?](#)” below).

### **Do the Skin Appendages (Hair Follicles, Sebaceous Glands, Apocrine, and Eccrine Sweat Glands) Have a Role in Topical Drug Absorption?**

Yes they do. Skin appendages that originate in the dermis are *sub-anatomical pathways*, whereby drugs and chemicals can be transported through the skin. Diffusion of chemicals through skin appendages is termed “*shunt diffusion*.” Hair follicles can contribute to the total skin surface area for drug absorption. Skin appendages are especially important for the penetration and skin storage of larger molecules (e.g., proteins), as discussed in section “[How does substantivity and binding to the different skin components affect topical absorption?](#)” below. Little data exists regarding transport through the eccrine, apocrine, and sebaceous glands.

### **How Do the Skin Sites of Application Affect Absorption?**

There is marked *regional variability* in absorption: absorption rates vary at different anatomical skin sites—in general, faster if hair follicles are present in large numbers and somewhat slower if the stratum corneum is thick. More specifically, the scrotum has

the highest rate of topical absorption due to having both a very thin stratum corneum and a rich blood supply. The next highest body areas for absorption are the forehead, scalp, and neck. These regional differences may partially relate to skin thickness and the number of cell layers in the stratum corneum. Body areas with the lowest topical absorption rates include the palms and soles.

## What Population Variability Factors Affect Topical Absorption?

**Ethnicity** Although the skin is approximately equally thick in persons of different pluralistic societies, the stratum corneum in blacks has more cell layers and a higher lipid content than in whites [10]. These differences may lead to absorption differences. In addition, blacks and Hispanics have stronger irritant reactions than whites to sodium lauryl sulfate [11, 12], a surface-active agent often found in non-medicated and medicated shampoos. (Note that experimental data in comparing blacks and Hispanic skin is limited, and there is conflicting data. The interested reader can obtain more information from two textbooks detailing these points: Berardesca E, Leveque J-L, Maibach HI. *Ethnic Skin and Hair* 1st ed. CRC Press. Dec 2019. ISBN 9780367389994; and earlier edition Nov 2006 ISBN 978-0849330889 *Skin irritation may lead to inflammation and enhanced absorption of topical agents.*)

**Age** Age can significantly affect topical absorption. Aged skin is drier with less skin surface lipids [13]. It is also thinner and more friable—skin aging is associated with progressive dermal atrophy including atrophy of the skin's capillary network, resulting in a gradual reduction of blood supply to the skin [13]. All of these changes may potentially affect topical absorption. Overall, it paradoxically appears that the *permeability barrier function* of the skin is increased as we age. In particular, percutaneous absorption of less lipophilic substances (e.g., hydrocortisone, benzoic acid, acetylsalicylic acid, and caffeine) is reduced, while more lipophilic substances (e.g., testosterone and estradiol) are not [13].

However, increased friability may result in broken skin, resulting in the loss of permeability barrier function and increased percutaneous absorption.

At the other end of the age spectrum, that is, infants and children, topical absorption may be increased. In the preterm baby, the permeability barrier function of the skin is not yet intact. Prenatal skin undergoes developmental stages in utero (including permeability barrier development, e.g., proteolipid layer and pilo-sebaceous units), but some functions are not fully developed even in the neonate [14]. Importantly, the acid mantle is developed in the first 4 weeks after birth, and skin surface pH of both term newborns and premature neonates is less acidic than that of children and adults [15]. Newborn skin has higher permeability than topical agents. Pediatric skin is thinner, potentially allowing for an increase in the rate and amount of drug absorbed. In fact, pediatric and in particular neonatal and infant skins have skin surface conditions different from adult skin surface conditions, which may enhance absorption [16].

Skin hydration naturally differs with age. Although at birth the skin surface is rougher and drier compared with older children, within the first 30 days, the skin smoothens, and skin hydration increases [16, 17]. During the next 3 months, skin hydration continues to increase then exceeds that found in adults [17–19]—perhaps relating to sweat gland maturation in function [20]. The stratum corneum in infants 3–12 months of age is significantly more hydrated compared to adult skin [16, 17]. These factors may increase the potential for drug and chemical toxicities in neonates, infants, and children, and this should be kept in mind whenever the topical route is used. For example, increased topical absorption and toxicity have been reported in infants with the use of rubbing alcohol [21, 22], boric acid powders [23], and hexachlorophene baths, emulsions and soaps [24, 25]—thus, their use should be minimized. The evidence that rubbing enhances percutaneous penetration has recently been reviewed [26]. The preterm infant may be at even greater risk—even medications that are not normally administered topically due to their physicochemical characteristics may be absorbed enough to be efficacious or cause toxicity. For example, a theophylline gel (17 mg spread over an area 2 cm in



diameter) applied to the abdomens of premature infants produced therapeutic serum theophylline concentrations [27].

## How Do Skin Surface Conditions Affect Topical Drug Absorption?

**Hydration** Hydration is crucial (as discussed above with age comparisons). Well-hydrated skin often promotes topical absorption, and it is for this reason that occlusion is often intentional in product formulation, for example, ointments are often more potent than creams or lotions, also mentioned earlier, since occlusion creates a humectant effect. Formulation or application changes resulting in potency differences should be remembered when prescribing (e.g., clobetasol or hydrocortisone). For example, a tenfold increase in hydrocortisone absorption was seen when occlusion was applied for 24 h after topical administration [2, 28].

**Skin Temperature** Skin temperature also affects topical absorption: an increase in skin temperature—such as a febrile state or sometimes even when a heating pad is present—may increase topical absorption. For example, skin temperature at 40 °C increases the transdermal delivery of testosterone and fentanyl [29].

**Skin pH** The *skin pH* may affect topical absorption: a less acidic skin pH may enhance absorption. The normal stratum corneum is typically acidic and hence favors transport of chemicals and drugs whose pKas allow for greater unionized forms in an acidic environment. Abnormal stratum corneum frequently has higher pH (i.e., a more basic environment), and this would favor the penetration of chemicals and drugs whose pKa allows for greater unionized forms in a basic environment. Thus, the acid mantle of the intact adult skin (pH 4–5) would be an absorption barrier to most basic drugs and some acidic drugs.

Skin pH elevations can occur with occlusion [30] or with a change in the skin microbiome (e.g., caused by prolonged occlusion [30]). Even 1 day of occlusion (with plastic wrap) can cause a  $10^4$  increase in bacterial count (most significantly with Coagulase

negative *Staphylococci*), resulting in a corresponding increase in skin pH [30]. With 4 days of occlusion the skin pH can change from acidic to neutral (4.38–7.05) [30].

***Skin Surface Topography*** The *skin surface topography* can also affect topical absorption, since it affects lateral spread of drug or chemical (see section “[How does lateral spread affect percutaneous absorption?](#)”).

## How Does Skin Health and Skin Integrity Affect Topical Absorption?

Be cognizant that *any skin damage or trauma*—be it mechanical, chemical, biocidal, or clinical disease—may potentially enhance topical absorption [5, 31], and the effects may be more significant for hydrophilic (water-soluble) substances than lipophilic (oil-soluble) substances [31]. These effects are not only demonstrated in in vivo human studies measuring penetration through damaged or diseased skin [31], but also enhanced absorption has also been shown in in vitro studies using human models of damaged or diseased skin [32]. Even mild skin trauma such as adhesive tape stripping (which removes stratum corneum layers) may significantly enhance absorption. For example, penciclovir absorption was increased by 1300-fold and acyclovir absorption by 440-fold through tape stripping (to glistening but not broken skin) [33]. Skin compromised by sodium lauryl sulfate (a surfactant) was more permeable to various polyethylene glycols (of different molecular weights) [34].

***Skin Diseases*** Skin diseases such as psoriasis and atopic dermatitis [35] also compromise skin integrity, and topical drugs and chemicals may be absorbed faster and in greater amounts. There is some complexity though. For example, in atopic dermatitis (AD) patients (when compared to healthy individuals), increased absorption occurred not only through lesional skin but also through non-lesional skin [35–37]. Although non-lesional AD skin is “normal-appearing,” it still responds to petrolatum applied to it—by increasing stratum corneum thickness, reducing

T-cell infiltrates, upregulating antimicrobial peptides, etc. [35]. And both lesional and non-lesional skin of AD patients have higher *Staphylococcus aureus* levels than healthy controls, which correlates with disease severity [38].

However, it is AD patients with clinically active disease who demonstrated increased skin absorption (in both lesional and non-lesional skin)—patients with clinically inactive disease did not [36, 39, 40]. Furthermore, skin absorption increases significantly with the severity of AD [36, 41, 42].

Practically, this means that topical medications are better absorbed during dermatologic disease flare-ups—thus, (a) becoming more effective at that time, a useful phenomenon; (b) being potentially less effective when used as maintenance therapy, especially if intermittent (twice weekly) regimens are used, thus patient monitoring and follow-up during periods of inactive disease would be important; and (c) systemic toxicity from topical medications may be significantly increased during disease flare-ups, especially if higher potency agents within a class of medications are used (e.g., corticosteroids). Furthermore, absorption of and potential systemic toxicity of *any* chemical touching the skin may be similarly increased during a skin disease flare-up, such as in AD.

## **How Does Substantivity and Binding to the Different Skin Components Affect Topical Absorption?**

**Substantivity** Substantivity can be defined as the adherence of chemicals to the stratum corneum, that is more like adsorption. In practical terms, the substantivity of a sunscreen (as an example) would be that sunscreen's ability to remain effective during prolonged exercise, sweating, or swimming, and this may be a property of the active ingredient, the vehicle, or both. Obviously, the greater the substantivity, the greater the potential efficacy and systemic toxicity of a topical formulation that is meant for local/topical treatment or prevention (e.g., sunscreens, antibacterials, and antifungals).

**Binding** Binding can occur to various other skin proteins, lipids, or other substances, which have differing binding sites and chemical affinities [3]. Thus, binding is drug- or chemical-specific. Bindings to different skin components (such as eccrine and apocrine sweat glands and hair follicles) are also important to consider as the bound drug or chemical may serve as a skin reservoir. Further, drugs or chemicals stored in skin reservoirs may be absorbed systemically, potentially causing prolonged pharmacologic effect or toxicity. This is an area of current decontamination research, as bound substances may not be easily washed off or otherwise removed [3, 4]. (Washing is further discussed in section “Does washing affect topical absorption?”.)

## How Does Topical Application Result in Systemic Distribution of the Drug or Chemical?

**Systemic Distribution** First, drugs or chemicals are adsorbed to the superficial skin surface (substantivity being an issue here). Second, drugs or chemicals may penetrate and bind to various skin proteins, lipids, skin appendages, and other substances (binding affinity being an issue here). Third, drugs or chemicals penetrate deeper into the lower dermis where there is a vascular blood supply and partition into the bloodstream for systemic circulation [7]. The important issues here are affinity for blood components such as albumin or other plasma proteins (plasma protein binding) and local blood flow [7]. Vasodilatation enhances blood flow and may promote systemic distribution of a topically administered medication. Of note—some medications may have vasodilating properties—for example, transdermal nitroglycerin (a venodilator) acts within minutes and may be a temporary measure to provide sustained nitroglycerin blood concentrations before intravenous (IV) line insertion can be done to administer an IV nitroglycerin infusion. The converse should also be noted—some medications have vasoconstrictive effects (such as corticosteroids) and may inhibit systemic absorption. In addition to skin surfaces, drugs or chemicals may be applied to (or otherwise be in contact with) mucosal surfaces such as the eyes or nose—the nose has a highly vascular mucosa that almost guarantees systemic absorption.

Thus, there is potential for *systemic toxicity* from topical administration. As exposure from use of ophthalmic drops is to both the eye and surrounding skin, ophthalmic beta-blockers have caused bronchospasm, congestive heart failure and pulmonary edema, bradyarrhythmias and sinus arrest, CNS toxicity, impotence, and dyslipidemias [43–45]. Ophthalmic sulfonamides have induced Stevens-Johnson syndrome [46]. Topical corticosteroids have caused systemic side effects including HPA-axis suppression and adrenal insufficiency, Cushing’s syndrome, and hypertension [43]. Topical salicylates have caused a refractory hypoglycemia [47] by increasing glucose metabolism and reducing gluconeogenesis [43]. Significant systemic absorption of topical salicylates has resulted in systemic salicylate toxicity: tinnitus, hearing loss, blurred vision, sweating, tachypnea, diarrhea, nausea/vomiting, weakness, etc. [43]. Topical minoxidil 2% applied to the scalp may have caused cardiovascular adverse effects including palpitations, dizziness, hypotension, tachycardia, paroxysmal atrial fibrillation, and sinus arrhythmia [43]. There are many other drugs and chemicals applied topically, which may have increased systemic toxicity as skin barrier properties change.

*Inadvertent systemic toxicity* from cosmeceuticals and other products have occurred, for example, phenol can be cardiotoxic: a phenol and croton oil solution used in deep chemical peels caused cardiac arrhythmias including atrial and ventricular tachycardia, premature ventricular beats and bigeminy; people with diabetes mellitus, hypertension, and depression may be at higher risk [43]. There is also concern about mercury-containing skin care products (such as skin-lightening creams and soaps and local antiseptics) and their potential to cause neurotoxicity or nephrotoxicity with enough systemic absorption [43]. Arsenic is another toxic metal that is used (or is a contaminant) in cosmetics, medications, pigments, and natural health products that when applied onto skin over time or in sufficient amounts can result in systemic toxicity effects including psychoses, seizures, multi-organ failure, and death [43].

Be cognizant that *any* drug or chemical that touches the skin has the potential for percutaneous absorption that may result in systemic distribution and possible systemic toxicity.

## How, If at All, Does Exfoliation Affect Topical Absorption?

Exfoliation is part of a natural skin cell renewal process: keratinocytes begin as boxlike basal cells at the base of the epidermis and then migrate up toward the skin surface, flattening out to become a layer of overlapping corneocytes, which have no nuclei—thus termed dead skin cells—which are then “sloughed off,” that is, exfoliated. Drugs or chemicals bound to skin cells could either be *lost by the exfoliation process* or be *absorbed deeper into the dermis*; thus, exfoliation can affect drug bioavailability after topical administration. Urea, which is minimally absorbed topically, can be used as an exfoliation marker [48].

## Does Washing Affect Topical Absorption?

There are two opposing *wash effects* that can affect topical absorption of drugs and chemicals. Loss by exfoliation can be enhanced by washing [2] even hours after application [48] if there is drug remaining in the stratum corneum, and this would be a “*washing-off*” effect. Note that for highly lipid-soluble drugs or chemicals (e.g., pesticides), washing with soap and water may not be sufficiently effective in removing them [49].

In fact, the opposite may happen: washing the site of application in between doses may actually enhance topical absorption/penetration, and this would be a “*wash-in*” effect [50–52] (see also section “[Does rubbing or massaging affect topical absorption?](#)” below). Be aware that washing may promote drug or chemical penetrance through the skin leading to toxicity—for example with insect repellents [50–52]. Care should be taken when insect repellents are used, especially in children. The US Environmental Protection Agency (EPA) recommends that instructions on the label be followed [5] for insect repellent products, and they should be used according to the time of day when mosquitoes are most active—which may vary for the species and type of diseases transmitted [5]. Care should also be taken in the work environ-

ment if there is occupational exposure to chemicals: workers should be counselled to wear protective clothing and use protective equipment and warned about the “wash-in” phenomenon [5]. They should be aware that the mechanical friction from hand-washing may increase percutaneous absorption in particular of inorganic compounds [50].

## Does Rubbing or Massaging Affect Topical Absorption?

There are two important concepts here: *rub enhancement* and *rub resistance*, both of which occur with rubbing/massaging. One example of *rub enhancement* relates to sunscreen application and washing: the mechanical stress of skin washing can massage the sunscreen deeper into the hair follicle [53], and this washing/massaging may enhance transfollicular sunscreen absorption [50]. Massaging may also increase the follicular penetration depth of liposomes (used as drug carriers) [54, 55]. Massaging/rubbing reduces skin barrier function to facilitate penetration [55]. However, this effect differs between hydrophilic and lipophilic substances—lipophilic/organic substances are less affected, if at all.

With regard to *rub resistance*, this is a term used to describe whether a substance applied topically will still be effective after being rubbed with a textile (clothing, towel, etc.). Rub resistance would be an important factor for a sunscreen or a topical medication to possess, and a rub resistance factor (RRF) can be calculated to allow comparisons between products of the same class (e.g., sunscreens) [56]. Parameters that influence RRF include rubbing pressure, rubbing duration, rubbing speed, and the textile (composition, thickness, etc.) [56]. Obviously, the higher the RRF, the greater the amount of drug or chemical remaining on the skin and the greater the likelihood for percutaneous absorption.

## **Can Medications or Chemicals Be Transferred from One Person to Another Through Skin Contact, Clothing, or Contact with an Inanimate Surface?**

Yes. As briefly mentioned in section “[What effects do the conditions of drug exposure \(Dose, duration, surface area, and frequency of exposure\) have on drug absorption?](#)” above, inadvertent drug or chemical exposure can occur via transfer from one person to another—such as a mother wearing sunscreen and holding her baby with bare arms. Drug transfer can sometimes have serious consequences: a father who used testosterone cream without routine handwashing after application transferred enough testosterone over time to his infant son to cause precocious puberty—pronounced virilization in a 2-year-old boy [57]. The skin-to-skin contact time need not be lengthy: a controlled 15-min ventral forearm to ventral forearm rub/contact time transferred sufficient estradiol from donor volunteers to recipient volunteers for estradiol to be detected in the recipients’ urine [58]. There was also enough estradiol left on the sleeve of the donors for the possibility of transfer from clothing to occur [58]. Using a hair follicle drug screening test, a Department of Human Services detected methamphetamine in newborns and young children—postulating that “sweat glands glom onto meth which can then be transferred through skin-to-skin contact, like cuddling an infant [59].” However, besides sweat, other possibilities were children picking it up “from the environment, from the smoke or residue” [59]. Other examples include additional controlled studies confirming that skin-to-skin drug transfers exist [60, 61]. Skin-to-skin transfer can also occur in the same individual [61].

Practically, what does this mean? Anytime that a topical medication or chemical substance is used, we should be aware that transfer may occur from one person to another, including to infants who may be at greater risk of systemic toxicity—unless the substance is inert. Obviously, the other factors of percutaneous absorption would also apply to the transferred drug or chemical, and those factors would ultimately determine the clinical significance of the drug or chemical transfer.



## How Is Topical Absorption Affected If a Drug or Chemical Is Volatile?

**Volatility** means that a substance has the ability to spontaneously vaporize into the air, or, in the case of a topical agent applied on skin, to evaporate from skin over time. Medications or chemicals applied to skin are often in product formulations that are a mixture of active and inactive ingredients, some of which may be volatile while others are not. For volatile substances, the degree of volatility may vary from substance to substance and may be affected by other factors such as formulation (pH, etc.), environment (humidity, temperature, etc.), and skin characteristics (pH, hydration, skin temperature, etc.). Some substances may be volatile only when certain conditions are met. For example, methamphetamine HCl (a basic drug with a pKa of 9.9) in aqueous solution can change from a nonvolatile salt to a volatile free base when the pH of the solution exceeds 4 or 5 [62].

What implications does volatility of a drug or chemical have on percutaneous absorption? Important issues include the following: (a) For a multi-ingredient product, the contents of what is left behind may alter the function of the applied product, which may have implications for efficacy and safety [63]. (b) If the vehicle and not the active ingredient is volatile, over time, there will be a concentrating effect as more and more of the vehicle evaporates, potentially increasing the potency and/or toxicity of the active ingredient. This is important as volatile solvents are commonly used in drug and other formulations (cosmetic, patch test [64], etc.), for example, an acetone-based benzoyl peroxide product or an acetone-based patch test chemical [64]. (c) Skin patch testing detects contact irritants and allergens, and volatility can lead to false positives and false negatives—test vehicle evaporation leading to too high a test chemical concentration causing a false-positive result [64] and test chemical evaporation leading to too low a test chemical concentration causing a false-negative result [64, 65]. For example, fragrance chemicals are usually volatile substances and are common contact allergens often patch tested as “Fragrance mix 1” and “Fragrance mix 2.” A study of two

radiolabelled fragrance chemicals (geraniol and citronellol) detected that, due to evaporation, within 40 min geraniol lost up to 39% of its dose and citronellol up to 26% of its dose [65]. (d) Rapid volatilization reduces the dose and prevents oversaturation of skin's absorptive capacity. This allows for a direct relationship between dose and percutaneous absorption of volatile substances that is calculable (i.e., predictable). Two equations have been developed to correlate the relationship between volatilization and absorption for a small dose versus a large dose [66]. These equations may be useful in assessing the risk of topical products and their pharmacokinetics/pharmacodynamics/toxicities. An in-depth discussion of these equations is beyond the scope of this paper, and the interested reader should review the reference indicated [66].

Volatility is important in other ways. Mosquito repellents depend on volatility for their effects, and volatility remains a limiting efficacy factor (i.e., in providing sufficient biting protection from mosquitos). Traditional contact repellents such as *N,N*-diethyl-*meta*-toluamide (DEET) applied on human skin require frequent reapplication and may carry a risk of systemic absorption [67]. However, spatial repellents may prevent mosquito entry into particular areas or into a home and may be particularly useful in mosquito-borne disease endemic areas [67]. For example, metofluthrin-impregnated latticework plastic strips were capable of preventing the resting of *Aedes Aegypti* (L.) within residences in Vietnam for a minimum of 8 weeks after they were introduced [67, 68].

### **Does Metabolic Transformation Occur During Topical Absorption and If So, How and What? Does Cutaneous Metabolism Occur?**

Depending on the drug or chemical, *metabolic transformation* can occur in skin prior to systemic absorption, since there are metabolizing enzymes in skin. Both phase I (e.g., CYP450 enzymes) and phase II (e.g., N-acetyltransferase) enzymes have been found in skin—the mRNA and protein being detected more often than the

quantified enzyme activity (being much lower than in the liver and often at the limit of detection) [69]. Sometimes, UV light is required for transformation (see section “[Does photochemical transformation occur during topical absorption and if so, how and what?](#)”). Biotransformation changes the drug or chemical. This change can be in the drug’s physicochemical properties or in its pharmacodynamic activity, or it may be both. This can result in the following: (a) active agent becoming inactive (a degradation process); (b) inactive agent becoming active (an activation process for a pro-drug); (c) a lipophilic agent becoming more water soluble (via various metabolic pathways, e.g., oxidation, hydroxylation, and acetylation). These changes can affect the drug’s penetration through skin. For example, highly lipophilic compounds, often large, do not penetrate through skin well—a good thing). However, the highly lipophilic preservative butylparaben (one example) can be metabolized to p-hydroxybenzoic acid in skin—this metabolite is less lipophilic thus more readily penetrates through skin [2, 70]. Cutaneous metabolism of endogenous substrates such as vitamin A and vitamin D also occurs [2].

## **Does Photochemical Transformation Occur During Topical Absorption and If So, How and What?**

Similarly to section “[Does metabolic transformation occur during topical absorption and if so, how and what? Does cutaneous metabolism occur?](#)”, the effect of UV light on a drug or chemical applied to the skin can cause a *photochemical transformation* (degradation or activation, etc.) In particular, photochemical changes to a drug or chemical can induce a phototoxic or photoallergic reaction. A *phototoxic* reaction is caused by a drug or chemical absorbing UVA and causing direct damage to sun-exposed skin, whereas a *photoallergic* reaction requires the drug or chemical to be changed by UVA into an allergen—with skin damage occasionally spreading beyond the sun-exposed skin areas. *Photosensitivity*—an adverse cutaneous response to normally harmless doses of UV radiation—is a property related to the drug chemistry and can be seen with topical or systemic administra-

tion. Examples of phototoxic agents include amiodarone, tetracyclines (e.g., doxycycline), coal tar, psoralens, and sulfonamides. Examples of photoallergic agents include sulfonamides, sulfonylureas, thiazides, chloroquine, carbamazepine, etc. Practically, if a drug or chemical is known to cause photosensitivity, sun protection is recommended if used during the day; application/dosing at night rather than in more sunlit hours may minimize photosensitivity.

### **How Does Metabolism Affect Excretion Kinetics of the Drug or Chemical? And How Does Excretion Kinetics Relate to Topical Absorption?**

A drug or chemical can be excreted from the body unchanged, or it may undergo metabolic changes before excretion. Thus, the discussions in sections “[Does metabolic transformation occur during topical absorption and if so, how and what? Does cutaneous metabolism occur?](#)” and “[Does photochemical transformation occur during topical absorption and if so, how and what?](#)” regarding biotransformation in the skin will affect excretion kinetics. For example, a highly lipophilic drug or chemical that is biotransformed into a more water-soluble metabolite will not only be more easily absorbed through the skin; it will also be more easily excreted in the urine. Water-soluble drugs often do not require metabolic changes for urinary excretion, and a greater proportion of the administered dose may be excreted unchanged.

Metabolism and excretion are two mechanisms for elimination of drug or chemical, which can be affected by numerous factors [7]. Note that metabolism and excretion pharmacokinetics can differ greatly between structurally similar drugs or chemicals. Thus, depending on the substance, elimination (i.e., *drug clearance*) may or may not be in proportion to the dose absorbed. For researchers conducting in vivo studies, the clearance rate of the drug or chemical must be considered when estimating percutaneous absorption from blood or tissue samples [7].

## How Does Lateral Spread Affect Percutaneous Absorption?

*Lateral spread* is the ability of a topical agent to spread beyond the site of application, that is, the drug or chemical “flows” laterally on the skin surface from the application area to outside of it [71]. (Note that lateral spread is also more commonly used in describing earthquake phenomena.) Lateral spread of a topically applied drug or chemical is a competitive process to drug or chemical penetration into the stratum corneum [71, 72]. The spreading can reduce the amount of drug substance within the area of application, which can modify the desirable effect expected in the treated area [71]. *Time* is a factor: for example, a 10% urea in water solution applied to skin provided a 90.4% recovery rate at the site of application after 1 h versus a 79.6% recovery rate after 6 h [71]. Why is there less urea remaining at the site of application after 6 h than after 1 h? The cause is lateral spread and not percutaneous absorption as less than 1% of urea penetrates in vivo in man [73]. Thus, lateral spread is time dependent. Furthermore, *skin surface topography* can affect the degree of lateral spread: primary furrow networks such as fingerprints and palm prints can function as pathways for lateral spreading [72], whereas follicles and wrinkles can be reservoirs for drugs or chemicals, and little is known about lateral spread in these areas. Although there is no difference in lateral spread between forearm and back [72], little is known about other anatomical sites. Practically, we should be aware that lateral spread happens, and the lengthier the time from the time of application, the greater the effect of lateral spread, resulting in less and less drug or chemical remaining at the site of application for percutaneous absorption.

---

## **For Investigators, Does the Method of Determining Percutaneous Absorption Influence the Results and the Interpretation of Study Results?**

Based on what has been discussed from the 19 factors above, many issues can influence percutaneous absorption and, if not controlled for, can be confounders to study results. In particular, *in vivo* studies would be subject to many more confounding variables than *in vitro* studies. *In vitro* experiments can sometimes be better controlled than *in vivo* studies. Also, differences in experimental parameters such as animal species, anatomical site, vehicle, preparation of skin samples (*in vitro* studies), and other exposure conditions may affect the interpretation of and comparison between studies [2]. Furthermore, there are limits of quantification and limits of detection, which must be kept in mind when interpreting study results.

---

## **Summary**

In summary, percutaneous absorption is complex and requires more thought than just simply applying a topical formulation on the skin and assuming that it works. Many factors—at least the 20 that have been discussed here (Table 1.1)—need to be considered as they may affect the efficacy and/or toxicity of the medications and hence patient outcome.

**Table 1.1** Twenty clinically pertinent factors of percutaneous absorption

|    |                                                                                                                         |
|----|-------------------------------------------------------------------------------------------------------------------------|
| 1  | Relevant physicochemical properties (particle size/molecular weight, lipophilicity, pH, pKa, and partition coefficient) |
| 2  | Vehicle/formulation                                                                                                     |
| 3  | Conditions of drug exposure (dose, duration, surface area, and exposure frequency)                                      |
| 4  | Skin appendages (hair follicles and glands) as sub-anatomical pathways                                                  |
| 5  | Skin application sites (regional variation in penetration)                                                              |
| 6  | Population variability (prematurity, infants, and aged)                                                                 |
| 7  | Skin surface conditions (hydration, temperature, and pH)                                                                |
| 8  | Skin health and integrity (trauma and skin diseases)                                                                    |
| 9  | Substantivity and binding to different skin components                                                                  |
| 10 | Systemic distribution and systemic toxicity                                                                             |
| 11 | Exfoliation                                                                                                             |
| 12 | Washing-off and washing-in                                                                                              |
| 13 | Rubbing/massaging                                                                                                       |
| 14 | Transfer to others (from human to human and hard surface to human)                                                      |
| 15 | Volatility                                                                                                              |
| 16 | Metabolic biotransformation/cutaneous metabolism                                                                        |
| 17 | Photochemical transformation and photosensitivity                                                                       |
| 18 | Excretion kinetics                                                                                                      |
| 19 | Lateral spread                                                                                                          |
| 20 | Chemical method of determining percutaneous absorption                                                                  |

**Acknowledgments** This chapter was originally published in the American Journal of Clinical Dermatology (2020), Vol 21, No. 1, pp. 85–95. It has been reprinted with permission.

## References

1. Wester RC, Maibach HI. Cutaneous pharmacokinetics: 10 steps to percutaneous absorption. *Drug Metab Rev.* 1983;14(2):169–205.
2. Ngo MA, Maibach HI. Chapter 6: 15 factors of percutaneous penetration of pesticides, ACS symposium series. American Chemical Society; 2012. p. 67–86.

3. Hui X, Lamel S, Qiao P, Maibach HI. Isolated human/animal stratum corneum as a partial model for 15 steps in percutaneous absorption: emphasizing decontamination, Part I. *J Appl Toxicol*. 2013;33:157–72.
4. Hui X, Lamel S, Qiao P, Maibach HI. Isolated human and animal stratum corneum as a partial model for the 15 steps in percutaneous absorption: emphasizing decontamination, part II. *J Appl Toxicol*. 2013;33:173–82.
5. Li BS, Ngo MA, Maibach HI. Clinical relevance of complex factors of percutaneous penetration in man. *Curr Top Pharmacol*. 2017;21:85–107. Available at: [http://www.researchtrends.net/tia/title\\_issue.asp?id=11&in=0&vn=21](http://www.researchtrends.net/tia/title_issue.asp?id=11&in=0&vn=21)
6. Keurentjes AJ, Maibach HI. Percutaneous penetration of drugs applied in transdermal delivery systems: an in vivo based approach for evaluating computer generated penetration models. *Regul Toxicol Pharmacol*. 2019 Jul;18:104428.
7. Burton ME, Schentag JJ, Shaw LM, Evans WE. Applied pharmacokinetics and pharmacodynamics: principles of therapeutic drug monitoring. 4th ed. Lippincott, Williams, and Wilkins; 2006.
8. Marechal Y. The water molecule in (bio)macromolecules. In: The hydrogen bond and the water molecule: the physics and chemistry of water, aqueous and bio media. Elsevier; 2007. p. 249–75. <https://doi.org/10.1016/B978-044451957-3.50011-1>. ISBN 9780444519573, 0444519572;.
9. Wester RC, Noonan PK, Maibach HI. Frequency of application on percutaneous absorption of hydrocortisone. *Arch Dermatol*. 1977;113:620–2.
10. Berardesca E, Mariano M, Cameli N. Biophysical properties of ethnic skin. In: Vashi NA, Maibach HI, editors. *Dermatoanthropology of ethnic skin and hair*. Cham: Springer Nature, Springer International Publishing AG; 2017.
11. Berardesca E, Maibach HI. Racial differences in sodium lauryl sulfate induced cutaneous irritation: black and white. *Contact Derm*. 1988;18:65–70.
12. Berardesca E, Maibach HI. Sodium-lauryl-sulfate-induced cutaneous irritation. Comparison of white and Hispanic subjects. *Contact Derm*. 1988;19:136–40.
13. Roskos KV, Maibach HI, Guy RH. The effect of aging on percutaneous absorption in man. *J Pharmacokinetic Biopharm*. 1989;17(6):617–30.
14. Hoath SB, Maibach HI. Neonatal skin: structure and function. 2nd ed. CRC Press; 2003.
15. Mauro TM, Behne MJ. Chapter 3: Acid mantle. In: Hoath SB, Maibach HI, editors. *Neonatal skin: structure and function*. 2nd ed. CRC Press; 2003.
16. Nikolovski J, Stamatas GN, Kollias N, et al. Barrier function and water-holding and transport properties of infant stratum corneum are different from adult and continue to develop through the first year of life. *J Invest Dermatol*. 2008;128:1728–36.



17. Oranges T, Dini V, Romanelli M. Skin physiology of the neonate and infant: clinical implications. *Adv Wound Care*. 2015;4(10):587–95.
18. Hoeger PH, Enzmann CC. Skin physiology of the neonate and young infant: a prospective study of functional skin parameters during early infancy. *Pediatr Dermatol*. 2002;19:256–62.
19. Visscher MO, Chatterjee R, Munson KA, et al. Changes in diapered and non-diapered infant skin over the first month of life. *Pediatr Dermatol*. 2000;17:45–51.
20. Saijo S, Tagami HJ. Dry skin of newborn infants: functional analysis of the stratum corneum. *Pediatr Dermatol*. 1991;8:155–9.
21. Brayer C, Micheau P, Bony C, et al. Neonatal accidental burn by isopropyl alcohol. *Arch Pediatr*. 2004;11(8):932–5.
22. DeBellonia RR, Marcus S, Shih R, et al. Curanderismo: consequences of folk medicine. *Pediatr Emerg Care*. 2008;24(4):228–9.
23. George AJ. Toxicity of boric acid through skin and mucous membranes. *Food Cosmet Toxicol*. 1965;3:99–101.
24. Martin-Bouyer G, Toga M, Lebreton R, et al. Outbreak of accidental hexachlorophene poisoning in France. *Lancet Public Health*. 1982;319(8263):91–5.
25. Mullick FG. Hexachlorophene toxicity—human experience at the Armed Forces Institute of Pathology. *Pediatrics*. 1973;51(2):395.
26. Li BS, Cary JH, Maibach HI. Should we instruct patients to rub topical agents into skin? The evidence. *J Dermatolog Treat*. 2018;30:1–5.
27. Evans NJ, Rutter N, Hadgraft J, et al. Percutaneous administration of theophylline in the preterm infant. *J Pediatr*. 1985;107(2):307–11.
28. Zhai H, Maibach HI. Effects of skin occlusion on percutaneous absorption: an overview. *Skin Pharmacol Appl Ski Physiol*. 2001;14(1):1–10.
29. Shomaker TS, Zhang J, Ashburn MA. A pilot study assessing the impact of heat on the transdermal delivery of testosterone. *J Clin Pharmacol*. 2001;41(6):677–82.
30. Aly R, Shirley C, Cunico B, Maibach HI. Effect of prolonged occlusion on the microbial flora, pH, carbon dioxide and transepidermal water loss on human skin. *J Invest Dermatol*. 1978;71(6):378–81.
31. Gattu S, Maibach HI. Modest but increased penetration through damaged skin: an overview of the in vivo human model. *Skin Pharmacol Physiol*. 2011;24(1):2–9. (Published Dec 2010)
32. Gattu S, Maibach HI. Enhanced absorption through damaged skin: an overview of the in vitro human model. *Skin Pharmacol Physiol*. 2010;23:171–6.
33. Morgan CJ, Renwick AG, Friedmann PS. The role of stratum corneum and dermal microvascular perfusion in penetration and tissue levels of water-soluble drugs investigated by microdialysis. *Br J Dermatol*. 2003;148:434–43.

34. Jakasa I, Verberk MM, Bunge AL, et al. Increased permeability for polyethylene glycols through skin compromised by sodium lauryl sulfate. *Exp Dermatol*. 2006;15:801–7.
35. Jacob SE. Percutaneous absorption risks in atopic dermatitis. *Br J Dermatol*. 2017;177:11–2.
36. Halling-Overgaard AS, Kezic S, Jakasa I, et al. Skin absorption through atopic dermatitis skin: a systematic review. *Br J Dermatol*. 2017;177(1):84–106.
37. Garcia OP, Hansen SH, Shah VP, et al. Impact of adult atopic dermatitis on topical drug absorption: assessment by cutaneous microdialysis and tape stripping. *Acta Derm Venereol*. 2009;89:33–8.
38. Tauber M, Balica S, Hsu CY, et al. Staphylococcus aureus density on lesional and nonlesional skin is strongly associated with disease severity in atopic dermatitis. *J Allergy Clin Immunol*. 2016;137:1272–1274, e1–e3.
39. Jakasa I, de Jongh CM, Verberk MM, et al. Percutaneous penetration of sodium lauryl sulfate is increased in uninvolved skin of patients with atopic dermatitis compared with control subjects. *Br J Dermatol*. 2006;155:104–9.
40. Jakasa I, Verberk MM, Esposito M, et al. Altered penetration of polyethylene glycols into uninvolved skin of atopic dermatitis patients. *J Invest Dermatol*. 2007;127:129–34.
41. Hata M, Tokura Y, Takigawa M, et al. Assessment of epidermal barrier function by photoacoustic spectrometry in relation to its importance in the pathogenesis of atopic dermatitis. *Lab Invest*. 2002;82:1451–61.
42. Mochizuki J, Tadaki H, Takami S, et al. Evaluation of out-in skin transparency using a colorimeter and food dye in patients with atopic dermatitis. *Br J Dermatol*. 2009;160:972–9.
43. Alikhan FS, Maibach HI. Topical absorption and systemic toxicity. *Cutan Ocul Toxicol*. 2011;30(3):175–86.
44. Lewis PR, Phillips TG, Sassani JW. Topical therapies for glaucoma: what family physicians need to know. *Am Fam Phys*. 1982;1999(59):1871–9.
45. Goldberg I, Moloney G, McCluskey P. Topical ophthalmic medications: what potential for systemic side effects and interactions with other medications? *Med J Aust*. 2008;189:356–7.
46. Rubin Z. Ophthalmic sulfonamide-induced Stevens-Johnson syndrome. *Arch Dermatol*. 1977;113:235–6.
47. Raschke R, Arnold-Capell PA, Richeson R, et al. Refractory hypoglycemia secondary to topical salicylate intoxication. *Arch Intern Med*. 1991;151:591–3.
48. Zheng Y, Vieille-Petit A, Chodoutard S, Maibach HI. Dislodgeable stratum corneum exfoliation: role in percutaneous penetration? *Cutan Ocul Toxicol*. 2011;30(3):198–204.
49. Suny XX, Maibach HI. Skin decontamination. Heidelberg: Springer; 2019. (in press)

50. Rodriguez J, Maibach HI. Percutaneous penetration and pharmacodynamics: wash-in and wash-off of sunscreen and insect repellent. *J Dermatolog Treat*. 2016;27:11.
51. Moody RP. Letter to the editor: the safety of diethyltoluamide insect repellents. *JAMA*. 1989;262:28–9.
52. Moody RP, Benoit FM, Riedel R, Ritter L. Dermal absorption of the insect repellent DEET (N,N-diethyl-m-toluamide) in rats and monkeys: effect of anatomical site and multiple exposure. *J Toxicol Environ Health*. 1989;26:137–47.
53. Lademann J, Patzelt A, Schanzer S, et al. *In vivo* laser scanning microscopic investigation of the decontamination of hazardous substances from the human skin. *Laser Phys Lett*. 2010;7:884–8.
54. Trauer S, Richter H, Kuntsche J, et al. Influence of massage and occlusion on the ex vivo skin penetration of rigid liposomes and invasomes. *Eur J Pharm Biopharm*. 2014;86:301–6.
55. Phuong C, Maibach HI. Effect of massage on percutaneous penetration and skin decontamination: man and animal. *Cutan Ocul Toxicol*. 2016;35(2):153–6.
56. Delamour E, Miksa S, Lutz D, Guy C. How to prove ‘rub-resistant’ sun protection. *Cosmetics & Toiletries Science Applied* 2016. Available at: <https://www.cosmeticsandtoiletries.com/testing/efficacyclaims/How-to-Prove-Rub-resistant-Sun-Protection-373779591.html>. Accessed 12 Mar 2019.
57. Franklin SF, Geffner ME. Precocious puberty secondary to topical testosterone exposure. *J Pediatr Endocr Metab*. 2003;16:107–10.
58. Wester RC, Hui X, Maibach HI. *In vivo* human transfer of topical bioactive drug between individuals: estradiol. *J Invest Dermatol*. 2006;126:2190–3.
59. Linck M. Screens detect all: Mom, dad, kids, newborns all test positive for meth. *Sioux City Journal*, December 18, 2003. Available at: [https://siouxcityjournal.com/news/screens-detect-all-mom-dad-kids-newborns-all-test-postive/article\\_5c9a48cf-4855-5308-ba83-c11bf1b44239.html](https://siouxcityjournal.com/news/screens-detect-all-mom-dad-kids-newborns-all-test-postive/article_5c9a48cf-4855-5308-ba83-c11bf1b44239.html). Accessed 13 Mar 2019.
60. Dmochowski RR, Newman DK, Sand PK, et al. Pharmacokinetics of oxybutynin chloride topical gel. *Clin Drug Investig*. 2011;31(8):559–71.
61. Isnardo D, Vidal J, Panyella D, Vilaplana J. Nickel Transfer by Fingers *Actas Dermo-Sifiliográficas* (English Edition) 2015;106(5). <https://doi.org/10.1016/j.adengl.2015.04.011>.
62. Salocks CB, Hui X, Lamel S, et al. Dermal exposure to methamphetamine hydrochloride contaminated residential surfaces: surface pH values, volatility, and *in vitro* human skin. *Food Chem Toxicol*. 2012;50(12):4426–40.
63. Rouse NC, Maibach HI. The effect of volatility on percutaneous absorption. *J Dermatol Treat*. 2016;27(1):5–10.

64. Bruze M. Thoughts on how to improve the quality of multicentre patch test studies. *Contact Derm.* 2016;74:168–74.
65. Gilpin SJ, Hui X, Maibach HI. Volatility of fragrance chemicals: patch testing implications. *Dermatitis.* 2009;20(40):200–7.
66. Kasting GB, Miller MA. Kinetics of finite dose absorption through skin 2: volatile compounds. *J Pharm Sci.* 2006;95:268–80.
67. Norris EJ, Coats JR. Current and future repellent technologies: the potential of spatial repellents and their place in mosquito-borne disease control. *Int J Environ Res Public Health.* 2017;14(2):124–68.
68. Kawada H, Temu EA, Minjas JN, et al. Field evaluation of field repellency of metofluthrin impregnated latticework plastic strips against *Aedes aegypti* (L.) and analysis of environmental factors affecting its efficacy in My Tho City, Tien Giang, Vietnam. *Am J Trop Med Hyg.* 2006;75:1153–7.
69. Kazem S, Linssen EC, Gibbs S. Skin metabolism phase I and phase II enzymes in native and reconstructed human skin: a short review. *Drug Discovery Today* June 2019 ePub ahead of print. Available at: <https://www.sciencedirect.com/science/article/pii/S1359644618302198>.
70. Bando H, Mohri S, Yamashita F, et al. Effects of skin metabolism on percutaneous penetration of lipophilic drugs. *J Pharm Sci.* 1997;86(6):759–61.
71. Vieille-Petit A, Blickenstaff N, Coman G, Maibach H. Metrics and clinical relevance of percutaneous penetration and lateral spreading. *Skin Pharmacol Physiol.* 2015;28:57–64.
72. Jacobi U, Schanzer S, Weigmann H-J, et al. Pathways of lateral spreading. *Skin Pharmacol Physiol.* 2011;24:231–7.
73. Feldman RJ, Maibach HI. Absorption of some organic compounds through the skin in man. *J Invest Dermatol.* 1970;54:399–404.



# Pharmaceutical Compounding of Topical Dermatologic Treatments

# 2

Maggie Shukla, Heather Warren,  
and Stephen Coombs

## Contents

|                                                                                    |    |
|------------------------------------------------------------------------------------|----|
| Introduction.....                                                                  | 32 |
| Important Abbreviations.....                                                       | 33 |
| When to Compound.....                                                              | 34 |
| Quality Assurance [1, 2].....                                                      | 34 |
| Master Formula Creation [1, 2].....                                                | 36 |
| General Compounding Techniques and Equipment.....                                  | 36 |
| Compounding Bases.....                                                             | 39 |
| Considerations When Choosing an Appropriate Compounding<br>Base [1, 2, 10–12]..... | 40 |

---

M. Shukla · H. Warren

Compounding Wellness Sterile Lab, Mount Pearl, NL, Canada

e-mail: [maggiec@mun.ca](mailto:maggiec@mun.ca); [heatherw@compoundingwellness.ca](mailto:heatherw@compoundingwellness.ca)

S. Coombs (✉)

School of Pharmacy, Memorial University, St. John's, NL, Canada

Faculty of Medicine, Discipline of Family Medicine, Memorial  
University, St. John's, NL, Canada

e-mail: [n45sdc@mun.ca](mailto:n45sdc@mun.ca)

© The Author(s), under exclusive license to Springer Nature  
Switzerland AG 2025

R. M. Law, H. I. Maibach (eds.), *Handbook of Topical Drug  
Treatment in Dermatology*,

[https://doi.org/10.1007/978-3-031-93616-6\\_2](https://doi.org/10.1007/978-3-031-93616-6_2)

31

|                                                      |    |
|------------------------------------------------------|----|
| Excipients.....                                      | 45 |
| Active Pharmaceutical Ingredients.....               | 50 |
| Communication.....                                   | 62 |
| Considerations When Writing a Compounded Preparation |    |
| Prescription.....                                    | 63 |
| References.....                                      | 64 |

---

## Introduction

Pharmaceutical compounding is an integral part of pharmacy, medicine, and the healthcare system. Compounding in dermatology contributes to current therapeutics by personalizing treatments, filling therapeutic gaps, aiding adherence, and providing treatments during medication shortages. It can be defined as the process of combining, mixing, or altering ingredients to create medication tailored to the needs of a patient [1].

Pharmaceutical compounding can carry significant risk. Compounded medications are indicated for off-label use and not approved by national regulatory bodies such as the US Food and Drug Administration (FDA) or Health Canada. However, when appropriate standards of practice are considered, the benefits of administering a compounded medication can be much greater than the associated risks. Standards of practice for pharmaceutical compounding have become more stringent to ensure patient safety while preserving patient access. They are adopted and enforced primarily by state or provincial regulatory bodies.

In North America, United States Pharmacopeia (USP) includes General Chapter 795 directly addressing pharmaceutical compounding of non-sterile preparations and the National Association of Pharmacy Regulatory Authorities (NAPRA) developed the model standards of non-sterile preparations along with a guidance document [1, 2]. In general, these standards cover requirements for compounding personnel, training and skills assessment, policies and procedures, equipment, facility layout, and quality assurance.

When referring to this chapter, it is important to be cognizant of the fact that each country has different regulations pertaining to what active pharmaceutical ingredients (APIs) or bulk drug substances can be used when compounding. For example, the 503A compounding pharmacies bulk list (i.e., active pharmaceutical ingredient list) and the difficult to compound list have been created by the FDA. Before compounding, all compounders have a responsibility to ensure they are following their local compounding standards and regulations [3, 4].

Availability of evidence-based medicine is imperative to healthcare professional decision-making. Pharmaceutical compounding is a form of personalized medicine and therefore is often informed by lower-level evidence, such as case reports and case series. Depending on the frequency of use of a compounded preparation for a specific off-label indication, randomized controlled trials, systematic reviews, and other higher-level evidence may be available. However, higher-level evidence oftentimes requires a financial commitment unattainable for such personalized medicine. Nonetheless, when any level of evidence is combined with patient specific factors to support the use of a compounded medication, this shared decision should be made between the compounder, patient, and prescriber. The ability to offer compounded preparation options to patients can be a great tool for all healthcare professionals.

This chapter aims to cover common questions that may arise when recommending or writing a compounded prescription, preparing a compounded preparation, or discussing compounding options with a patient. The contents of this chapter are not a limitation to what compounding options are available for dermatology as pharmaceutical compounding is constantly evolving.

---

## Important Abbreviations

The following abbreviations are used throughout this chapter:

APIs: Active Pharmaceutical Ingredients

FDA: Food and Drug Administration

NAPRA: National Association of Pharmacy Regulatory Authorities

USP-NF: United States Pharmacopeia and the National Formulary

BUD: Beyond use date

IJPC: International Journal of Pharmaceutical Compounding

---

## When to Compound

When considering whether a compounded topical preparation for a patient is appropriate and beneficial, circumstances where compounding is inappropriate must be avoided. Table 2.1 is a useful tool to help guide the compounding decision-making process.

---

## Quality Assurance [1, 2]

As mentioned previously, compounding is not regulated by national regulatory bodies such as the US FDA or Health Canada. Quality assurance is a standard of practice in compounding, and these programs must be created and enforced by the compounders and their facilities. Quality assurance programs are additionally audited for compliance by state or provincial regulatory bodies.

A quality assurance program is developed and implemented to ensure processes are clearly defined, including application and verification of all activities, that affect the quality of the final compounded preparations. It also ensures protection of personnel who are compounding. Each verification step (carried out in accordance with the quality assurance program) should be documented. Quality assurance programs cover multiple components involved in the compounding process such as facility requirements, equipment used, personnel, the act of compounding itself, and final preparation verification. Within these components, there will be designated controls (e.g., skills assessment of personnel) and frequency at which reassessment or certification should be carried out (e.g., yearly).



**Table 2.1** When compounding is appropriate or inappropriate [1, 2, 5, 6]

| Appropriate                                                                                                                                                                                                                                                                                                | Inappropriate                                                                                                                                                                                                |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Customizing a compounded preparation for a patient by:<br>Adjusting the dosage of the API<br>Choosing the most appropriate base for the condition being treated<br>Combining APIs that work synergistically together                                                                                       | Compounding a product that is the same as a product that is currently available on the market (i.e., duplication of a manufactured product)                                                                  |
| Providing pharmaceutical dosage forms that are not available commercially (e.g., preparing a topical solution of an API when only oral capsules are commercially available)                                                                                                                                | Compounding beyond the scope of practice; this refers to compounding without the appropriate knowledge, expertise and equipment/facilities required to provide a quality, safe, effective compounded product |
| Meeting the needs of a patient requiring products for rare disease states, also known as orphan diseases, for which the pharmaceutical industry is not currently developing products                                                                                                                       | Compounding without a developed formula or without appropriate references and supporting documentation to develop your own formula                                                                           |
| Offering a different dosage strength than those available by manufacturers. Dosage adjustment may be needed to optimize the risk-benefit profile specific to the patient                                                                                                                                   | Compounding a product that includes an API deemed ineffective or unsafe for human use or has been discontinued from the market after being found unsafe or ineffective                                       |
| Providing a compounded alternative when a product is not currently available because of manufacturer shortage, or the product is withdrawn from the market (i.e. for reasons other than medication safety issues)                                                                                          | Compounding with an API that has been excluded for use in compounding by your specific regulatory body (e.g., FDA, Health Canada)                                                                            |
| Altering the preparation such that application is conducive to adherence, either by modifying the physical properties of the formulation (e.g., change base from ointment to cream) or combining several active ingredients into a single formulation (e.g., combining an antifungal and a corticosteroid) |                                                                                                                                                                                                              |
| Removing or exchanging excipients or bases due to allergy, intolerance, or a possible drug interaction                                                                                                                                                                                                     |                                                                                                                                                                                                              |

---

## Master Formula Creation [1, 2]

Compounders develop master formulas for each compounded preparation. These formulas are specific to each compounding facility and follow requirements described in compounding standards of practice and their quality assurance program. A literature search should be completed to gather all information available regarding a specific ingredient or compound and listed as references in the master formula. Likewise, there are multiple resources to aid in formula creation (e.g., USP-NF, Remington, Trissel's, The Merck Index, IJPC, and Compounding Today). There are also formulas created by compounding supply companies who have carried out the majority of the physiochemical research required and make up the bulk of a master formula.

---

## General Compounding Techniques and Equipment

To prepare a topical dermatological preparation that is both pharmaceutically elegant and optimally formulated the compounder must employ specific techniques during the mixing process. This may include the use of compounding equipment that not only produces a product with more favorable characteristics (e.g., small particle size of APIs) but also makes the compounding process more efficient. Table 2.2 describes some of the most common compounding techniques used when preparing topical preparations. Table 2.3 outlines equipment that can be used.

**Table 2.2** Commonly used techniques when compounding topical preparations [7, 8]

| Technique                           | Definition                                                                                                                                                                    | How is this achieved?                                                                                                                                                                                                                                                                                             |
|-------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Geometric addition/<br>dilution     | The standard procedure is used to achieve a homogenous blend when two or more components are mixed. This ensures active ingredients are evenly dispersed within a preparation | The compounder starts with ingredients of the smallest quantity and effectively “dilutes” it by adding an equal portion of another ingredient of the next smallest quantity. This is continued incrementally by doubling the portions mixed. The procedure is repeated until all the ingredients are incorporated |
| Trituration/<br>milling             | The act of reducing the particle size of a powder                                                                                                                             | Can be achieved by the continuous grinding or rubbing of the powder in a mortar with a pestle<br>Trituration may be achieved by levigation or wetting<br>May be achieved mechanically through the use of equipment (e.g., ointment mill)                                                                          |
| Levigation                          | The process of decreasing the particle size of powders via trituration with a mortar and pestle and a small amount of liquid in which the substance is insoluble              | The specific liquid used is called a levigating agent and is viscous in nature. It has a low surface tension to easily wet the solid particles. Such agents also act as a lubricant as they also allow a smoother incorporation of solids in the preparation                                                      |
| Pulverization<br>by<br>intervention | Used with hard crystalline powders that do not crush or triturate easily, or for gummy type substances                                                                        | A solvent, such as alcohol or acetone, that will dissolve the compound is mixed in a mortar with the powder. The evaporation of the solvent is carried out afterward                                                                                                                                              |
| Spatulation                         | The mixing of powders and semisolids (ointments, creams, etc.) using a spatula                                                                                                | A spatula is used to continuously heap the powders and/or solids together and then smoothing the mass out on a glass or paper slab<br>This process does not reduce particle size, so this must be previously accomplished if required                                                                             |

**Table 2.3** Commonly used equipment for compounding of topical preparations [2, 8, 9]

| Equipment                          | Explanation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Mortar and pestle                  | <p>A set of two simple tools used to prepare ingredients or substances by crushing and grinding them into a fine paste or powder</p> <p>The mortar is the bowl, and the pestle is the blunt, club shaped object</p> <p>Pharmaceutical mortar and pestles are typically made of either ceramic, glass, or a more porous porcelain. The correct mortar and pestle type should be chosen based on the ingredients to be grinded; harder ingredients may require a more porous mortar and pestle</p> <p>The ingredient to be ground, which may be wet or dry, is placed in the mortar where the pestle is pounded, pressed, and rotated into the substance until the desired texture is achieved</p>           |
| Ointment slab and spatula          | <p>Ointment slabs provide a clean, hard surface for the mixing of preparations</p> <p>Types of ointment slabs include reusable glass slabs or disposable parchment paper slabs that require less cleaning in between preparations</p> <p>Typically, a spatula is used to mix the preparation on the slab</p>                                                                                                                                                                                                                                                                                                                                                                                               |
| Electronic mortar and pestle (EMP) | <p>The device uses both horizontal and vertical mixing movements via mixing blades contained in a polypropylene jar to produce a homogeneous preparation</p> <p>The mixing blade rotates at speeds between 200 and 2500 rpm depending on the specific brand and engine size</p> <p>The shear force between the blade and side of the EMP jar results in some particle size reduction, although powders that are crystalline and granular may still need to be triturated before incorporation</p> <p>It provides time-efficient preparation</p> <p>It is more costly than the traditional mortar and pestle set and requires regular maintenance, as well as specialized blades and containers for use</p> |

(continued)

**Table 2.3** (continued)

| Equipment          | Explanation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ointment mill      | Used for intensive trituration and dispersion of ointments, creams, pastes, gels, and suspensions<br>A preparation is run through the mill where there are generally three rollers made either from a ceramic or aluminum oxide material<br>The preparation is fed through the instrument on the roller furthest from the operator. The preparation passes through the two gaps formed between the three rollers. The shearing action of the rollers results in the reduction of particle size and dispersion of powders<br>The range of function of ointment mills varies between brands<br>Cost is a considerable factor when purchasing |
| Electronic balance | A requirement to participate in pharmaceutical compounding, used to accurately weigh material<br>Replaces traditional torsion balances and weight systems<br>The lowest amount of material that can be weighed accurately on a scale, as well as the scale's sensitivity, must be considered by compounders, as there is great variation between scale models                                                                                                                                                                                                                                                                              |

## Compounding Bases

The quality and efficacy of topical compounded preparations is largely influenced by the base chosen. The compounder must consider if the selected base is appropriate for the indication and the patient and if it can properly deliver the APIs to the site of action. Commercial cosmetic creams tend to be a poor choice for compounding. Many times, they already contain a large number of ingredients and are not generally designed to hold additional APIs. Therefore, it is a good idea to use an innovative proprietary compounding base that has been designed specifically to deliver the APIs required. These proprietary bases are also commonly fragrance free, hypoallergenic, preservative-free, and alcohol-free. However, to ensure informed decision-making while compounding, these bases should be used by compounders that have access to their composition.

Numerous bases have been preformulated by compounding supply companies for specific conditions; examples include muco-adhesive gels that prolong contact time between an API and

the area of treatment and bases containing excipients that work synergistically with the API.

---

### **Considerations When Choosing an Appropriate Compounding Base [1, 2, 10–12]**

- Carrying capacity of the base
  - Does the active ingredient have a salt concentration that the base can support?
  - Is there more than one ingredient?
  - How much of the API can be incorporated into the base without the preparation breaking, rendering the compound unusable?
- Beyond use date (BUD)
  - Is the base anhydrous? This generally extends the BUD the compounder can give (e.g., USP 795 states in the absence of stability data, the BUD 6 months or not later than the time remaining until the earliest expiration date of any API, whichever is earlier).
  - Does the base contain water? This generally shortens the BUD the compounder can give (e.g., USP 795 states in the absence of stability data, the BUD is not later than 30 days).
- Site of action
  - Where will the cream be applied? (e.g., skin and mucosal)
  - Is the area covered in hair or a smooth surface?
  - What is the surface area to be covered?
  - Does the area contain thick or thin skin?
  - Is the preparation intended to sit on top of skin locally, or is deeper penetration required to be effective (i.e., topical or transdermal delivery)?

- Patient preference
  - Nongreasy preparation?
  - Gluten free, vegan, nonallergenic?
  - An easily spreadable preparation?
  - A lower-cost preparation?
- Intended use of the compounding preparation
  - Provide moisture while healing?
  - Act as an occlusive?
  - Decrease exudate and promote wound healing?
  - Act as an adhesive to hold drugs at site of action?
  - Deeply penetrate through various layers of skin?
- Chemical properties of the API(s)
  - Hydrophilic or hydrophobic (or both)?
  - Acidic or basic (i.e., pH)?
  - Crystalline, powder, or liquid?
  - Stability at different temperatures and in different bases?
  - Molecular weight?
  - Partition coefficient?
- Integrity of the skin
  - Is the skin barrier damaged (e.g., open wound)?
  - Is the skin red, irritated, or dry?
  - Is there an exudate being produced?
  - Is there scar tissue?
  - Is the skin considered thick (e.g., soles and palms) or thin (e.g., genital area and eyelids)?
  - What is the patient's age (e.g., very old, very young)?

Tables 2.4 and 2.5 outline the most commonly used compounding bases and provide supplemental information on each.

**Table 2.4** Ointment bases [7, 10–12]

| Ointments                  |                                                                                                                                                              |                                                                 |                                                                                    |                                                        |
|----------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|------------------------------------------------------------------------------------|--------------------------------------------------------|
| Ointment type              | Properties                                                                                                                                                   | Uses                                                            | Levitating agents that can be used to incorporate solid API into base <sup>a</sup> | Examples                                               |
| Oleaginous base            | Anhydrous<br>Do not absorb water<br>Forms occlusive film on skin<br>Not water washable                                                                       | Protectant, emollient, drug carrier for hydrophobic API(s) only | Mineral oil                                                                        | Petrolatum, wax, synthetic esters, white soft paraffin |
| Absorption base            | Oleaginous base plus a water-in-oil emulsifier<br>Can incorporate aqueous solution and/or alcohol<br>Not easily water washable                               | Protectant, emollient, drug carrier                             | Mineral oil                                                                        | Anhydrous lanolin, hydrophilic petrolatum USP          |
| Water-in-oil emulsion base | Contains water<br>Oleaginous base plus water-in-oil emulsifier plus water<br>Allows easier incorporation of an aqueous solution<br>Not easily water washable | Emollient, drug carrier                                         | Mineral oil, glycerin, propylene glycol                                            | Hydrous lanolin, cold cream USP                        |



| Ointment type                                                   | Properties                                                                                                                                                                                                                                                                                                                                      | Uses                    | Levitating agents that can be used to incorporate solid API into base <sup>a</sup> | Examples                                          |
|-----------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|------------------------------------------------------------------------------------|---------------------------------------------------|
| Oil-in-water emulsion base (also known as water removable base) | <p>Contains water</p> <p>Oleaginous base plus oil-in-water emulsifier plus water</p> <p>Leaves a hydrophobic film on the surface of skin when the water evaporates</p> <p>Water washable</p> <p>Has a cream like appearance</p> <p>Can be further diluted with water</p> <p>Can absorb serous discharge caused by dermatological conditions</p> | Emollient, drug carrier | Glycerin<br>propylene glycol, polysorbate 80                                       | Vanishing cream, hydrophilic ointment USP         |
| Water-soluble base                                              | <p>Contains water</p> <p>Nongreasy</p> <p>Nonocclusive</p> <p>Lipid-free and water-soluble</p> <p>Water washable</p> <p>Has a cream like appearance</p> <p>Can be further diluted with water</p>                                                                                                                                                | Drug carrier            | Glycerin<br>Propylene glycol<br>Polyethylene glycol                                | Polyethylene glycol ointment USP, Emollient cream |

<sup>a</sup>Levitating agents included in this table are not exhaustive and are included only to provide suggestions

**Table 2.5** Other types of bases [11–13]

| Base type | Important points                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Creams    | <p>A highly viscous emulsion base is commonly referred to as a cream</p> <p>A semisolid base that may contain one or more ingredients dissolved or dispersed</p> <p>Either a w/o (i.e., oily creams) or o/w (i.e., aqueous creams) emulsion base</p> <p>Water-soluble drugs are dispersed in aqueous creams</p> <p>Lipid-soluble drugs are dispersed in oily creams</p> <p>Creams are more fluid than ointments</p> <p>Creams are desirable for the patient because they have an elegant appearance, are more readily spread on the skin, and are less greasy, and they rub into the skin leaving little or no trace</p> |
| Lotions   | <p>Low-to-medium viscosity topical preparation, usually applied to unbroken skin</p> <p>An insoluble fine powder drug can be suspended or dispersed into a lotion</p> <p>Is easily spreadable and therefore can be used in hair covered areas and large areas</p> <p>Has no emollient or skin protective properties</p>                                                                                                                                                                                                                                                                                                  |
| Gels      | <p>Semisolid base that consists of small or large molecules in an aqueous liquid vehicle. The aqueous vehicle has been thickened with a gelling agent</p> <p>Nongreasy, easy to apply and wash off</p> <p>Once on the skin, it changes from a semisolid state to a liquefied state and then dries to a nonocclusive film</p> <p>Easy to apply to hair covered areas and can be used in mucosal areas</p> <p>Has no emollient or skin protective properties</p> <p>Compounded gels can be useful in wound care, as they are easily applied over the affected area</p>                                                     |
| Solutions | <p>A nonaqueous, aqueous, or hydroalcoholic liquid, which contains solutes that are dissolved to the point of clarity</p> <p>Is very easily spreadable, oftentimes leading to messy applications</p> <p>Very simple to compound</p> <p>Solutions are commonly used when compounding preparations for dermatological conditions affecting the scalp and ears</p>                                                                                                                                                                                                                                                          |

## Excipients

Active pharmaceutical ingredient is the term generally used to describe the substances in drugs that are responsible for the beneficial health effects experienced by patients [5]. Therefore, all other ingredients are referred to as either inactive, non-medicinal, or excipients. Excipients are important for the integrity of the compounded preparation, functioning as stabilizers and therapeutically enhancing the API in the final dosage form [14]. Excipients used in compounding should be of pharmaceutical grade (e.g., USP-NF). Table 2.6 outlines common excipients and possible functions. To note, colorants are also excipients but not listed in Table 2.6 as they are most often approved dyes.

Considerations when choosing specific excipients:

- Patient preference
- Drug properties (hydrophilic, lipophilic, pH, and solubility)
- Desired viscosity of final preparation
- Desired consistency of final preparation
- Patient specific sensitivities
- Area of application
- Site of action (e.g., topical, transdermal)
- Cosmeceutical elegance (e.g., color and odor)

**Table 2.6** Excipients commonly used in topical compounded preparations [14–20]

| Example excipients                                                                                                                                                                                               | Functional category                          | Details                                                                                                                                                                                                                                                   |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Alpha hydroxyl acids<br>(lactic acid)<br>Glycerin<br>Propylene glycol<br>Sorbitol<br>Urea                                                                                                                        | Humectant                                    | Hygroscopic substances that promote water retention and prevent drying of preparations. May be helpful in enhancing active ingredient solubility and, thus, its ability to penetrate the skin<br>Should be stored in tight, light-resistant containers    |
| Propylene glycol<br>monostearate<br>Emulsifying wax<br>Diethylene glycol<br>monoethyl ether<br>Polysorbate 20/80/60<br>Docusate sodium<br>Poloxamer<br>Sodium lauryl sulfate<br>Sorbitan monopalmitate<br>Acacia | Emulsifying/solubilizing agent<br>Surfactant | Reduce interfacial tension resulting in stabilizing an emulsion. In hydrophobic materials, these agents enhance solubility and wetting<br>Selection of an appropriate surfactant is important for establishing the hydrophilic lipophilic balance system. |

|                                                                                                                                                                                                                                                                                |                                                        |                                                                                                                                                                                                                                                                                                                                                              |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>Ethanol</p> <p>Isopropyl alcohol</p> <p>Propylene glycol (adjunct for synergism)</p> <p>Polyethylene glycol</p> <p>Isopropyl palmitate</p> <p>Isopropyl myristate</p> <p>Azone</p> <p>Dimethyl sulfoxide (DMSO)</p> <p>Limonene</p> <p>Menthol</p> <p>Urea</p> <p>Water</p> | <p>Permeation enhancer</p> <p>Penetration enhancer</p> | <p>Enhances diffusion or solubility in order to pass through the stratum corneum</p> <p>Should be nontoxic, nonirritating, and nonallergenic</p> <p>Menthol, urea, and DMSO have the highest irritation potential</p> <p>If larger amounts of alcohol-based enhancers are required in a particular formula, there is potential for excessive skin drying</p> |
| <p>Imidurea</p> <p>Sorbic acid</p> <p>Benzoid acid</p> <p>Boric acid</p> <p>Imidurea propyl paraben</p> <p>Benzalkonium chloride</p> <p>Methyl paraben</p>                                                                                                                     | <p>Preservative</p>                                    | <p>Inhibits bacterial and fungal growth. However, these ingredients frequently cause allergic contact dermatitis and sensitive patients may need them removed</p>                                                                                                                                                                                            |

(continued)

**Table 2.6** (continued)

| Example excipients                                                                                                                                                                                                                                                       | Functional category      | Details                                                                                                             |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|---------------------------------------------------------------------------------------------------------------------|
| Guar gum<br>Xanthan gum<br>Gelatin<br>Carbomer<br>Sodium carboxyl methyl cellulose<br>Carrageenan<br>Colloidal silicon dioxide<br>Carboxymethylcellulose sodium<br>Hydroxyethyl cellulose<br>Hydroxypropyl cellulose<br>Hydroxypropyl methylcellulose<br>Methylcellulose | Thickening/gelling agent | Used to increase viscosity. Enables easier application of drugs to various parts of the body so they do not run off |
| Cetyl alcohol<br>Cetyl esters wax<br>Microcrystalline wax<br>Paraffin<br>Stearyl alcohol<br>White wax<br>Yellow wax                                                                                                                                                      | Stiffening agent         | Used to increase thickness or hardness of a preparation, usually an ointment                                        |

|                                                      |                  |                                                                                                                                                                                                                                                                                                      |
|------------------------------------------------------|------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ethylene diamine<br>tetraacetate                     | Chelating agent  | Enhances stability by minimizing metal-catalyzed degradation                                                                                                                                                                                                                                         |
| Butylated hydroxytoluene<br>Butylated hydroxyanisole | Antioxidant      | Decreases oxidative deterioration; oxidative deterioration may manifest as an unpleasant odor, discoloration, and even slight loss of activity<br>During product formulation, antioxidants should be used in their lowest effective concentrations and incorporated early in the preparation process |
| Mineral oil<br>Propylene glycol<br>Glycerin          | Levigating agent | Liquid used as an intervening agent to reduce the particle size of a powder by grinding                                                                                                                                                                                                              |

## Active Pharmaceutical Ingredients

Compounding in dermatology contributes to current therapeutics by personalizing treatments, filling therapeutic gaps, aiding adherence, and serving as an adjunct to commercially available therapies to further meet specific patient needs. Therefore, a compounded preparation could be requested for any indication (Table 2.7).

- As mentioned previously, a compounder cannot compound a preparation that is identical to a commercially available product. For more information on when and when not to compound a preparation, see Table 2.1—When compounding is appropriate or inappropriate.
- The strengths included in this table are not all inclusive, and the upper range may not be appropriate for all patients or for all indications.
- Combining APIs can result in synergisms that serve to potentiate efficacy and reduce the toxicity of the APIs when they are used separately. However, not all APIs can be combined; assessment of physicochemical properties and other stability information or prior clinical experience at minimum would be required before combining ingredients for the first time.



**Table 2.7** Examples of active pharmaceutical ingredients used in compounded topical dermatology preparations<sup>a</sup> [21–23]

| API            | APIs expanded if applicable   | Commonly requested strengths | Requested indications                                                                                           | Other notes |
|----------------|-------------------------------|------------------------------|-----------------------------------------------------------------------------------------------------------------|-------------|
| Acid (hydroxy) | Glycolic acid (alpha hydroxy) | 2–70%                        | Acne<br>Pre-peel preparations, skin cleansers, skin bleaching/skin lightening                                   |             |
|                | Lactic acid (alpha hydroxy)   | 2–12%                        | Facial peels, pre-peel preparations,<br>Skin cleansers,<br>Skin bleaching/skin lightening,<br>Keratosis pilaris |             |
|                | Mandelic acid (alpha hydroxy) | 2–10%                        | Pre-peel preparation<br>Mild facial peel                                                                        |             |
|                | Salicylic acid (beta hydroxy) | 0.5–60%                      | Keratosis pilaris, skin cleansers, warts                                                                        |             |
|                |                               | 2–5%                         | Warts                                                                                                           |             |
| Acyclovir      |                               |                              |                                                                                                                 |             |
| Amitriptyline  |                               | 2–5%                         | Shingles/post herpetic neuralgia                                                                                |             |

(continued)

**Table 2.7** (continued)

| API        | APIs expanded if applicable | Commonly requested strengths | Requested indications                | Other notes |
|------------|-----------------------------|------------------------------|--------------------------------------|-------------|
| Antibiotic | Ciprofloxacin               | 2%                           | Wound care <sup>b</sup>              |             |
|            | Clindamycin                 | 1–2%                         | Acne                                 |             |
|            | Erythromycin                | 2–4%                         | Acne                                 |             |
|            | Gentamicin                  | 0.2–0.5%                     | Wound care <sup>b</sup>              |             |
|            | Metronidazole               | 0.75–1%                      | Rosacea, Wound care <sup>b</sup>     |             |
|            | Mupirocin                   | 2–5%                         | Wound care <sup>b</sup>              |             |
| Antifungal | Tobramycin                  | 5%                           | Wound care <sup>b</sup>              |             |
|            | Clotrimazole                | 1–2%                         | Fungal infection                     |             |
|            | Itraconazole                | 1–2%                         | Nail fungus, wound care <sup>b</sup> |             |
|            | Nystatin                    | 100,000–200,000 units/gm     | Fungal infection                     |             |
|            | Terbinafine                 | 2–3%                         | Fungal infection Nail fungus         |             |
|            | Ketoconazole                | 2%                           | Fungal infection Nail fungus         |             |

|                       |                       |            |                                                                                 |             |
|-----------------------|-----------------------|------------|---------------------------------------------------------------------------------|-------------|
| Ascorbic acid         |                       | 5–20%      | Antiaging,<br>Skin bleaching/skin<br>lightening                                 |             |
| Azelaic acid          |                       | 1.5–18%    | Acne,<br>Hair loss                                                              |             |
| Azelastine            |                       | 0.1–0.175% | Eczema, psoriasis,<br>and allergic contact<br>dermatitis                        |             |
| Benzoyl peroxide      |                       | 2.5–20%    | Acne,<br>Skin cleansers                                                         |             |
| Calcineurin inhibitor | Tacrolimus            | 0.03–0.1%  | Atopic dermatitis,<br>eczema, lichen<br>planus, geographic<br>tongue, psoriasis |             |
|                       | Sirolimus (rapamycin) | 0.1–1%     | Eczema,<br>angiofibromas caused<br>by tubular sclerosis<br>complex              | (continued) |

**Table 2.7** (continued)

| API            | APIs expanded if applicable | Commonly requested strengths | Requested indications                                                                                      | Other notes                                                                        |
|----------------|-----------------------------|------------------------------|------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|
| Caffeine       |                             | 1–3%                         | Androgenetic alopecia, prevent rosacea and skin cancer. Improve skin circulation and contains antioxidants |                                                                                    |
| Camphor        |                             | 0.25–3%                      | Counterirritant                                                                                            |                                                                                    |
| Capsaicin      |                             | 0.25–0.75%                   | Post-herpetic neuralgia                                                                                    |                                                                                    |
| Cimetidine     |                             | 10–15%                       | Warts                                                                                                      |                                                                                    |
| Coal tar       |                             | 1–5%                         | Eczema<br>Psoriasis                                                                                        | Available as pure coal tar or liquor carbonis detergens (LCD) usually 20% coal tar |
| Cholestyramine |                             | 5–10%                        | Wound care <sup>b</sup>                                                                                    |                                                                                    |

|                 |                            |             |                                                        |                             |
|-----------------|----------------------------|-------------|--------------------------------------------------------|-----------------------------|
| Corticosteroid  | Betamethasone valerate     | 0.05–0.1%   | Scars                                                  |                             |
|                 | Betamethasone dipropionate | 0.05%       | Scars                                                  |                             |
|                 | Clobetasol propionate      | 0.025–0.05% | Eczema<br>Psoriasis                                    |                             |
|                 | Desonide                   | 0.05%       | Eczema<br>Psoriasis                                    |                             |
|                 | Fluocinolone acetonide     | 0.01–0.025% | Skin bleaching/skin lightening                         |                             |
|                 | Hydrocortisone             | 0.05–2.5%   | Wound care <sup>b</sup> , anti-itch, anti-inflammatory |                             |
|                 | Mometasone                 | 0.1%        | Eczema<br>Psoriasis                                    |                             |
|                 | Triamcinolone              | 0.05–0.5%   | Skin bleaching/skin lightening, scarring               |                             |
| Cromolyn sodium |                            | 0.21–10%    | Eczema                                                 | Adjunct to topical steroids |

(continued)

**Table 2.7** (continued)

| API                           | APIs expanded if applicable | Commonly requested strengths | Requested indications                  | Other notes          |
|-------------------------------|-----------------------------|------------------------------|----------------------------------------|----------------------|
| Cyanocobalamin                |                             | 0.07–1%                      | Eczema<br>Psoriasis                    | A non-steroid option |
| Deoxy-D-glucose               |                             | 0.2–2%                       | Warts                                  |                      |
| Diclofenac                    |                             | 1–3%                         | Actinic keratosis                      |                      |
| Diltiazem                     |                             | 2%                           | Wound care <sup>b</sup>                |                      |
| Dimethyl/ethanolamine (DMAE)  |                             | 2.28–5%                      | Skin firming<br>Skin masks             |                      |
| Diphenhydramine               |                             | 1–2%                         | Eczema<br>Psoriasis<br>Scars, pruritus |                      |
| Diphenylcyclopropanone (DCPC) |                             | 0.0001–4%                    | Alopecia areata                        |                      |
| Estrinol                      |                             | 0.01–0.2%                    | Antiaging                              |                      |
| Finasteride                   |                             | 0.05–0.1%                    | Androgenetic alopecia                  |                      |
| 5-Fluorouracil                |                             | 1–5%                         | Skin cancer, warts                     |                      |
| Gabapentin                    |                             | 2–10%                        | Shingles/post herpetic neuralgia       |                      |
| Glycopyrrolate                |                             | 0.25–2%                      | Hyperhidrosis                          |                      |
| Hyaluronic acid               |                             | 0.1–0.5%                     | Antiaging                              |                      |

|                   |  |                 |                                                                                                                                       |
|-------------------|--|-----------------|---------------------------------------------------------------------------------------------------------------------------------------|
| Hydroquinone      |  | 2–10%           | Melasma<br>Skin bleaching/skin<br>lightening                                                                                          |
| Ichthammol        |  | 10–20%          | Topical drawing<br>salve used for minor<br>skin infections and<br>irritations. Also used<br>to treat eczema,<br>dermatitis, psoriasis |
| Imiquimod         |  | 5%              | Actinic keratosis<br>Warts                                                                                                            |
| Insulin (topical) |  | 0.1–10 units/cm | Wound care <sup>b</sup>                                                                                                               |
| Ivermectin        |  | 1%              | Rosacea                                                                                                                               |
| Ketoprofen        |  | 2–10%           | Shingles<br>Wound care <sup>b</sup>                                                                                                   |
| Ketotifen         |  | 0.05%           | Eczema<br>Psoriasis<br>Rosacea                                                                                                        |
| Kojic acid        |  | 0.05–6%         | Skin masks, skin<br>lightening                                                                                                        |

(continued)

**Table 2.7** (continued)

| API                   | APIs expanded if applicable | Commonly requested strengths | Requested indications                                                                                                      | Other notes                                                                                                 |
|-----------------------|-----------------------------|------------------------------|----------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|
| Menthol               |                             | 0.25–10%                     | Counterirritant                                                                                                            | Maximum 1% in a transdermal base                                                                            |
| Methotrexate          |                             | 1%                           | Eczema<br>Psoriasis                                                                                                        |                                                                                                             |
| Methoxsalen           |                             | 0.1–1%<br>10 mg capsules     | Atopic dermatitis,<br>psoriasis, vitiligo                                                                                  | Capsules NOT oral, to be opened for PUVA therapy                                                            |
| Minoxidil             |                             | 5–10%                        | Androgenetic alopecia                                                                                                      |                                                                                                             |
| Misoprostol           |                             | 0.0024%                      | Ulcers,<br>Wound care <sup>b</sup>                                                                                         |                                                                                                             |
| Naltrexone (low dose) |                             | 0.1–0.2%                     | Eczema, pruritis<br>Psoriasis<br>Hailey-Hailey disease<br>Neuropathic itch<br>Vitiligo<br>Warts<br>Wound care <sup>b</sup> | Prolonged use (greater than 2 weeks) without cycling may exacerbate condition, frequent monitoring required |
| Niacinamide           |                             | 2–5%                         | Acne<br>Rosacea                                                                                                            |                                                                                                             |



|                 |            |            |                                                                               |                                                            |
|-----------------|------------|------------|-------------------------------------------------------------------------------|------------------------------------------------------------|
| Nifedipine      |            | 0.2–5%     | Reynolds<br>Wound care <sup>b</sup>                                           |                                                            |
| Pentoxifyline   |            | 0.3–1%     | Burns<br>Contractures                                                         |                                                            |
| Phenytol        |            | 1–5%       | Wound care <sup>b</sup>                                                       |                                                            |
| Pyrogallol acid |            | 10–25%     | Corns<br>Warts                                                                |                                                            |
| Resorcinol      |            | 1–14%      | Facial peel<br>Antiaging                                                      |                                                            |
| Retinoid        | Adapalene  | 0.1–0.3%   | Acne                                                                          | Ingredient as a<br>commercially<br>available cream<br>only |
|                 | Tazarotene | 0.045–0.1% | Acne                                                                          | Ingredient as a<br>commercially<br>available cream<br>only |
|                 | Tretinoin  | 0.025–0.1% | Acne<br>Facial peels, hair loss<br>Skin bleaching/skin<br>lightening<br>Warts |                                                            |

(continued)

**Table 2.7** (continued)

| API                                        | APIs expanded if applicable | Commonly requested strengths | Requested indications                                                          | Other notes                                     |
|--------------------------------------------|-----------------------------|------------------------------|--------------------------------------------------------------------------------|-------------------------------------------------|
| Sildenafil                                 |                             | 1–5%                         | Reynauds<br>Wound care <sup>b</sup>                                            |                                                 |
| Silver sulfadiazine                        |                             | 1%                           | Wound care <sup>b</sup>                                                        |                                                 |
| Simvastatin/cholesterol                    |                             | 2%/2%                        | Porokeratosis                                                                  |                                                 |
| Spironolactone                             |                             | 1–5%                         | Acne, androgenetic alopecia                                                    |                                                 |
| Sucralfate                                 |                             | 4%                           | Wound care <sup>b</sup>                                                        |                                                 |
| Sulfur                                     |                             | 2–10%                        | Skin cleanser<br>Scabies<br>Seborrheic dermatitis                              | Can also be used adjunctively in acne compounds |
| Tea tree oil (also known as melaleuca oil) |                             | 1–5%                         | Antibacterial use to treat warts, acne, nail fungus, topical fungal infections | Often used in combination with other APIs       |
| Tranexamic acid                            |                             | 3–10%                        | Epistaxis<br>Melasma<br>Wound care                                             |                                                 |
| Tranilast                                  |                             | 1%                           | Eczema psoriasis<br>Scars                                                      | A non-steroid option                            |

|                      |             |         |                                     |                                                                                 |
|----------------------|-------------|---------|-------------------------------------|---------------------------------------------------------------------------------|
| Tofacitinib          |             | 2%      | Alopecia and vitiligo               | JAK inhibitor                                                                   |
| Topical anesthetics  | Benzocaine  | 0.5–20% | Numbing agent                       | Toxicity may occur if higher strengths are used over large area and/or occluded |
|                      | Bupivacaine | 0.25–2% | Numbing agent                       |                                                                                 |
|                      | Lidocaine   | 2–5%    | Shingles<br>Wound care <sup>b</sup> |                                                                                 |
|                      | Prilocaine  | 1–10%   | Numbing agent                       |                                                                                 |
|                      | Tetracaine  | 0.5–4%  | Numbing agent                       |                                                                                 |
| Trichloroacetic acid |             | 7–20%   | Facial peels, warts                 |                                                                                 |
| Urea                 |             | 10–40%  | Moisturizer                         |                                                                                 |
| Vitamin A palmitate  |             | 0.3%    | Antiaging                           |                                                                                 |
| Vitamin E acetate    |             | 0.6–1%  | Antiaging                           |                                                                                 |
| Zinc                 |             | 2–25%   | Wound care <sup>b</sup>             | Different salts (oxide, sulfate) use different strength                         |

<sup>a</sup>This table is not inclusive and is based primarily on formulas produced by compounding supply companies [22, 23] and the clinical experience of the authors and their peers. Performing a literature search will provide information on individual APIs or compounded preparations; however, referencing each API or compounded preparation is outside the scope of this chapter. The requested indications are used off-label when compounding and API efficacy and adverse effects will vary per person and per master formulation

<sup>b</sup>Superficial wound care is non-sterile, and deep wounds may require sterile preparations

## Communication

Communication and shared decision-making are essential components of the patient care process. This involves identifying plausible treatment plans, working with patients to decide which plan is optimal for them, and following up regularly to address any barriers to implementation or adherence. When prescribing compounded preparations, there are additional elements to consider to optimize the ability to achieve goals of therapy. Maintaining open lines of communication between prescriber, patient, and pharmacist and frequent engagement within this triad will aid in the facilitation of high-quality health care [25]. Here are some examples of these considerations:

### Prescriber/patient:

- When deciding on therapy, notify patients that the product being prescribed will need to be compounded. Given that not all pharmacies are equipped to be able to compound, as well as the fact that compounding takes time, this will help to establish realistic expectations.
- Patients should be consulted on topical product characteristics that are acceptable for their individual circumstances. For example, would the greasy appearance of an ointment base be suitable for multiple daily applications?

### Prescriber/pharmacist [24, 25]:

- Constructive communication is imperative for ensuring and improving the quality of prescriptions for compounded preparations. If incompatibilities in prescription ingredients exist, or if there are compounding strategies that may offer greater benefits than what is prescribed, for example. Timely communication ensures quality patient care.
- In keeping with the above, getting to know local practitioners as well as the breadth of compounding services offered will facilitate enhanced collaboration and communication. Ultimately, this will allow for pre-emptive discovery and management of issues related to prescriptions for compounded preparations.

- Providing rationale for recommendations can be more productive than just providing an answer; therapeutic relationships may be strengthened through demonstration of critical thinking and reasoning skills.

#### Pharmacist/patient:

- Patient counselling and education is certainly not a foreign topic to pharmacists, and this holds true in the realm of compounding. As there is no manufacturer provided information for patients to refer to, it is essential that they are counselled on the appropriate use, storage, and expiry (beyond use date) of the preparations dispensed. National and state/provincial regulations should be consulted to ensure any verbal or written information provided is acceptable.
- To reiterate, explaining that a preparation is compounded can help to establish realistic expectations for prescription wait times and help to avoid misconceptions that may hinder the patient-pharmacist relationship.
- Educating patients about the potential adverse effects of compounded preparations, including how they can be managed, is paramount to optimizing adherence. This should occur at the time of dispensing, as well as on subsequent follow-up.
- Follow-up should be tailored to each individual patient's needs. Goals of follow-up should include assessing degree of efficacy, identifying adverse effects, reviewing application technique, and inquiring about factors that may contribute to noncompliance.

---

### **Considerations When Writing a Compounded Preparation Prescription**

Ultimately, one of the tangible products of the communication between a prescriber and a pharmacist is a prescription for a compounded preparation. Although legal requirements vary between provinces/states and countries, there are best practices for compounding prescription writing that are universal:

- Identifying that the prescribed preparation is to be compounded (e.g., compounded medication, to compound). This indicates to both the patient and the compounding pharmacist that this is indeed the expectation.
- Explicitly writing APIs with their desired final concentrations/strengths in the compound is important to avoid confusion, as well as potential dilution, if assuming commercially available products will be used in the compounding process instead of pharmaceutical grade powders.
- With regard to the compounding base, if a specific brand product is not desired, including the type of base, and/or the desired site of action may be appropriate (e.g., topical lotion and transdermal cream).
- Specifically identify the area of application (e.g., trunk and legs), the amount to apply (e.g., sparingly and liberally), and duration of therapy.
- If the compounded preparation is to be applied on an as needed basis, it is important to indicate the maximum total daily dose (i.e., maximum number of daily applications).
- It may be helpful to include brief instruction on how to manage some potential adverse effects (e.g., discontinue use if experiencing extreme irritation, redness, or burning).
- Diligently assess the quantity of compounded preparation that will be required to treat the affected area and appropriate duration of therapy to prevent product wastage, and excessive use and cost.
- BUDs should always be considered when prescribing durations of therapy and quantities to dispense.

---

## References

1. USP. General Chapter 795 Pharmaceutical Compounding Non Sterile Preparations. The United States Pharmacopeial Convention. 2022. <https://www.usp.org/compounding/general-chapter-795>. Accessed 15 Jan 2022.
2. NAPRA. Model Standards for Pharmacy Compounding of Non-Sterile preparations. <https://napra.ca/general-practice-resources/model-standards-pharmacy-compounding-non-sterile-preparations>. The National Association of Pharmacy Regulatory Authorities. 2018. Accessed 15 Jan 2022.

3. FDA. Bulk Drug Substances Used in Compounding. U.S. Food and Drug Administration. 2021. <https://www.fda.gov/drugs/human-drug-compounding/bulk-drug-substances-used-compounding>. Accessed 20 Jan 2022.
4. FDA. Drug products that present demonstrable difficulties for compounding Under the Federal Food, Drug, and Cosmetic Act. U.S. Food and Drug Administration. 2017. <https://www.federalregister.gov/documents/2017/07/28/2017-15900/drug-products-that-present-demonstrable-difficulties-for-compounding-under-the-federal-food-drug-and>. Accessed 22 Jan 2022.
5. Health Canada. Policy on manufacturing and compounding drug products in Canada (POL-0051). January 2009. <https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/policy-manufacturing-compounding-drug-products.html>. Accessed 20 Jan 2022.
6. Sánchez-Regana M, Llambí-Mateos F, Salleras-Redonnet M, Iglesias Sancho M, Collgros Totosaus H, Umbert-Millet P. Compounding as a current therapeutic option in dermatology, vol. 104. Spain: Actas Dermo-Sifiliográficas; 2013. p. 738–56.
7. Nagel K, Ali F, Al-Khudari S, Patel A, Patel N, Desai P. Extemporaneous compounding of medicated ointments. *IJPC*. 2010;14(6):472–8.
8. Nguyen T, Ullmann P. Compounding from basics to modern technology. *Medisca*. 2018. <https://www.medisca.com.au/Pages/Education/Files/AJP%20Oct%202018%20-%20Practice%20Update%20-%20Basic%20Skills%20to%20Modern%20Technology.pdf>. Accessed 20 Jan 2022.
9. PCCA. Gako Unguator Electronic Mortar & Pestles. 2019. Available from: [https://www.pccarx.com/Documents/C-Files/95002\\_emp.pdf](https://www.pccarx.com/Documents/C-Files/95002_emp.pdf). Accessed 20 Jan 2022.
10. Campbell E, Elston D, Straughan C. A review of the clinical indications, general principles and techniques related to compounding. *J Am Acad Dermatol*. 2020;83(1):179–83.
11. Weiss S. Conventional topical delivery systems. *Dermatol Ther*. 2011;24:471–6.
12. Conway J, Brown M. A flowchart for selecting an Ointment Base. *Am J Pharm Educ*. 2014;78(1):16.
13. Fiorillo L, Romano G. Gels in medicine and surgery: current trends and future perspectives. *Gels*. 2020;6(4):48.
14. Allen LV. Excipients used in nonsterile compounding, part 1. *IJPC*. 2019;23:305–11.
15. Allen LV. Excipients used in nonsterile compounding, part 8: humectants. *IJPC*. 2021;25:126–8.
16. Allen LV. Excipients used in nonsterile compounding, part 7: compounding with surfactants. *IJPC*. 2020;24:388–95.
17. Allen LV. Excipients used in nonsterile compounding, part 3: preservatives. *IJPC*. 2019;23:472–7.

18. Allen LV. Excipients used in nonsterile compounding, part 4: antioxidants and chelating agents. *IJPC*. 2020;24:38–43.
19. Newton SJ. Chemical penetration enhancers. *IJPC*. 2013;17:370–4.
20. Allen LV. Excipients used in nonsterile compounding, part 6: compounding with viscosity-increasing agents. *IJPC*. 2020;24:206–12.
21. The National Academies of Sciences, Engineering, and Medicine, et al. Compounded topical pain creams: review of select ingredients for safety, effectiveness and use. The National Academies Press. 2020; <https://doi.org/10.17226/25689>. Accessed 30 Jan 2022.
22. Medisca formulation support. Medisca, Canada. 2022. <https://www.medisca.ca/compounding-services/dashboard>. Accessed 26 Jan 2022.
23. PCCA formula search. PCCA, Canada. 2022. <https://www.pccarx.com/Search/Formula>. Accessed 26 Jan 2022.
24. Salzmann S, Salzmann M, Staubach P. Compounded preparations in dermatology – analysis of prescribing habits in everyday clinical practice in Germany. *J Dtsch Dermatol Ges*. 2020;18(4):334–40.
25. Cormier M. Bedside manner: not just for doctors anymore. *IJPC*. 2015;19(2):115–8.





Le Hanh Dung Do, Rebecca M. Law ,  
and Howard I. Maibach

## Contents

|                                                 |    |
|-------------------------------------------------|----|
| Introduction.....                               | 68 |
| Key Concepts.....                               | 68 |
| History and Definition of Pharmacogenomics..... | 68 |
| Current Databases.....                          | 69 |
| Regulations.....                                | 71 |
| Clinical Use Examples.....                      | 76 |
| Challenges to Test Utilization.....             | 76 |
| Conclusion.....                                 | 78 |
| References.....                                 | 79 |

---

L. H. D. Do (✉)

Roger Williams Medical Center, Providence, RI, USA

e-mail: [dolehanhdung@gmail.com](mailto:dolehanhdung@gmail.com)

R. M. Law

School of Pharmacy and Faculty of Medicine (Discipline of Family  
Medicine), Memorial University of Newfoundland, St. John's, NL, Canada

e-mail: [rlaw@mun.ca](mailto:rlaw@mun.ca); [rlawUCSF@gmail.com](mailto:rlawUCSF@gmail.com)

H. I. Maibach

Department of Dermatology, University of California San Francisco  
(UCSF), San Francisco, CA, USA

e-mail: [howard.maibach@ucsf.edu](mailto:howard.maibach@ucsf.edu)

© The Author(s), under exclusive license to Springer Nature  
Switzerland AG 2025

R. M. Law, H. I. Maibach (eds.), *Handbook of Topical Drug  
Treatment in Dermatology*,

[https://doi.org/10.1007/978-3-031-93616-6\\_3](https://doi.org/10.1007/978-3-031-93616-6_3)

---

## Introduction

Pharmacogenomics is rapidly becoming a clinically useful and sometimes necessary consideration in the selection of appropriate pharmacotherapy. This includes the use of drug treatments in dermatology, both topical and systemic. This chapter provides a general discussion about pharmacogenomics (definition, the aims, and limitations of pharmacogenomics) and provides the currently available databases and resources on pharmacogenomics and FDA-approved pharmacogenomic tests and biomarkers of dermatologic drugs, for topical and/or systemic use. The goal is for clinicians to gain an understanding of how and when to use pharmacogenomic tests for various dermatologic conditions.

---

## Key Concepts

- Pharmacogenomics is a science that can help to predict drug effects—both efficacious or adverse drug effects—in the human body. The predictions are based on variations in the patients' genetic makeup. These may relate to metabolic enzymes/enzymatic activity differences or HLA markers for increased risk for a particular adverse drug reaction, such as a severe cutaneous adverse reaction (SCAR). Thus, pharmacogenomics may help clinicians select the drugs and doses suited for a particular patient.
- Pharmacogenomic tests are selectively approved by the FDA, but not all are covered by insurance.
- Clinicians need to acknowledge the aim and limitations of those tests to effectively use them in clinical decision-making.

---

## History and Definition of Pharmacogenomics

Since the 1950s, various authors have theorized that there is individual genetic susceptibility/variability in response to certain agents. Friedrich Vogel first used the terminology “pharmacogenetics” to describe drug response across patients and populations

[1]. In 1962, Pare et al. reported on the similarity in antidepressant response among first-degree relatives [2]. In 1994, O-Reilly et al. also found familial tendency to respond to certain antidepressants [3]. Beyond psychiatry, Smith et al. found a binomial distribution in various subjects' responses to an antihypertensive drug and suggested that its metabolism was controlled by an autosomal gene [4]. However, the lack of true genetic data led to difficulties in proving these seemingly genetically linked hypotheses.

In April 2003, the National Human Genome Research Institute proclaimed the completion of the Human Genome Project, which enabled researchers to accelerate studies on gene-drug interactions [5]. This became the foundation on which many studies on gene-disease associations and gene-drug interactions have been built. Based on a quick search of the keyword "pharmacogenomics" on PubMed, one can see a great acceleration on this topic since 2004.

The National Institutes of Health (NIH) defined pharmacogenomics as a field that studies how a person's genes affect their response to drugs, thus helping clinicians choose appropriate drugs and doses for their patients [6]. Therefore, healthcare providers should be aware of the available pharmacogenomic databases and their interpretations.

---

## Current Databases

Do and Maibach [7] provided a comprehensive summary of US-based available databases, where clinicians can look up drug-gene interactions. Table 3.1 was reproduced with permission from their publication, with recently expanded additional sources.

FDA's Table of Pharmacogenomic Biomarkers in Drug Labels lists FDA-approved therapeutic products with pharmacogenomic information found in the drug labeling [8]. Biomarkers in the table include germline or somatic gene variants, functional deficiencies with a genetic etiology, and gene expression differences. This guides clinicians with decisions regarding clinical response variability, genotype-specific dosing, and risk for adverse events. This list has expanded from 100 medications in 2007 [9] to more than 260 in 2018 and currently to 483 in 2021.

**Table 3.1** Online resources with drug-gene associations

| Online resources                                         | Goals of site                                                                                                                                                                                                                                                  | Dosing guidelines | Lab test recommendation |
|----------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|-------------------------|
| FDA's table of pharmacogenomic biomarkers in drug labels | Official recommendations for clinicians practicing in the United States                                                                                                                                                                                        | Yes               | Yes                     |
| <a href="#">CPIC</a>                                     | Evidence-based recommendations for clinicians                                                                                                                                                                                                                  | Yes               | Yes                     |
| <a href="#">PharmGKB</a>                                 | Clinical implementation                                                                                                                                                                                                                                        | Yes               | Yes                     |
| eMERGE-PGX                                               | Develop and validate electronic phenotyping algorithms for large-scale, high-throughput genomics research<br>Assess health impact, cost effectiveness, and ethical, legal, and social implications of reporting genetic variants on a broader population scale | No                | No                      |
| <a href="#">DGIdb</a>                                    | Research                                                                                                                                                                                                                                                       | No                | No                      |
| UK Biobank                                               |                                                                                                                                                                                                                                                                |                   | Yes                     |

In 2000, the NIH founded the Pharmacogenomics Research Network (PGRN) and their products: Clinical Pharmacogenomics Implementation (CPIC), Pharmacogenomics Knowledge Base (PharmGKB), Pharmacogenomics iPSC Library & Services (PiLS), Functionalization of Variants in Clinically Actionable Pharmacogenes (F-CAP), and the Drug–Gene Interaction Database (DGIdb, [www.dgldb.org](http://www.dgldb.org)), all of which aimed to amass discoveries worldwide, thus organizing and providing the hub for all clinicians and researchers.

Until 11/2021, CPIC had curated 443 peer-reviewed gene-drug clinical practice guidelines in one place, along with their lab test recommendations [10]. PharmGKB provides more comprehensive variant-drug phenotype summaries based on peer-reviewed

publications, including associations that may not yet reach the requirement for an implementation guideline. Their clinical guideline annotations included 733 annotated drugs from not just CPIC but also the Royal Dutch Association for the Advancement of Pharmacy-Pharmacogenetics Working Group (DPWG), the Canadian Pharmacogenomics Network for Drug Safety (CPNDS), and other professional societies including the French National Network of Pharmacogenetics (RNPGx), the Cystic Fibrosis Foundation, and the American College of Rheumatology [11]. DGIdb organizes drug-gene interactions and potential protein-protein interactions under drug effects on an even larger scale, as it includes 30 sources and 56,309 interaction claims, which may or may not be relevant to clinical practice [12].

The eMERGE-PGx project was a US-based multicenter pilot of adopting pharmacogenetic sequencing to clinical practice. This project concluded its Phase III in 2019, with the goal to develop and validate electronic phenotyping algorithms while assessing health impact, cost-effectiveness, ethical, and legal implications of reporting genetic variants [13]. SPHINX is a searchable website of observed inherited variants among eMERGE-PGx project's 33,966 subjects [14].

UK Biobank provides one of the largest pharmacogenomic data based on around 500,000 European volunteers. In a 2021 study, McInnes et al. found that 99.5% of participants have at least one pharmacogenomic variant, leading to about 12 drugs among the 14 tested drugs that needed to be changed or alternate dosage [15]. Therefore, understanding pharmacogenetics and interpreting related tests is essential to optimizing prescribing practices.

---

## Regulations

Similar to other genetic tests, results about patients' pharmacogenomics are protected under the Genetic Information Nondiscrimination Act (GINA), passed in 2008, to prevent employers from using genetic information to make career decisions [16]. Note that, although GINA applies to health insurance,

it does not apply to life, disability, or long-term care insurance. Having this understanding may help physicians and patients make informed decisions when ordering these tests.

Table 3.2 in this chapter consolidates dermatologic drugs, their biomarkers, and indications from FDA’s Table of Pharmacogenomic Biomarkers in Drug Labeling, CPIC, and PharmGKB, along with their PGx levels from PharmGKB: testing required, testing recommended, actionable PGx, and Informative PGx. Further definitions of these levels can be found on the PharmGKB website [30].

**Table 3.2** FDA-approved pharmacogenomic biomarkers of dermatologic drugs, their PGx levels, and indications (updated 2022)

| Bio markers | Drugs and their PGx levels | FDA approved indications in dermatology                                                                                                                  | Off-label use in dermatology |
|-------------|----------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|
| BRAF        | Binimetinib                | Melanoma, with BRAF V600E, BRAF V600K, or NRAS mutation<br><br>Non-small cell lung cancer with BRAF V600E mutation                                       |                              |
|             | Cobimetinib                | Histiocytic neoplasms<br>Melanoma                                                                                                                        |                              |
|             | Dabrafenib                 | Melanoma, with BRAF V600E or BRAF V600K mutation<br><br>Non-small cell lung cancer, solid tumors, and anaplastic thyroid cancer with BRAF V600E mutation |                              |
|             | Encorafenib                | Colorectal cancer, melanoma, or non-small cell lung cancer with BRAF V600E mutation<br><br>Melanoma with BRAF V600K mutation                             |                              |
|             | Nivolumab                  | Colorectal cancer (microsatellite instability-high or mismatch repair deficient)<br><br>Esophageal cancer (adenocarcinoma or squamous cell carcinoma) or |                              |

(continued)

Table 3.2 (continued)

|          |                                                       |                                                                                                                                                                                                                                                                                                                                                           |                                                                   |
|----------|-------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|
|          |                                                       | gastroesophageal junction cancer or gastric cancer<br><br>Head and neck cancer (squamous cell carcinoma)<br><br>Hepatocellular carcinoma<br><br>Hodgkin lymphoma (classical)<br><br>Malignant pleural mesothelioma<br><br>Melanoma<br><br>Merkel cell carcinoma<br><br>Non-small cell lung cancer<br><br>Renal cell carcinoma<br><br>Urothelial carcinoma |                                                                   |
|          | Trametinib                                            | Melanoma, with BRAF V600E or BRAF V600K mutation<br><br>Non-small cell lung cancer, solid tumors, and anaplastic thyroid cancer with BRAF V600E mutation<br><br>Ovarian carcinoma                                                                                                                                                                         |                                                                   |
|          | Vemurafenib<br>Testing required                       | Erdheim-Chester Disease with BRAF V600 mutation                                                                                                                                                                                                                                                                                                           | Unresectable or metastatic melanoma with BRAF V600E mutation [31] |
| CYP2 C19 | Drospirenone and Ethinyl Estradiol<br>Informative PGx | Contraception                                                                                                                                                                                                                                                                                                                                             | Acne vulgaris [32]; pyoderma gangrenosum [33]                     |
| CYP2 D6  | Cevimeline<br>Actionable PGx                          | Xerostomia in Sjögren's syndrome [34]                                                                                                                                                                                                                                                                                                                     | Limited information                                               |
|          | Terbinafine<br>Informative PGx                        | Tinea pedis, tinea cruris, tinea corporis                                                                                                                                                                                                                                                                                                                 | Limited information                                               |

(continued)

**Table 3.2** (continued)

|                   |                                    |                                                                                                                                                                   |                                                                                                                                           |
|-------------------|------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|
|                   | Pimozide <b>Testing required</b>   | None in dermatology                                                                                                                                               | Delusions of parasitosis, body dysmorphic disorder, metastatic melanoma, trichotillomania, and trigeminal and postherpetic neuralgia [35] |
|                   | Propranolol <b>Informative PGx</b> | None in dermatology                                                                                                                                               | Infantile hemangiomas [36]<br>Decrease recurrence and death in patients with thick cutaneous melanoma [37]                                |
| CYP2 D6, CYP2 C19 | Doxepin <b>Actionable PGx</b>      | Atopic dermatitis or lichen simplex chronicus                                                                                                                     | Urticaria [38]                                                                                                                            |
| DPYD              | Fluorouracil <b>Actionable PGx</b> | Multiple actinic or solar keratoses, superficial basal cell carcinomas when conventional methods are impractical, (multiple lesions or difficult treatment sites) | Keloids and Hypertrophic Scars [39]                                                                                                       |
| G6PD              | Articaine and Epinephrine          | Dental, gum                                                                                                                                                       |                                                                                                                                           |
|                   | Bupivacaine                        | Local analgesia/anesthesia                                                                                                                                        |                                                                                                                                           |
|                   | Chloroquine <b>Actionable PGx</b>  | None in dermatology                                                                                                                                               | Lupus erythematosus, dermatomyositis, polymorphous light eruption, granuloma annulare [40]                                                |
|                   | Dapsone <b>Actionable PGx</b>      | Oral: dermatitis herpetiformis, leprosy<br>5% Gel: topical treatment of acne vulgaris.                                                                            | Chronic inflammatory dermatoses; used as an adjunctive treatment modality [41]                                                            |
|                   | Lidocaine <b>Actionable PGx</b>    | Local anesthetic                                                                                                                                                  |                                                                                                                                           |
|                   | Mepivacaine                        | Dental anesthesia                                                                                                                                                 |                                                                                                                                           |

(continued)



**Table 3.2** (continued)

|                                   |                                    |                                                                                                                   |                                                                                                                                                                                           |
|-----------------------------------|------------------------------------|-------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                   |                                    | Local or regional anesthesia                                                                                      |                                                                                                                                                                                           |
|                                   | Oxymetazoline and Tetracaine       | Persistent facial erythema associated with rosacea in adults                                                      |                                                                                                                                                                                           |
|                                   | Ropivacaine                        | Surgical anesthesia (nerve block or field block)                                                                  |                                                                                                                                                                                           |
| HLA-B                             | Abacavir Testing recommended       | HIV-1 treatment, used in combination with other medications as part of highly active antiretroviral therapy       | Limited information                                                                                                                                                                       |
| IL12A<br>,<br>IL12B<br>,<br>IL23A | Ustekinumab                        | Hidradenitis suppurativa<br><br>Plaque psoriasis<br><br>Psoriatic arthritis                                       |                                                                                                                                                                                           |
| MS4<br>A1                         | Rituximab Informative PGx          | None in dermatology                                                                                               | Autoimmune bullous disorders, pemphigus foliaceus, mucous membrane pemphigoid, epidermolysis bullosa acquisita; chronic Graft-Versus-Host-Disease, dermatomyositis [42]                   |
| PML-RARA                          | Tretinoin (topical)                | Acne vulgaris<br><br>Palliation of fine wrinkles, mottled hyperpigmentation, and tactile roughness of facial skin |                                                                                                                                                                                           |
| TPMT                              | Azathioprine Testing recommended   | None in dermatology                                                                                               | Immunosuppressant, used in severe atopic dermatitis, bullous pemphigoid, parthenium dermatitis, chronic actinic dermatitis, leprosy type 1 reactions, cutaneous vasculitis, vitiligo [43] |
|                                   | Mercaptopurine Testing recommended |                                                                                                                   |                                                                                                                                                                                           |

(continued)

---

## Clinical Use Examples

Biomarker screening is recommended by the Food and Drug Administration (FDA) and by Health Canada in drug selection to minimize the risk of severe cutaneous adverse reactions (SCARs) in patients being prescribed an anticonvulsant (carbamazepine or phenytoin). Some of the examples are HLA-B\*15:02AQ4, HLA-A\*31:01, HLA-B\*15:11 for carbamazepine, and HLA-B\*15:02 and CYP2C9 genotypes for phenytoin [31, 32]. The HLA-B\*15:02 variant is common to both carbamazepine and phenytoin and more often found in people of Southeast Asian descent; these individuals are at higher risk of SCARs such as SJS/TEN. Allopurinol is another example where HLA biomarkers may predict a higher risk of developing a SCAR in susceptible populations.

---

## Challenges to Test Utilization

Clinicians can use the aforementioned databases to discuss with their patients and order FDA- approved biomarkers. Factors that affect the utilization of the results may include insurance coverage, clinicians' and patients' knowledge, and the presentation of test results from laboratories [33].

## Insurance Coverage

Many studies have been published on cost-effectiveness and improved health outcomes, two important criteria for insurance coverage. In 2017, Verbelen et al. provided a review of pharmacoeconomic studies of PGx-guided treatment [34]. Among the 137 available associations in the FDA table at that time, only ~18% (57% of 44 evaluations) favored PGx testing. One example is a systematic testing for HLA-B\*57 when prescribing abacavir, by Ruiz-Iruela et al. in Spain [35]. The same conclusion in testing for HLA-B\*1502 was found by Dong et al. in Singapore [36].

However, Rosenblat et al. found cost-effectiveness of pharmacogenomics, as well as the demonstration of improved health outcomes, is not yet supported with replicated evidence [37].

In 2016, Marshall et al. published results from an online survey on the willingness to pay out of pocket for PGx tests [38]. People with older age and higher income are associated with willingness to pay, but this association declined with more exposure to testing details and higher cost.

## Clinicians and Patients' Knowledge

Clinicians need to understand the aim and limitations of these tests to effectively utilize them and discuss them with their patients. Pharmacogenomic tests are dependent on the pharmacokinetic aspects of the drug (how the human body affects a drug), which predicts drug absorption, distribution, metabolism, and elimination, hence affecting drug accumulation in the body. For example, the CYP2C9 gene, responsible for phenytoin metabolism, is highly polymorphic with over 50 known alleles. This variation is likely contributing to the pharmacogenetic variability in phenytoin metabolism. For the specific HLA markers, for example, [Phenytoin Therapy and HLA-B\\*15:02 and CYP2C9 Genotypes](#) with HLA-B\*15:02 being strongly associated with phenytoin or carbamazepine-induced SJS/TEN as discussed above, testing for HLA-B\*15:02 is recommended for all patients with ancestry in populations with increased frequency of HLA-B\*15:02 (such as Southeast Asian) prior to drug use (FDA).

Secondly, pharmacogenomic tests aim for genotypes, not phenotypes. This means they will not provide information whether the tested genes are expressed in the patients. Furthermore, even if that information is known now, there is no guarantee that these genes will keep their expressions in the future.

Thirdly, even if a gene's expression is known both now and later, there are still uncertainties about its relation with other genes/genes' expressions. The human body is complex with many interactions on many levels.

Currently, in the United States, there are at least 34 laboratories that provided pharmacogenomic tests approved by the FDA [39]. A DNA sample (blood/saliva/cheek swab) is collected from the patient, and the results will be available in a few days or within 2–3 weeks.

In 2014, Brewer et al. found that women were interested in genomic testing, and many believed that extensive tamoxifen metabolizers had better breast cancer prognosis [40, 41]. This observation was consistent with previous studies by Tzeng et al. and O'Neill et al. [42, 43]. Note that these studies were conducted on female subjects; thus, they may or may not be applicable to the general population (i.e., males may rarely develop breast cancer).

## Test Result Presentation

Since pharmacogenomic testing is novel and not widely used, the laboratories should provide the results in a way that accommodates the comprehension of clinicians and patients. One way is to use infographics [44]. Haga found many laboratories used a tricolor system to categorize medications as high risk, moderate risk, and normal in their results. They also used symbols, such as “X,” flags, or checkmarks to inform the level of urgency/risk.

---

## Conclusion

Since the completion of the Human Genome Project in 2003, pharmacogenomics has been extensively studied to aid drug and dosing choices. The FDA-approved biomarkers and other policies have brought pharmacologic tests to clinical settings, thus requiring clinicians and patients' knowledge to fully utilize these tools.

## References

1. Pirmohamed M. Pharmacogenetics: past, present and future. *Drug Discov Today*. 2011;16(19–20):852–61. <https://doi.org/10.1016/j.drudis.2011.08.006>.
2. Pare CM, Rees L, Sainsbury MJ. Differentiation of two genetically specific types of depression by the response to anti-depressants. *Lancet*. 1962;2(7270):1340–3. [https://doi.org/10.1016/s0140-6736\(62\)91019-x](https://doi.org/10.1016/s0140-6736(62)91019-x).
3. O'Reilly RL, Bogue L, Singh SM. Pharmacogenetic response to antidepressants in a multicase family with affective disorder. *Biol Psychiatry*. 1994;36(7):467–71. [https://doi.org/10.1016/0006-3223\(94\)90642-4](https://doi.org/10.1016/0006-3223(94)90642-4).
4. Mahgoub A, Idle JR, Dring LG, Lancaster R, Smith RL. Polymorphic hydroxylation of debrisoquine in man. *Lancet*. 1977;2(8038):584–6. [https://doi.org/10.1016/s0140-6736\(77\)91430-1](https://doi.org/10.1016/s0140-6736(77)91430-1).
5. The Human Genome Project. 22 December 2020. <https://www.genome.gov/human-genome-project>. Accessed 31 Oct 2021.
6. Pharmacogenomics. <https://www.nigms.nih.gov/education/fact-sheets/Pages/pharmacogenomics.aspx>. Accessed 31 Oct 2021.
7. Do LHD, Maibach H. Pharmacogenomics/updated for precision medicine in dermatology. *Journal of Dermatological Treatment*. 2018;30(4):410–413. <https://doi.org/10.1080/09546634.2018.1527434>.
8. Table of Pharmacogenomic Biomarkers in Drug Labeling | FDA. 20 August 2021. <https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling>. Accessed 3 Jan 2022.
9. Drozda K, Müller DJ, Bishop JR. Pharmacogenomic testing for neuropsychiatric drugs: current status of drug labeling, guidelines for using genetic information, and test options. *Pharmacotherapy*. 2014;34(2):166–84. <http://doi.org.ucsf.idm.oclc.org/10.1002/phar.1398>
10. CPIC. <https://cpicpgx.org/>. Accessed 1 Jan 2022.
11. Clinical Guideline Annotations – PharmGKB. <https://www.pharmgkb.org/guidelineAnnotations>. Accessed 1 Jan 2022.
12. Cotto KC, Wagner AH, Feng Y-Y, et al. DGIdb 3.0: a redesign and expansion of the drug–gene interaction database. *Nucleic Acids Res*. 2018;46(Database issue):D1068–73. <https://doi.org/10.1093/nar/gkx1143>.
13. Electronic Medical Records and Genomics (eMERGE) Network. 23 February 2020, <https://www.genome.gov/Funded-Programs-Projects/Electronic-Medical-Records-and-Genomics-Network-eMERGE>. Accessed 3 Jan 2022.
14. SPHINX. <https://www.emergesphinx.org/>. Accessed 3 Jan 2022.
15. Pharmacogenetics at Scale: An Analysis of the UK Biobank – PubMed. <https://pubmed.ncbi.nlm.nih.gov/33237584/>. Accessed 3 Jan 2022.

16. Public Law 110–233 110th Congress An Act – [Govinfo.gov](https://www.govinfo.gov/link/plaw/110/public/233). 21 May 2008, <https://www.govinfo.gov/link/plaw/110/public/233>. Accessed 1 Jan 2022.
17. Roos WP, Quiros S, Krumm A, et al. B-Raf inhibitor vemurafenib in combination with temozolomide and fotemustine in the killing response of malignant melanoma cells. *Oncotarget*. 2014;5(24):12607–20.
18. Trivedi MK, Shinkai K, Murase JE. A review of hormone-based therapies to treat adult acne vulgaris in women. *Int J Women's Dermatol*. 2017;3(1):44–52. <https://doi.org/10.1016/j.ijwd.2017.02.018>.
19. Jourabchi N, Rhee SM, Lazarus GS. Premenstrual flares of pyoderma gangrenosum controlled with use of a combined oral contraceptive and antiandrogen (ethinyl estradiol/drospirenone). *Br J Dermatol*. 2016;174(5):1096–7. <https://doi.org/10.1111/bjd.14332>.
20. Greenfield NP, Maibach H. Pharmacogenomic biomarkers in dermatologic drugs. *J Dermatolog Treat*. 2013;24(6):408–10. <https://doi.org/10.3109/09546634.2012.697989>.
21. Lorenzo CR, Koo J. Pimozide in dermatologic practice: a comprehensive review. *Am J Clin Dermatol*. 2004;5(5):339–49.
22. Hagen R, Ghareeb E, Jalali O, Zinn Z. Infantile hemangiomas: what have we learned from propranolol? *Curr Opin Pediatr*. 2018;30:499. <https://doi.org/10.1097/MOP.0000000000000650>.
23. De Giorgi V, Grazzini M, Benemei S, Marchionni N, Botteri E, Pennacchioli E, Geppetti P, Gandini S. Propranolol for off-label treatment of patients with melanoma: results from a cohort study. *JAMA Oncol*. 2018;4(2):e172908. <https://doi.org/10.1001/jamaoncol.2017.2908>.
24. Gupta MA, Gupta AK. Antidepressant drugs in dermatology. *Skin Therapy Lett*. 2001;6(8):3–5.
25. Shah VV, Aldahan AS, Mlacker S, Alsaidan M, Samarkandy S, Nouri K. 5-fluorouracil in the treatment of keloids and hypertrophic Scars: a comprehensive review of the literature. *Dermatol Ther (Heidelb)*. 2016;6(2):169–83. <https://doi.org/10.1007/s13555-016-0118-5>.
26. Callen JP. Safe use of systemic agents in dermatology – Chicagodermin.
27. Wozel G, Blasum C. Dapsone in dermatology and beyond. *Arch Dermatol Res*. 2014;306(2):103–24. <https://doi.org/10.1007/s00403-013-1409-7>.
28. Gleghorn K, Wilson J, Wilkerson M. Rituximab: uses in dermatology. *Skin Therapy Lett*. 2016;21(5):5–7.
29. Schram ME, Borgonjen RJ, Bik CMJM, et al. Off-label use of azathioprine in dermatology: a systematic review. *Arch Dermatol*. 2011;147(4):474–88. <https://doi.org/10.1001/archdermatol.2011.79>.
30. Drug Label Information and Legend – PharmGKB. <https://www.pharmgkb.org/page/drugLabelLegend>. Accessed 4 Jan 2022.
31. Dean L. Carbamazepine therapy and HLA genotype. 2015 Oct 14 [Updated 2018 Aug 1]. In: Pratt VM, Scott SA, Pirmohamed M, et al.,

- editors. Medical genetics summaries [Internet]. Bethesda: National Center for Biotechnology Information (US); 2012. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK321445/>.
32. Dean L, Kane M. Phenytoin therapy and HLA-B\*15:02 and CYP2C9 genotype. 2016 Sep 22 [updated 2021 Apr 7]. In: Pratt VM, Scott SA, Pirmohamed M, Esquivel B, Kattman BL, Malheiro AJ, editors. Medical genetics summaries [Internet]. Bethesda: National Center for Biotechnology Information (US); 2012. PMID: 28520374.
  33. Integrating pharmacogenetic testing into primary care – NCBI. 3 November 2017, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6919655/>. Accessed 3 Jan 2022.
  34. Verbelen M, Weale ME, Lewis CM. Cost-effectiveness of pharmacogenetic-guided treatment: are we there yet? *Pharmacogenomics J*. 2017;17(5):395–402. <https://doi.org/10.1038/tpj.2017.21>.
  35. HLA-B\*57: 01 genotyping in the prevention of hypersensitivity.... <https://www.x-mol.com/paperRedirect/1212907309917609986>. Accessed 14 Jan 2022.
  36. Dong D, Sung C, Finkelstein EA. Cost-effectiveness of HLA-B\*1502 genotyping in adult patients with newly diagnosed epilepsy in Singapore. *Neurology*. 2012;79(12):1259–67. <https://doi.org/10.1212/WNL.0b013e31826aac73>.
  37. Rosenblat JD, Lee Y, McIntyre RS. Does Pharmacogenomic testing improve clinical outcomes for major depressive disorder? A systematic review of clinical trials and cost-effectiveness studies. *J Clin Psychiatry*. 2017;78(6):720–9. <https://doi.org/10.4088/JCP.15r10583>.
  38. Marshall DA, Gonzalez JM, Johnson FR, MacDonald KV, Pugh A, Douglas MP, Phillips KA. What are people willing to pay for whole-genome sequencing information, and who decides what they receive? *Genet Med*. 2016;18(12):1295–302. <https://doi.org/10.1038/gim.2016.61>.
  39. Haga SB. Educating patients and providers through comprehensive pharmacogenetic test reports. *Pharmacogenomics*. 2017;18(11):1047–50. <https://doi.org/10.2217/pgs-2017-0088>.
  40. N.T. Brewer, J.T. DeFrank, W.K. Chiu, J.G. Ibrahim, C.M. Walko, P. Rubin, O.A. Olajide, S.G. Moore, R.E. Raab, D.R. Carrizosa, S.W. Corso, G. Schwartz, J.M. Peppercorn, H.L. McLeod, L.A. Carey, W.J. Irvin Jr.; Patients' Understanding of how genotype variation affects benefits of tamoxifen therapy for breast cancer. *Public Health Genomics* 2014; 17 (1): 43–47. <https://doi.org/10.1159/000356565>.
  41. Lautenbach DM, Christensen KD, Sparks JA, Green RC. Communicating genetic risk information for common disorders in the era of genomic medicine. *Annu Rev Genomics Hum Genet*. 2013;14:491–513. <https://doi.org/10.1146/annurev-genom-092010-110722>.

42. Tzeng JP, Mayer D, Richman AR, Lipkus I, Han PK, Valle CG, Carey LA, Brewer NT. Women's experiences with genomic testing for breast cancer recurrence risk. *Cancer*. 2010;116(8):1992–2000. <https://doi.org/10.1002/cncr.24990>.
43. O'Neill SC, Brewer NT, Lillie SE, Morrill EF, Dees EC, Carey LA, Rimer BK. Women's interest in gene expression analysis for breast cancer recurrence risk. *J Clin Oncol*. 2007;25(29):4628–34. <https://doi.org/10.1200/JCO.2006.09.6255>.
44. McCrorie AD, Donnelly C, McGlade KJ. Infographics: healthcare communication for the digital age. *Ulster Med J*. 2016;85(2):71–5.





# Clinical Pharmacology of Dermatology Products in Pediatric Drug Development

# 4

Gilbert J. Burckart, Elimika Pfuma Fletcher,  
and Chinmay Shukla

## Contents

|                                                              |    |
|--------------------------------------------------------------|----|
| Introduction.....                                            | 84 |
| Lessons Learned from Pediatric Drug Development Studies..... | 84 |
| Pediatric and Dermatology Trial Design Elements.....         | 86 |
| Summary.....                                                 | 92 |
| References.....                                              | 92 |

---

Disclaimer: The opinions expressed are those of the authors and may not reflect the position of the US Food and Drug Administration.

---

G. J. Burckart (✉) · E. P. Fletcher · C. Shukla  
Office of Clinical Pharmacology, Office of Translational Sciences,  
Center for Drug Evaluation and Research, US Food and Drug  
Administration, Silver Spring, MD, USA  
e-mail: [gilbert.burckart@fda.hhs.gov](mailto:gilbert.burckart@fda.hhs.gov); [elimika.fletcher@fda.hhs.gov](mailto:elimika.fletcher@fda.hhs.gov);  
[Chinmay.Shukla@fda.hhs.gov](mailto:Chinmay.Shukla@fda.hhs.gov)

© The Author(s), under exclusive license to Springer Nature  
Switzerland AG 2025  
R. M. Law, H. I. Maibach (eds.), *Handbook of Topical Drug  
Treatment in Dermatology*,  
[https://doi.org/10.1007/978-3-031-93616-6\\_4](https://doi.org/10.1007/978-3-031-93616-6_4)

83

## Introduction

Pediatric dermatology is a relatively young medical specialty in spite of the fact that a significant percentage of pediatric medical and emergency room visits are related to dermatologic diseases or dermatologic manifestations of a disease. The subspecialty of pediatric dermatology was only certified as a subspecialty in 2000 [1], which was about the time that pediatric patients were just starting to be included in pediatric drug development studies. Therefore, the understanding of the specific aspects of pediatric drug development (determining the pediatric dose, proving efficacy, and assuring safety) was evolving as the specialty of pediatric dermatology was evolving. Twenty years later, the clinical pharmacology aspects of pediatric drug development have built a knowledge base for many therapeutic areas, including dermatology, that has allowed for a high success rate for pediatric therapeutic trials. The following narrative provides (a) the lessons learned from pediatric drug development studies and (b) their application to clinical pharmacology studies of therapy for pediatric dermatologic diseases in drug development.

---

## Lessons Learned from Pediatric Drug Development Studies

Although pediatric patients were very much involved in some of the early incidents that produced federal legislation related to drug development, such as the elixir of sulfanilamide tragedy of 1937 that led to the 1938 Food Drug and Cosmetic Act, there was no requirement to include children in drug development studies through the twentieth century [2]. Therefore, children were “therapeutic orphans,” and physicians had to rely on off-label use of drugs to treat pediatric patients.

Off-label drug use for pediatric patients was common practice in all therapeutic areas until recently. Approximately 80% of all drugs were not labeled for pediatric use from initial assessments in 1973 through the year 2000 [3]. Even when focusing only on

new molecular entities, 71% of new molecular entities were without pediatric drug labeling by the US Food and Drug Administration in the period of 1991–1994. Without adequate drug development trials, the efficacy of off-label drug use is in question, and the poor safety record of off-label drug use has been established.

Off-label drug use is well known in dermatology practice both for pediatric patients and adults [4]. The off-label use of botulinum toxin, topical calcineurin inhibitors, and topical vitamin D analogues is particularly common. A 2002 report that surveyed dermatologic prescribing from 1990 to 1997 found that 73% of prescriptions for rosacea and 52% of prescriptions for actinic keratosis were off-label [5]. With the availability of more potent systemic therapies available for dermatologic diseases, off-label drug use carries a substantial safety risk, especially in pediatric patients.

The drug development system for pediatric patients started to change in 1997 with the Food and Drug Administration Modernization Act (FDAMA) of 1997. In this update to the Food Drug and Cosmetic Act, an additional 6 months of patent exclusivity was provided for sponsors who performed pediatric studies that were requested by the FDA under a formal Written Request. This section of FDAMA had a 5-year sunset and was renewed in 2002 under the Best Pharmaceuticals for Children Act (BPCA). At about the same time, the US Department of Health and Human Services and the US Congress worked together to create an act, which would require pediatric studies when the disease indication intended by the sponsor for adult patients also occurred in pediatric patients. This law was called the Pediatric Research Equity Act (PREA) and was passed into law in December 2003. Both BPCA and PREA were renewed in 2007 and eventually made permanent under the FDA Safety and Innovation Act of 2012. BPCA and PREA have worked together over the last two decades to study the pediatric use of almost 900 products.

A separate route of pediatric drug approval comes from the 1982 Orphan Drug Act. If a disease affects less than 200,000 patients in the United States, a drug to treat this disease can get orphan drug status, which carries with it some drug development incentives. An orphan drug is exempt from PREA studies, so this is considered a separate route for pediatric drug approval.

Multiple indicators appeared during the 1997–2007 period to demonstrate that there were serious problems in undertaking pediatric drug development. Pediatric drug development was a new science, but considerable work had been performed during the prior three decades to prepare for the pediatric drug development endeavor. The ethics of including children in drug studies had been worked out in the 1970s through the cooperation of the American Academy of Pediatrics and the National Institutes of Health with the US FDA [2]. Also, basic studies of drug pharmacokinetics and metabolism were conducted by investigators such as Dr. Sumner Yaffe and by the Pediatric Pharmacology Research Units supported by the NIH. Even so, the failure rate for these early studies (inability to label for pediatric use) was an unacceptable 42% for products already shown to be effective in adults [6].

Over the past decade, many of the problems that have plagued pediatric drug development, in terms of understanding trial design, pediatric dosing, and the application of modeling and simulation to pediatric drug development, have been worked out. The following discussion focuses on those trial design, dosing, and application of modeling in pediatrics and provides examples of pediatric dermatology drug development programs.

---

## **Pediatric and Dermatology Trial Design Elements**

***Trial Endpoints*** The choice of a primary endpoint in a pediatric drug development trial has a significant impact on the success of the trial in demonstrating efficacy. Green et al. examined 9 years of pediatric trials from 2007 to 2016 and recorded the primary endpoints of trials and their success in obtaining pediatric labeling for the use of the drug [7]. Sixty percent of the 234 trials examined utilized the same primary endpoint in both the pediatric and the adult efficacy trial. When the trial used the same endpoint in the pediatric trial as it did in the adult trial, the

trial was significantly more successful in obtaining pediatric labeling.

The reason for this is most likely that adult endpoints have been validated as fit-for-purpose over multiple trials. New endpoints specific to pediatric patients are less likely to have long-term experience in drug development. Table 4.1 lists three products used in pediatric dermatology drug development that were studied with subjective, objective, and both types of endpoints [7]. All of the endpoints are clinical and did not use surrogate endpoints [8]. All three products were successful in obtaining pediatric labeling for these products.

**Combined Pediatric and Adult Efficacy Trials** In the early programs in pediatric drug development, a long lag time was observed between the adult approval and pediatric labeling for the drug's use. These lag times averaged more than 9 years and sometimes stretched to 15–20 years. One of the methods to decrease this lag time was to include pediatric patients in adult phase 3 trials whenever possible. The US FDA now routinely encourages this when the pediatric disease and response to therapy is expected to be or considered the same in adults and in at least some subgroup of pediatric patients. Adolescent patients are the most commonly

**Table 4.1** Pediatric dermatology examples of successful trials using subjective, objective, and both endpoints

| Indication                   | Primary endpoints                                                                                                                                     | Subjective/objective/both |
|------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| Chronic idiopathic urticaria | Change from baseline to week 12 in weekly itch severity score                                                                                         | Subjective                |
| Head lice                    | The proportion within each treatment group of index patients who are lice free (without live lice) on day 15                                          | Objective                 |
| Tinea pedis                  | Complete cure at day 43, which is 2 weeks post treatment and is defined as score of 0 on all signs and symptoms and negative KOH and negative culture | Both                      |

chosen group of pediatric patients to be included in phase 3 adult drug development trials.

Tanaudommongkon et al. examined these combined pediatric and adult trials from 2012 to 2018 [9]. They identified 72 products with 156 combined and adult trials studied under both BPCA/PREA and under the Orphan Drug Act. The majority of products and trials under BPCA/PREA combined only the adolescents (12–18 years old) with the adults, but the majority of products and trials under the Orphan Drug Act utilized the entire pediatric age group.

This review found that 23 dermatology drug products were included in this review under BPCA/PREA. Of those products, four (17%) included pediatric patients in the drug development trials. Considering the overlap between dermatology and allergy treatment guidelines [10], four biological products in the products studied under BPCA/PREA for allergy were identified and one included both adult and pediatric patients.

Under the Orphan Drug Act, the Tanaudommongkon et al. study [9] identified 25 biological orphan drug products that treated allergy. Only one of the 25 products had combined adult and pediatric drug development trials.

***Placebo-Controlled Trials*** The choice of a control group is a critically important design consideration for a drug development trial, and a placebo-controlled trial is the gold standard for most drug development programs. Considering the ethical challenges associated with pediatric placebo-controlled trials, the design of such a trial is an important consideration [11].

In the discussion of the ethical considerations with pediatric placebo-controlled trials in drug development, Momper et al. [11] identified 96 placebo-controlled trials in pediatric patients for 67 unique products. The report listed three pediatric dermatology products with placebo-controlled trials in pediatric patients: adapalene and benzoyl alcohol for acne in patients aged 9–11 years, etanercept for chronic severe plaque psoriasis in 4–17 years of age, and ustekinumab for moderate to severe plaque psoriasis in pediatric patients aged 12 years and older. None of these products used the agent as an add-on medication, and no use of rescue medication was designed into the protocols.

The placebo response rate between pediatric patients and adults is always an important consideration in study design. If the pediatric placebo response rate is much greater in pediatric patients than in adults, it may be difficult to identify a significant therapeutic effect of the drug. For drugs with pediatric placebo-controlled trials having an identical study design and endpoint, etanercept in plaque psoriasis serves as an example with a pediatric placebo response rate of 11.4% (12/105 patients) in comparison to the adult response rate of 4% (6/168 patients). For products with an identical study design but different pediatric and adult endpoints, ustekinumab serves as an example and has almost identical physician's global assessment (PGA) score: 5.4% in pediatric patients and 4–5% in adult patients. When separate pediatric placebo-controlled trials for adapalene and benzoyl alcohol for acne were developed with the same endpoint as adult trials, the results for the placebo response rate were quite different. For example, for the changes in non-inflammatory counts from baseline to week 12, the pediatric placebo response rate was 2.3%, whereas the adult placebo response rate was 23–27%.

So while identical study designs and endpoints should produce similar placebo response rates in adults and pediatric patients, the placebo response rate in prior dermatologic trials has been unpredictable. This fact reinforces the need for a pediatric study control group whenever possible to have reliable study results and to make decisions about product efficacy.

***Enrichment of the Patient Study Population*** Enrichment of the study population to assure that it represents the patient population of interest and represents the patient population most likely to respond to the drug is another important aspect of drug development trial design. The strategies are typically broken into three categories including practical, prognostic, and predictive enrichment strategies. An extensive guidance document from the US FDA is available to read more about these approaches to enriching the patient population [12]. Pharmacogenomic information in FDA labels is also part of enrichment criteria, do pertain to pediatric products, and include dermatologic products [13].

Green et al. investigated the enrichment strategies in pediatric drug development by examining 112 efficacy studies conducted from 2012 to 2016 [14]. Overall, if the trial utilized all three enrichment strategies in trial design, the success rate for pediatric labeling was 87.5%, whereas programs that used no enrichment strategies had a 65.4% rate of success for pediatric labeling. Therefore, proper enrichment strategies are considered crucial for developing pediatric efficacy trials that will successfully lead to pediatric labeling for use.

Included in this analysis [14] were four pediatric dermatologic trials for three products. All three of these products were successfully labeled for pediatric use. However, the use of enrichment criteria in these studies was quite narrow, with only two prognostic strategies used in these trials.

***Exposure-Response and Modeling and Simulation*** An exposure-response (E-R) analysis is not always conducted during drug development but can be a powerful tool for dose-finding and in comparing the adult and the pediatric responsiveness to a drug in a given disease state. When using another tool that facilitates pediatric drug development, or efficacy extrapolation from adults to pediatric patients, an E-R analysis can help to assure that the response to the drug or biological agent is similar between adults and pediatric patients.

Zhang et al. examined 313 pediatric drug development programs from 2007 to 2018 and found that 84 programs contained an E-R analysis [15]. In 48 of those programs, the E-R analysis was determined to support decision-making related to dosing, extrapolation and trial design, or assessment of a new formulation or dosing regimen. In the two dermatology examples provided in the E-R assessments, both programs used E-R analysis to perform dose selection. The two examples were omalizumab in chronic idiopathic urticaria and terbinafine in tinea capitis. Infliximab is approved to treat plaque psoriasis in adults, and a standard dose results in enough of a wide range of concentrations to perform an E-R analysis [16].

The relationship between plasma concentrations and effect in dermatology may be different from many other therapeutic



areas. While the examples provided above do represent situations in which the plasma concentration of systemic therapy may be related to the response in pediatric dermatology, plasma concentrations after the topical application of a drug are generally used in the safety analysis. The goal of topical drug therapy is often to minimize systemic absorption, and consequently low concentrations of drug would be expected systemically. However, the use of refined techniques such as microdialysis have been used to characterize the transfer process between plasma and skin and may be useful in preclinical and clinical studies during drug development [17].

Biological products make up an increasing part of the pharmacologic armamentarium for severe pediatric dermatologic diseases. Monoclonal antibodies and Fc-fusion proteins have a very different pharmacokinetic profile than do small molecule drugs, but it is still possible to perform an E-R analysis. Liu et al. found that 12 of 20 pediatric drug development programs used E-R analysis as part of their development programs [12].

Modeling and simulation (M&S) play an increasing part in pediatric drug development programs. The use of M&S allows for the optimal use of all data available, thereby decreasing the number of pediatric patients who have to be enrolled in a clinical study. This is not only an ethical imperative but also allows the extension of indications in FDA labeling for pediatric age groups who may not have been studied but are expected to have the same response as other pediatric populations.

Bi et al. have reviewed the applications of M&S to pediatric drug development and reviewed the use of M&S in approvals of 105 pediatric indications from 2017 to 2019 [18]. They found that 9.5% of programs used topical therapy, but did not use M&S. This study points to one of the critical problems in pediatric dermatology and drug development, which is the alternate way that plasma drug concentrations are used to make adequate predictions. As mentioned above, more intensive preclinical and clinical studies of drug transfer between skin and plasma [17] may assist in this process.

## Summary

Drug development studies in pediatric patients have evolved in about the same time frame as the medical specialty of pediatric dermatology. Over this 20-year period, drug development studies of pediatric dermatology products have been complicated by a number of factors. While the efficacy trial design has a number of elements that have to be carefully planned, such as endpoints and enrichment of the study population, drug dosing and drug safety are the most critical factors to be addressed in pediatric dermatology drug development studies. The maximal use study is a critical part of the pediatric safety assessment. The observed higher systemic exposure observed in pediatric patients after topical application and its implications on safety have to be carefully considered at the time of drug approval, and products must be appropriately labeled with the available systemic exposure data to inform the prescribing clinicians. The use of more potent systemic therapies for pediatric dermatologic diseases suggests that other techniques such as exposure-response analyses may be necessary going forward. Studies of HPA axis suppression are necessary when appropriate and should be refined to provide more interpretable safety information. Studies of pediatric growth remain an essential part of the evaluation of corticosteroid products. Overall, the clinical pharmacology of drug development studies in pediatrics and pediatric dermatology have advanced considerably over the past 20 years, and this knowledge must be applied to future drug development studies in pediatric dermatology.

---

## References

1. Prindaville B, Antaya RJ, Siegfried EC. Pediatric dermatology: past, present, and future. *Pediatr Dermatol.* 2015;32:1–12.
2. Burckart GJ, Kim C. The revolution in pediatric drug development and drug use: therapeutic orphans no more. *J Pediatr Pharmacol Ther.* 2020;25:565–73.
3. Wilson JT. An update on the therapeutic orphan. *Pediatrics.* 1999;104:585–90.

4. Franca K, Litewka S. Controversies in off-label prescriptions in dermatology: the perspective of the patient, the physician, and the pharmaceutical companies. *Int J Dermatol*. 2019;58:788–94.
5. Sugarman JH, Fleischer AB Jr, Feldman SR. Off-label prescribing in the treatment of dermatologic disease. *J Am Acad Dermatol*. 2002;47:217–23.
6. Wharton GT, Murphy MD, Avant D, et al. Impact of pediatric exclusivity on drug labeling and demonstrations of efficacy. *Pediatrics*. 2014;134:e512–8.
7. Green DJ, Burnham JM, Schuette P, et al. Primary endpoints in pediatric efficacy trials submitted to the US FDA. *J Clin Pharmacol*. 2018;58:885–90.
8. Green DJ, Sun H, Burnham J, et al. Surrogate endpoints in pediatric studies submitted to the US FDA. *Clin Pharmacol Ther*. 2019;105:555–7.
9. Tanaudommongkon I, John Miyagi S, Green DJ, et al. Combined Pediatric and Adult Trials Submitted to the US Food and Drug Administration 2012–2018. *Clin Pharmacol Ther*. 2020;108:1018–25.
10. Mohan GC, Lio PA. Comparison of dermatology and allergy guidelines for atopic dermatitis management. *JAMA Dermatol*. 2015;151:1009–13.
11. Momper JD, Green DJ, Park K, Burckart GJ, Snyder DL. Ethical considerations for pediatric placebo-controlled trials: FDA outcomes and perspectives. *Ther Innov Regul Sci*. 2021;55:282–303.
12. Liu XI, Dallmann A, Wang YM, et al. Monoclonal antibodies and fusion proteins for pediatric use: dosing, immunogenicity, and modeling and simulation in data submitted to the US Food and Drug Administration. *J Clin Pharmacol*. 2019;59:1130–43.
13. Green DJ, Mummaneni P, Kim IW, Oh JM, Pacanowski M, Burckart GJ. Pharmacogenomic information in FDA-approved drug labels: application to pediatric patients. *Clin Pharmacol Ther*. 2016;99:622–32.
14. Green DJ, Liu XI, Hua T, et al. Enrichment strategies in pediatric drug development: an analysis of trials submitted to the US Food and Drug Administration. *Clin Pharmacol Ther*. 2018;104:983–8.
15. Zhang Y, Wang Y, Khurana M, et al. Exposure-response assessment in pediatric drug development studies submitted to the US Food and Drug Administration. *Clin Pharmacol Ther*. 2020;108:90–8.
16. Zhang Q, Travis J, Rothwell R, et al. Applying the noninferiority paradigm to assess exposure-response similarity and dose between pediatric and adult patients. *J Clin Pharmacol*. 2021;61(Suppl 1):S165–74.
17. Shukla C, Patel V, Juluru R, Stagni G. Quantification and prediction of skin pharmacokinetics of amoxicillin and cefuroxime. *Biopharm Drug Dispos*. 2009;30:281–93.
18. Bi Y, Liu J, Li L, et al. Role of model-informed drug development in pediatric drug development, regulatory evaluation, and labeling. *J Clin Pharmacol*. 2019;59(Suppl 1):S104–11.



# Clinical Pharmacology of Topical Therapy in Pediatrics

# 5

Chinmay Shukla, Aaron Park,  
Elimika Pfuma Fletcher,  
and Gilbert J. Burckart

## Contents

|                                                               |     |
|---------------------------------------------------------------|-----|
| Introduction.....                                             | 96  |
| Pediatric Maximal Use Trial.....                              | 99  |
| Sunscreen.....                                                | 102 |
| Pediatric Dermatology Safety Assessment: Corticosteroids..... | 102 |
| Educating the Caregiver.....                                  | 106 |
| Summary.....                                                  | 107 |
| References.....                                               | 107 |

Disclaimer: The opinions expressed are those of the authors and may not reflect the position of the US Food and Drug Administration.

C. Shukla · E. P. Fletcher · G. J. Burckart (✉)  
Office of Clinical Pharmacology, Office of Translational Sciences,  
Center for Drug Evaluation and Research, US Food and Drug  
Administration, Silver Spring, MD, USA  
e-mail: [Chinmay.Shukla@fda.hhs.gov](mailto:Chinmay.Shukla@fda.hhs.gov); [elimika.fletcher@fda.hhs.gov](mailto:elimika.fletcher@fda.hhs.gov);  
[gilbert.burckart@fda.hhs.gov](mailto:gilbert.burckart@fda.hhs.gov)

A. Park  
Acelyrin Inc., McLean, Virginia, USA

## Introduction

The previous introductory chapter introduced the current scenario of pediatric drug development for dermatological products. This chapter will look into the need for pharmacokinetic (PK) assessment in pediatric subjects and will delve into the details of the clinical pharmacology study design of topical products in pediatric subjects. In particular, this chapter focuses on the several design elements that create the building blocks of the maximal usage trial (MUSt), and some of these individual components are supported by examples to enhance the understanding of these concepts. The MUSt study is the primary clinical pharmacology study for topical dermatological products.

***Pediatric Dosing and Ontogeny*** Developmental, anatomical, and physiological differences in pediatric patients and adults or across pediatric ages increase the complexity of dose selection for pediatric patients. Many drugs are initially developed in adults, and data from adults is used to inform dosing for pediatric studies. The most common strategy for selecting initial doses to be studied in pediatric patients reported by Green et al. [1], for drugs submitted for pediatric indications between 2012 and 2020 was previous experience with the product, followed by allometric scaling (19%) and exposure matching with adults (15%). The most common pivotal support for doses approved for pediatric patients was based on titration to target response (33%), pharmacokinetic (PK) or pharmacodynamic data (30%), and exposure matching (20%). The use of PK or exposure matching approaches are not applicable for topical dermatology products for which the exposure at the site of action is more relevant and systemic exposure may be minimal or not directly related to efficacy.

Ontogeny in the skin (larger surface to body volume, skin differences in water loss, and thinner stratum corium) can result in differences in systemic absorption of a topical product in pediatrics compared to adults or among pediatrics of varying ages and sizes [2]. For any systemic absorption that occurs, ontogeny in drug metabolism, transport, and excretion (e.g., renal function) may result in differences in elimination of the drug product in

pediatrics. In addition to potential differences in the systemic exposure (PK), the susceptibility to adverse events resulting from systemic absorption may differ in pediatric patients.

***Pediatric Dosing of Topical products in Dermatology*** Vinueza et al. reported that for locally acting drugs with pediatric indications approved since 2002 (about a third were dermatological products), 75% were labeled at the same dose as adults [3]. Topical dermatological product dosing is usually the same as adult dosing in terms of the specific number of times the drug is recommended to apply (e.g., apply to affected area twice a day). However, the dosing for most topical dermatology products is not precise (does not specify a mg, ml, or specific amount or thickness). A few drugs attempt to add some specificity to their recommendations (e.g. use thin layer, use pea-sized amount, do not exceed a percentage of total body surface area, and do not exceed a certain amount in a week), but the clinical application of such instructions may not be precise or interpreted in a consistent manner. Even if in most cases the instructions for use (dosing) are the same for pediatric and adult dosing, the amount of drug an individual applies may differ based on the skin surface area affected and other factors.

Considering the lack of precision in the dosing for most topical products and the ontogeny in skin and PK, a labeled dose and instructions for use that is similar to adults can result in differences in overall exposure on the skin and systemically. In addition, some indications may involve a greater portion of the body (more affected area) compared to adults (e.g., eczema). For these reasons, pediatric assessments related to PK, safety, and in some cases efficacy are needed in drug development [4].

A drug development program in pediatric dermatology may rely on the efficacy results from the sponsor's trials but may also require additional PK and/or safety studies in pediatrics both for local adverse events and systemic absorption and effects. In some situations, pharmacodynamic and efficacy studies in pediatrics are performed. The PK component of a pediatric topical drug development program is generally performed in a Maximal

Usage Trial (MUsT) to assess potential for systemic exposure, as detailed in the next section. In general, when topical product has more than one indication, the MUsT study may be performed in the indication/population for which highest potential for dermal absorption is expected. For example, PK assessment under maximal use conditions for the indication of eczema may support the localized indication of hand eczema without a separate PK assessment. However, if PK labeling of specific products related to the indication is desired due to a lower anticipated lower systemic exposure, a separate PK study under maximal use conditions would be desired. If there is a plan to extrapolate systemic exposure between different diseases, then that extrapolation plan should be discussed and agreed upon with the FDA. Differences in the formulation can impact the absorption of a drug and is an important consideration in choosing the formulation to study or the need for additional MUsT studies [4]. Pivotal MUsT studies are recommended to be conducted with the to-be-marketed formulation.

In addition to ontogeny that can result in differences in the PK, safety, and efficacy of a topical product in pediatrics compared to adults, some particular circumstances can be of greater concern or interest in pediatric assessments. Characteristics of the disease such as the extent the skin barrier is damaged can increase the chances of systemic exposure. Another consideration is whether a drug is dosed chronically versus acutely or as needed (topical antibiotic for minor scrapes). The risk of drug accumulation with more chronic treatment is a concern, and safety evaluations during drug development may be useful. Concerns related to chronic use highlight the utility of well-designed maximal use trials to inform the risk. The risk of systemic absorption as well is of particular interest including for agents such as corticosteroids for which additional safety assessments such as HPA axis effect are performed to assess the risk of any systemic exposure.

Dosing considerations of topical dermatologic products in pediatrics are important in drug development to ensure efficacy and safety. Dosing of these products also has clinical implications beyond safety and efficacy. The dosing informs the quantity needed to be prescribed to a patient. As mentioned, the amount of drug

applied can differ, and quantifying specific amounts that may be needed by a patient can be challenging especially for chronic use. Nelson et al. and others have proposed rules or BSA estimates to estimate quantities needed for topical agents such as methods based on BSA in an individual or average BSA by age and gender [5]. Some have argued that quantities prescribed could affect the amount a person decides to apply (over or under dosing) based on the perception of available drug for application in a time period.

---

## **Pediatric Maximal Use Trial**

The purpose of MU<sub>s</sub>T is to assess the systemic exposure of a topical product applied under maximal usage conditions with the aim of informing the systemic safety of such products. While the concepts and the purpose of MU<sub>s</sub>T do not change, the nature of disease manifestation will dictate the design of pediatric maximal usage trials, and this could make pediatric study design different from adult study design in certain instances. For example, atopic dermatitis is more common in pediatric patients compared to adults; hence, the minimum body surface area (BSA) that a drug is applied to in MU<sub>s</sub>T is larger in pediatric subjects compared to adults. Conversely, some diseases like psoriasis and onychomycosis usually manifest the opposite way with lower BSA involvement in pediatric subjects compared to adults. Hence, MU<sub>s</sub>T design of pediatric subjects in such diseases needs lesser % BSA involvement compared to adults. Such factors are considered to inform the design of a pediatric MU<sub>s</sub>T, and FDA encourages sponsors to discuss the MU<sub>s</sub>T study design with them prior to initiating the study. In diseases that are uncommon in pediatric subjects, such as, actinic keratosis, pediatric MU<sub>s</sub>T assessment is generally not needed.

In general, MU<sub>s</sub>T study design involves assessment of the systemic exposure at steady state following the application of the to-be-marketed formulation. The goal is to maximize drug absorption with the goal of capturing the worst-case scenario by designing the study to incorporate elements such as upper range of disease severity, % BSA in the upper range, frequency, and dura-



tion of dosing that would be recommended in the approved labeling, amount of dose applied within the upper range, and the use of highest proposed strength if multiple strengths of the product are going to be marketed [6]. The PK information from adult subjects could be used to inform the sampling scheme in pediatric subjects, and generally sparse PK assessment especially in younger pediatric subjects would be acceptable in lieu of serial PK sampling. If waiver of PK assessment in pediatric subjects is desired, then a formal request should be submitted to the FDA for review and concurrence.

Pediatric MUSt study could be conducted as a separate study or can be assessed in a subgroup of subjects within the Phase 3 trials. If a separate study is conducted, then the study's therapy should generally be continued despite the PK assessment completion in pediatric subjects. The goal of PK assessment only for a topical product is not generally considered a reasonable ethical approach for pediatric patients due to the lack of any potential clinical benefit for the enrolled pediatric subjects.

It is critical to assess PK of the topical product under maximal usage conditions in pediatric subjects within the upper range of disease severity. Exposing healthy pediatric subjects is not justifiable ethically and scientifically as disease skin is expected to have different drug permeation potential compared to healthy skin. In an example to illustrate the difference in the systemic exposure between healthy and disease skin, the systemic exposure of luliconazole cream is shown in Fig. 5.1 [7]. As illustrated in Fig. 5.1, the systemic exposure of luliconazole in subjects with tinea cruris is approximately more than fourfold higher compared to that observed following application to the healthy skin. It should be noted that the systemic exposure in healthy subjects was lower in spite of applying to larger body surface area and using approximately more than threefold higher dose than the dose used in patients with tinea cruris. This example illustrates the importance of assessing the systemic exposure in subjects with disease in the MUSt instead of healthy subjects in both adult and pediatric subjects as drug permeation properties of diseased skin could be different from healthy skin.

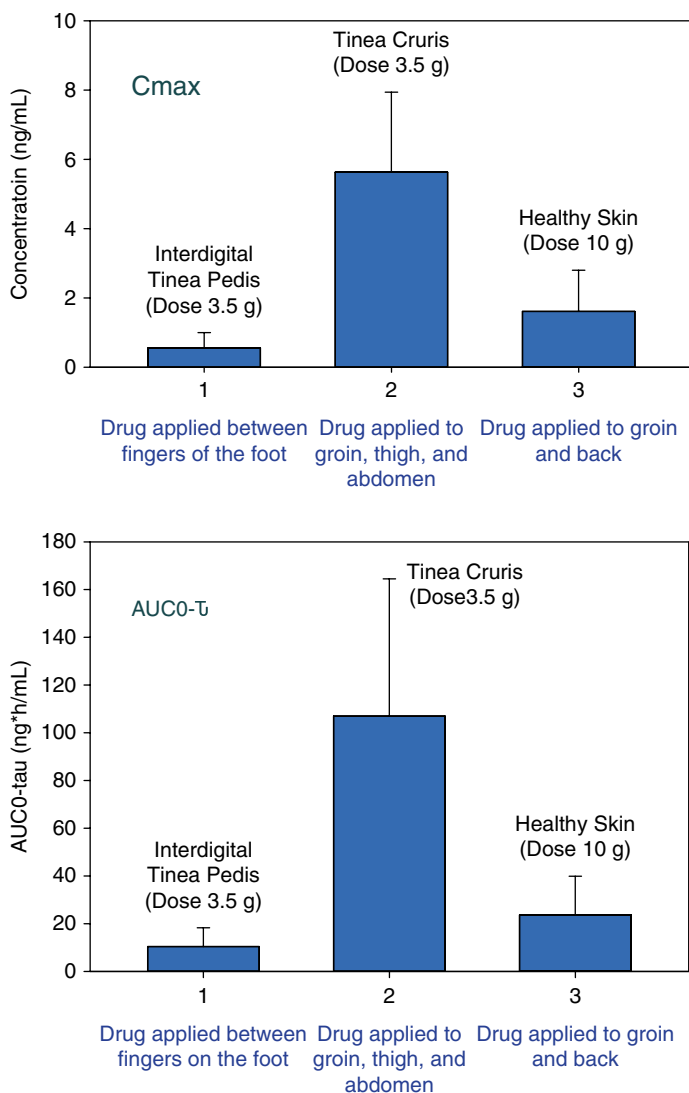


**Fig. 5.1** Systemic exposure of luliconazole cream, 1% in healthy adult subjects and in adult patients with tinea cruris and tinea pedis [7]

## Sunscreen

Sunscreens are marketed in a wide variety of formulations, and the active moieties for sunscreens are usually regulated under the monograph pathway. Monograph approval is for the active moiety, which when used under the conditions specified under the monograph could be marketed in a variety of formulations without the need for FDA approval of an individual formulation. In contrast, the NDA pathway is for a specific formulation, and the sponsor would need separate FDA approval to market each of the different formulations.

MUsT assessment is now an integral part of generally regarded as safe and effective (GRASE) determination under a monograph. For sunscreen products, initial MUsT assessment is recommended to be conducted in adults only by applying the product to at least 75% BSA [4]. The need for pediatric assessment should be considered only if substantial systemic exposure is observed in adult subjects, and this determination should be made in collaboration with FDA.

---

## Pediatric Dermatology Safety Assessment: Corticosteroids

For several dermatological diseases like atopic dermatitis, psoriasis, and acne vulgaris, topical corticosteroids usually are the first line of therapy, unless the disease severity calls for systemic intervention. Hypothalamic pituitary adrenal (HPA) axis suppression is one of the serious adverse effects of corticosteroids. It becomes critical to monitor and assess HPA axis function especially in pediatric subjects during treatment because, in addition to other adverse effects, it impacts growth. Since HPA axis suppression is a systemic adverse effect, when assessed under maximal usage conditions, it has been used as a surrogate for systemic exposure in the times when bioanalytical technology had its limitations toward quantification due to lack of sensitivity. Today, with advancing bioanalytical capabilities, it is now increasingly possible to quantify systemic concentrations of topically applied corticosteroids.

The US FDA has been inconsistent in providing guidance related to conducting HPA axis suppression studies in adults and in pediatric patients. Burnham et al. have documented the HPA axis studies submitted to the FDA from 2002 to 2018 [8]. At one point, seven separate FDA Guidances for Industry were active, but several guidances have now been withdrawn. The active guidance related to pediatric patients is titled “Guidance for Industry: Orally Inhaled and Intranasal Corticosteroids: Evaluation of the Effects on Growth in Children” and is dated March 2007 [9]. Burnham et al. [8] found that of 83 corticosteroid product studies conducted in pediatric patients, 37 conducted HPA axis suppression studies, and 46 did not. Five different methods were used to assess HPA axis suppression in corticosteroid safety studies. The primary approach used in dermatology drug development studies has been ACTH stimulation tests.

There are several examples of topical corticosteroids where higher HPA axis suppression rates were observed in pediatric subjects compared to adults, and also, an increase in the incidence of the rate of HPA axis suppression has been observed with a decrease in age. Although it is a huge challenge to tease out which intrinsic or extrinsic factor (e.g., ontogenetic difference, dose, disease severity, and % BSA exposed) actually contributed to an increase in the incidence of HPA axis suppression, the available data suggests that HPA axis suppression should ideally be assessed in pediatric subjects to inform the safety of the topical corticosteroid product.

Diprolene AF Cream (betamethasone), 0.05%, is approved for the treatment of corticosteroid-responsive dermatoses in subjects 13 years of age and older, and the rate of HPA axis suppression is shown in Table 5.1. The data suggests an increase in the HPA axis suppression rate with decrease in age. Although the goal of this

**Table 5.1** Rate of HPA axis suppression for Diprolene AF (betamethasone) cream [15, 16]

| Age group                            | 3 months to 1 year | 2–5 years | 6–8 years | 9–12 years |
|--------------------------------------|--------------------|-----------|-----------|------------|
| % subjects with HPA axis suppression | 50                 | 38        | 32        | 17         |

chapter is to not provide an exhaustive list of products showing differences in the rate of HPA axis suppression in adults and pediatric subjects, another example is Clobex (clobetasol) lotion, which showed a 64% HPA axis suppression rate in adolescent subjects 12–17 years old with atopic dermatitis following 2 weeks of drug application compared to a rate of 56% in adults. Due to unfavorable benefit-risk, topical corticosteroids with a high incidence of HPA axis suppression are usually not approved for use in the pediatric population, or they could be approved only in older pediatric subjects (i.e., adolescent) and not younger ones [10].

Sometimes, pediatric studies of topical corticosteroids are conducted in a stepwise manner starting from adolescent subjects and then going down in age sequentially. The rate of HPA axis suppression determined in the older pediatric cohort would inform the progression of the study in the next lower age cohort. The study progression would be stopped if the rate of HPA axis suppression is high in the older pediatric cohort with the aim of lowering the risk to the younger age study participants.

One example that supports this strategy is Topicort (desoximetasone) Spray where the HPA axis suppression potential was assessed via cosyntropin stimulation testing at baseline and following 4 weeks of twice daily dosing in an open-label, sequential cohort, safety trial in 100 subjects 2–17 years of age with moderate to severe plaque psoriasis with at least 10% of their body surface area involved. The results indicated that, overall, 36% of pediatric subjects 2–17 years of age demonstrated HPA axis suppression defined as a serum cortisol level  $\leq 18$  mcg/dL 30-min post cosyntropin stimulation. The proportion of subjects demonstrating HPA axis suppression was 35% in Cohort 1 (12–17 years of age) and 43% in Cohort 2 (6 years to less than 12 years of age). Due to the high incidence of HPA axis suppression observed in subjects 6–17 years of age, trial enrollment in the youngest cohort (2–5 years of age) was discontinued early [11].

There are several topical retinoid and retinoid like products (e.g., TAZORAC (tazarotene) gel and cream, AVAGE (tazarotene) cream, and ARAZLO (tazarotene) lotion) approved for the treatment of several dermatological diseases like acne vulgaris, plaque

psoriasis, and hyper- and hypopigmentation. Products of this class carry the risk of teratogenicity and the PK assessment in adult and pediatric subjects under maximal usage conditions are used to assess safety margins based on animal toxicity data. A MUSt study in 24 subjects (18 adolescent +6 adult) 12 years of age and older was a pivotal study to support the prescription (Rx) to over-the-counter (OTC) switch of Differin (adapalene) Gel, 0.1% for the treatment of acne vulgaris. The systemic exposure observed in the MUSt was used to assess the safety margin based on animal toxicity data and the wide margin of safety (at least 70-fold) supported the Rx to OTC switch of Differin Gel, 0.1% making the first retinoid like product to be available OTC [12].

To enhance the favorability of benefit-risk, the systemic exposure information in both adult and pediatric subjects could be used to inform the % BSA and dosing limitation in the drug product labeling. Ruxolitinib cream is the first topical JAK inhibitor class of product to be approved for the treatment of mild to moderate atopic dermatitis [13]. Based on the systemic exposure from MUSt in both adults and adolescent subjects, the approved labeling has a % BSA limitation of up to 20% and dosing limitation to not use more than 60 g per week. With additional data in younger pediatric subjects, the % BSA and dosing limitation would need to be revisited to ensure a favorable benefit-risk in the younger pediatric population.

Another example is abametapir lotion, a pediculicide product approved for the treatment of head lice infestation [14]. This product showed that the systemic exposure in subjects less than 1 year of age was approximately between three- to fourfold higher compared to the systemic exposure in subjects 3–17 years of age following application of the product to the entire scalp and hair and rinsing it off after 10 min (Table 5.2). This example suggests that ontogenetic differences, especially surface area-to-volume ratio, could be the reason for the increased systemic exposure in younger pediatric subjects. This suggests that obtaining PK under maximal usage conditions in pediatric subjects of all age ranges would be essential to inform systemic safety and labeling of the product, and extrapolating from older age cohorts would be very challenging.

**Table 5.2** Abametapir PK parameters in pediatric subjects with headlice infestation from trials B and C [14]

| Study | Age group   | n  | C <sub>max</sub> (ng/mL) mean (%CV) | AUC <sub>0-8h</sub> (ng <sup>*</sup> h/mL) mean (%CV) |
|-------|-------------|----|-------------------------------------|-------------------------------------------------------|
| B     | 6 months to | 1  | 418                                 | 1057                                                  |
| C     | <1 year     | 5  | 228 (50%)                           | 688 (43%)                                             |
| B     | 1 year to   | 3  | 209 (62%)                           | 446 (65%)                                             |
| C     | <2 years    | 8  | 147 (49%)                           | 406 (37%)                                             |
| B     | 2 years to  | 6  | 206 (66%)                           | 633 (57%)                                             |
| C     | <3 years    | 8  | 160 (48%)                           | 602 (51%)                                             |
| B     | 3 years to  | 12 | 121 (60%)                           | 330 (49%)                                             |
| C     | 17 years    | 7  | 52 (45%)                            | 194 (39%)                                             |

The few examples presented here suggest that assessment of PK in pediatric subjects would be needed not only for assessment of systemic safety but also to inform labeling to ensure safety of the patients. Although some of the products approved in pediatric subjects have shown higher systemic exposure than adults, one should not interpret this as the approved product being unsafe in the pediatric population compared to adults. The observed higher systemic exposure and its implications on safety were carefully considered at the time of drug approval and products are appropriately labeled with the available systemic exposure data to inform the prescribing physician.

## Educating the Caregiver

For topical dermatological products, the target site is the skin, and the drug is administered directly at the target site. Systemic absorption, though not desired, does occur, and this leads to the need to address the systemic safety of these products. Pediatric subjects should not be considered as miniature adults as in several cases, we have observed higher systemic exposure in pediatric patients compared to adults following topical application of dermatological products.

Educating the caregiver to the correct use of the product as well as making sure they comprehend the label to understand the limitation of use in terms of % BSA, dosing, approved indica-

tions, approved age range, etc. is critical, especially in case of younger pediatric patients who are not old enough to self-administer the medication correctly.

---

## Summary

The need for clinical pharmacology studies for topical dermatologic agents in pediatric subjects has been met with some criticism. However, several examples discussed in this chapter do suggest that there is significant value in pediatric MUSt studies related to support for drug approval, safety, and dosing instructions in terms of limitations of % BSA and amount applied. The pediatric population is vulnerable to multiple adverse effects, and the risks of extrapolation of safety and/or efficacy from the adult population are well known. Product labeling claims for the pediatric use of topical dermatologic products that are supported by data inform the safe use of the product and do guide health-care providers toward not only prescribing the optimal treatment but also educate the caregiver. Hence, conducting adequately designed MUSt studies in pediatric patients pre-approval does support the safe use of the topical dermatological products, and the FDA encourages sponsors to discuss the MUSt study design prior to initiating this study. The ultimate mission of the FDA is to protect and promote the health and well-being of the American people, and this goal in pediatric dermatology can be achieved through the performance of controlled clinical trials especially in the pediatric patient population.

---

## References

1. Green FG, Park K, Burckart GJ. Methods used for pediatric dose selection in drug development programs submitted to the US FDA 2012–2020. *J Clin Pharmacol*. 2021;61(Suppl 1):S28–35.
2. Nikolovski J, Stamatias GN, Kollias N, Wiegand BC. Barrier function and water-holding and transport properties of infant Stratum Corneum are different from adult and continue to develop through the first year of life. *J Invest Dermatol*. 2008;128:1728–36.



3. Vinueza G, Ramamoorthy A, Burckart GJ, Madabushi R, Zineh I, Pfuma Fletcher E. Deriving pediatric doses for locally-acting drugs: a US Food & Drug Administration evaluation. In: American Association of Colleges of Pharmacy Annual Meeting; 2021.
4. US Food and Drug Administration: Guidance for Industry: Maximal Usage Trials for Topically Applied Active Ingredients Being Considered for Inclusion in an Over-The – Counter Monograph: Study Elements and Considerations. 2019. Access at: <https://www.fda.gov/media/125080/download>. Accessed 26 Nov 2021.
5. Nelson AA, Miller AD, Fleischer AB, Balkrishnan R, Feldman SR. How much of a topical agent should be prescribed for children of different sizes? *J Dermatolog Treat*. 2006;17:224–8.
6. Bashaw ED, Tran DC, Shukla CG, Liu X. Maximal usage trial: an overview of the Design of Systemic Bioavailability Trial for topical dermatological products. *Ther Innov Regul Sci*. 2015;49:108–15.
7. US Food and Drug Administration: Clinical Pharmacology Review: Luliconazole cream 1%. 2012. Access at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2013/204153Orig1s000ClinPharmR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204153Orig1s000ClinPharmR.pdf). Accessed 26 Nov 2021.
8. Burnham JM, Green DJ, Ray A, et al. Hypothalamic-pituitary-adrenal Axis pediatric safety studies submitted to the FDA. *Ther Innov Regul Sci*. 2021;55:622–30.
9. US Food and Drug Administration: Guidance for Industry: Orally Inhaled and Intranasal Corticosteroids: Evaluation of the Effects on Growth in Children. 2007. Access at: <https://www.fda.gov/media/71624/download>. Accessed 27 Nov 2021.
10. US Food and Drug Administration: CLOBEX (clobetasol propionate) Lotion. 2012. Access at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2012/021535Orig1s003,%20021644Orig1s0031bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021535Orig1s003,%20021644Orig1s0031bl.pdf). Accessed 27 Nov 2021.
11. US Food and Drug Administration: TOPICORT (desoximetasone) topical spray. 2021. Access at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2021/204141s0091bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/204141s0091bl.pdf). Accessed 27 Nov 2021.
12. US Food and Drug Administration: Nonprescription Drugs Advisory Committee Meeting, April 15, 2016: Consideration of adapalene gel 0.1% for over-the-counter use for the treatment of acne in consumers 12 years and older. 2016. Access at: <https://www.fda.gov/media/96934/download>. Accessed 27 Nov 2021.
13. US Food and Drug Administration: OPZELURA (ruxolitinib phosphate). 2021. Access at: <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=215309>. Accessed 27 Nov 2021.
14. US Food and Drug Administration: XEGLYZE (abametapir). 2020. Access at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2020/2069661bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/2069661bl.pdf). Accessed 27 Nov 2021.

15. US Food and Drug Administration: DIPROLENE AF (augmented betamethasone dipropionate) cream. 2019. Access at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/019555s035lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/019555s035lbl.pdf). Accessed 27 Nov 2021.
16. US Food and Drug Administration: Joint Meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee and the Nonprescription Drugs Advisory Committee; Notice of Meeting: Adapted from presentation by Denise Cook, MD. 2005. Access at: <https://www.federalregister.gov/documents/2005/02/17/05-3055/joint-meeting-of-the-dermatologic-and-ophthalmic-drugs-advisory-committee-and-the-nonprescription>. Accessed 27 Nov 2021.



# Topical Drug Use in the Elderly

# 6

Rebecca M. Law  and Meghan T. Greene

## Contents

|                                                                                                             |     |
|-------------------------------------------------------------------------------------------------------------|-----|
| Factors Relating to Topical Drug Absorption in the Elderly.....                                             | 111 |
| Disease States (Chronic Diseases) in the Elderly That May<br>Affect Topical Drug Efficacy and Toxicity..... | 113 |
| References.....                                                                                             | 114 |

---

## Factors Relating to Topical Drug Absorption in the Elderly

### 1. Skin

Skin changes due to aging can significantly affect topical absorption of drugs and chemicals.

---

R. M. Law (✉)

School of Pharmacy and Faculty of Medicine (Discipline of Family  
Medicine), Memorial University of Newfoundland, St. John's, NL, Canada  
e-mail: [rlaw@mun.ca](mailto:rlaw@mun.ca); [rlawUCSF@gmail.com](mailto:rlawUCSF@gmail.com)

M. T. Greene

Faculty of Medicine, Memorial University of Newfoundland,  
St. John's, NL, Canada  
e-mail: [meghan.greene@mun.ca](mailto:meghan.greene@mun.ca)

© The Author(s), under exclusive license to Springer Nature  
Switzerland AG 2025

R. M. Law, H. I. Maibach (eds.), *Handbook of Topical Drug  
Treatment in Dermatology*,  
[https://doi.org/10.1007/978-3-031-93616-6\\_6](https://doi.org/10.1007/978-3-031-93616-6_6)

111

Aged skin is drier with less skin surface lipids [1, 2]. It is also thinner and more friable—skin aging is associated with progressive dermal atrophy. This includes atrophy of the skin's capillary network, resulting in a gradual reduction of blood supply to the skin [1, 2]. All of these changes may potentially affect topical absorption.

Overall, it paradoxically appears that the permeability barrier function of the skin is increased as we age. In particular, percutaneous absorption of less lipophilic substances (e.g., hydrocortisone, benzoic acid, acetylsalicylic acid, and caffeine) is reduced, while more lipophilic substances (e.g., testosterone and estradiol) are not [1, 2].

However, increased friability may result in broken skin, resulting in the loss of permeability barrier function and increased percutaneous absorption. There may be significant systemic drug concentration to result in systemic pharmacologic effect and/or adverse effect from topical drug application (refer to Chap. 1: Factors Affecting Percutaneous Penetration: Twenty clinically pertinent factors/observations for percutaneous absorption in humans for more information).

Moisture-associated skin damage occurs in the elderly population secondary to prolonged exposure to moisture in an occluded environment (e.g., if incontinence products are used). This damage results in disruption of skin barrier function.

## 2. Renal Function

Age-related renal impairment may have an effect on excretion of drugs applied on skin, if significant systemic absorption occurs. This is specific to each drug and the amount of drug absorbed systemically may be different based on drug formulation and the physicochemical properties of the drug and other factors [2]. Please refer to specific drug monographs for more information.

Age-related renal impairment may potentially also have an effect on topical absorption of drugs if significant hypoalbuminemia is present. See Chap. 7: Systemic Considerations Relating to Topical Drug Treatment for More Information.

### 3. Hepatic Function

Age-related hepatic dysfunction may have an effect on metabolism of drugs applied on skin, if significant systemic absorption occurs and if the drug is metabolized by the liver. Metabolism also occurs in the skin [2] for some drugs, and many drugs may not be metabolized at all.

Thus, the impact of age-related changes in hepatic function is specific to each drug. Furthermore, the amount of drug absorbed systemically may be different based on drug formulation and the physicochemical properties of the drug and other factors [2]. In addition, patients with severe liver disease may develop the hepato-renal syndrome: even if the drug is metabolized, renal excretion may be impaired. Please refer to specific drug monographs for more information.

---

## **Disease States (Chronic Diseases) in the Elderly That May Affect Topical Drug Efficacy and Toxicity**

### 1. Xerosis and Pruritus

Xerosis or dry skin is caused by diminished natural moisturizing factors, sebum, and lipid production [3]. As we age sebaceous gland function decreases, particularly on the extremities, leading to less endogenous emolliation. Xerosis often occurs on the arms, legs and trunk [4]. Comorbid conditions and medications can also contribute to xerosis and pruritus. Hypothyroidism, renal or hepatic insufficiency, and peripheral neuropathies can be associated with xerosis. The chronic state of inflammation or associated excoriations due to xerosis may affect topical drug efficacy.

### 2. Frailty

Patients with moderate to severe frailty due to physical and/or cognitive deficits may have difficulty applying topical medications adequately or appropriately, thus impacting their use. Decreased dexterity or impaired vision may impact the patient's ability to apply topical medications.

### 3. Weakened Immune Response

A weakened immune system can alter skin barrier function. Without the appropriate immune response, the skin barrier of elderly patients may allow more microorganisms to penetrate the skin causing more frequent bacterial, viral, or fungal infections [3]. These disruptions to the skin barrier function could impact the efficacy of topical drugs in the older adult population.

### 4. Socioeconomic Factors

Compliance or accessibility to topical medications can be impacted by socioeconomic factors such as cost of medication or availability of home care to assist with medication application.

---

## References

1. Roskos KV, Maibach HI, Guy RH. The effect of aging on percutaneous absorption in man. *J Pharmacokinet Biopharm.* 1989;17(6):617–30.
2. Law RM, Ngo MA, Maibach HI. Twenty clinically pertinent factors/observations for percutaneous absorption in humans. *Am J Clin Dermatol.* 2020;21(1):85–95.
3. Humbert P, Dreno B, Krutmann J, et al. Recommendations for managing cutaneous disorders associated with advancing age. *Clin Interv Aging.* 2016;11:141–8.
4. Chang ALS, Wong JW, Endo JO, Norma RA. Geriatric dermatology review: major changes in skin function in older patients and their contribution to common clinical challenges. *J Am Med Dir Assoc.* 8:110.



# Systemic Considerations Relating to Topical Drug Treatment

# 7

Amanda Tzenov and Rebecca M. Law 

## Contents

|                                                                                   |     |
|-----------------------------------------------------------------------------------|-----|
| Introduction.....                                                                 | 116 |
| Pregnancy.....                                                                    | 116 |
| Systemic Metabolism and Excretion of Drugs.....                                   | 120 |
| Potential Drug Interactions of Topical Drugs with Systemic<br>Drug Treatment..... | 121 |
| Systemic Toxicity from Topical Drug Treatment.....                                | 123 |
| References.....                                                                   | 124 |

---

A. Tzenov (✉)

Faculty of Medicine, Memorial University of Newfoundland,  
St. John's, NL, Canada  
e-mail: [Amanda.Tzenov@mun.ca](mailto:Amanda.Tzenov@mun.ca)

R. M. Law (✉)

School of Pharmacy and Faculty of Medicine (Discipline of Family  
Medicine), Memorial University of Newfoundland, St. John's, NL, Canada  
e-mail: [rlaw@mun.ca](mailto:rlaw@mun.ca); [rlawUCSF@gmail.com](mailto:rlawUCSF@gmail.com)

© The Author(s), under exclusive license to Springer Nature  
Switzerland AG 2025

115

R. M. Law, H. I. Maibach (eds.), *Handbook of Topical Drug  
Treatment in Dermatology*,

[https://doi.org/10.1007/978-3-031-93616-6\\_7](https://doi.org/10.1007/978-3-031-93616-6_7)

## Introduction

There are numerous factors that affect percutaneous absorption after topical application of a drug. Twenty factors have been discussed in Chap. 1 [1]. With significant percutaneous absorption, systemic drug concentrations leading to systemic pharmacologic effects and adverse effects may be seen. This is drug and sometimes formulation specific and is discussed in more detail in individual drug monographs in this textbook.

Systemic considerations include potential issues relevant to pregnancy, lactation, renal dysfunction, hepatic dysfunction, potential drug interaction, and altered physiologic states such as hypoalbuminemia.

---

## Pregnancy

### Physiologic Changes in Pregnancy

The body undergoes a tremendous number of physiologic changes during pregnancy, which include things like increased total body water, decreased plasma protein, physiologic anemia due to maternal blood volume increasing more so than red blood cell increase, increased blood flow to the kidneys, and decreased gastric emptying, to name a few [2]. There are particular cutaneous changes that occur during pregnancy as well, which can contribute to the absorption and therefore the systemic effects of a variety of topical medications [3]. Pigment changes, striae, increased telangiectasias, and telogen effluvium are common, as is increased hair growth and nail changes [4]. Preexisting skin changes may also be exacerbated or improved during pregnancy, and it is often difficult to determine the course during pregnancy. For example, psoriasis improves for some patients during pregnancy but might worsen for others and in fact might vary from one pregnancy to the next in the same patient [5]. The treatment of these preexisting skin conditions also warrants more careful consideration during pregnancy due to the above noted changes.



## Systemic Absorption in Pregnancy

Because of the changes noted above, systemic absorption can be altered for topical drug treatments in pregnancy (either increased or decreased, depending on numerous factors discussed in Chap. 1). This section will look at specific topical dermatologic drugs in pregnancy and their unique systemic absorption during pregnancy. It will also review the effects of this systemic absorption on the patient as well as potential teratogenicity [6, 7].

*Drugs with significant systemic absorption after topical administration (and effects of same including potential teratogenicity):*

Acne vulgaris is often worsened during pregnancy, and one of the treatments often asked about in practice is topical retinoids [8]. Oral retinoids are very effective in treating acne vulgaris but are contraindicated in pregnancy due to their teratogenicity including neurological and cardiovascular sequelae (among others) [9]. **Topical retinoids** carry with them the same concerns. For example, tazarotene is contraindicated in pregnancy due to the above noted risks. Other topical retinoids include adapalene, isotretinoin, tretinoin, and trifarotene. A systematic review by Kaplan et al. [8] noted that while inadvertent exposure may not increase rates of major malformations, the study was not powered to justify their use in pregnancy. Refer to Chap. 23: Retinoids for their drug monographs.

Treatment of acne during pregnancy has been summarized [10]. Some other topical acne treatments to be mindful of in pregnancy include **salicylic acid** and **glycolic acid**, which are keratolytic agents. While animal studies have shown teratogenicity with systemic salicylic acid [11], the recommendation for topical salicylic acid is to limit duration of use and to a small area, and to avoid occlusion, which can increase systemic absorption [7]. Topical antibiotics (i.e., erythromycin and clindamycin) are safer to use in pregnancy [7], classified as a Category B by the US FDA (in the former Pregnancy Risk classification scheme).

**Topical Corticosteroids (TCS)** are used for a large number of skin conditions, including those that can first appear or worsen during pregnancy (including eczema, lupus, and atopic eruptions during pregnancy). An updated Cochrane Review from 2015 concluded that there is no association between TCS exposure (regardless of potency) in pregnancy and pregnancy outcomes [12]. There was a “probable” association between low birth weight and use of potent to very potent corticosteroids if the cumulative dosage was very large [12]. That said, there are guidelines published in the British Journal of Dermatology that review the appropriate use of TCS in pregnancy [13]. They note that whenever possible, mild/moderate TCS should be used in preference to more potent corticosteroids. These more potent TCS should be reserved for second-line therapy for as short a time as possible. The theoretical risk of adverse events is increased in areas of high absorption (i.e., genitals, eyelids, and flexures). Refer to Chap. 17: Corticosteroids for a potency table for TCS.

**5-Fluorouracil (5-FU)** is a topical cream used in the treatment of actinic keratoses, basal cell carcinomas, and squamous cell carcinomas of the skin. Since it is an antineoplastic agent and interferes with DNA synthesis, there is a risk of fetal harm, and therefore, its use is contraindicated in pregnancy [6]. A number of studies have demonstrated fetal harm when 5-FU is used inadvertently during pregnancy [14]. Refer to Chap. 13: Antineoplastic Agents for its drug monograph.

Given that melasma is a common dermatological condition in pregnancy, it is worthwhile to mention the use of *hydroquinone* topically. Hydroquinone is a first-line agent for melasma and is a bleaching agent [15]. There have been teratogenic and carcinogenic effects following oral administration in animal studies, and since it is readily absorbed cutaneously, it is not recommended for use in pregnancy [15]. Resolution of melasma can occur without treatment but may be slow, and sun avoidance or use of barriers (i.e., physical sunscreen) is also key [16]. Topical retinoids have also been used for melasma, but as discussed above, their use in

pregnancy should be avoided [8, 9]. Refer to Chap. 20: Pigmenting and Depigmenting Agents for the hydroquinone drug monograph.

Musculoskeletal (MSK) aches and pains are common in pregnancy. *Topical non-steroidal anti-inflammatory drugs (NSAIDs)* are used in nonpregnant adults to treat musculoskeletal pain; however, evidence in pregnant patients is lacking. Health Canada has recommended avoidance of oral NSAIDs at 20 weeks or later in pregnancy unless advised otherwise by a healthcare professional [17]. A recent systematic review examined the available evidence and safety of topical NSAIDs for the treatment of MSK issues in pregnancy and found that there is no evidence [18].

**Tacrolimus** is a calcineurin inhibitor and therefore an immunosuppressant agent. It is used for a number of skin conditions, including atopic and allergic dermatitis, lichen planus, psoriasis, pyoderma gangrenosum, and vitiligo [19]. While there are no studies of topical tacrolimus in pregnancy, manufacturers advise avoidance of topical calcineurin inhibitors during pregnancy. Given that the absorption of topical calcineurin inhibitors is quite low [20], topical tacrolimus is generally considered safe in pregnancy, if used on small areas for short durations [21]. Refer to Chap. 17 Atopic Dermatitis: Topical Agents for Drug Monographs on Tacrolimus and Pimecrolimus

## Dermatologic Conditions in Pregnancy

There are some dermatologic conditions that commonly occur in pregnancy. Pruritus occurs more commonly in pregnancy. It affects up to 20% of pregnant women. Consequences may include affecting the woman's sleep and quality of life, as well as the pruritus being associated with either inconsequential or a more serious medical condition [22, 23]. Several pruritic skin disorders are unique to pregnancy. These include intrahepatic cholestasis of pregnancy (ICP), pruritic urticarial papules and plaques of pregnancy (PUPPP), pemphigoid gestationis (PG), and atopic eruption of pregnancy [22]. ICP has been associated with adverse fetal outcomes including preterm labor and fetal death [22, 23].

Other dermatologic conditions or changes in pregnancy include melasma, striae, and hyperpigmentation (linea nigra, acanthosis nigricans, darkened areolas, and darkened skin folds). The hyperpigmentation is suspected to be due to melanocyte sensitivity to hormones that increase during pregnancy (including estrogen and progesterone) [3]. Increased androgens lead to worsening of acne vulgaris [10]. Increased hair growth (thickness/diameter, anagen/telogen ratio, and growth rate) is related to the effects of estrogen, progesterone, prolactin, and growth factors on the hair follicles [24]. With the increase in plasma volume, as well as the effects of the gravid uterus on venous return, both venous stasis and varicose veins can become more problematic [25].

---

## Systemic Metabolism and Excretion of Drugs

Metabolism and excretion are two mechanisms for elimination of drugs or chemicals, which can be affected by numerous factors. Metabolism and excretion pharmacokinetics can differ greatly between structurally similar drugs or chemicals. Thus, depending on the substance, elimination (i.e., drug clearance) may or may not be in proportion to the dose absorbed. Even for researchers conducting *in vivo* studies, the clearance rate of the drug or chemical must be considered when estimating percutaneous absorption from blood or tissue samples [1, 26].

## Renal Dysfunction

The major organ for drug excretion from the body is the kidneys. If enough drug is absorbed systemically after topical administration, elimination and renal clearance would be needed, and the significance of renal impairment would need to be considered. This differs between drugs—some drugs may be extensively metabolized prior to drug excretion, while other drugs may be minimally metabolized (if at all) and be 99–100% cleared from the kidneys unchanged.

Furthermore, drug metabolism often changes a drug into a more hydrophilic metabolite, which is then excreted by the kidneys. In renal dysfunction, the metabolite may accumulate and—if it is an active metabolite, that is, it has pharmacologic activity—may add to the original drug's pharmacologic effects and/or adverse effects [26].

Thus, whether the original drug is excreted unchanged or is metabolized, renal dysfunction may be a concern. How drug usage is affected by renal dysfunction is further discussed in each drug monograph.

## **Hepatic Dysfunction**

The liver is the major organ for metabolism of drugs and chemicals. However, metabolism can occur in other organs including the skin [1]. Similarly to drug excretion, metabolism is drug specific: the degree of metabolism differs from one drug to another, and some drugs may not be metabolized at all.

For drugs that are extensively metabolized by the liver, significant hepatic dysfunction may reduce the amount of drug metabolized, resulting in potential for increased pharmacologic effect and/or toxic effects.

Furthermore, cirrhosis of the liver—or even acute hepatic injury—may result in hepatorenal syndrome, causing functional renal failure [27]. Thus, even drugs that are not metabolized by the liver but are excreted unchanged by the kidneys may be affected by acute or chronic liver injury.

---

## **Potential Drug Interactions of Topical Drugs with Systemic Drug Treatment**

Obviously, the use of two topical drugs may result in a potential drug interaction. With enough drug through percutaneous absorption, a topical drug may also interact with a systemic drug, resulting in a clinically significant drug interaction.

## Topical Miconazole and Warfarin

Warnings by USFDA and Health Canada about this drug interaction were first raised in 2001, when case reports surfaced (two in the United States and one in Canada) about *vaginal* miconazole increasing INR resulting in associated bleeding tendencies (bruising, gingival bleeding, and nosebleeds) [28].

Subsequently, other similar case reports appeared. A potentially life-threatening case involved a patient using a tube of miconazole oral gel, which he purchased on his own from a community pharmacy two weeks prior to the interaction being discovered. The patient was on warfarin for atrial fibrillation, and his INR had previously been well controlled within the 2–3 range. In this instance, the patient's INR was found to be 8 then increased to 15, and he had presented with hematuria [29, 30].

## Topical Econazole and Warfarin

Other topical azoles have been reported to interact with warfarin as well. Topical econazole cream prescribed twice daily for at least one week beyond clearing or a minimum of two weeks, (for a *Candida* infection on the scrotum and inner thighs), led to a marked increase in bruising within the first week of use, a large ecchymosis on the hip from a trivial injury, and a bleed for over 24 h from a small superficial cut on the hand. The patient's INR had increased from 2.2 to 12 while using topical econazole [31]. Previous to this, the patient's INR had been within a stable range (1.8–3) for three years on the same dose of warfarin [31].

The case report further noted that this patient had previously used topical miconazole without a similar effect [31].

## Hypoalbuminemia Effects on Drug-Binding Interactions

Serum albumin is a plasma protein, which binds to acidic or neutral drugs and other substances, keeping them in the systemic circulation but not actively producing an effect. In states of

hypoalbuminemia (such as malnutrition and chronic kidney disease), if a drug is highly bound to serum albumin, there will be less binding, thus releasing more free drug into the circulation, potentially enhancing pharmacologic effect and toxicities including drug interactions [26]. Warfarin, for example, is a drug highly bound to serum albumin. Thus, in states of hypoalbuminemia, there is a greater potential for increased INR and potential drug-drug interactions. Other drugs with high binding to serum albumin include salicylates, phenytoin, and many more.

### Systemic Toxicity from Topical Drug Treatment

In summary, it is possible for topical drug treatments to have systemic toxicity (Table 7.1). The risk varies from drug to drug and may be formulation dependent as well as dependent on many other factors affecting percutaneous absorption as discussed, including patient-specific factors such as renal and hepatic dysfunction. Skin-to-skin transfer of a topical drug can result in systemic toxicity in another person. A father using testosterone

**Table 7.1** Some examples of systemic toxicity from topical drug treatments

| Topical drug                          | Systemic adverse effect                                                                                                           |
|---------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|
| Clindamycin                           | Pseudomembranous colitis [33, 34]                                                                                                 |
| Corticosteroids                       | HPA-axis suppression, adrenal insufficiency, Cushing's syndrome, hypertension [1, 35]                                             |
| EMLA cream (prilocaine and lidocaine) | Methemoglobinemia [31]                                                                                                            |
| Minoxidil                             | Palpitations, hypotension, tachycardia, paroxysmal atrial fibrillation, sinus arrhythmia [1, 35]                                  |
| Salicylates                           | Refractory hypoglycemia, tinnitus, hearing loss, blurred vision, sweating [1, 35]                                                 |
| Ophthalmic sulfonamides               | Stevens-Johnson syndrome [1, 35]                                                                                                  |
| Testosterone                          | Hyperandrogenic effects, including acne, hirsutism, menstrual irregularities [31], and precocious puberty upon skin transfer [32] |

cream without routine handwashing after application transferred enough testosterone over time to his infant son to cause precocious puberty—pronounced virilization in a 2-year-old boy [32].

The use of topical drugs in pregnancy must include considerations of potential risks to the fetus as discussed above. Please refer to each drug monograph for more specific discussion.

---

## References

1. Law RM, Ngo MA, Maibach HI. Twenty clinically pertinent factors/observations for percutaneous absorption in humans. *Am J Clin Dermatol*. 2020;21(1):85–95.
2. Constantine M. Physiologic and pharmacokinetic changes in pregnancy. *Front Pharmacol*. 2014;5:1–5.
3. Panicker VV, Riyaz N, Balachandran PK. A clinical study of cutaneous changes in pregnancy. *J Epidemiol Glob Health*. 2017;7(1):63–70. <https://doi.org/10.1016/j.jegh.2016.10.002>. Epub 2016 Nov 19. PMID: 27870929; PMCID: PMC7320517.
4. Motosko CC, Bieber AK, Pomeranz MK, Stein JA, Maritres KJ. Physiologic changes of pregnancy: a review of the literature. *Int J Women's Dermatol*. 2017;3(4):219–24.
5. Simionescu AA, Danciu BM, Stanescu AMA. State-of-the-art review of pregnancy-related Psoriasis. *Medicina*. 2021;57:804. <https://doi.org/10.3390/medicina57080804>.
6. Patel V, Schwartz RA, Lambert WC. Safety of topical dermatologic medications in pregnancy. *J Drugs Dermatol*. 2016;15(7)
7. Putra IB, Jusuf NK, Dewi NK. Skin changes and safety profile of topical products during pregnancy. *J Clin Aesthet Dermatol*. 2022;15(2):49–57. PMID: 35309882; PMCID: PMC8884185
8. Kaplan YC, Ozsarfaty J, Etwel F, Nickel C, Nulman I, Koren G. Pregnancy outcomes following first-trimester exposure to topical retinoids: a systematic review and meta-analysis. *Br J Dermatol*. 2015;173(5):1132–41. <https://doi.org/10.1111/bjd.14053>.
9. Choi JS, Koren G, Nulman I. Pregnancy and isotretinoin therapy. *CMAJ*. 2013;185(5):411–3. <https://doi.org/10.1503/cmaj.120729>.
10. Kong YL, Tey HL. Treatment of acne vulgaris during pregnancy and lactation. *Drugs*. 2013;73(8):779–87. Retrieved from <https://qe2a-proxy.mun.ca/login?url=https://www.proquest.com/scholarly-journals/treatment-acne-vulgaris-during-pregnancy/docview/1466259872/se-2>.
11. Akhavan A, Bershadt S. Topical acne drugs: review of clinical properties, systemic exposure, and safety. *Am J Clin Dermatol*. 2003;4(7):473–92. <https://doi.org/10.2165/00128071-200304070-00004>. PMID: 12814337



12. Chi C, Wang S, Wojnarowska F, Kirtschig G, Davies E, Bennett C. Safety of topical corticosteroids in pregnancy. *Cochrane Database Syst Rev*. 2015, Issue 10. Art. No.: CD007346; <https://doi.org/10.1002/14651858.CD007346.pub3>.
13. Chi C, Kirtschig G, Aberer W, Gabbud JP, Lipozencic J, Karpati S, Hausteiner UF, Zuberbier T, Wojnarowska F. Evidence-based (S3) guideline on topical corticosteroids in pregnancy. *Br J Dermatol*. 2011;165(5):943–52.
14. Efudex (Fluorouracil) product monograph. (2014). Valeant Canada LP. 2150 St Elzear Blvd West. Laval, Quebec. H7L 4A8. Canada. Retrieved from [https://pdf.hres.ca/dpd\\_pm/00026974.PDF](https://pdf.hres.ca/dpd_pm/00026974.PDF).
15. Bio LL, Cies JJ. Lack of pregnancy warnings on over-the-counter dermatologic products containing potentially harmful hydroquinone. *J Perinatol*. 2017;37:778–81.
16. Handel AC, Miot LDB, Miot HA. Melasma: a clinical and epidemiological review. *An Bras Dermatol*. 2014;89(5):771–82.
17. Health Canada Advisory (Oct 30, 2020). RA-74239. Use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) beyond 20 weeks of pregnancy and risk of kidney damage in unborn babies, leading to low amniotic fluid. Retrieved from <https://recalls-rappels.canada.ca/en/alert-recall/use-non-steroidal-anti-inflammatory-drugs-nsaids-beyond-20-weeks-pregnancy-and-risk> on October 24, 2023.
18. Shi C, et al. Multidisciplinary guidelines for the rational use of topical non-steroidal anti-inflammatory drugs for musculoskeletal pain. *J Clin Med*. 2023;12(4):1544.
19. Tacrolimus (topical): Drug Information. UpToDate. Wolters Kluwer. Retrieved from [https://www.uptodate.com/contents/tacrolimus-topical-drug-information?search=tacrolimus&source=panel\\_search\\_result&selectedTitle=1~145&usage\\_type=panel&showDrugLabel=true&display\\_rank=1](https://www.uptodate.com/contents/tacrolimus-topical-drug-information?search=tacrolimus&source=panel_search_result&selectedTitle=1~145&usage_type=panel&showDrugLabel=true&display_rank=1) on October 24, 2023.
20. Undre NA, Moloney FJ, Ahmadi S, Stevenson P, Murphy GM. Skin and systemic pharmacokinetics of tacrolimus following topical application of tacrolimus ointment in adults with moderate to severe atopic dermatitis. *Br J Dermatol*. 2009;160(3):665–9. <https://doi.org/10.1111/j.1365-2133.2008.08974.x>. Epub 2008 Dec 12. PMID: 19076975.
21. Heilskov S, Deleuran M, Vestergaard C. Immunosuppressive and immunomodulating therapy for atopic dermatitis in pregnancy: an appraisal of the literature. *Dermatol Ther (Heidelb)*. 2020;10(6):1215–28.
22. Law RM, Law DTS, Maibach HI. Chapter e-121: Dermatologic drug reactions, contact dermatitis, and common skin conditions. In: DiPiro's pharmacotherapy: a pathophysiologic approach. 12th ed. McGraw-Hill Medical; 2023. p. 1693.
23. Bergman H, Melamed N, Koren G. Pruritus in pregnancy: treatment of dermatoses unique to pregnancy. *Can Fam Phy*. 2013;59(12):1290–4.
24. Grymowicz M, Rudnicka E, Podfigurna A, Napierala P, Smolarczyk R, Smolarczyk K, Meczekalski B. Hormonal effects on hair follicles. *Int J*

- Mol Sci. 2020;21(15):5342. <https://doi.org/10.3390/ijms21155342>. PMID: 32731328; PMCID: PMC7432488.
25. Goulart VB, Cabral ACV, Reis ZS, et al. Anatomical and physiological changes in the venous system of lower limbs in pregnant women and findings associated with the symptomatology. *Arch Gynecol Obstet*. 2013;288:73–8. <https://doi-org.qe2a-proxy.mun.ca/10.1007/s00404-013-2728-9>
  26. Burton ME, Schentag JJ, Shaw LM, Evans WE. *Applied pharmacokinetics and pharmacodynamics: principles of therapeutic drug monitoring*. 4th ed. Lippincott, Williams, and Wilkins; 2006.
  27. Ranasinghe IR, Sharma B, Bashir K. Hepatorenal syndrome. NIH National Library of Medicine StatPearls. Last update Aug 8, 2023. [https://www.ncbi.nlm.nih.gov/books/NBK430856/#:~:text=Hepatorenal%20syndrome%20\(HRS\)%20is%20a%20multiorgan%20condition%20affecting%20the%20kidneys,observed%20in%20the%20late%201800s](https://www.ncbi.nlm.nih.gov/books/NBK430856/#:~:text=Hepatorenal%20syndrome%20(HRS)%20is%20a%20multiorgan%20condition%20affecting%20the%20kidneys,observed%20in%20the%20late%201800s). Accessed 4 Dec 2023.
  28. O'Reilly M. Drug advisory: the interaction between warfarin and vaginal miconazole. *JAMC*. 2001;165(7):938.
  29. Filmer S. Warfarin and oral miconazole: a major interaction overlooked in practice. *Pharm J*. 2012;288:527.
  30. Miki A, Ohtani H, Sawada Y. Warfarin and miconazole oral gel interactions: analysis and therapy recommendations based on clinical data and a pharmacokinetic model. *J Clin Pharm Ther*. 2011;36:642–50.
  31. Lang PG, LeClercq AH. Increase in anticoagulant effect of warfarin in a patient using econazole cream. *J Am Acad Dermatol*. 2005;55(5 Supplement):S117–9.
  32. Franklin SF, Geffner ME. Precocious puberty secondary to topical testosterone exposure. *J Pediatr Endocr Metab*. 2003;16:107–10.
  33. Trexler M, Fraser T, Jones M. Fulminant pseudomembranous colitis caused by clindamycin phosphate vaginal cream. *Am J Gastroenterol*. 1997;92:2112–3.
  34. Parry MF, Rha CK. Pseudomembranous colitis caused by topical clindamycin phosphate. *Arch Dermatol*. 1986;122:583–4.
  35. Alikhan FS, Maibach HI. Topical absorption and systemic toxicity. *Cutan Ocul Toxicol*. 2011;30(3):175–86.

---

## Part II

# Drug Monographs



# Topical Drug Treatments for Acne

# 8

Brian W. Connor, Jason Ya,  
and Lisa E. Maier

## Contents

|                      |     |
|----------------------|-----|
| Introduction.....    | 129 |
| Drug Monographs..... | 132 |
| References.....      | 174 |

---

## Introduction

Acne vulgaris is a common inflammatory disorder primarily affecting the sebaceous follicles of face, chest and back. Although acne can affect any age, it is more common in adolescence and

---

B. W. Connor  
Schweiger Dermatology Group, New York, NY, USA  
e-mail: [bwconnor@uw.edu](mailto:bwconnor@uw.edu)

J. Ya  
Department of Dermatology, Stanford University School of Medicine,  
Redwood City, CA, USA  
e-mail: [jasonya@uw.edu](mailto:jasonya@uw.edu)

L. E. Maier (✉)  
Department of Dermatology, UW Medicine, Seattle, WA, USA  
e-mail: [lemaier@uw.edu](mailto:lemaier@uw.edu)

early adulthood. Various clinical features can be seen in acne including comedones, inflammatory lesions (papules, pustules, and nodules), scars, and dyspigmentation. Acne pathogenesis is complex, but there appear to be several key pathogenic steps that contribute to the development of acne. These include abnormal follicular keratinization resulting in follicular hyperkeratosis, overabundant sebum production, follicular colonization by the skin flora resident bacteria *Cutibacterium acnes* and subsequent inflammatory response surrounding the sebaceous follicle. The microcomedone, characterized by follicular hyperkeratosis and sebum, is considered the precursor lesion for comedones, papules, pustules, and nodules. Microcomedones progress to comedones or inflammatory lesions as they become increasingly filled with sebum, keratin, and *C. acnes* and other bacteria. Rupture of the distended sebaceous follicle aggravates the inflammatory response and results more severe inflammatory lesions and nodules [1].

Androgen hormones are thought to play an important role in the development of acne by driving sebum production and contributing to follicular hyperkeratosis. Other factors such as decreased linoleic acid and increased IL-1- $\alpha$  and FGFR-2 signaling may also contribute to microcomedone development. *C. acnes* contributes to follicular inflammation, by activating the innate and adaptive immune responses. Some of the possible mechanisms by which this occurs includes *C. acnes* ability to break down sebum to inflammatory free fatty acids, the production of enzymes that trigger rupture of comedones, activating the expression of Toll-like receptors and activating of NOD-like receptor protein 3 of inflammasomes in neutrophils and monocytes. *C. acnes* contributes to a Th1/Th17 adaptive immune response [2].

Currently available topical acne treatments are not curative but aim to reduce acne lesions and subsequently minimize scarring and dyspigmentation. Treatment choice is based on the types of lesions present, the location, and extent of involvement. Topical-only therapy is generally appropriate for milder and more limited forms of acne. Various topical agents may be combined to achieve greater control of acne and to limit the development of bacterial resistance—topical antibiotic monotherapy should be avoided to prevent development of bacterial resistance. When combining therapies, special attention should be given to overlapping or potentiating adverse

effects, such as skin irritation. In more severe or widespread presentations of acne, topical can be combined with oral therapies (e.g., oral antibiotics, spironolactone, and oral contraceptives).

Topical medications that improve comedonal acne include topical retinoids, azelaic acid, benzoyl peroxide, sulfur, salicylic acid, and clascoterone. Most of these work by decreasing follicular hyperkeratosis. Medications that treat inflammatory lesions include benzoyl peroxide, sodium sulfacetamide-sulfur, clascoterone, and topical antibiotics such as erythromycin, clindamycin, minocycline, and dapsone. These typically work by reducing inflammation and decreasing bacteria in the sebaceous follicle [3]. Because microcomedone formation is a key step in acne pathogenesis, it is often recommended to use a product that reduces follicular hyperkeratosis even in the management of primarily inflammatory acne. Some products such as benzoyl peroxide and clascoterone improve both comedonal and inflammatory acne equally.

Commercially available combination topical therapies combining a retinoid and antibiotic such as benzoyl peroxide + clindamycin gel and tretinoin + clindamycin gel can target both inflammatory and comedonal acne and help limit bacterial resistance to the antibiotic component [3]. Although these combination products are often easier for patients to use, depending on availability, cost, tolerability, and clinical presentation, the practitioner can combine more than one individual topical agent in the patient's daily treatment regimen (e.g., benzoyl peroxide wash qam and tretinoin 0.025% cream qhs). Data regarding comparative efficacy of different topical medications is limited, although one recent meta-analysis suggested that topical treatments with antibiotics were not more effective than those that did not contain antibiotics. This study did not include all topical therapies, notably omitting topical dapsone, topical minocycline, clascoterone, and some topical retinoids (trifarotene and tazarotene) [4].

There are a variety of topical agents such as resorcinol and tea tree oil that are used in over-the-counter products worldwide but for which supporting evidence for efficacy is minimal. We have briefly included these medications in this chapter given their common use.

## Drug Monographs

### Adapalene

#### Classification and Mode of Action

- Retinoic acid derivative: Adapalene is a retinoid-like substance that modulates cellular differentiation, keratinization, and inflammation. Topical adapalene may normalize the differentiation of follicular epithelial cells resulting in decreased microcomedone formation. Adapalene is better than tretinoin or tazarotene in reducing inflammatory acne lesions and total lesion count and causes less irritation.

#### Indications and Dermatological Uses

- *Clinical indications (FDA)*: Acne vulgaris
- *Off-label common uses*: Rosacea

#### Formulations/Presentation

- US: 0.1% gel, 0.1% cream, 0.1% lotion, 0.1% pad, 0.1% solution
- Canada: 0.1% cream, 0.1% gel

#### Dosages and Suggested Regimens

- Apply once daily before bedtime
- No suggested dosage adjustment for renal or hepatic impairment due to low systemic absorption

#### Baseline Investigations and Considerations

- None

#### Pharmacokinetics

- Minimal topical absorption, even after chronic use (trace amounts measured in serum). Elimination half-life between 7 and 51 h (gel). Excreted in bile.
- Onset of effect: between 8 and 12 weeks.

## Use in Special Populations

### Pediatrics:

- Approved for use in children. May cause mild hyperglycemia, which is more common in children. Avoid internal use.

### Pregnancy and Lactation:

- Listed as FDA pregnancy classification C (former classification system).
- Unknown whether adapalene is present in breast milk.

### Renal Insufficiency:

- Not evaluated; dose adjustment is not expected to be needed.

### Hepatic Insufficiency:

- Not evaluated; dose adjustment is not expected to be needed.

## Monitoring

- Skin irritation/dryness
- Initial acne flare
- Severe skin reactions (exfoliation and desquamation)
- Allergy (angioedema, lip swelling, facial edema—reported postmarketing with gel)

## Contraindications and Cautions

- Accidental ingestion especially of large amounts of products containing propylene glycol may result in toxicity (metabolic acidosis/lactic acidosis, hyperosmolality, respiratory depression, and seizures). Fatalities have been reported in neonates given large amounts of propylene glycol internally (po or IV).

## Important Drug Interactions

- Other topical medications, which may cause skin irritation, will potentially exacerbate the skin irritation. (e.g., benzoyl peroxide, medicated soaps, and cleansers).
- Other topical medications (or cosmetics) containing alcohol, acetone, or astringents may exacerbate adapalene's drying effect.
- Adapalene may increase the levels/effects of aminolevulinic acid (topical or systemic). Avoid concomitant use.
- Levels/effects of adapalene may be increased by concomitant use of multivitamins with minerals (i.e., ADEK, folate, or iron).



## **Adverse Effects and Their Management**

- Skin irritation can occur. Less skin irritation than other retinoids, that is, tretinoin. Erythema, stinging/burning, dryness, or pruritus may occur especially during the initial 2–4 weeks of use. These may lessen with continued use.
- May cause initial exacerbation of acne.
- May cause increased sensitivity to UV rays. Use sunscreen and avoid sunlamp use.
- Hypersensitivity reactions including facial and eyelid edema and swelling have been reported. Use must be discontinued immediately as anaphylactoid/anaphylactic reactions may occur.

## **Carcinogenicity**

- Unknown. Carcinogenicity studies conducted in mice at topical doses of 0.3, 0.9, and 2.6 mg/kg/day and in rats at oral doses of 0.15, 0.5, and 1.5 mg/kg/day (approximately 4–75 times the maximal daily human topical dose). In the oral study, positive linear trends were observed in the incidence of follicular cell adenomas and carcinomas in the thyroid glands of female rats and in the incidence of benign and malignant pheochromocytomas in the adrenal medullas of male rats.
- No photocarcinogenicity studies were conducted. Animal studies have shown an increased tumorigenic risk with similar drugs (e.g., retinoids). Although the significance of these studies to human use is not clear, patients should be advised to avoid or minimize exposure to either sunlight or artificial UV irradiation sources.

## **Patch Test Concentration**

- 0.1% and 0.01% pet

## **Essential Patient Information**

- Avoid contact with broken, sunburned, eczematous, or abraded skin.
- Avoid contact with eyes, lips, or other mucous membranes (e.g., inside nose).

- Avoid using products including cosmetics which contain alpha hydroxyl or glycolic acid, as they may further irritate the skin.
- Do not ingest. For external use only.
- Use sun protection. Apply sunscreen with SPF 30 daily. If there is a sunburn, discontinue use until sunburn has healed.

## Benzoyl Peroxide

### Classification and Mode of Action

- Releases oxygen free radicals that both break down keratin (comedolytic) and result in a bactericidal effect on pathogenic skin bacteria.

### Indications and Dermatological Uses

- *Clinical indications (FDA):* Acne vulgaris, inflammatory rosacea, folliculitis, pseudofolliculitis barbae
- *Off-label common uses:* N/A

### Formulations/Presentations

US: Many prescription brands, generic, and OTC products exist. Multiple different formulations exist including cleansing bars, creams, gels, foams, liquid washes, foaming cloths, masks, and shaving creams. Some representative brands and strengths are listed below. Microencapsulated benzoyl peroxide is a novel prescription-only formulation in which benzoyl peroxide is encapsulated by silica microcapsules. This is used alone as a 5% cream for rosacea or in a combination product with tretinoin.

- Cream: 10% (Clearskin)
- Cream: Microencapsulated benzoyl peroxide 5% cream (Epsolay)
- Gel: 2.5%, 5%, 10% (BP Gel, Acne-Clear, Acne Medication, Persa-Gel)
- Foam: 5.2%, 5.5%, 5.3%, 9.8% (BenzePro, Riax)
- Liquid Wash: 2.5%, 3.5%, 4%, 5%, 5.25%, 6%, 7%, 10% (Panoxyl, Neutrogena Clear Pore, Benzac, BenzePro, Benziq Wash, BP Wash, PR Benzoyl peroxide wash)

- Liquid extended release Wash: 4.4% (Advanced Acne Wash)
- Lotion: 5%, 8%, 10% (Acne Medication 5, Acne Medication 10, Zaclar Cleansing)
- Foaming cloths: 6% (BenzePrO, BPO foaming cloths)
- Cleansing bar: 5%, 10% (Panoxyl)
- Masks: 2.5% (Rapid Clear Daily leave on mask)
- Shaving creams: 5%, 10% (BenzaShave)

Canada: Numerous prescription and OTC products similar to the United States

### **Dosages and Suggested Regimens: Adult**

Topical formulations:

- Apply sparingly once daily. Can increase to twice daily if necessary. Decrease application frequency or active ingredient strength for skin dryness/irritation.

Topical cleansers:

- Wash affected areas once to twice daily. Decrease application frequency and/or active ingredient strength for skin dryness/irritation.

### **Baseline Investigations and Considerations**

- None

### **Pharmacokinetics**

- Absorption: Approximately 5% through the skin. Gel-based products are more penetrating.
- Metabolism: Converted to benzoic acid in the skin. Cleared renally.

### **Use in Special Populations**

Pregnancy:

- Safety studies have not been conducted in human or animal models. In general, topical agents are preferred in treating acne in pregnant patients. Among the topical options, benzoyl peroxide is a preferred agent [17, 25].

**Lactation:**

- While the manufacturer recommends caution in using benzoyl peroxide in breastfeeding patients, the World Health Organization considers use of the topical medication compatible with breastfeeding [27]. As above, topical agents are preferable to systemic acne medications in breastfeeding patients, and benzoyl peroxide is a preferred agent [17, 25].

**Renal insufficiency:**

- There are no dosing adjustments provided on the manufacturer's label.

**Hepatic insufficiency:**

- There are no dosing adjustments provided on the manufacturer's label.

**Monitoring**

- No specific monitoring guidelines

**Contraindications and Cautions**

- Hypersensitivity to benzoyl peroxide or any component of the product's formulation. Consult product label for comprehensive ingredient list, as inactive ingredients can vary significantly between products.
- Benzoyl peroxide can bleach or discolor hair and fabrics.
- Hypersensitivity reactions: Rare but potential life-threatening allergic reactions have been reported with over-the-counter benzoyl peroxide products. Allergic reactions can occur to active ingredients (benzoyl peroxide), inactive ingredients, or both. Treatment should be discontinued in the setting of urticaria or significant skin pain/irritation. Patients should seek emergency medical assistance in the setting of anaphylaxis. The FDA recommends spot treatment (one to two areas) with small amount of product for the first few applications to mitigate this risk.
- Skin irritation/erythema
- Only for external use: do not apply to eyes, lips, or other mucosal surfaces.
- Avoid use of benzoyl peroxide containing products in neonates.

## Important Drug Interactions

The frequency of the following potential drug interactions is not defined.

- Dapsone (topical): Concurrent use may cause temporary discoloration (yellow-orange) of face/hair.
- Sodium sulfacetamide-sulfur: Concurrent use may cause temporary discoloration (yellow-orange) of face/hair
- Tretinoin (topical): Concurrent application of non-microencapsulated formulations of benzoyl peroxide may decrease effectiveness of tretinoin. Do not apply both medications at the same time. Generally, it is recommended to apply benzoyl peroxide products in the morning and topical retinoid products at night (as the latter can cause some photosensitivity).
- Topical anesthetics (benzocaine, tetracaine, procaine, pramoxine, prilocaine, and lidocaine): Concurrent use may decrease effectiveness of anesthetic.

## Adverse Effects and Their Management

- Bleaching of hair and clothing may occur.
- Dry skin, desquamation, burning, or stinging (irritant dermatitis). This can be minimized by decreasing concentration or frequency of benzoyl peroxide use. Additionally, this is often soothed and improved by using a light non-comedogenic moisturizer. Discontinue if significant discomfort develops. Use with caution in patients with dry skin and atopic dermatitis.
- Allergic contact dermatitis. Patch testing may be indicated for diagnosis.
- Photosensitivity/rare phototoxicity

## Essential Patient information

- Bleaching and staining of fabrics may occur. Cotton fabrics appear to be more affected than synthetic fabrics. Washing fabrics within 8 h of contact with benzoyl peroxide may decrease staining. Wait until product is completely dry if

leave-on product, or make sure washed off completely (if short contact foam, cleansing wash/bar, shave cream) prior to putting on clothes.

- Discontinue if significant redness, scaling, and irritation develops. Let your clinician know if this occurs.
- Practice sun protection while using this medication including sunscreen when appropriate.
- Do not mix with other acne medications unless directed by your clinician.

### **Carcinogenicity**

- In animal studies, benzoyl peroxide has been shown to promote tumor progression and to increase photocarcinogenicity (including in over-the-counter combination products). In one study, BPO in acetone administered twice a week over 20 weeks induced squamous cell skin cancers. These studies have not been performed or replicated in humans, and the clinical significance remains unknown.

### **Patch Test Concentration**

- 1.0% pet. (Chemotechnique, SmartPracticeEurope, SmartPracticeCanada); great risk of irritant reactions

## **Clascoterone**

### **Classification and Mode of Action**

- Topical acne medication; androgen receptor antagonist
- MOA: Competitive androgen receptor antagonist. By competing with dihydrotestosterone for androgen receptor binding, clascoterone limits downstream sebum production and curbs local inflammation.

### **Indications and Dermatological Uses**

- *Clinical indications (FDA)*: Acne vulgaris (patients 12 years of age and older)
- *Off-label common uses*: N/A

**Formulations/Presentation**

- US: Cream 1% (Winlevi) clascoterone 1%; inactive ingredients

**Dosages and Suggested Regimens: Adult**

- Acne vulgaris: Gently cleanse acne prone area with mild soap and water. Gently dry skin, then apply thin, even layer to the affected area(s) twice daily, morning and evening.

**Pharmacokinetics**

- Absorption: Systemic absorption reaches steady state by day 5. In general, metabolites of clascoterone were below or near detectable levels in the serum (0.5 ng/mL) in patients >12 years of age.
- Elimination: Cortexolone is the possible primary metabolite. In vitro studies indicate at least partial hepatic metabolism.
- Excretion: Has not been characterized yet in human studies

**Use in Special Populations****Pregnancy**

- There are no data evaluating the safety of using Clascoterone cream in pregnant adults.
- There are animal studies suggesting fetal pregnancy complications and pregnancy loss attributed to dosing above maximal recommended dose. As such, it is most prudent to recommend against use in pregnancy.

**Lactation:**

- There are no data evaluating the safety of using topical Clascoterone in breastfeeding patients.
- The potential risks and benefits of androgen blockage and the risks and benefits of breastfeeding while using this medication should be discussed with each patient individually.
- Additionally, assessing lactating patients need for the medication while breastfeeding an infant should be addressed.

**Pediatric use:**

- Safety and efficacy have been reported with using topical Clascoterone in children age 12 and older for acne vulgaris.

- There are no safety/efficacy data available for children under 12 years of age.
- It is important to note that Hypothalamic-pituitary-adrenal (HPA) axis suppression was noted in 2/22 (9%) of adolescents. Both affected children had axis function return to normal one month after stopping the medication.

#### Geriatric use:

- To date, there is not sufficient data in the safe use of Clascoterone in patients older than 65.
- Recommend caution in starting geriatric patients on this medication, with consideration for lower dosing/frequency of application.

#### Renal and hepatic insufficiency

- There are no dosing adjustments provided on the manufacturer's label.

### Monitoring

- No specific monitoring guidelines

### Contraindications and Cautions

- HPA axis suppression observed.
- Hyperkalemia, caution when using in patient with underlying heart disease
- Caution with use in pregnant, lactating, pediatric and elderly patients
- Not approved for use in children under the age of 12
- Do not apply to open wounds or abraded, eczematous, or sun-burned skin.

### Important Drug Interactions

- No clinical studies evaluating drug-drug interactions have been completed to date.

### Adverse Effects and Their Management

- Skin irritation: erythema, pruritus, scaling/dry texture (~7–12%), edema, and stinging/burning (>3%). In phase 3 clinical trials, these occurred with a similar frequency as the



vehicle control arm. If this occurs and is significant, consider decreasing frequency, medication holidays, and/or discontinuation.

- Less commonly observed local cutaneous side effects in the phase 3 clinical trials included striae rubrae (2.5%) and telangiectasia (1.2%). In phase 3 clinical trials, these occurred with a similar frequency as the vehicle control arm. A 9-month safety trial did not show increase in striae rubra, telangiectasia, or atrophy in subjects treated with topical Clascoterone. If new atrophy, striae, or telangiectasia is observed, discontinue use.
- In the long-term safety trial, one patient developed depigmented hair in the area treated with Clascoterone cream.
- HPA axis suppression was observed in PK studies (adult: 1/20 subjects, pediatric: 2/22). If symptoms of HPA axis suppression develop, discontinue medication. Risk of systemic Clascoterone absorption increases with occlusion, use on large body surface area, and prolonged use. Of note, clinical trials did not show systemic antiandrogen activity.

### **Essential Patient Information**

- Do not apply to open wounds or abraded, eczematous, or sunburned skin.
- Do not apply to mucous membranes.
- Avoid concomitant use of potentially drying and irritating skin products (e.g., astringents, drying soaps, and cleansers)
- Notify clinician if symptoms of HPA-axis suppression occur including weakness, malaise, fatigue, nausea, abdominal pain, headache, and poor weight gain.

### **Carcinogenesis**

- In a 2-year long rat study, daily application of Clascoterone cream (0.1%, 1%, 5%) was not carcinogenic. An Ames reverse mutation assay showed that Clascoterone was not mutagenic.

### **Patch Test Concentration**

- N/A

## Common Brand Names

- Winlevi

## Clindamycin

### Classification and Mode of Action

- Topical acne product; topical antibiotic, lincosamide
- Reversibly binds the bacterial 50S ribosomal subunit, preventing protein synthesis. This effect can be either bacteriostatic or bactericidal depending on the drug concentration used and organism targeted.

### Indications and Dermatological Uses

- *Clinical indications (FDA)*: Inflammatory lesions of acne vulgaris
- *Off-label common uses*: Hidradenitis suppurativa, rosacea (inflammatory lesions), folliculitis

### Formulations/Presentation (Vaginal Creams/Suppositories Not Outlined)

US:

- Foam, 1% (Evoclin, Generic)
- Gel, 1% (Cleocin-T, Clindagel, Generic)
- Pledgets and Swab, 1% (Clindacin ETZ, Clindacin Pac—available in Kit with acne wash, Clindacin-P, Generic)
- Lotion, 1% (Cleocin-T, Generic)
- Solution, 1% (Cleocin-T, Generic)
- Foam, 1% (Evoclin)
- Generic: 1%

Canada:

- Solution, 1% (Clinda-T, Dalacin T, Generic)
- Gel, 1% (Biacna, Generic)

## Dosages and Suggested Regimens

Acne vulgaris:

- Gel, pledgets, lotion, and solution: Apply a thin film to acne-prone areas twice daily
- Gel (Clindagel) and foam (Evoclin): Apply to acne-prone areas once daily

Hidradenitis suppurativa (off-label use):

- Solution: apply twice daily to affected area(s)

Rosacea (off-label use):

- Lotion: Apply twice daily to the face

Folliculitis (off-label use):

- Gel, lotion, solution: apply twice a day to affected area  $\times$  7–10 days

## Pharmacokinetics

- Absorption: Topical solution, lotions, gels, or foams have minimal systemic absorption. As such, there is no relevant data on systemic metabolism, half-life, or time to peak serum concentration.
- Excretion: Urine ( $<0.2\%$  with topical preparations)

## Use in Special Populations

Pregnancy:

- Clindamycin crosses the placenta when administered through oral or parenteral routes. The amount of clindamycin present systemically is significantly less when administered topically.
- If antibiotic treatment for acne vulgaris is deemed necessary during pregnancy by patient and clinician, topical clindamycin is a reasonable option to consider. However, pregnant patients should avoid repetitive application inflamed or open skin and should not apply to large surface areas, just locally to affected skin.

Lactation:

- While clindamycin is present in breast milk following oral and IV dosing, it is not presently known if clindamycin is present in breast milk following topical application. In gen-

eral, it is known that there is very minimal systemic absorption of topical clindamycin, which should minimize potential exposure to breastfeeding infant.

- Consider monitoring breastfeeding infants for diarrhea and hematochezia if clindamycin is indicated for a breastfeeding mother.
- To decrease level of systemic exposure, breastfeeding patients should avoid repetitive application to inflamed or open skin and should not apply to large surface areas.
- The manufacturer states the decision to continue or discontinue breastfeeding should be made after a discussion of the potential risks of exposure to the infant and potential benefits to the breastfeeding mother.

Pediatric use:

- Safety and efficacy in children under 12 years of age have not been established.

Renal insufficiency:

- There are no dosing adjustments provided on the manufacturer's label.

Hepatic insufficiency:

- There are no dosing adjustments provided on the manufacturer's label.

## Monitoring

- No specific monitoring guidelines

## Contraindications and Cautions

- Hypersensitivity to clindamycin, lincomycin, or any component of the product's formulation
- History of antibiotic-associated colitis
- Regional enteritis
- Ulcerative colitis
- *Caution:* Given the risk of bacterial resistance, it is recommended clindamycin be used in combination with other agents, such as topical benzoyl peroxide, topical retinoids, and/or systemic antibiotics.

## Important Drug Interactions

The frequency of the following potential drug interactions is not defined.

- Erythromycin (systemic): May reduce the therapeutic effect of topical clindamycin. Avoid concurrent use in treating acne vulgaris.
- Erythromycin (topical): May reduce the therapeutic effect of topical clindamycin. Avoid concurrent use (especially at the same application site) in treating acne vulgaris.
- Neuromuscular-blocking agents: Topical clindamycin may enhance the effect of neuromuscular-blocking agents.

## Adverse Effects and Their Management

- Local skin irritation (itching, burning, dryness, redness, and peeling/desquamation). Discontinue if this occurs. This may occur with any of the formulations but may be less frequent with the foam when used in acne vulgaris.
- Oily skin
- Hypersensitivity: Allergic contact dermatitis or urticaria. Discontinue therapy if this occurs.
- Rare diarrhea, bloody diarrhea, nausea, and abdominal discomfort. Discontinue if this occurs. *C. difficile* colitis has rarely been reported with topical clindamycin.
- Gram-negative folliculitis. If suspected, discontinue clindamycin, culture skin pustule if possible, and start therapy for gram-negative folliculitis.

## Essential Patient Information

- Topical clindamycin should be used whenever possible with other topical acne treatments such as benzoyl peroxide or topical retinoids to minimize bacterial resistance.
- Foam is flammable and should not be used around open fire, flame, or smoking.
- Let your clinician know if you have worsening acne despite treatment with topical clindamycin. In some cases, this may indicate gram-negative folliculitis, which requires a different approach to treatment.

**Carcinogenicity**

- Daily application of topical clindamycin at 3–15 times higher doses than commercially available resulted in no significant increase in tumors in animal studies.

**Patch Test Concentration**

- Phosphate, 10.0% pet. (Chemotechnique)

**Common Brand Names**

Cleocin; Cleocin-T; Clindacin ETZ; Clindacin Pac; Clindacin-P; Clindagel; Clindesse; Evoclin; Clinda-T; Dalacin T [DSC]; Dalacin Vaginal; TARO-Clindamycin

**Dapsone****Classification and Mode of Action**

- Sulfone, unknown but thought to work as an anti-inflammatory agent.

**Indications and Dermatological Uses**

- *Clinical indications (FDA)*: topical treatment of acne vulgaris
- *Off-label common uses*: none

**Formulations/Presentation**

- US: Acne 5% or 7.5% gel (Aczone, generic)
- Canada: 5% gel (Aczone)

**Dosages and Suggested Regimens**

- Acne vulgaris: apply approximately a pea-sized amount of gel in a thin layer to the entire face once daily. A thin layer can also be applied to other affected areas.

**Baseline Investigations and Considerations**

- None

## Pharmacokinetics

### Absorption:

- The systemic exposure from dapsone gel, 7.5% is expected to be about 1% of that from a 100 mg oral dose.

## Use in Special Populations

### Pregnancy:

- There are no available data on dapsone use in pregnant women to inform risk for adverse developmental outcomes.
- In animal studies on rats, maternal toxicity and developmental effects were seen at a dapsone dose of 30 mg/kg/day (approximately 563 times the systemic exposure with maximum recommended human dose of dapsone gel, 7.5%).

### Lactation:

- There is no information regarding the presence of topical dapsone in breastmilk, the effects on the breastfed infant, or the effects on milk production.
- Orally administered dapsone appears in human milk and could result in hemolytic anemia and hyperbilirubinemia, especially in infants with G6PD deficiency.
- The manufacturer states that the decision to use dapsone should include a discussion of the developmental and health benefits of breastfeeding, along with the mother's clinical need for treatment, and any potential adverse effects on the child from dapsone or the underlying maternal condition.

### Pediatric use:

- Dapsone gel, 7.5%, is safe to use for the topical treatment of acne vulgaris in patients 9 years of age or older.
- Safety and effectiveness of dapsone gel, 7.5%, have not been established in patients below age 9 years.

Renal insufficiency: There are no dosing adjustments provided on the manufacturer's label.

Hepatic insufficiency: There are no dosing adjustments provided on the manufacturer's label.

## Monitoring

- No specific monitoring guidelines

## Contraindications and Cautions

- No contraindications
- Temporary yellow or orange discoloration of the skin and facial hair may be seen when benzoyl peroxide is applied after dapsone.
- *Caution:* Cases of methemoglobinemia have been reported with twice daily dapsone gel, 5%, treatment. Patients with G6PD deficiency or congenital or idiopathic methemoglobinemia are more susceptible. Avoid use in these patients.
- *Caution:* Dose-related hemolysis and hemolytic anemia have been seen with oral dapsone treatment. There was no evidence of clinically relevant hemolysis or hemolytic anemia in clinical trials with topical dapsone, but some subjects with G6PD deficiency using dapsone gel, 5%, twice daily did show laboratory changes suggestive of hemolysis. Avoid use in patients who are taking oral dapsone or antimalarials due to potential for hemolytic reactions. Additionally, combination of dapsone gel, 7.5%, with trimethoprim/sulfamethoxazole (TMP/SMX) may increase the likelihood of hemolysis in patients with G6PD deficiency.

## Important Drug Interactions

- No formal drug-drug interaction studies have been conducted with dapsone gel, 7.5%.
- Trimethoprim-sulfamethoxazole (TMP/SMX): When combined with double strength (160 mg/800 mg) TMP/SMX, levels of dapsone and its metabolites were increased. However, the systemic exposure with dapsone gel, 7.5%, is still expected to be about 1% of that from the 100 mg oral dose when administered with TMP/SMX.
- Drugs that induce methemoglobinemia: The risk for developing methemoglobinemia may be increased when administered with drugs that induce methemoglobinemia, such as sulfonamides, acetaminophen, phenytoin, and others.



## **Adverse Effects and Their Management**

- Skin irritation, peeling, dryness, erythema, pruritus, dermatitis, and swelling of the face, lips, and eyes. If this occurs and is severe or intolerable, discontinue therapy.
- Methemoglobinemia. May present initially as cyanosis of mucous membranes, lips, and nail beds. Discontinue topical dapsone if this occurs.
- Respiratory: Nasopharyngitis, sinusitis, and cough were reported in less than 5% of subjects in the Aczone 5% clinical trials. Unclear if these symptoms are truly related to the topical dapsone. If it occurs, consider discontinuing. If not severe, can consider retreat topical dapsone once symptoms resolve.
- Headache was also noted in 4% of patients in the Aczone clinical trials. Unclear if these symptoms are truly related to the topical dapsone. If it occurs, consider discontinuing. If not severe, can consider retreat topical dapsone once symptoms resolve.
- In clinical trials of Aczone 5% the following severe adverse events were reported: suicide attempt, tonic clonic movements, abdominal pain, severe vomiting, and pancreatitis. This was not reported in the Aczone 7.5%.
- Orally administered dapsone has been associated with hemolytic anemia, agranulocytosis, motor peripheral neuropathy, and severe cutaneous drug reactions. These were not observed in clinical trials of topical dapsone.

## **Carcinogenicity**

- No carcinogenesis observed when rats were exposed to systemic dapsone in doses up to 340 times the systemic exposure observed in humans as a result of the use of the maximum recommended human dose of Aczone gel, 7.5%. Dermal studies in Tg.AC transgenic mice showed no induction of carcinogenesis with topically applied dapsone 3%, 5% and 10%.
- Ames test of Dapsone did not show mutagenesis; however, it did induce structural chromosomal aberrations in Chinese hamster ovary cells.

**Patch Test Concentration**

- N/A

**Essential Patient Information**

- Seek immediate medical attention if cyanosis develops while using this medication.

**Erythromycin****Classification and Mode of Action**

- Topical acne product; topical antibiotic, macrolide
- MOA: Reversibly binds the bacterial 50S ribosomal subunit, preventing protein synthesis. Alcohol component can be quite drying.

**Indications and Dermatological Uses**

- *Clinical indications (FDA):* Acne vulgaris
- Note: The AAD recommends against use as monotherapy given risk for bacterial resistance (AAD [48]).
- *Off-label common uses:* Rosacea, perioral dermatitis

**Formulations/Presentation (Vaginal Creams/Suppositories Not Outlined)**

US:

- Gel: 2% (Erygel, Generic)
- Swab: 2% (Generic)
- Solution: 2% (Erythra-Derm, Generic)

Canada:

- Gel: 3% with 5% benzoyl peroxide (Benzamycin)

**Dosages and Suggested Regimens**

Prior to treatment, wash affected areas with soap and water and rinse and pat dry. Avoid contact with mucous membranes.

- Gel: Apply thin film to acne-prone areas once to twice daily. May take 6–8 weeks before effect is appreciated. Discontinue if no improvement after 6–8 weeks.

- Pads: Rub pad over acne prone areas twice daily. More than one pad can be used, if necessary.
- Solution: Apply to the affected area twice daily. Frequency of application may be limited by skin dryness.

### **Baseline Investigations and Considerations**

- None

### **Pharmacokinetics**

- Absorption: Topical formulations have minimal systemic absorption. As such, there is no relevant data on systemic metabolism, half-life, or time to peak serum concentration.

### **Use in Special Populations**

#### **Pregnancy:**

- The amount of erythromycin available systemically after being applied topically is exceedingly low. Systemic absorption is required for the medication to cross the placenta.
- Because the risk to the fetus is low, antibiotic treatment for acne vulgaris with topical erythromycin is a reasonable option to consider.

#### **Lactation:**

- Currently, it is not known if erythromycin is present in breast milk after topical application. As above, amount of erythromycin systemically available after topical application is exceedingly low and is thus considered generally compatible to use in lactating patients.

#### **Pediatric use:**

- Safety and efficacy in patients less than 12 years of age have not been established.

#### **Renal insufficiency:**

- There are no dosing adjustments provided on the manufacturer's label.

#### **Hepatic insufficiency:**

- There are no dosing adjustments provided on the manufacturer's label.

**Monitoring**

No specific monitoring guidelines

**Contraindications and Cautions**

- Hypersensitivity to erythromycin, macrolide antibiotics, or any component of its formulation
- Pseudomembranous colitis. Discontinue if patient develops diarrhea, abdominal pain, hematochezia, or melena
- Given the risk of bacterial resistance, it is recommended clindamycin be used in combination with other agents, such as topical benzoyl peroxide, topical retinoids, and/or systemic antibiotics.
- Topical gel may be flammable.
- May cause significant skin dryness and/or redness when used in combination with other topical acne products.
- Keep away from broken/damaged skin. Do not apply to any mucous membranes, including eyes, nose, mouth, etc.

**Important Drug Interactions**

The frequency of the following potential drug interactions is not defined.

- Clindamycin (topical): May reduce the therapeutic effect of topical clindamycin. Avoid concurrent use in treating acne vulgaris.
- Isotretinoin (topical): May enhance the adverse effects of topical erythromycin, see below.

**Adverse Effects and Their Management**

- Local skin effects: Skin peeling, xerosis, itching, burning, redness, irritation, and oily skin. Discontinue if symptoms are significant.
- May irritate eyes and mucosal surfaces if used on nearby skin or mucosal surface itself.
- Generalized urticaria and other hypersensitivity reactions have been reported. Discontinue if this occurs.
- Superinfection of skin by non-susceptible organisms may occur with the use of topical antibiotics. If this occurs, discontinue therapy and treat superinfection

## **Carcinogenesis**

- No investigations into the carcinogenic potential of topical erythromycin have been performed. Studies of rats exposed to oral erythromycin (base) over 2 years did not show tumorigenicity.

## **Patch Test Concentration**

- 2% pet. (SmartPractice Canada, SmartPracticeEurope), 1% pet. (SmartPracticeCanada), 10.0% pet (Chemotechnique). 1% may sometimes be too low.

## **Common Brand Names**

- Erygel

## **Minocycline**

### **Classification and Mode of Action**

- Tetracycline class antibiotic. Bacteriostatic medication that suppresses bacterial protein synthesis. Antibiotic effect against skin flora including some strains of *Cutibacterium acnes*.
- Minocycline also has anti-inflammatory effects, which may help improve acne. Some proposed anti-inflammatory mechanisms include inhibition of matrix metalloproteinases, suppression of neutrophil chemotaxis, and downregulation of inflammatory cytokines.

### **Indications and Dermatological Uses**

- *Clinical indications (FDA)*: Inflammatory lesions of rosacea and acne
- *Off-label common uses*: N/A

### **Formulations/Presentation**

- US:
  - Rosacea: Topical foam 1.5%, 15 mg minocycline/gram (Zilxi)
  - Acne: foam 4%, 40 mg minocycline/gram (Amzeeq)

## Dosages and Suggested Regimens

- Acne: Shake can before use. Apply a “cherry-sized” amount of foam once a day to affected areas of face at least 1 h before bedtime. Additional amount of foam can be used to other acne affected areas (e.g., chest, back, neck, shoulders, and arms).
- Rosacea: Shake can before use. Apply a “cherry-sized” amount of foam once a day to affected areas of face at least 1 h before bedtime. Additional amount of foam can be used if needed to cover the entire affected area.

## Baseline Investigations and Considerations

- None

## Pharmacokinetics

### Absorption:

- Minocycline 4% foam (Amzeeq): Following application once daily for 21 days, systemic minocycline exposure was 730–765 times lower than minocycline administered orally.
- Minocycline 1.5% foam (Zilxi): When 2 g applied to the whole face, a very low amount absorbed in plasma (day 1: C<sub>max</sub> 1.30 ng/mL and day 14: 0.75 ng/mL). Systemic accumulation was not observed.

## Use in Special Populations

### Pregnancy:

- Safety in pregnant women has not been established, but systemic absorption of topical minocycline foam is low. Administration of oral minocycline can result in skeletal defects, permanent discoloration of teeth and bone growth inhibition.

### Lactation:

- Safety in lactation has not been established. Accumulation of minocycline in breast milk after topical application has not been studied. Recommend avoidance in lactation.

**Pediatric use:**

- Safety has not been established in children younger than 9 years old. Recommend avoiding use in this age group given risks of permanent tooth discoloration, tooth enamel hypoplasia, and potential bone growth abnormalities with oral administration of tetracycline antibiotics.

**Renal:** No dose adjustments have been recommended by the manufacturer.

**Hepatic:** No dose adjustments have been recommended by the manufacturer.

**Monitoring**

- Skin sensitivity
- Photosensitivity
- Diarrhea
- Headache with visual changes
- Skin discoloration

**Contraindications and Cautions**

- The propellant used in the can is flammable. Advise patients during and immediately after application to avoid open flames and smoking.

**Important Drug Interactions**

- Anticoagulants. Tetracycline class antibiotics can reduce prothrombin activity. Patients on tetracycline class antibiotics and anticoagulants may require a decrease in the dose of their anticoagulant.
- Penicillin. Avoid concomitant use. Tetracycline class antibiotics can affect penicillin bactericidal activity.
- Benzoyl peroxide. If applied together, benzoyl peroxide can inactivate minocycline foam.

**Adverse Effects and Their Management**

- May cause application site discomfort, skin dryness, and erythema. Discontinue if significant.
- Headache was the most common side effect with minocycline 4% foam in the clinical studies affecting 3% of subjects com-

pared to 2% of vehicle treated patients. If persistent or “unusual” headaches (particularly if associated with changes in vision) develop, the medication should be discontinued.

- May cause temporary yellow tint of skin and nails that can be washed off with soap and water. Wait at least 1 h after application before washing off.
- May discolor fabrics.
- Orally administered minocycline has been associated with multiple adverse reactions. These have not been demonstrated with topical application; however, patients and prescribers should be aware of these side effects. If they occur, the topical minocycline foam should be discontinued. These side effects include: *Clostridioides difficile* associated diarrhea, hepatotoxicity, autoimmune syndromes (fevers, arthralgia, malaise, and rash), central nervous system effects, intracranial hypertension, hyperpigmentation of scars, skin, teeth and gums, superinfection by non-susceptible organisms, and hypersensitivity reactions (e.g., anaphylaxis, Stevens-Johnson syndrome, drug reaction with eosinophilia, and other serious cutaneous eruptions).
- May increase the risk of superinfection by minocycline non-susceptible microbes and fungi. Discontinue topical minocycline if this occurs and start therapy for the superinfection.
- Possible photosensitivity. Orally administered minocycline is associated with photosensitivity; however, studies of minocycline foam application under ultraviolet light did not show development of phototoxicity or photoallergy.

### **Carcinogenicity**

- Carcinogenicity studies are available in rats. One study showed that orally administered minocycline in doses up to 200 mg/kg/day for 104 weeks was associated with follicular cell tumors (adenomas and carcinomas) of the thyroid gland in both male and female rats. Another study that administered oral minocycline up to 150 mg/kg/day for 104 weeks showed no increase in neoplasms.

### **Patch Test Concentration**

- N/A



## Essential Patient Information

- Patients should be advised to practice diligent sun protection and minimize exposure to natural or artificial ultraviolet light. Discontinue minocycline foam if sunburn occurs.
- Avoid open flames and smoking during and immediately after application.
- At home, store at temperatures below 25 °C (77 °F) for 90 days. Do not store in refrigerator. Do not expose to temperatures above 49 °C (120 °F). Do not store near flame.
- Foam should be applied at approximately the same time each day. Avoid bathing, swimming, or showering for at least 1 h after application.
- Don't use on mucous membranes or ocular mucosa.
- May take up to 3 months to see full benefit of minocycline 1.5% foam.
- Wait at least 8 h between application of minocycline foam and any benzoyl peroxide product.
- Avoid use in children under 9 years old.

## Resorcinol

### Classification and Mode of Action

- Isomer of hydroquinone.
- Reducing agent with antibacterial and keratolytic properties by disrupting hydrogen bonds of keratin.

### Indications and Dermatological Uses

- *Clinical indications (FDA)*: Topical treatment of acne vulgaris and seborrheic dermatitis
- *Off-label common uses*: Post-inflammatory hyperpigmentation/erythema, acne scarring, and analgesia

### Formulations/Presentation

- US: There are a variety of over-the-counter formulations. Examples include Resorcinol 2% ointment (Resinol) or 2% cream with 2%, 5%, or 8% sulfur (Rezamid, Acnomel, and other generic).
- Resorcinol is also used in a variety of chemical peels.

## Dosages and Suggested Regimens

- Acne vulgaris:
  - 2% ointment: apply to affected area not more than three to four times daily
  - 2% cream: cover the entire affected area with a thin layer one to three times a day

## Pharmacokinetics

Absorption:

- Dermal absorption appears to be low (<1%) when applied on intact skin.

## Use in Special Populations

Pregnancy:

- Contraindicated in pregnancy due to lack of study data.

Lactation:

- No data available.

Pediatric use:

- Safety and effectiveness of topical resorcinol in pediatric patients have not been established.

Renal insufficiency: There are no dosing adjustments provided on the manufacturer's label.

Hepatic insufficiency: There are no dosing adjustments provided on the manufacturer's label.

## Monitoring

- No specific monitoring guidelines.

## Contraindications and Cautions

- *Contraindications:* Pregnancy and skin type VI, due to lack of data regarding complications.
- Resorcinol should not be applied to large areas of the body, for prolonged periods, or in high concentrations due to potential for interference with thyroid function or production of methemoglobinemia.
- May produce hyperpigmentation and darken lighter hair colors.

**Important Drug Interactions**

- There have been no formal studies of the interaction of topical resorcinol with other drugs.

**Adverse Effects and Their Management**

- No manufacturer studies of adverse effects available.
- Adverse effects that have been reported include hyperpigmentation, burning sensations, and paresthesias.

**Carcinogenicity**

- In studies of oral administration to male and female rats at doses of 50 mg/kg or greater, there was no evidence of carcinogenic activity.

**Patch Test Concentration**

- 1% pet. (Chemotechnique, SmartPracticeCanada), 2% pet (SmartPracticeEurope, SmartPracticeCanada)

**Essential Patient Information**

- N/A

**Retinoids**

See under Chap. [22](#): Retinoids

**Salicylic Acid**

See under Chap. [21](#): Psoriasis

**Sulfur and Sulfacetamide****Classification and Mode of Action**

- Sulfur is a chemical element thought to have antibacterial effects by conversion of sulfur to pentathionic acid.

- May suppress *C. acnes* proliferation in sebaceous follicle.
- Also thought to possess keratolytic action when reduced via direct interaction with keratinocytes to form hydrogen sulfide.
- May also have effect on decreasing facial demodex counts.
- Sodium sulfacetamide is a sulfonamide that has a bacteriostatic effect by restricting synthesis of folic acid through competition with para-aminobenzoic acid.

### Indications and Dermatological Uses

- *Clinical indications (FDA)*: Acne vulgaris, rosacea (inflammatory papules and pustules), seborrheic dermatitis
- *Off-label common uses*: perioral dermatitis, scabies, superficial fungal infections, secondary bacterial infections due to organisms susceptible to sulfonamides

### Formulations/Presentation

- Available products include combination sulfur and sulfacetamide, sulfacetamide-only and sulfur-only in a variety of formulations. Some formulations contain additional ingredients such as salicylic acid, resorcinol, sunscreen, tints, bakuchiol, and urea.
- US:
  - Sulfur and sulfacetamide sodium products:
    - Cleanser, topical:
      - Sulfur 5% and sulfacetamide sodium 10%: AVAR, Clenia, Prascion, Rosanil. Generic formulations available
      - Sulfur 2% and sulfacetamide sodium 10%; AVAR LS, Generic formulations available
      - Sulfur 4.8% and sulfacetamide sodium 9.8%; Prascion cleanser. Generic formulations available.
    - Cream, topical:
      - Sulfur 5% and sodium sulfacetamide 10% : AVAR-e, AVAR-e Green (corrective cream), Clenia, SSS, Virtisulf. Generic formulations available.
      - Sulfur 2% and sulfacetamide sodium 10%: AVAR-e LS, Generic formulations available.

- Sulfur 4.8% and sulfacetamide sodium 9.8%: Generic formulations available.
- Foam, topical:
  - Sulfur 5% and sulfacetamide sodium 10%: SSS. Generic formulations available.
  - Sulfur 5% and sulfacetamide sodium 9.5%: AVAR
  - Sulfur 2% and sulfacetamide sodium 10%: AVAR LS
- Lotion, topical:
  - Sulfur 4.8% and sulfacetamide sodium 9.8%; Generic.
- Gel, topical:
  - Sulfur 5%, sodium sulfacetamide 10% and urea 10%; Rosula, Generic.
- Cleansing cloth:
  - Sulfur 5% and sulfacetamide sodium 10%; Rosula.
  - Sulfur 4.8% and sulfacetamide sodium 9.8%; Generic.
  - Sulfur 4% and sulfacetamide sodium 10%; Sumaxin, Generic.
- Suspension, topical:
  - Sulfur 4% and sulfacetamide sodium 8%; SulfaCleanse 8/4, Sumaxin TS, Generic.
- Wash:
  - Sulfur 1% and sulfacetamide sodium 10%: BP 10-1, Sulfamez wash, Generic.
  - Sulfur 4% and sulfacetamide sodium 10%: BP cleansing Wash
  - Sulfur 4.5% and sulfacetamide sodium 10%: Rosula wash
  - Sulfur 4.5% and sulfacetamide sodium 9%: Sumadan, Sumadan XLT
  - Sulfur 4% and sulfacetamide sodium 9%: Sumaxin, Generic.
- Sodium sulfacetamide only products:
  - Lotion, external:
    - 10% sulfacetamide sodium: Klaron, Generic (indicated for acne)
    - 9.8% sulfacetamide sodium: Ovace Plus

- Liquid:
  - 10% sulfacetamide sodium: Ovace Plus Wash, Ovace Wash, Seb-Prev Wash, Generic.
  - Combination therapy of sodium sulfacetamide 10% -Bakuchiol: APOP gel.
- Cream, external
  - 10% sodium sulfacetamide: Ovace Plus (indicated for seborrheic dermatitis/scaling dermatoses and bacteria infections)
- Foam, external
  - 9.8% sodium sulfacetamide: Ovace Plus
- Wash/cleansing gel, external (indicated for seborrheic dermatitis):
  - 10% sodium sulfacetamide: Ovace Plus Wash cleansing gel, SEB-Prev, Generic.
- Shampoo:
  - 10% sodium sulfacetamide: Ovace Plus
  - 9.8% sodium sulfacetamide: Generic.
- Sulfur products (also comes with salicylic acid for seborrheic dermatitis):
  - Sulfur is found in many over-the-counter formulations such as bar soaps, cleansers, creams, lotions and masks.
  - Precipitated sulfur can be compounded as a 2–9% topical gel, cream, body wash and lotion for treatment of acne, seborrheic dermatitis, scabies.
  - Many additional over-the-counter formulations of sulfur or sodium sulfacetamide available.
  - Combination sodium sulfacetamide-sulfur is typically only found in prescription products.
- Canada:
  - Sulfur products (also comes with salicylic acid for seborrheic dermatitis):
    - Sulfur is found in many over-the-counter formulations such as bar soaps, cleansers, creams, lotions, and masks.
    - Precipitated sulfur can be compounded as a 2–9% topical gel, cream, body wash, and lotion for treatment of acne, seborrheic dermatitis, and scabies.

- Many additional over-the-counter formulations of sulfur or sodium sulfacetamide available.
- Combination sodium sulfacetamide-sulfur is typically only found in prescription products

### **Dosages and Suggested Regimens**

- Different products have different regimens, so it is important to read the package insert before applying.
- Acne/rosacea:
  - Sodium sulfacetamide-sulfur lotion and cream: apply one to three times daily to affected skin after cleansing.
  - Sodium sulfacetamide-sulfur cleansing cloth: use one to two times a day. Moisten cloth with water, massage skin for 10–20 s then rinse skin completely.
  - Sodium sulfacetamide-sulfur washes, cleansers, and suspensions: Use to wash affected areas one to two times a day.
  - Sodium sulfacetamide-sulfur foam:
    - SSS foam: Apply one or two times a day after washing affected areas. May use in a wash-off application (product washed off after 1–2 min) or as a leave-on application (product is not washed off).
    - Avar foam: Apply one to three times a day. After washing skin, apply product to affected area and wait 10 min. Rinse off with water.
  - Sodium sulfacetamide lotion: Apply a thin film to affected areas twice daily.
- Seborrheic dermatitis:
  - Sodium sulfacetamide lotion, foam, and cream: Apply a thin film to affected areas twice daily.

### **Pharmacokinetics**

#### **Absorption:**

- After topical application, approximately 1% of sulfur is systematically absorbed. Systemic absorption of sulfacetamide after topical administration is unknown.

## Use in Special Populations

### Pregnancy:

- There have not been any animal reproductive studies for topical sulfur or sulfacetamide. The manufacturer recommends administration to a pregnant woman only if clearly needed.

### Lactation:

- Systemically administered sulfonamides are capable of producing kernicterus in infants of lactating women. Excretion in human milk following topical use of sulfur sulfacetamide is unknown.

### Pediatric use:

- Safety in children under 12 years is unknown.
- Some formulations contain benzyl alcohol which can cause fatal “gasping syndrome” in neonates.

Renal insufficiency: There are no dosing adjustments provided on the manufacturer’s label.

Hepatic insufficiency: There are no dosing adjustments provided on the manufacturer’s label.

## Monitoring

- No specific monitoring guidelines.

## Contraindications and Cautions

- *Contraindications:* Hypersensitivity to sulfonamides, sulfur, or any other component of the preparation.
- *Caution:* Sulfonamide class mediations have been associated with severe reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Sensitivity reactions have been reported in individuals with no prior history of sulfonamide hypersensitivity. Discontinue use at the first sign of any such reactions.
- *Caution:* Klaron lotion contains sodium metabisulfite, which may cause anaphylactic symptoms and life-threatening asthmatic episodes in susceptible persons.



### **Important Drug Interactions**

- Concomitant use of benzoyl peroxide and sulfacetamide can result in orange-brown staining on skin or clothing.
- Do not concomitantly use with preparations containing silver.
- There have been no formal studies of the interaction of topical sulfur/sulfacetamide with other drugs.

### **Adverse Effects and Their Management**

- Rare local side effects reported including pruritus, dryness, and erythema. If irritation develops, stop the use of medication.
- Use around the eyes may irritate conjunctiva.
- Case reports of Stevens-Johnson syndrome and erythema multiforme following ophthalmic use of sodium sulfacetamide.
- May stain clothes and skin if used together with benzoyl peroxide. Use at a separate time from benzoyl peroxide application.

### **Carcinogenicity**

- Long-term studies in animals have not been performed to evaluate carcinogenic potential.

### **Patch Test Concentration**

- Sulfacetamide: 5% pet.

## **Tea Tree Oil**

### **Classification and Mode of Action**

- Tea tree oil is derived by distillation of leaves from the tea tree.
- This distillate contains over 100 monoterpenoid, sesquiterpenoid, and alcohol compounds. Up to 90% is composed of terpinene-4-ol, 1,8-cineole, alpha-terpineol, terpinolene, and alpha- and gamma-terpinene.
- The primary component is terpinene-4-ol, and some products are standardized to this component.
- Tea tree oil has been found to have activity against *C. acnes*.

## Indications and Dermatological Uses

- *Clinical indications (FDA):* none
- *Off-label common uses:* acne, onychomycosis, tinea pedis, oral candidiasis, molluscum contagiosum, and seborrheic dermatitis

## Formulations/Presentation

- US: Tea tree oil is available over the counter as a natural health product in numerous formats, including as undiluted product, gel, shampoo, body wash, mouth rinse, spray, or cream at varying concentrations from 5% to 50%. It is marketed both alone and in combination with other topical acne treatments.

## Dosages and Suggested Regimens

- Acne vulgaris: various concentrations of different vehicle: typically applied twice daily (left on or washed off) for 8 weeks

## Pharmacokinetics

- There is insufficient reliable information to comment on the pharmacokinetics of tea tree oil.

## Use in Special Populations

Pregnancy:

- Possibly safe when used topically and appropriately.

Lactation:

- Possibly safe when used topically and appropriately.

Pediatric use:

- Possibly safe when used topically and appropriately.

Renal insufficiency: There are no dosing adjustments provided on the manufacturer's label.

Hepatic insufficiency: There are no dosing adjustments provided on the manufacturer's label.

## Monitoring

- No specific monitoring guidelines.

**Contraindications and Cautions**

- Contraindications: None reported.
- Tea tree oil can be potentially toxic if ingested.
- Multiple dermatologic conditions including skin irritation, allergic contact dermatitis, systemic contact dermatitis, linear IgA disease, erythema multiforme-like reactions, and systemic hypersensitivity reactions have been reported to parallel increased levels of tea tree oil use.
- In particular, there is substantial literature to support tea tree oil as a known cause of allergic contact dermatitis.

**Important Drug Interactions**

- There have been no formal studies of the interaction of topical tea tree oil with other drugs.

**Adverse Effects and Their Management**

- No manufacturer studies of adverse effects available. The most commonly reported adverse effects include allergic reactions, burning, dryness, irritation, pruritus, redness, and stinging.

**Carcinogenicity**

- There is no available data in the literature on carcinogenic potential of tea tree oil.

**Patch Test Concentration**

- N/A

**Essential Patient Information**

- Do not consume this medication orally.

**Common Brand Names**

- N/A

## Acne Combination Products

### Classification and Mode of Action

- Topical combination acne medications.
- In general, there are three main classes of topical combination acne products. For the products listed below, see individual drug monographs outlining each active ingredient for more detailed information, including mechanism of action, indications, contraindications/cautions, drug-drug interactions, considerations in special populations, and pharmacokinetic properties. See combination product label for specific application instructions.

The five main classes of topical combination acne medications are as follows:

- Benzoyl peroxide (BPO) and topical antibiotic (clindamycin or erythromycin)
- Adapalene and benzoyl peroxide (BPO)
- Clindamycin and tretinoin
- Tretinoin and microencapsulated benzoyl peroxide
- Clindamycin, adapalene, and benzoyl peroxide

### Indications and Dermatological Uses

- *Clinical indications (FDA):* Acne vulgaris
- *Off-label common uses:* Combination clindamycin and benzoyl peroxide has been used off-label for rosacea

### Formulations/Presentation

- Many formulations with differing vehicles exist. Some formulations report to have better tolerability.

#### Clindamycin and Benzoyl Peroxide

US:

- Clindamycin phosphate 1.2% and benzoyl peroxide 2.5% gel (Acanya, generic)
- Clindamycin phosphate 1% and benzoyl peroxide 5% gel (BenzaClin, pump dispenser available, generic)
- Clindamycin phosphate 1.2% and benzoyl peroxide 5% gel (Neuac, Duac, generic)

- Clindamycin phosphate 1.2% and benzoyl peroxide 3.75% gel (Onexton)
- Generic formulations of clindamycin phosphate 1% and BPO 5% gel, clindamycin 1.2% and BPO 2.5%, and clindamycin phosphate 1.2% and BPO 5% are available
- Neuac: Clindamycin phosphate 1.2% and benzoyl peroxide 5% kit

Canada:

- Clindamycin phosphate 1% and benzoyl peroxide 5% gel (BenzaClin, Clindoxyl, Generic)
- Clindamycin phosphate 1% and benzoyl peroxide 3% gel (Clindoxyl ADV)

Erythromycin and benzoyl peroxide

US:

- Erythromycin 3% and benzoyl peroxide 5% gel (Benzamycin, Generic)

Canada:

- Erythromycin 3% and benzoyl peroxide 5% gel (Benzamycin)

Adapalene and benzoyl peroxide

US:

- Adapalene 0.1% and benzoyl peroxide 2.5% gel (Epiduo)
- Adapalene 0.3% and benzoyl peroxide 2.5% gel (Epiduo Forte)

Canada:

- Adapalene 0.1% and benzoyl peroxide 2.5% gel (Taro-Adapalene/Benzoyl Peroxide)
- Adapalene 0.3% and benzoyl peroxide 2.5% gel (Taro-Adapalene/Benzoyl Peroxide Forte)

Clindamycin and Tretinoin

US:

- Clindamycin phosphate 1% and tretinoin 0.025% gel (Ziana, Generic)

Canada:

- Clindamycin phosphate 1% and tretinoin 0.025% gel (Biacna)

Tretinoin and microencapsulated benzoyl peroxide

US and Canada:

- Tretinoin 0.1% and microencapsulated benzoyl peroxide 3% cream (Twynéo)

Clindamycin, adapalene, and benzoyl peroxide

US and Canada:

- Clindamycin phosphate 1.2%, adapalene 0.15%, benzoyl peroxide 3.1% gel (Cabtreo)

## **Dosages and Suggested Regimens**

Acne:

- Clindamycin and benzoyl peroxide (BPO) Gel:
  - Clindamycin 1.2% and BPO 2.5% & 3.75%: Apply to affected area(s) once daily. Avoid contact with eyes or mucous membranes.
  - Clindamycin 1.2% and BPO 5%: Apply to the affected area(s) once daily at night. Avoid contact with eyes and mucous membranes.
  - Clindamycin 1% and BPO 5% (BenzaClin): Apply to affected area(s) twice daily. Avoid contact with eyes or mucous membranes.
- Erythromycin and BPO Gel: Apply thin layer twice daily. Avoid contact with eyes or mucous membranes.
- Adapalene and BPO: Apply a thin layer to affected area (face and/or body) once daily after washing. Avoid eyes and mucous membranes.
- Clindamycin and tretinoin: Apply pea-sized amount QHS at bedtime. Do not apply to eyes or mucous membranes.
- Clindamycin, adapalene, and benzoyl peroxide: Apply a thin layer to affected area once a day. Avoid the eyes, mucous membranes, nasal creases, and areas of damaged skin or areas affected by eczema or sunburn.

Rosacea (off-label use):

- Clindamycin 1% and BPO 5%: Apply to affected area(s) once daily Avoid contact with eyes and mucous membranes.
- Erythromycin and BPO Gel: Apply thin layer twice daily. Avoid contact with eyes or mucous membranes

## **Use in Special Populations**

Pregnancy:

- No adequate studies of these products in pregnant women
- Manufacturer recommend only to consider if potential benefit justifies potential fetal risk
- Extrapolating from mouse data for topical retinoids, the theoretical risk of topical retinoids in pregnancy generally outweighs potential benefits

Lactation:

- There are no robust data on the presence of topical retinoids, benzoyl peroxide or topical antibiotic metabolites in human breast milk, the effects on breastfed infants or effects on milk production

Pediatric use:

- Safety and efficacy of benzoyl peroxide (BPO) and topical antibiotics (clindamycin or erythromycin) have not been established in children less than 12 years of age.
- Safety and efficacy of adapalene and BPO has not been established in children less than 9 years of age.
- Safety and efficacy of clindamycin and tretinoin have not been established in children less than 9 years of age.

Renal: No dose modifications are mentioned in the manufacturer's prescribing information.

Hepatic: No dose modifications are mentioned in the manufacturer's prescribing information.

## **Monitoring**

- Hypersensitivity
- Skin irritation
- Photosensitivity

**Contraindications and Cautions\***

- All benzoyl peroxide-containing products may have a bleaching effect on hair/fabric
- Use of benzoyl peroxide with topical sulfone products may cause yellow-orange discoloration at the application site(s)
- Benzoyl peroxide-containing products may enhance the adverse/toxic effects of dapsone and diminish the therapeutic effects of topical isotretinoin.
- Diarrhea may result with the use of topical clindamycin. Topical clindamycin should be discontinued if diarrhea occurs.
- Erythromycin may diminish the therapeutic effect of clindamycin. Do not use together in combination.
- Avoid/limit UV-exposure after application of topical retinoids (adapalene/tretinoin). Nighttime application is one strategy to achieve this goal. Wear SPF 30+ sunscreen when exposure cannot be completely avoided
- Ziana (along with any clindamycin-containing topical medication) is contraindicated in patients with regional enteritis, ulcerative colitis, or history of antibiotic-associated colitis.
- Ziana has also been reported to cause nasopharyngitis, pharyngolaryngeal pain, cough, and sinusitis in >1% of patients.
- Skin irritation, dermatitis, dryness, erythema, and burning sensations are all possible side effect of the aforementioned combination products.
- Avoid all medications to which patients have known hypersensitivity reactions, including topical medications.

\*See individual drug monographs for comprehensive listing of contraindications/cautions

**Carcinogenicity**

Clindamycin/benzoyl peroxide:

In one study of mice treated with clindamycin phosphate and benzoyl peroxide gel 1.2%/5% at up to 16 times the highest recommended human dose for two years, no increase in skin tumors was observed. A 2-year study in rats treated with a different formulation of 1% clindamycin and 5% benzoyl peroxide demonstrated dose dependent increase in keratoacanthoma incidence in males. A study of hairless mice exposed to chronic



concurrent topical treatment with clindamycin and benzoyl peroxide gel 1.2%/5% and ultraviolet radiation showed a decrease in the median time to onset of skin tumor formation and number of tumors per mouse increased.

### **Patch Test Concentration**

- See individual ingredients

### **Common Brand Names**

Clindamycin and Benzoyl Peroxide:

- Acanya, BenzaClin, Neuac, Onexton, Clindoxyl, Clindoxyl ADV

Erythromycin and Benzoyl Peroxide:

- Benzamycin

Adapalene and Benzoyl Peroxide:

- Epiduo Forte

Clindamycin and Tretinoin:

- Ziana

---

## **References**

1. Goh C, Cheng C, Agak G, Zaenglein AL, Graber EM, Thiboutot DM, Kim J. Acne Vulgaris. In: Kang S, Amagai M, Bruckner AL, Enk AH, Margolis DJ, McMichael AJ, Orringer JS, editors. Fitzpatrick's Dermatology, 9e. McGraw Hill; 2019. Accessed 06 Mar 2022.
2. Kistowska M, et al. Propionibacterium acne Promotes Th17 and Th17/Th1 responses in Acne Patient. *J Investig Dermatol.* 2015;135(1):110–8.
3. Eichenfield DZ, Sprague J, Eichenfield LF. Management of Acne Vulgaris: a review. *JAMA.* 2021;326(20):2055–67.
4. Stuart B, et al. Topical preparations for the treatment of mild-to-moderate acne vulgaris: systematic review and network meta-analysis. *Br J Dermatol.* 2021;185(3):512–525
5. Barbieri JS, Drucker AM. The need for comparative effectiveness data to guide management of acne vulgaris. *Br J Dermatol.* 2021;185(3):476–7.

## Drug Monographs: Adapalene

6. FDA drug monograph (Adapalene). Available from [https://www.access-data.fda.gov/drugsatfda\\_docs/label/2007/020380s004lbl.pdf](https://www.access-data.fda.gov/drugsatfda_docs/label/2007/020380s004lbl.pdf). Accessed 12 Aug 2023.
7. LexiComp drug monograph (Adapalene). Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2023 UptoDate, Inc.
8. Brogden R, Goa K. Adapalene: a review of its pharmacological properties and clinical potential in the management of mild to moderate acne. *Drugs*. 1997;53(3):511–9.
9. Altinyazar HC, Koca R, Tekin NS, et al. Adapalene vs metronidazole gel for the treatment of rosacea. *Int J Dermatol*. 2005;44(3):252–5.
10. Autret E, Berjot M, Jonville-Bera AP, et al. Anophthalmia and agenesis of optic chiasma associated with adapalene gel in early pregnancy. *Lancet*. 1997;350(9074):339.
11. Shehab N, Lewis CL, Streetman DD, et al. Exposure to the pharmaceutical excipients benzoyl alcohol and propylene glycol among critically ill neonates. *Pediatr Crit Care Med*. 2009;10(2):256–9.
12. Kong YL, Tey HL. Treatment of acne vulgaris during pregnancy and lactation. *Drugs*. 2013;73(8):779–87.
13. Eichenfield LF, Krakowski AC, Piggott C, et al. Evidence-based recommendations for the diagnosis and treatment of pediatric acne. *Pediatrics*. 2013;131(Suppl 3):S163–86.
14. Asai Y, Baibergenova A, Dutil M, et al. Management of acne: Canadian clinical practice guideline. *CMAJ* 2016.
15. Maguiness S. Acne. 5-minute video available from the Society for Pediatric Dermatology Website at <https://tinyurl.com/saa9t4s>. Accessed 12 Aug 2023.

## Drug Monographs: Benzoyl Peroxide

16. Burkhart CG, Burkhart CN. Decreased efficacy of topical anesthetic creams in presence of benzoyl peroxide. *Dermatol Surg*. 2005;31(11 Pt 1):1479–80.
17. Chien AL, Qi J, Rainer B, Sachs DL, Helfrich YR. Treatment of acne in pregnancy. *J Am Board Fam Med*. 2016;29(2):254–62.
18. deGroot AC. Chapter 3: Monographs of topical drugs that have caused contact allergy/allergic contact dermatitis. In: *Monographs in contact allergy*, volume 3. Topical drugs. CRC Press; 2021.
19. Del Rosso J, Sugarman J, Green L, Lain T, Levy-Hacham O, Mizrahi R, Gold LS. Efficacy and safety of microencapsulated benzoyl peroxide and microencapsulated tretinoin for the treatment of acne vulgaris: results

- from two phase 3 double-blind, randomized, vehicle-controlled studies. *J Am Acad Dermatol*. 2023;89(4):719–27.
20. Edwards T, Cardwell LA, Patel N, Feldman SR. Benzoyl peroxide gel stains synthetic fabrics less than they stain cotton. *J Am Acad Dermatol*. 2021;85(2):481–2.
  21. FDA Drug Safety Communication. <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM402663.pdf>. 26957383
  22. FDA drug monograph Epsolay. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2023/214510Orig1s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/214510Orig1s000lbl.pdf). Accessed 11 Mar 2025.
  23. Foti C, Romita P, Borghi A, Angelini G, Bonamonte D, Corazza M. Contact dermatitis to topical acne drugs: a review of the literature. *Dermatol Ther*. 2015;28(5):323–9.
  24. Kong YL, Tey HL. Treatment of acne vulgaris during pregnancy and lactation. *Drugs*. 2013;73(8):779–87.
  25. Leachman SA, Reed BR. The use of dermatologic drugs in pregnancy and lactation. *Dermatol Clin*. 2006;24(2):167–97.
  26. LexiComp drug monograph Benzoyl peroxide. Available from: LexiComp Online at [online.lexi.com](http://online.lexi.com). Copyright 2023 UpToDate, Inc.
  27. World Health Organization (WHO). Breastfeeding and maternal medication, recommendations for drugs in the Eleventh WHO Model List of Essential Drugs. [Breastfeeding and maternal medication \(who.int\). https://www.who.int/publications/i/item/55732](https://www.who.int/publications/i/item/55732) (2002 Feb 25). Accessed 8 Aug 2023.

## Drug Monographs: Clascoterone

28. FDA drug monograph Clascoterone. Available from: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2020/213433s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213433s000lbl.pdf). Accessed 8 Aug 2023.
29. Eichenfield L, Hebert A, Gold LS, Cartwright M, Fragasso E, Moro L, Mazzetti A. Open-label, long-term extension study to evaluate the safety of clascoterone (CB-03-01) cream, 1% twice daily, in patients with acne vulgaris. *J Am Acad Dermatol*. 2020;83(2):477–85.
30. Hebert A, Thiboutot D, Stein Gold L, Cartwright M, Gerloni M, Fragasso E, Mazzetti A. Efficacy and safety of topical Clascoterone cream, 1%, for treatment in patients with facial Acne: Two Phase 3 randomized clinical trials. *JAMA Dermatol*. 2020;156(6):621–30.

## Drug Monographs: Clindamycin

31. deGroots AC. Chapter 3: Monographs of topical drugs that have caused contact allergy/allergic contact dermatitis. In: Monographs in contact allergy, volume 3. Topical drugs. CRC Press; 2021.
32. FDA drug monograph Cleocin-T and clindamycin phosphate gel. Available from: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/050537s040,050600s017,050615s0181bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/050537s040,050600s017,050615s0181bl.pdf) and [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2001/507821bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2001/507821bl.pdf). Accessed 8 Aug 2023.
33. FDA drug monograph EVOCLIN foam. Available from: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2012/050801s0151bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/050801s0151bl.pdf). Accessed 8 Aug 2023.
34. LexiComp drug monograph Clindamycin. Available from: LexiComp Online at [online.lexi.com](https://online.lexi.com). Copyright 2023 UpToDate, Inc.
35. Barza M, Goldstein JA, Kane A, et al. Systemic absorption of Clindamycin hydrochloride after topical application. *J Am Acad Dermatol*. 1982;7(2):208–14.
36. Rehms W. Folliculitis. Merck Manual Professional Version. Kenilworth, NJ. <https://www.merckmanuals.com/professional/dermatologic-disorders/bacterial-skin-infections/folliculitis#>. Accessed 8 Aug 2023.
37. World Health Organization (WHO). Breastfeeding and maternal medication, recommendations for drugs in the Eleventh WHO Model List of Essential Drugs. [Breastfeeding and maternal medication \(who.int\). https://www.who.int/publications/i/item/55732](https://www.who.int/publications/i/item/55732) (2002 Feb 25). Accessed 8 Aug 2023.
38. Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol*. 2016;74(5):945–973. e33.

## Drug Monographs: Dapsone

39. FDA drug monograph ACZONE (dapsone) gel. Available from: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/021794s0161bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021794s0161bl.pdf) and [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/207154s0001bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/207154s0001bl.pdf). Accessed 8 Aug 2023.
40. LexiComp drug monograph Dapsone (topical). Available from: LexiComp Online at [online.lexi.com](https://online.lexi.com). Copyright 2022 UpToDate, Inc. Accessed 3 Mar 2022.
41. Nickles MA, Lake E. Topical dapsone in the treatment of acne: a systematic review. *Int J Dermatol*. 2022; <https://doi.org/10.1111/ijd.16074>. Epub ahead of print. PMID: 35132625.

42. Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol*. 2016;74(5):945–73. e33. <https://doi.org/10.1016/j.jaad.2015.12.037>. Epub 2016 Feb 17. Erratum in: *J Am Acad Dermatol*. 2020 Jun;82(6):1576. PMID: 26897386.

## Drug Monographs: Erythromycin

43. Akhavan A, Bershad S. Topical Acne drugs: review of clinical properties, systemic exposure, and safety. *Am J Clin Dermatol*. 2003;4(7):473–92.
44. deGroot AC. Chapter 3: Monographs of topical drugs that have caused contact allergy/allergic contact dermatitis. In: *Monographs in contact allergy*, Volume 3. Topical drugs. CRC Press; 2021.
45. FDA Monograph ERYGEL. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/anda/97/64184ap.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/anda/97/64184ap.pdf). Accessed 17 Mar 2022.
46. FDA Monograph ERYTHROMYCIN PLEDGETS USP 2%. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/anda/96/064126ap.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/anda/96/064126ap.pdf). Accessed 17 Mar 2022.
47. Manders SM, Lucky AW. Perioral dermatitis in childhood. *J Am Acad Dermatol*. 1992;27(5 pt 1):688–92.
48. Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol*. 2016;74(5):945–73.

## Drug Monographs: Minocycline

49. FDA drug monograph. AMZEEQ. Available from: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/212379s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212379s000lbl.pdf). Accessed 11 Aug 2023.
50. FDA drug monograph. ZILXI. Available from: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2020/213690s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213690s000lbl.pdf). Accessed 11 Aug 2023.
51. Dosik J, Ellman H, Stuart I. Topical minocycline foam 4%: results of four phase 1 studies evaluating the potential for phototoxicity, photoallergy, sensitization, and cumulative irritation. *J Immunotoxicol*. 2019;16(1):133–9.
52. Gold LS, Del Rosso JQ, Kircik L, Bhatia ND, Hooper D, Nahm WK, Stuart I. Minocycline 1.5% foam for the topical treatment of moderate to severe papulopustular rosacea: results of 2 phase 3, randomized, clinical trials. *J Am Acad Dermatol*. 2020;82(5):1166–73.
53. Jones TM, Ellman H, deVries T. Pharmacokinetic comparison of once-daily topical minocycline foam 4% vs oral minocycline for moderate-to-severe acne. *J Drugs Dermatol*. 2017;16:1022–8.

54. Jones TM, Stuart I. Safety and pharmacokinetics of FMX103 (1.5% Minocycline topical foam) in subjects with moderate-to-severe Papulopustular Rosacea under maximum-use treatment conditions. *J Clin Aesthet Dermatol.* 2021;14(3):E53–7.
55. Onge ES, Mobley WC. Minocycline topical foam: a new drug for the treatment of Acne. *Ann Pharmacother.* 2021;55(1):105–10.
56. Stein Gold L, Del Rosso JQ, Kircik L, et al. Open-label extension study evaluating long-term safety and efficacy of FMX103 1.5% Minocycline topical foam for the treatment of moderate-to-severe papulopustular Rosacea. *J Clin Aesthet Dermatol.* 2020;13(11):44–9.

## Drug Monographs: Resorcinol

57. deGroots AC. Chapter 3: Monographs of topical drugs that have caused contact allergy/allergic contact dermatitis. In: *Monographs in contact allergy*, volume 3. Topical drugs. CRC Press; 2021.
58. Martindale resorcinol monograph. Accessed 3/3/2022.
59. Alikhan A, Maibach HI. Keratolytic treatment of acne. In: *Textbook of cosmetic dermatology*. Essay. CRC Press; 2017.
60. Resinol label information. Available from: <https://resical.com/resinol-medicated-ointment/label-information/>. Accessed 3/3/2022.
61. Tinted acne treatment – resorcinol 2.00% sulfur 8.00% cream. Available from: <https://dailymed.nlm.nih.gov/dailymed/getFile.cfm?setid=30e7d8f7-ca10-436a-8cce-25f97a7163a9&type=pdf>. Accessed 3/3/2022
62. Substance evaluation conclusion – Resorcinol. Finland. Available from: [https://s3-us-west-2.amazonaws.com/drugbank/cite\\_this/attachments/files/000/000/062/original/SEV-203-585-2-1\\_conclusion\\_and\\_report\\_public\\_5148\\_en.pdf?1526062531](https://s3-us-west-2.amazonaws.com/drugbank/cite_this/attachments/files/000/000/062/original/SEV-203-585-2-1_conclusion_and_report_public_5148_en.pdf?1526062531). Accessed 3/3/2022.
63. National Toxicology Program. Toxicology and Carcinogenesis Studies of Resorcinol (CAS No. 108-46-3) in F344 Rats and B6C3F1 Mice (Gavage Studies). *Natl Toxicol Program Tech Rep Ser.* 1992;403:1–234. PMID: 12621515

## Drug Monographs: Sulfur and Sulfacetamide

64. deGroots AC. Chapter 3: Monographs of topical drugs that have caused contact allergy/allergic contact dermatitis. In: *Monographs in contact allergy*, volume 3. Topical drugs. CRC Press; 2021.
65. FDA drug monograph Klaron. Available from: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2010/019931s0191bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/019931s0191bl.pdf). Accessed 8/11/2023.

66. Sarac G. A comparison of the efficacy and tolerability of topical agents used in facial Demodex treatment. *J Cosmet Dermatol*. 2019;18(6):1784–7.
67. Liu H, Yu H, Xia J, Liu L, Liu GJ, Sang H, Peinemann F. Topical azelaic acid, salicylic acid, nicotinamide, sulphur, zinc and fruit acid (alpha-hydroxy acid) for acne. *Cochrane Database Syst Rev*. 2020;5(5):CD011368.
68. Ovace Plus Wash. Available from: <https://ovace.com/wp-content/uploads/2020/10/Ovace-Combined-PI.pdf>. Accessed 11 Aug 2023.
69. Natural medicines monograph sulfur. Available from: <https://naturalmedicines.therapeuticresearch.com/>. Accessed 3/3/2022.
70. Martindale sulfur monograph. Available from: <https://about.medicinescomplete.com/publication/martindale-the-complete-drug-reference/>. Accessed 3/3/2022.
71. LexiComp drug monograph Sulfur and Sulfacetamide. Available from: LexiComp Online at [online.lexi.com](https://online.lexi.com). Copyright 2022 UpToDate, Inc. Accessed 3/3/2022.
72. AVAR Cleanser. Available from: [https://avarinfo.com/wp-content/uploads/2020/10/AVAR\\_PI\\_R2016.pdf](https://avarinfo.com/wp-content/uploads/2020/10/AVAR_PI_R2016.pdf). Accessed 11 Aug 2023.
73. Dubina M, Fleischer AB. Interaction of topical sulfacetamide and topical dapsone with benzoyl peroxide. *Arch Dermatol*. 2009;145(9):1027–9.
74. Wolf K, Silapunt S. The use of sodium sulfacetamide in dermatology. *Cutis*. 2015;96(2):128–30. PMID: 26367751
75. Sodium sulfacetamide 10% and Sulfur 5% emollient foam- sulfacetamide sodium and sulfur aerosol, foam. Acella Pharmaceuticals, LLC. Available from: <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=79ffd6f1-f3ad-4b4b-bc23-abd9295c5f2d&type=display>. Accessed 11 Aug 2023.
76. Yuen MV, Gianturco SL, Pavlech LL, et al. Precipitated Sulfur: summary report. 2020. Available from: [https://archive.hshsl.umaryland.edu/bitstream/handle/10713/12274/Precipitated%20sulfur\\_Final\\_2020\\_02.pdf?sequence=6](https://archive.hshsl.umaryland.edu/bitstream/handle/10713/12274/Precipitated%20sulfur_Final_2020_02.pdf?sequence=6). Accessed 11 Aug 2023.

## Drug Monographs: Tea Tree Oil

77. Natural medicines monograph Tea tree oil. Available from: <https://naturalmedicines.therapeuticresearch.com/>
78. Hammer KA. Treatment of acne with tea tree oil (melaleuca) products: a review of efficacy, tolerability and potential modes of action. *Int J Antimicrob Agents*. 2015;45(2):106–10. <https://doi.org/10.1016/j.ijantimicag.2014.10.011>. Epub 2014 Nov 13. PMID: 25465857.

79. Pazyar N, Yaghoobi R, Bagherani N, Kazerouni A. A review of applications of tea tree oil in dermatology. *Int J Dermatol*. 2013;52(7):784–90. <https://doi.org/10.1111/j.1365-4632.2012.05654.x>. Epub 2012 Sep 24. PMID: 22998411.
80. de Groot AC, Schmidt E. Tea tree oil: contact allergy and chemical composition. *Contact Dermat*. 2016;75(3):129–43. <https://doi.org/10.1111/cod.12591>. Epub 2016 May 13. PMID: 27173437.
81. Bergfeld WF, Belsito DV, Cohen DE, et al. Safety assessment of *Melaleuca alternifolia* (Tea Tree)-derived ingredients as used in cosmetics. Available from: [https://www.cir-safety.org/sites/default/files/Tea%20Tree\\_0.pdf](https://www.cir-safety.org/sites/default/files/Tea%20Tree_0.pdf). Accessed 11 Aug 2023.
82. Tea tree oil. National Center for Complementary and Integrative Health. Available from: <https://www.nccih.nih.gov/health/tea-tree-oil>. Accessed 11 Aug 2023.

## Drug Monographs: Acne Combination Products

83. Breneman D, Savin R, VandePol C, Vamvakias G, Levy S, Leyden J. Double-blind, randomized, vehicle-controlled clinical trial of once-daily benzoyl peroxide/clindamycin topical gel in the treatment of patients with moderate to severe rosacea. *Int J Dermatol*. 2004;43(5):381–7.
84. FDA drug monograph Epiduo Forte (adapalene and benzoyl peroxide). Available from: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2015/207917Orig1s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207917Orig1s000lbl.pdf) Accessed 12 Aug 2023.
85. FDA drug monograph Ziana (clindamycin phosphate 1.2% and tretinoin 0.025%). Available from: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2006/050802lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/050802lbl.pdf) Accessed 12 Aug 2023.
86. FDA drug monograph Neuac. Available at [https://www.medimetriks.com/sites/default/files/pi-files/Neuac\\_pi\\_website.pdf](https://www.medimetriks.com/sites/default/files/pi-files/Neuac_pi_website.pdf). Accessed 13 Aug 2023.
87. FDA drug monograph Twynéo. Available at [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2021/214902s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214902s000lbl.pdf)
88. FDA drug monograph Cabtreo. Available at [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2023/216632s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216632s000lbl.pdf). Accessed 11 Mar 2025.
89. LexiComp drug monograph Clindamycin and benzoyl peroxide. Available from: LexiComp Online at [online.lexi.com](https://online.lexi.com). Copyright 2023 UpToDate, Inc.
90. LexiComp drug monograph Erythromycin and benzoyl peroxide. Available from: LexiComp Online at [online.lexi.com](https://online.lexi.com). Copyright 2023 UpToDate, Inc.



91. Leyden JJ, Thiboutot D, Shalita A. Photographic review of results from a clinical study comparing benzoyl peroxide 5%/clindamycin 1% topical gel with vehicle in the treatment of rosacea. *Cutis*. 2004;73((6) (suppl)):11–7. [PubMed 15228129]
92. Oztürkcan S, Ermertcan AT, Sahin MT, Afşar FS. Efficiency of benzoyl peroxide-erythromycin gel in comparison with metronidazole gel in the treatment of acne rosacea. *J Dermatol*. 2004;31(8):610–7.



# Rosacea and Topical Drug Treatments

# 9

Lisa E. Maier, Brian W. Connor,  
and Jason Ya

## Contents

|                    |     |
|--------------------|-----|
| Brimonidine.....   | 185 |
| Oxymetazoline..... | 190 |
| Metronidazole..... | 194 |
| Ivermectin.....    | 199 |
| Azelaic Acid.....  | 202 |
| References.....    | 206 |

---

L. E. Maier (✉)  
Department of Dermatology, UW Medicine, Seattle, WA, USA  
e-mail: [lemaier@uw.edu](mailto:lemaier@uw.edu)

B. W. Connor  
Schweiger Dermatology Group, New York, NY, USA  
e-mail: [bwconnor@uw.edu](mailto:bwconnor@uw.edu)

J. Ya  
Department of Dermatology, Stanford University School of Medicine,  
Redwood City, CA, USA  
e-mail: [jasonya@uw.edu](mailto:jasonya@uw.edu)

Rosacea is a common chronic inflammatory condition with multiple clinical features that typically affects the skin of the face. It may also affect the eyes, but this is beyond the scope of this handbook. The etiology of rosacea is unknown, but aberrant immune and neurovascular responses to various external triggers such as microbes, ultraviolet light, and extremes of temperature in genetically susceptible individuals are thought to be contributory [1].

As outlined by National Rosacea Society Expert Committee in 2017, diagnostic features for rosacea include (1) fixed centrofacial erythema that may wax and wane in intensity or (2) phymatous changes (often characterized by thickened and irregularly textured skin, patulous follicles, and nodular hyperplasia). Patients should have one or both of these features to be diagnosed with rosacea. Other major features that may be present with these diagnostic features include papules and pustules, flushing, and telangiectasia. Patients with rosacea may also have secondary features of edema, rough and scaly texture, and symptoms of burning or stinging. Various rosacea clinical features may be present in different combinations in different individuals [2].

Available rosacea treatments are not curative but aim to manage specific rosacea clinical features—most commonly fixed erythema and papules and pustules. Telangiectasia, phymatous changes, and flushing typically are unaffected by topical treatment. Topical vasoconstrictors such as topical brimonidine and oxymetazoline specifically target fixed erythema. Reduction of the inflammatory lesions (papules and pustules) is typically achieved with the use of topical antimicrobials and anti-inflammatories including metronidazole, azelaic acid, ivermectin, topical minocycline, and microencapsulated benzoyl peroxide [4]. Secondary features of rosacea such as edema, burning and stinging, and dry texture may improve as treatment of the inflammatory lesions and transient erythema improve. To control various clinical features of rosacea, more than one topical therapy may be used, or they may be combined with systemic rosacea treatments and/or laser/light devices [3].

**Topical Treatments for Non-transient Erythema of Rosacea**

- Brimonidine
- Oxymetazoline

**Topical Treatments for Inflammatory Lesions of Rosacea**

- Metronidazole
- Azelaic acid
- Ivermectin
- Topical minocycline\*
- Sodium sulfacetamide and sulfur\*
- Microencapsulated benzoyl peroxide\*
- Less commonly used antimicrobials and antiparasitic agents:
  - Clindamycin\*
  - Erythromycin\*
  - Dapsone\*
  - Benzoyl peroxide\*
  - Permethrin\*\*

\*Drug monograph for this agent is in the acne section of this chapter.

\*\*Drug monograph for this agent is in the parasitic agents chapter.

---

**Brimonidine****Classification and Mode of Action**

- Selective alpha-2 adrenergic receptor
- Temporary reduction in non-transient erythema occurs due to vasoconstrictive effects
- The greatest reduction in erythema is observed around 3–6 h, and there is a diminishment of effect by 12 h.

## Indications and Dermatological Uses

- *Clinical indications (FDA)*: Treatment of fixed centrofacial erythema associated with rosacea in adults (18 years or older)
- *Off-label common uses*: N/A

## Formulations/Presentation

- US: MIRVASO (brimonidine) topical gel, 0.33%
- Canada: ONRELTEA (brimonidine) topical gel, 0.33%
- Europe: MIRVASO (as above)

## Dosages and Suggested Regimens

- Apply pea size amount in a thin layer to the face (forehead, bilateral cheeks, nose, and chin) once a day. Typically, this is applied in the morning.

## Baseline Investigations and Considerations

- None

## Pharmacokinetics

- Absorption: A very small amount of topical absorption is noted with use topically to the cutaneous face (non-mucosal surfaces). Absorption is less than noted with ocular administration of brimonidine. No drug accumulation was noted in plasma.
- In a clinical trial, 1 g of brimonidine 0.33% topical gel was applied to the entire face of 24 adult subjects with rosacea associated facial erythema for 29 days. Pharmacokinetic assessments performed on day 1, day 15, and day 29 demonstrated the greatest mean plasma concentration (C<sub>max</sub>) and area under the

concentration-time curve (AUC) on day 15 ( $C_{\max}$   $46 \pm 62$  pg/mL and AUC  $417 \pm 264$  pg.hr/mL). At day 29, the systemic drug exposure was lower, suggesting that there was no further drug accumulation. Topical application to the face was compared to a single day of ocular application of 0.2% ophthalmic drops (applied every 8 h for three doses). Day 15 topical brimonidine gel  $C_{\max}$  and AUC were approximately twofold lower than those found with single day ocular use.

- Metabolism: hepatically metabolized
- Excretion: Urinary excretion.

## Use in Special Populations

- Pregnancy:
  - No adequate studies of use in pregnant women.
  - Manufacturer recommends only to use if potential benefit justifies potential fetal risk.
  - Ocular administration of brimonidine is considered first line for the treatment of glaucoma but is typically discontinued late in the third trimester due to potential for induction of newborn central nervous system. Effect of topical administration is unknown.
- Lactation:
  - Unknown if excreted in breast milk.
  - Manufacturer recommends avoidance during breastfeeding.
- Pediatric use:
  - Not indicated for use in children under the age of 18; ONRELTEA gel is contraindicated in children under 2 years of age.
  - Concerns for possible systemic absorption of brimonidine gel in 2–12 years old age group.
  - In a clinical trial, two young children who accidentally ingested MIRVASO gel experienced serious adverse reactions including respiratory distress requiring intubation, sinus bradycardia, lethargy, and confusion.

- Renal: No dose modifications are mentioned in the manufacturer's prescribing information.
- Hepatic: No dose modifications are mentioned in the manufacturer's prescribing information.

## Monitoring

- Skin irritation
- Worsening of erythema and flushing
- Allergic contact dermatitis
- Undesirable pallor
- Symptoms of low blood pressure (e.g., dizziness or lightheadedness, fatigue, fainting, and blurred vision)

## Contraindications and Cautions

- Hypersensitivity: Avoid use in patients with known hypersensitivity to brimonidine or the components of the gel.
- Vascular insufficiency: Due to potential to potentiate vascular insufficiency, use with caution in patients with cerebral or coronary insufficiency, scleroderma, Raynaud phenomenon, thromboangiitis obliterans, depression, and Sjögren syndrome.
- Cardiovascular disease: Due to potential to decrease blood pressure, use with caution in patients with cardiovascular disease that is unstable, uncontrolled or severe.
- Keep out of reach of children and avoid ingestion as this can result in serious side effects (difficulty breathing, bradycardia, confusion, fatigue, restlessness, muscle spasms, or twitching).

## Important Drug Interactions

- *Anti-hypertensives and cardiac glycosides:* As a class, Alpha-2 agonists can reduce blood pressure. Patients on beta-blockers, other anti-hypertensives, and/or cardiac glycosides should be monitored while using Mirvaso.

- *CNS depressants*: Drug-drug interactions studies have not been conducted with MIRVASO topical gel, but consideration of possibility of additive or potentiating effects with CNS depressants (alcohol, opiates, sedatives, anesthetics, and barbituates) has been advised.
- *Monoamine oxidase inhibitors monoamine oxidase (MAO) inhibitors*: Theoretically, MAO inhibitors may interfere with brimonidine metabolism. This could result in increased systemic side effects such as low blood pressure and potentially result in an increased systemic side effect such as hypotension.

## Adverse Effects and Their Management

- Worsening of facial erythema compared to baseline may occur in an estimated 20% of patients. This may occur within 3–6 h of application, also known as “paradoxical erythema,” or present as redness that is greater than baseline after the medication fully wears off. Typically, this resolves with discontinuation of therapy, although some patients may be able to “treat through” and eventually tolerate the medication. Occasionally, more profound or prolonged redness, edema, warmth, pruritus, burning, and stinging can occur. In these cases, cool compresses, aspirin, or other NSAID can be used to manage discomfort. Antihistamines may help with pruritus and edema.
- More frequent or new onset flushing may also occur during therapy (30 min to hours). Typically resolves with discontinuation of therapy.
- Patients may experience temporary cosmetically undesirable facial pallor after application.
- Allergic contact dermatitis to both the active ingredient, brimonidine, and the inactive ingredients has been reported. Additionally, angioedema, throat tightening, tongue swelling, and urticaria may also rarely occur. Discontinue use if significant hypersensitivity reactions occur.



## Patch Test Concentration

- 1%, 5%, and 10% pet.

## Essential Patient Information

- Erythema reduction is temporary with brimonidine gel. Studies demonstrate recurrence of erythema within 8–12 h of initial application.
- Redness reduction is temporary and not curative.
- Brimonidine gel will not treat inflammatory lesions (papules and pustules) or phymatous changes associated with rosacea. Any inflammatory lesions if not treated by other methods may temporarily appear accentuated due to the reduction of surrounding erythema.
- Worsening redness, more frequent or new onset flushing may occur during therapy. If prolonged redness, burning, stinging, or warmth occurs, patients should contact their prescribing clinician.
- Do not use on broken skin or mucous membranes.

---

## Oxymetazoline

### Classification and Mode of Action

- $\alpha_{1A}$ -adrenergic receptor agonist.
- Temporary reduction in non-transient erythema reduction occurs due to vasoconstrictive effects.
- Greatest reduction in erythema is observed around 6–9 h, and there is a diminishment of effect by 12 h.
- Based on available study data, use of topical oxymetazoline appears to produce less “rebound erythema” (worsening of baseline erythema or flushing) than topical brimonidine.
- Best results may come from daily, long-term, continued use of oxymetazoline over weeks to months rather than intermittent use.

## Indications and Dermatological Uses

- *Clinical indications (FDA)*: Topical treatment of rosacea related non-transient facial erythema
- *Off-label common uses*: N/A

## Formulations/Presentation

- US: RHOFADÉ.
- Each gram of Rhofade contains 10 mg of oxymetazoline hydrochloride, equivalent to 8.8 mg of oxymetazoline-free base.

## Dosages and Suggested Regimens

- Oxymetazoline 1% cream. Apply a pea-sized amount to face (forehead, nose, bilateral cheeks, and chin) once daily. Avoid eyes and lips.

## Baseline Investigations and Considerations

- None

## Pharmacokinetics

- Absorption: A very small amount of percutaneous absorption occurs with use of oxymetazoline 1% cream when applied to the face to treat rosacea associated facial erythema. Specifically, when 0.3 g was applied to the face of adult rosacea patients, the mean concentration (C<sub>max</sub>) after first dose application was  $60.5 \pm 53.9$  pg/mL.
- The mean area under the concentration-time curves from time 0–24 h (AUC<sub>0–24 h</sub>) after first dose was  $895 \pm 798$  pg·h/mL. After 28 days of daily applications, the mean C<sub>max</sub> and

AUC<sub>0-24 h</sub> were  $66.4 \pm 67.1$  pg/mL and  $1050 \pm 992$  pg\*h/mL, respectively. Researchers also evaluated twice daily applications for 28 days and found that the mean C<sub>max</sub> and AUC<sub>0-24 h</sub> were  $68.8 \pm 61.1$  pg/mL and  $1530 \pm 922$  pg\*h/mL, respectively.

- Distribution: Approximately 57% is bound to plasma protein.
- Metabolism: Minimally metabolized.
- Excretion: Has not been characterized in humans.

## Use in Special Populations

- Pregnancy:
  - There is no available data on use in pregnant women. Intranasal use of oxymetazoline in the second trimester may be potentially associated with renal collecting system anomalies. No adverse developmental effects noted in pregnant rats and rabbits when exposed to oral oxymetazoline up to three times and 73 times the maximum recommended human dose.
- Lactation:
  - No available data on the effects of topical oxymetazoline cream on lactation or its presence in human breast milk. Oxymetazoline has been found in the milk of lactating rats.
- Pediatric use:
  - Safety and effectiveness of oxymetazoline cream has not been studied in pediatric patients.
- Renal insufficiency:
  - No dose modifications are mentioned in the manufacturer's prescribing information.
- Hepatic insufficiency:
  - No dose modifications are mentioned in the manufacturer's prescribing information.

## Monitoring

- None

## Contraindications and Cautions

- **Hypersensitivity:** Avoid use in patients with known hypersensitivity to oxymetazoline or the components of the cream.
- **Vascular insufficiency:** Due to potential to potentiate vascular insufficiency, use with caution in patients with cerebral or coronary insufficiency, scleroderma, Raynaud phenomenon, thromboangiitis obliterans, depression, and Sjögren syndrome.
- **Cardiovascular disease:** Due to potential to decrease blood pressure, use with caution in patients with cardiovascular disease that is unstable, uncontrolled, or severe.
- **Narrow angle glaucoma:** Angle closure may occur with use of oxymetazoline.

## Important Drug Interactions

- **MAO inhibitors.** May potentiate vasoconstrictive effects.
- **Antihypertensives/cardiac glycosides.** May affect blood pressure.

## Adverse Effects and Their Management

- **Local application site adverse effects** may occur including application site dermatitis, erythema, pruritus, pain, worsening of inflammatory lesions, and photosensitivity. This typically resolves with treatment discontinuation. May require treatment of persistent dermatitis with topical steroid or topical calcineurin inhibitor. Worsening of inflammatory lesions of rosacea may require therapy with topical or oral therapies that target inflammatory lesions.
- **Worsening of facial erythema and flushing** during treatment or when the medication effect wears off. One 52-week open-label study of daily oxymetazoline cream observed this phenomenon in less than 1% of patients.

## Patch Test Concentration

- N/A

## Essential Patient Information

- Avoid ocular exposure. Wash hands immediately after applying cream to prevent inadvertent ocular exposure.
- Redness reduction is temporary and not curative.
- Oxymetazoline cream will not treat inflammatory lesions (papules and pustules) or phymatous changes associated with rosacea. Any inflammatory lesions if not treated by other methods may temporarily appear accentuated due to the reduction of surrounding erythema.
- Worsening redness, more frequent or new onset flushing may occur during therapy. If prolonged redness, burning, stinging, or warmth occurs, patients should contact their prescribing clinician.
- Do not use on broken skin or mucous membranes.
- At initial use, priming of a new RHOFADÉ dispenser is required. To do this, pump the dispenser three times and discard the product. Product can be used normally thereafter.
- Keep away from children.

---

## Metronidazole

### Classification and Mode of Action

- Metronidazole is an antibiotic with effects against anaerobic bacteria and protozoa. Mechanism of action in the treatment of rosacea is unknown. Effects may be related to anti-inflammatory, antioxidant, and/or antimicrobial properties.
- Often used as a first-line topical treatment for papulopustular rosacea.
- Less irritating than azelaic acid in the treatment of rosacea, with equal to slightly lower effectiveness as azelaic acid.

- Less effective than topical ivermectin in the treatment of moderate to severe inflammatory rosacea.
- Onset of effect within 2–4 weeks, but greatest results are noted after 8 weeks of treatment.

## Indications and Dermatological Uses

- *Clinical indications (FDA):* Rosacea (topical), bacterial vaginosis (intravaginal), trichomoniasis (intravaginal)
- *Off-label common uses:* Periorificial dermatitis (topical)

## Formulations/Presentation

- US:
  - External: 0.75% gel, 0.75% lotion, 0.75% cream, 1% cream, 1% gel (Metrogel, Metrocream, Metrolotion, Noritate cream, generic)
  - Vaginal: 0.75% vaginal gel, 1.3% vaginal gel
- Canada:
  - External: 0.75% gel, 1% gel and cream (Metrocream, Metrogel, Noritate)
  - Vaginal: 0.75% gel, 10% cream
- Europe:
  - External: 0.75% topical gel and cream (UK: Metrogel, Acea, Rozex)
  - Vaginal: 0.75% vaginal gel (UK: Zidoval)

## Dosages and Suggested Regimens

### Rosacea:

- External 0.75% gel, cream or lotion: apply a thin film to the affected area twice a day. Apply in the morning and evening.
- External 1% gel or cream: apply a thin film to the affected area once a day

Periorificial dermatitis (off label):

Adult:

- External 0.75% gel, cream, or lotion: apply a thin film to the affected area twice a day. Apply in the morning and evening.
- External 1% gel or cream: apply a thin film to the affected area once a day

Pediatric (6 months or older):

- Safety and effectiveness in pediatric patients have not been established. In clinical practice, this has been used to manage pediatric rosacea and perioral dermatitis.

## **Baseline Investigations and Considerations**

- None

## **Pharmacokinetics**

Absorption:

- Topical (external) administration of metronidazole is absorbed systemically in negligible amounts. Administration of a 1 g dose of metronidazole 1% gel resulted in absorption of less than 1% of a 250 mg oral dose. Maximum plasma concentration occurred 6–10 h after application.

Metabolism: Hepatic (30–60%)

Excretion: Urine (unchanged (20%) and metabolites (40–60%), feces (6–15%))

## **Use in Special Populations**

Pregnancy:

- Topical use for the treatment of rosacea is considered compatible with pregnancy. Although metronidazole has been found to cross the placenta with oral administration, there is

less absorption systemically with topical application. Based on available studies, there has not been an increased risk of adverse events to the fetus following maternal use of metronidazole.

**Lactation:**

- Topical use for the treatment of rosacea is considered compatible with lactation. Metronidazole has been found in breast milk after oral administration; however, there is less absorption with topical application.

**Pediatric use:**

- Safety data is limited; however, several studies support its use in this population.

**Renal insufficiency:**

- No adjustments recommended.

**Hepatic insufficiency:**

- No adjustment recommended; however, use with caution in severe liver impairment.

## **Monitoring**

- Skin irritation (scaling, itching, burning, stinging, and dryness)
- Eye irritation
- Contact dermatitis (identified post-marketing); may cross react with imidazoles such as clotrimazole and tioconazole

## **Contraindications and Cautions (Topical Non-Vaginal Metronidazole)**

- Contact with ocular mucosa should be avoided, as topical metronidazole can cause tearing and conjunctivitis of the eyes.
- Per manufacturer, topical metronidazole should be used with caution in patients with a history of, or active blood dyscrasia. Likelihood of worsening blood cell dyscrasia is low due to low systemic absorption.



- Use caution in patients with underlying neurologic disorders. Peripheral neuropathy can occur with systemic metronidazole use and has been reported rarely with topical use in the post-approval period.
- Use caution in patients with severe liver impairment.
- Oral metronidazole has a black box warning due to potential carcinogenesis demonstrated with high dose, long-term use in mice and rats. Carcinogenesis has not been demonstrated in humans. Black box warning has not been assigned to the topical and vaginal forms of metronidazole. No definitive carcinogenic effect has been noted with long term real-life clinical use of topical metronidazole.

## **Important Drug Interactions**

- Although drug interactions are less likely with topical administration due to less systemic absorption, metronidazole may interact with the following:
- Coumarin and warfarin: may potentiate the anticoagulant effect
- Alcohol: disulfuram-like reaction

## **Adverse Effects and Their Management**

- Skin irritation
- Allergic contact dermatitis
- Eye irritation
- Post marketing adverse effects reported include tingling or numbness of extremities, metallic taste, headache, nausea, and constipation.

## **Patch Test Concentration**

- 1% pet

---

## Essential Patient Information

- Avoid contact with the eyes.
- Gently cleanse affected area(s) before applying.
- Do not ingest. For external use only.
- Inflammatory lesions of rosacea can re-occur with discontinuation of treatment; thus, chronic treatment may be needed to control the condition.

---

## Ivermectin

### Classification and Mode of Action

- Postulated to have antiparasitic effect against *Demodex* mites and anti-inflammatory actions.
- Antiparasitic effect via binding to glutamate-gated chloride channels in invertebrate muscle and nerves. *For more information about use as a ectoparasiticide, please refer to Chap. 19: Ectoparasiticides, Ivermectin monograph.*
- More effective than metronidazole in reducing inflammatory lesions of moderate to severe papulopustular rosacea.

### Indications and Dermatological Uses

- *Clinical indications (FDA):* Rosacea, head lice
- *Off-label common uses:* N/A

### Formulations/Presentation

- US: Rosacea: 1% cream (Soolantra, Generic)  
Head lice: 0.5% lotion (Sklice, Generic)
- Canada: Rosacea: 1% cream (Rosiver)
- Europe: 1% cream (Efacti, Soolantra)

## **Dosages and Suggested Regimens for Rosacea**

- Once a day application to the affected area of the face. Avoid eyes and lips.

## **Baseline Investigations and Considerations**

- None

## **Pharmacokinetics**

Absorption:

- Low transepidermal absorption when used topically on the face for rosacea. Steady state of a low systemic level was achieved by 2 weeks. Over 52 weeks of use, there was no additional plasma accumulation. After a 10 min exposure in 6 months to 3 years old, ivermectin lotion absorption was very low compared to oral administration.

Metabolism: Hepatic, metabolized by CYP3A4

Excretion: Fecal

## **Use in Special Populations**

Pregnancy:

- Insufficient information about safety in pregnant people. Animal studies have demonstrated the potential for adverse developmental effects with oral administration of ivermectin.

Lactation:

- Insufficient information about safety of topical ivermectin in lactation. Orally administered ivermectin is found in low concentrations in human breast milk. Rat studies demonstrated potential for neonatal toxicity when ivermectin is absorbed during nursing.

Pediatric use: Insufficient information about safety of ivermectin in pediatric patients

Renal insufficiency: No alterations in dosing recommended in renal insufficiency

Hepatic insufficiency: No alterations in dosing recommended in hepatic insufficiency

## **Monitoring**

- N/A

## **Contraindications and Cautions**

- None

## **Important Drug Interactions**

- None described

## **Adverse Effects and Their Management**

- A localized burning sensation may occur with application. Rosacea patients in general may be sensitive to topical medications application to the skin. To minimize this possibility, make sure to wait at least 30 min after washing prior to applying the topical cream.
- Dry skin has been reported. Consider addition of light emollient cream if this occurs.
- Eye irritation and conjunctivitis may occur. Recommend avoiding using near the eyes.
- Irritant and allergic contact dermatitis has been reported.

## Patch Test Concentration

- N/A

## Essential Patient Information

- Do not ingest.
- Avoid contact with eyes and lips.
- Not for vaginal use.

---

## Azelaic Acid

### Classification and Mode of Action

- Dicarboxylic acid
- Possible anti-inflammatory and antioxidative effects
  - Inhibits serine protease kallikrein-5 involved in the production of cathelicidin, a pro-inflammatory antimicrobial peptide involved in rosacea pathogenesis
  - Activation of PPAR $\gamma$  resulting in anti-inflammatory activity
  - Inhibition of IL-1, IL-6 and TNF- $\alpha$  expression
  - Decreasing reactive oxygen species
- Antimicrobial activity against *Staphylococcus epidermidis* and *Cutibacterium acnes*
- Comparative efficacy in rosacea
  - Available studies have shown equal or greater efficacy compared to topical metronidazole.
  - Azelaic acid gel is more likely to be irritating to the skin compared to topical metronidazole and topical ivermectin.
  - Azelaic acid 15% foam may be better tolerated than metronidazole cream and gel.
- Comparative efficacy in acne vulgaris:
  - Azelaic acid 20% cream twice a day was less effective than once daily application combination benzoyl peroxide 3% plus clindamycin 1%.

## Indications and Dermatological Uses

- *Clinical indications (FDA)*: Inflammatory lesions of rosacea, inflammatory lesions of acne vulgaris
- *Off-label common uses*: Melasma, hyperpigmentation, perioral dermatitis

## Formulations/Presentation

- US: Rosacea: 15% gel (Finacea, generic) or foam (Finacea foam), acne: 20% cream or lotion (Azelex, generic); also available in OTC products up to 10%
  - Finacea gel: 0.15 gm azelaic acid per gram of gel.
  - Finacea foam: 1 g of Finacea Foam contains 0.15 g of azelaic acid.
  - Azelex cream: 0.2 g (azelaic acid) per gram of cream.
- Canada: 15% gel (Finacea)
- Europe: 15% gel (Finacea), 20% cream (Skinoren)

## Dosages and Suggested Regimens

- Rosacea: apply gel or foam to affected areas twice a day (morning and evening)
- Acne vulgaris: apply thin film to affected areas twice daily (morning and evening)

## Baseline Investigations and Considerations

- None

## Pharmacokinetics

### Absorption:

- Approximately 4% of topically applied azelaic acid 20% cream. Studies of the use of azelaic acid 15% gel did not show an increase plasma azelaic acid concentration beyond the normal range.

### Metabolism:

- Negligible cutaneous metabolism occurs after topical application.

### Excretion:

- Mainly excreted unchanged in the urine but undergoes some  $\beta$ -oxidation to shorter chain dicarboxylic acids.

## Use in Special Populations

### Pregnancy:

- There are no adequate and well-controlled studies in pregnant women. The manufacturer recommends use during pregnancy only if clearly needed. However, because less than 4% is absorbed systemically, exposure to fetus is thought to be minimal. Azelaic acid is typically considered by the dermatologic community to be a low-risk treatment option for acne vulgaris and rosacea in pregnant people.

### Lactation:

- Passage of drug into maternal milk may occur. However, as less than 4% of a topical dose is systemically absorbed, this is not expected to cause a significant change in baseline azelaic acid levels in the milk.
- The manufacturer recommends caution when administering to nursing mothers.

### Pediatric use:

- Safety and effectiveness of topical azelaic acid in pediatric patients has not been established. However, based on available studies and guidelines, it is likely safe in children aged 12 and older with same dosing as in adults.

Renal insufficiency: No dosing adjustments are provided on the manufacturer's label.

Hepatic insufficiency: No dosing adjustments are provided on the manufacturer's label.

## Monitoring

- No specific monitoring guidelines.

## Contraindications and Cautions

- *Contraindications:* Hypersensitivity to any of its components.
- This product is not well studied in patients with dark complexion. Monitor these patients for early signs of hypopigmentation as there have been isolated reports of hypopigmentation after use of azelaic acid.
- Temporary skin irritation may occur when applied to broken or inflamed skin, usually at the start of treatment. This typically subsides if treatment is continued. If it continues, reduce to once daily use or stop treatment until these effects have subsided.
- The propellant in Finacea foam is flammable. Avoid fire, flame, and smoking during and immediately following application.

## Important Drug Interactions

- There have been no formal studies of the interaction of topical azelaic acid with other drugs.

## Adverse Effects and Their Management

- Skin erythema, dryness, peeling, stinging, pruritus, and pain at application site. Patients may tolerate foam better than gel formulation.
- Eye irritation—avoid contact with eyes and periorbital skin.
- Post marketing rash, hypersensitivity and worsening of asthma has been reported. If this occurs discontinue therapy.
- Rare cases of hypopigmentation and vitiligo.



- Rare hypertrichosis.
- Rare exacerbation of recurrent herpes labialis.
- Foam only: avoid flames/fire and smoking during and immediately after application.

## Patch Test Concentration

- N/A

## Essential Patient Information

- To minimize irritation to skin, avoid alcohol containing toners, astringents, and cleansers. Also avoid abrasive cleansers.
- Avoid concomitant use of other topical acid containing products and peels such as glycolic acid, lactic acid, salicylic acid, alpha-hydroxy acids, and beta-hydroxy acids unless directed by clinician. Combining use may increase the risk of skin irritation.
- Concomitant use with topical retinoids may increase the risk of skin irritation.

## Additional Rosacea Topical Therapies

*FDA approved:* Topical Minocycline—see section on Acne

*Other:* Sulfur and sulfacetamide, dapsone, clindamycin, erythromycin—see section on Acne; Topical Permethrin—see section on Parasitic treatment

---

## References

1. Buddenkotte J, Steinhoff M. Recent advances in understanding and managing rosacea. *F1000 Research*. 2018;7(F1000 Faculty Rev-1885) <https://doi.org/10.12688/f1000research.16537>.
2. Gallo RL, Granstein RD, Kang S, Mannis M, Steinhoff M, Tan J, Thiboutot D. Standard classification and pathophysiology of rosacea: the 2017 update by the National Rosacea Society Expert Committee. *J Am Acad Dermatol*. 2018;78(1):148–55.

3. Thiboutot D, Anderson R, Cook-Bolden F, Draelos Z, Gallo RL, Granstein RD, Kang S, Macsai M, Gold LS, Tan J. Standard management options for rosacea: the 2019 update by the National Rosacea Society Expert Committee. *J Am Acad Dermatol*. 2020;82(6):1501–10.
4. Desai SR, Baldwin H, Del Rosso JQ, Gallo RL, Bhatia N, Harper JC, York JP, Gold LS. Microencapsulated Benzoyl Peroxide for Rosacea in context: a review of the current treatment landscape. *Drugs*. 2024;84(3):275–84.

## Brimonidine

5. FDA drug monograph. Mirvaso. Available from: [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/2047081bl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/2047081bl.pdf). Accessed 1/2/2022.
6. Anton C. de Groot – Monographs in contact allergy volume 3: topical drugs. Chapter 3.
7. Onreltea product monograph. Galderma Canada. Available at <https://www.galderma.com/sites/default/files/inline-files/Onreltea%20English%20PM.pdf>. Accessed 1/2/2022.
8. Okwundu N, Cline A, Feldman SR. Difference in vasoconstrictors: oxymetazoline vs. brimonidine. *J Dermatolog Treat*. 2021;32(2):137–43.
9. Sethi HS, Naik M, Gupta VS. Management of glaucoma in pregnancy: risks or choices, a dilemma? *Int J Ophthalmol*. 2016;9(11):1684–90.
10. Tanghetti EA, Jackson JM, Belasco KT, Friedrichs A, Hougier F, Johnson SM, Kerdel FA, Palceski D, Hong HC, Hinek A, Cadena MJ. Optimizing the use of topical brimonidine in rosacea management: panel recommendations. *J Drugs Dermatol*. 2015;14(1):33–40.

## Oxymetazoline

11. FDA drug monograph RHOFADE. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/208552s0001bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208552s0001bl.pdf). Accessed 1/2/2022.
12. LexiComp drug monograph (name of monograph). Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2021 UptoDate, Inc.
13. Draelos ZD, Gold MH, Weiss RA, et al. Efficacy and safety of oxymetazoline cream 1.0% for treatment of persistent facial erythema associated with rosacea: findings from the 52-week open label REVEAL trial. *J Am Acad Dermatol*. 2018;78:1156–63.
14. Okwundu N, Cline A, Feldman SR. Difference in vasoconstrictors: oxymetazoline vs. brimonidine. *J Dermatolog Treat*. 2021;32(2):137–43.

## Metronidazole

15. deGroot AC. Chapter 3: Monographs of topical drugs that have caused contact allergy/allergic contact dermatitis. In: Monographs in contact allergy, volume 3. Topical drugs. CRC Press; 2021.
16. FDA drug monograph METROGEL 1%. Available from: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2005/0217891bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/0217891bl.pdf). Accessed 12 Aug 2023.
17. FDA drug monograph Metrogel 0.75%. Available from: <https://www.galderma.com/sites/default/files/inline-files/METROGEL-PM-E-Feb-22-2018.pdf>. Accessed 12 Aug 2023.
18. FDA drug monograph MetroLotion 0.75%. Available from: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/1998/209011bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/1998/209011bl.pdf). Accessed 12 Aug 2023.
19. FDA monograph NORITATE cream 1%. Available from: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2003/020743s0021bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2003/020743s0021bl.pdf). Accessed 12 Aug 2023.
20. LexiComp drug monographs (metronidazole – topical and systemic). Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2023 UptoDate, Inc.
21. Hernández Ceruelos A, Romero-Quezada LC, Ruvalcaba Ledezma JC, López Contreras L. Therapeutic uses of metronidazole and its side effects: an update. *Eur Rev Med Pharmacol Sci*. 2019;23(1):397–401.
22. Jarmuda S, O'Reilly N, Żaba R, Jakubowicz O, Szkaradkiewicz A, Kavanagh K. Potential role of Demodex mites and bacteria in the induction of rosacea. *J Med Microbiol*. 2012;61(Pt 11):1504–10.
23. Kellen R, Silverberg NB. Pediatric periorificial dermatitis. *Cutis*. 2017;100(6):385–8.
24. Kroshinsky D, Glick SA. Pediatric rosacea. *Dermatol Ther*. 2006;19(4):196–201.
25. Mostafa FF, El Harras MA, Gomaa SM, et al. Comparative study of some treatment modalities of rosacea. *J Eur Acad Dermatol Venereol*. 2009;23:22.
26. Miyachi Y. Potential antioxidant mechanism of action for metronidazole: implications for rosacea management. *Adv Ther*. 2001;18:237.
27. Murase JE, Heller MM, Butler DC. Safety of dermatologic medications in pregnancy and lactation: Part I. Pregnancy. *J Am Acad Dermatol*. 2014;70(3):401.
28. Taieb A, Ortonne JP, Ruzicka T, Roszkiewicz J, Berth-Jones J, Peirone MH, Jacovella J. Ivermectin Phase III study group. Superiority of ivermectin 1% cream over metronidazole 0.75% cream in treating inflammatory lesions of rosacea: a randomized, investigator-blinded trial. *Br J Dermatol*. 2015;172(4):1103–10.
29. Wolf JE Jr, Kerrouche N, Arsonnaud S. Efficacy and safety of once-daily metronidazole 1% gel compared with twice-daily azelaic acid 15% gel in the treatment of rosacea. *Cutis*. 2006;77:3.

30. Ziel K, Yelverton CB, Balkrishnan R, Feldman SR. Cumulative irritation potential of metronidazole gel compared to azelaic acid gel after repeated applications to healthy skin. *J Drugs Dermatol*. 2005;4:727.

## Ivermectin

31. FDA drug monograph SOOLANTRA cream. Available from [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2014/2062551bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/2062551bl.pdf). Accessed 12 Aug 2023.
32. FDA drug monograph SKLICE lotion. Available from [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/202736s0031bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/202736s0031bl.pdf). Accessed 12 Aug 2023.
33. [https://www.ema.europa.eu/en/documents/psusa/ivermectin-topical-use-list-nationally-authorised-medicinal-products-psusa/00010376/201610\\_en.pdf](https://www.ema.europa.eu/en/documents/psusa/ivermectin-topical-use-list-nationally-authorised-medicinal-products-psusa/00010376/201610_en.pdf). Accessed 12 Aug 2023.
34. LexiComp drug monograph (Ivermectin). Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2023 UptoDate, Inc.
35. Benkali K, Rony F, Graeber M, Jacovella J, Chappuis JP, Peirone MH, Poncet M, Delage S, Bouer R, Wagner N. Clinical pharmacokinetics profile of ivermectin 1% cream after dermal applications on the face. *World J Dermatol*. 2016;5(1):57–64.
36. González Canga A, Sahagún Prieto AM, Díez Liébana MJ, Fernández Martínez N, Sierra Vega M, García Vieitez JJ. The pharmacokinetics and interactions of ivermectin in humans—a mini-review. *AAPS J*. 2008;10(1):42–6.
37. Schaller M, Gonser L, Belge K, et al. Dual anti-inflammatory and anti-parasitic action of topical ivermectin 1% in papulopustular rosacea. *J Eur Acad Dermatol Venereol*. 2017;31:1907–11.
38. Taieb A, Ortonne JP, Ruzicka T, et al. Superiority of ivermectin 1% cream over metronidazole 0.75% cream in treating inflammatory lesions of rosacea: a randomized, investigator-blinded trial. *Br J Dermatol*. 2015;172:1103.

## Azelaic Acid

39. FDA drug monograph FINACEA gel, 15%. Available from: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2010/021470s0051bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021470s0051bl.pdf). Accessed 12 Aug 2023.
40. FDA drug monograph FINACEA foam. Available from: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2015/207071s0001bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207071s0001bl.pdf). Accessed 12 Aug 2023.

41. FDA drug monograph AZELEX (azelaic acid cream). Available from: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2003/20428slr016\\_azelex\\_jbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2003/20428slr016_azelex_jbl.pdf). Accessed 12 Aug 2023.
42. Afarideh M, Rodriguez Baisi KE, Davis DMR, Hand JL, Tollefson MM. Trends in utilization of non-first-line topical acne medications among children, adolescents, and adults in the United States, 2012–2016. *Pediatr Dermatol*. 2021;38(5):1066–73.
43. Coda AB, Hata T, Miller J, et al. Cathelicidin, kallikrein 5, and serine protease activity is inhibited during treatment of rosacea with azelaic acid 15% gel. *J Am Acad Dermatol*. 2013;69(4):570–7.
44. Koh YP, Tian EA, Oon HH. New changes in pregnancy and lactation labelling: review of dermatologic drugs. *Int J Womens Dermatol*. 2019;5(4):216–26.
45. Jansen T, Melnik BC, Schadendorf D. Steroid-induced periorificial dermatitis in children-clinical features and response to azelaic acid. *Pediatr Dermatol*. 2010;27(2):137–42.
46. Mastrofrancesco A, Ottaviani M, Aspite N, Cardinali G, Izzo E, Graupe K, Zouboulis CC, Camera E, Picardo M. Azelaic acid modulates the inflammatory response in normal human keratinocytes through PPARgamma activation. *Exp Dermatol*. 2010;19(9):813–20.
47. Schaller M, Sebastian M, Ress C, et al. A multicentre, randomized, single-blind, parallel-group study comparing the efficacy and tolerability of benzoyl peroxide 3%/clindamycin 1% with azelaic acid 20% in the topical treatment of mild-to-moderate acne vulgaris. *J Eur Acad Dermatol Venereol*. 2016;30(6):966–73.
48. Schulte BC, Wu W, Rosen T. Azelaic acid: evidence-based update on mechanism of action and clinical application. *J Drugs Dermatol*. 2015;14(9):964–8.
49. Täuber U, Weiss C, Matthes H. Percutaneous absorption of azelaic acid in humans. *Exp Dermatol*. 1992;1(4):176–9.
50. Williamson T, LaRose A, Cameron J, et al. Rosacea treatment satisfaction: matching adjusted indirect treatment comparison analysis of metro-nidazole gel or cream vs azelaic acid foam. *J Drugs Dermatol*. 2020;19(3):295–304.
51. Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol*. 2016;74(5):945–73. e33. <https://doi.org/10.1016/j.jaad.2015.12.037>. Epub 2016 Feb 17. Erratum in: *J Am Acad Dermatol*. 2020 Jun;82(6):1576.



# Topical Drug Treatment in Actinic Keratosis

# 10

Chavy Chiang and Anuk Burli

## Contents

|                                   |     |
|-----------------------------------|-----|
| Aminolevulinic Acid.....          | 212 |
| Tirbanibulin.....                 | 215 |
| Fluorouracil (5-FU).....          | 218 |
| Diclofenac (Alternate Agent)..... | 222 |
| References.....                   | 222 |

Treatment options for actinic keratosis include topical aminolevulinic acid in conjunction with photodynamic therapy or fluorouracil (covered under antineoplastics). Ingenol mebutate was previously approved and marketed as Picato gel for treatment of actinic keratosis but was withdrawn by its manufacturer LEO Pharma in October 2020 after studies showed a potential increased

---

C. Chiang (✉)  
Department of Dermatology, University of Rochester Medical Center,  
Rochester, NY, USA  
e-mail: [chavyz@gmail.com](mailto:chavyz@gmail.com)

A. Burli  
Department of Dermatology, Stanford University School of Medicine,  
Redwood City, CA, USA  
e-mail: [anukb@stanford.edu](mailto:anukb@stanford.edu)

© The Author(s), under exclusive license to Springer Nature  
Switzerland AG 2025  
R. M. Law, H. I. Maibach (eds.), *Handbook of Topical Drug  
Treatment in Dermatology*,  
[https://doi.org/10.1007/978-3-031-93616-6\\_10](https://doi.org/10.1007/978-3-031-93616-6_10)

211

risk of nonmelanoma skin cancer. Topical tirbanibulin, a first-in-class microtubule inhibitor, was approved by the FDA in 2020 for treatment of actinic keratosis.

---

## Aminolevulinic Acid

### Classification and Mode of Action

- Photosensitizing agent. Following topical application, aminolevulinic acid is metabolized to photosensitizer protoporphyrin IX (PpIX), which accumulates in the skin. Light exposure of proper wavelength and energy excites PpIX and generates cytotoxic reactive oxygen species (AMELUZ: combine with red light from BF-RhodoLED® lamp at a dose of 37 J/cm<sup>2</sup>; LEVULAN KERASTICK: combine with blue light from BLU-U Blue Light Photodynamic Therapy Illuminator at a dose of 10 J/cm<sup>2</sup>).

### Indications and Dermatological Uses

- *Clinical indications (FDA)*: Actinic keratosis
- *Off-label common uses*: Actinic cheilitis (level of evidence: C), basal cell skin cancer, superficial, low risk (level of evidence: G), squamous cell skin cancer in situ, low risk (Bowen disease; level of evidence: G)

### Formulations/Presentation

- US: 10% gel (AMELUZ), 20% solution (LEVULAN KERASTICK)
- Canada: 20% solution (LEVULAN KERASTICK)
- Europe: 7.8% gel (AMELUZ)

## Dosages and Suggested Regimens

- **Gel:** Apply gel, amounting 1 mm in thickness, to cover lesion(s) and 5 mm of surrounding skin. Application area and amount should not exceed 20 cm<sup>2</sup> and 2 g, respectively. Allow gel to dry for 10 min and then use light-blocking, occlusive dressing to cover the application area for 3 h. Remove dressing and wipe off remaining gel afterward and treat with red light illumination. Lamp head should be positioned 5–8 cm from the skin surface. Lesions may be retreated if they have not completely resolved in 3 months following initial treatment.
- **Solution:** Apply to lesion and uniformly wet the surface, including edges without excess running or dipping. Do not apply solution to surrounding healthy skin. For face or scalp lesions, repeat application once more after initial application as dried. Administer blue light treatment 14–18 h afterward. For upper extremity lesions, occlude upper extremity with low-density polyethylene plastic wrap and secure wrap with an elastic net dressing. After 3 h, remove dressing, rinse with water, pat dry, and treat with blue light. Lesions may be retreated once if they have not completely resolved in 8 weeks following initial treatment.
- Significant drug interactions exist, which may require dose/frequency adjustment or avoidance. Consult drug interactions database for guidance/information.

## Baseline Investigations and Considerations

### Pharmacokinetics (Percutaneous Absorption, Distribution, Metabolism, Excretion) as Relevant

- Two grams of AMELUZ applied under occlusion over 20 cm<sup>2</sup> for 3 h in 12 adults with subsequent photodynamic therapy yielded a mean  $\pm$  SD area under the concentration time curve and maximum concentration of  $142.83 \pm 75.50$  ng/mL and  $27.19 \pm 20.02$  ng/mL, respectively, for baseline-corrected aminolevulinic acid. Mean  $\pm$  SD baseline plasma levels measured  $20.16 \pm 16.53$  ng/mL. The median time to reach maximum concentration (T<sub>max</sub>) was 3 h.



## Use in Special Populations

- No lactation or pediatric data.
- Unknown risk of fetal exposure upon maternal use.
- *Renal insufficiency*: No data.
- *Hepatic insufficiency*: No data.

## Monitoring

- Educate patients on proper post-treatment care.

## Contraindications and Cautions

- Skin photosensitivity to light
- Known hypersensitivity to porphyrins
- Porphyrria

## Important Drug Interactions

- No formal studies conducted.
- Use of other known photosensitizing agents, such as St. John's wort, griseofulvin, thiazide diuretics, sulfonyleureas, phenothiazines, quinolones, and tetracyclines may enhance phototoxic reaction to photodynamic therapy.

## Adverse Effects and Their Management

- Erythema, edema, stinging/burning, scaling/crusting, itching, erosion, hypo/hyperpigmentation, oozing/vesiculation/crusting, scaling, and dryness.

## Patch Test Concentration

- 20% water; a concentration of 10% in petrolatum causes irritant reactions.

## Essential Patient Information

- Avoid exposing treated skin to sun and prolonged or intense light for 48 h after treatment.
- Avoid medications that may enhance phototoxic reaction.

---

## Tirbanibulin

### Classification and Mode of Action

- Microtubule inhibitor. Blocks polymerization of tubulin.

### Indications and Dermatological Uses

- *Clinical indications (FDA)*: Actinic keratosis (of face and scalp)
- *Off-label common uses*: None

### Formulations/Presentation

- US: 1% ointment (KLISYRI)

### Dosages and Suggested Regimens

- Apply evenly to cover up to 25 cm<sup>2</sup> of affected area once daily for five consecutive days, using one single-dose packet per application.

## Baseline Investigations and Considerations

### Pharmacokinetics (Percutaneous Absorption, Distribution, Metabolism, Excretion) as Relevant

- Topical application of a mean daily dose of 138 mg (range: 54–295 mg) of KLISYRI to 25 cm<sup>2</sup> of facial skin or balding scalp once daily for five consecutive days achieved steady state concentration by 72 h, with a mean±SD trough concentration ( $C_{\text{trough}}$ ) of  $0.11 \pm 0.08$  ng/mL. Low systemic exposure was demonstrated on Day 5, with mean ± SD maximum plasma concentration ( $C_{\text{max}}$ ) measuring  $0.34 \pm 0.30$  ng/mL and  $0.18 \pm 0.10$  ng/mL. Mean±SD area under the plasma concentration from time zero to 24 h ( $AUC_{24}$ ) measured  $5.0 \pm 3.9$  h\*ng/mL and  $3.2 \pm 1.9$  h\*ng/mL in facial- and scalp-treated subjects, respectively. Median time to reach  $C_{\text{max}}$  ( $T_{\text{max}}$ ) was about 7 h.
- Plasma protein binding measures 88% and is unaffected by concentrations within the range of 0.01–10 µg/mL.
- Topical treatment to adult subjects with actinic keratosis induced detectable levels of two pharmacologically inactive metabolites, KX2-5036 and KX2-5163, with respective maximum plasma concentrations measuring 0.09 ng/mL and 0.12 ng/mL. In vitro data indicate that when 1 or 10 µM tirbanibulin are incubated with hepatocytes, KX2-5036, KX-5163, and other unidentified metabolites are generated. In vitro, tirbanibulin is largely metabolized by CYP3A4, with a smaller contribution by CYP2C8.
- Excretion data not fully characterized in humans.

### Use in Special Populations

- No human pregnancy, human lactation, or pediatric data available.
- *Renal insufficiency*: not evaluated.
- *Hepatic insufficiency*: not evaluated.

## **Monitoring**

- Local skin reactions
- Ophthalmic reactions

## **Contraindications and Cautions**

- None.

## **Important Drug Interactions**

- No data.

## **Adverse Effects and Their Management**

- Local skin reactions can occur, including erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, erosions/ulcerations.

## **Patch Test Concentration**

- N/A

## **Essential Patient Information**

- Apply to skin only.
- Do not use more than needed to cover treatment area.
- Do not apply in, around, or near eyes, mouth, or lips.

## Fluorouracil (5-FU)

### Classification and Mode of Action

- Antineoplastic. Fluorouracil prevents methylation of deoxy-uridylic acid to thymidylic acid to block DNA and, to a lesser extent, RNA synthesis, particularly so in rapidly growing cells.

### Indications and Dermatological Uses

- *Clinical indications (FDA)*: Actinic keratosis. Basal cell carcinoma, superficial.
- *Off-label common uses*: Penile carcinoma in situ (level of evidence: C). Squamous cell carcinoma in situ (Bowen disease; level of evidence: C)

### Formulations/Presentation

- US: 0.5% cream (Carac or generic), 1% cream (Fluoroplex or generic), 4% cream (Tolak—contains peanut oil), 5% cream (Efudex or generic), 2% solution (generic), 5% solution (generic)
- Canada: 4% cream (Tolak—contains peanut oil), 5% cream (Efudex)
- Europe: Not on LexiComp

### Dosages and Suggested Regimens

- Actinic keratosis:
  - 0.5% cream: apply thin film once daily to lesions for up to 4 weeks, as tolerated
  - 1% cream: apply twice daily to lesions for 2–6 weeks
  - 4% cream: apply once daily to lesions for 4 weeks as tolerated

- 5% cream, 2% or 5% solution: apply sufficiently to cover lesions twice daily for 2–4 weeks, until the inflammatory response reaches the erosion stage, then stop. Complete healing may take 1–2 months post-treatment cessation to be evident.
- Basal cell carcinoma:
  - 5% cream or solution: Apply sufficiently to cover lesions twice daily for at least 3–6 weeks; treatment can be extended up to 10–12 weeks.
- Penile carcinoma in situ (off-label):
  - 5% cream: Apply to and leave on lesion for 12 h every 48 h for 28 days
- Squamous cell carcinoma in situ (Bowen disease; off-label):
  - 5% cream: Apply twice daily to lesion for 9 weeks

## **Baseline Investigations and Considerations**

### **Pharmacokinetics (Percutaneous Absorption, Distribution, Metabolism, Excretion) as Relevant**

- Approximately 6% absorbed systemically for 5% cream, with a time to peak of about 1 h.
- After bolus intravenous injection, fluorouracil distributes throughout the body in sites including the intestinal mucosa, bone marrow, liver, cerebrospinal fluid, and brain tissue following bolus injection.
- After bolus intravenous injection, 5–20% of parent drug is excreted unchanged in the urine in 6 h, while the remaining is metabolized primarily by the liver. Metabolites of 5-FU, such as urea and  $\alpha$ -fluoro- $\beta$ -alanine, are excreted in urine over 3–4 h.

## **Use in Special Populations**

- Unknown if excreted in human milk; decision to discontinue nursing or use of drug should be made.

- May cause fetal harm when used by pregnant women. Miscarriages, ventricular septal defects, and cleft lips and palates have been reported when pregnant women were topically or parenterally exposed.
- No safety or efficacy data in children.
- *Renal insufficiency*: No data.
- *Hepatic insufficiency*: No data.

## Monitoring

- Dihydropyrimidine dehydrogenase enzyme deficiency
- Hypersensitivity or local skin reactions

## Contraindications and Cautions

- Not to be used in pregnant women or women planning to become pregnant.
- Not to be used in patients with dihydropyrimidine dehydrogenase enzyme deficiency, as fluorouracil is largely metabolized by this enzyme and life-threatening toxicity has been reported.

## Important Drug Interactions

- Brivudine (not approved by FDA): May enhance 5-FU toxicity.

## Adverse Effects and Their Management

- Burning, crusting, allergic contact dermatitis, erosions, erythema, hyperpigmentation, irritation, pain, photosensitivity, pruritus, scarring, rash, soreness, and ulceration.
- Ulcerations, other local reactions, cases of miscarriage, and a birth defect (ventricular septal defect) have been reported when Efudex was applied to mucous membrane areas.

- Leukocytosis is most frequent hematological side effect.
- Other adverse reactions: emotional upset, insomnia, irritability, medicinal taste, stomatitis, eosinophilia, thrombocytopenia, toxic granulation, alopecia, blistering, bullous pemphigoid, discomfort, ichthyosis, scaling, suppuration, swelling, telangiectasia, tenderness, urticaria, skin rash, conjunctival reaction, corneal reaction, lacrimation, nasal irritation, herpes simplex.

## Patch Test Concentration

- Commercial 5% cream “as is”; 5-FU 50 mg/mL (5%) and 10 mg/mL (1%) in saline or 5% pet; if negative and contact allergy is strongly suspected, or with 7+ patch tests, perform intradermal tests with 5-FU 10 mg/mL (1%) saline with reading at Day 2.

## Essential Patient Information

- Do not apply to eyelids, into eyes, nose, or mouth. Miscarriage and birth defects have been reported following mucous membrane application during pregnancy.
- Wash hands immediately after if using fingers to apply the medication.
- Use by pregnant women may cause harm to fetus. Contraception use advised in females of reproductive potential during and for one month following last dose of medication.
- Four percent cream contains peanut oil and can cause hypersensitivity reactions as well as ophthalmic reactions.
- Avoid sun exposure, sun lamps, and tanning beds during and immediately following treatment since ultraviolet rays can increase reaction intensity.
- Skin reaction caused by treatment may be unsightly during treatment and for several weeks upon completion of therapy.



## Diclofenac (Alternate Agent)

Refer to *Chap. 11: Analgesics* for the Diclofenac drug monograph.

---

## References

### Aminolevulinic Acid

1. [https://www.ema.europa.eu/en/documents/product-information/ameluzepar-product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/ameluzepar-product-information_en.pdf).
2. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/020965s0151bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020965s0151bl.pdf).
3. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/208081s0001bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208081s0001bl.pdf).
4. Lexicomp: Aminolevulinic acid. Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2024 UptoDate, Inc.
5. De Groot AC. Patch testing. 3rd edition. Volume 3 Chapter 3
6. De Groot AC. Patch testing, 4th edition: update 2018–2022. Wapserveen: Acdegroot Publishing, 2022 (37 pages). ISBN/EAN 978-90-813233-7-6.

### Tirbanibulin

7. Lexicomp: Tirbanibulin LexiComp drug monograph (name of monograph). Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2024 UptoDate, Inc.
8. Kempers S, DuBois J, Forman S, et al. Tirbanibulin Ointment 1% as a novel treatment for actinic keratosis: Phase 1 and 2 results. *J Drugs Dermatol*. 2020;19(11):1093–100. <https://doi.org/10.36849/JDD.2020.5576>.

## Fluorouracil (5-FU)

9. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/012209s040lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/012209s040lbl.pdf).
10. LexiComp drug monograph Fluorouracil. Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2024 UptoDate, Inc.
11. De Groot AC. Patch testing, 3rd edition. Volume 3 Chapter 3
12. De Groot AC. Patch testing, 4th edition: update 2018–2022. Wapserveen: Acdegroot Publishing, 2022 (37 pages). ISBN/EAN 978-90-813233-7-6.



# Topical Analgesics

# 11

Sheeva Shahinfar, Rebecca M. Law ,  
and Howard I. Maibach

## Contents

|                 |     |
|-----------------|-----|
| Capsaicin.....  | 226 |
| Diclofenac..... | 231 |
| References..... | 238 |

---

S. Shahinfar (✉)

Texas A&M University College of Medicine, Bryan, TX, USA

e-mail: [sheeva.shahinfar@tamu.edu](mailto:sheeva.shahinfar@tamu.edu)

R. M. Law (✉)

School of Pharmacy and Faculty of Medicine (Discipline of Family  
Medicine), Memorial University of Newfoundland, St. John's, NL, Canada

e-mail: [rlaw@mun.ca](mailto:rlaw@mun.ca); [rlawUCSF@gmail.com](mailto:rlawUCSF@gmail.com)

H. I. Maibach

Department of Dermatology, University of California San Francisco  
(UCSF), San Francisco, CA, USA

e-mail: [howard.maibach@ucsf.edu](mailto:howard.maibach@ucsf.edu)

© The Author(s), under exclusive license to Springer Nature  
Switzerland AG 2025

225

R. M. Law, H. I. Maibach (eds.), *Handbook of Topical Drug  
Treatment in Dermatology*,

[https://doi.org/10.1007/978-3-031-93616-6\\_11](https://doi.org/10.1007/978-3-031-93616-6_11)

## Capsaicin

### Classification and Mode of Action

- A compound originally discovered in chili peppers.
- Initially recognized in its ability to produce pain with its burning and irritant effects. Over time, capsaicin's analgesic properties have also been recognized.
- Mechanism of action: not entirely understood. It is believed that a high or repeated dose of capsaicin induces a refractory state in TRPV1 receptors.
  - TRPV1 receptors are ion channels part of the transient receptor potential (TRP) family and implicated in nociception along pain pathways.
  - Capsaicin-induced refraction leads to desensitization and eventual inhibition of receptor function. Part of this process includes a decrease in nociceptive peptides (e.g., Substance P) on nerves that express TRPV1.
  - It has been hypothesized that initial stimulation with capsaicin produces pain via antagonism of TRPV1 receptors. Repeated stimulation with capsaicin causes a refractory state in TRPV1 receptors and depletes neurons of substance P, leading to the desensitization and analgesic effect.

### Indications and Dermatological Uses

- *Clinical indications (FDA):* neuropathic pain (post-herpetic)
- *Off-label common uses:* psoriasis pain, intractable pruritus, neuropathic post-surgical pain, notalgia paresthetica, apocrine chromhidrosis, lipodermatosclerosis, prurigo nodularis, lichen simplex chronicus, aquagenic pruritus, alopecia areata
  - Level of evidence for psoriasis: B
  - Level of evidence for intractable pruritus: B

## Formulations/Presentation

- US: Qutenza® 8% patch (available as cream, gel, liquid, lotion, patch for non-dermatologic clinical indications).
- Canada: Cream (0.025%, 0.05%, 0.075%), gel (0.025%), patch (0.025%). Note: Capsaicin (Qutenza®) is not approved for use in post-herpetic neuralgia in Canada.
- Europe: Qutenza® 8% patch (available as cream, gel, liquid, lotion, patch for non-dermatologic clinical indications).

## Dosages and Suggested Regimens

- Qutenza®: Health professional should apply patch in-office to most painful areas for 60 min. A maximum of four patches can be applied at once. Repeat treatment every 3 months as needed for pain. Do not apply sooner than 3 months after application.
- Cream for off-label use: Apply a thin film of substance to the affected area three to four times a day for pain.

## Baseline Investigations and Considerations

### Pharmacokinetics (Percutaneous Absorption, Distribution, Metabolism, Excretion) as Relevant

- Qutenza® patch showed low and transient systemic absorption (<5 ng/mL) in one out of three patients when evaluated after 60 min of application. Most patients with higher concentrations had a noticeable drop in concentration (below the quantifiable limit) at 3–6 h after a 60-min application cycle.
- Half-life seen at 1.64 h.
- Onset of action at 1 week after application. Cream's onset of action seen with 2–4 weeks of regular, directed application.

## Use in Special Populations

- **Pregnancy:** Systemic absorption is limited after topical application. Fetal exposure is not anticipated with maternal use of topical medication. Plasma concentration is below quantifiable level at 3–6 h after 60-min patch application.
- **Lactation:** Systemic absorption is limited after topical application. Exposure to infant via breast milk is not anticipated. According to manufacturer, breastfeeding decision while using topical therapy should consider risks of infant exposure, benefits of infant breastfeeding, and benefits of topical treatment for mother. Avoid application to the nipple or surrounding areas to decrease infant exposure.
- **Children:** Qutenza® 8% patch is not approved for use in children.
  - Off-label lotion (0.025%) use: children 8+ years old may apply to affected area three to four times per day.
  - Off-label patch (0.0375%) use: children 8+ years old may apply 1 patch to affected area, maximum use of three patches/day.
  - Off-label patch (0.03%) use: children 8+ years old may apply one patch to affected area for <8 h, maximum use of four patches/day, do not use more than five consecutive days.
  - Off-label patch (0.0225%) use: children 8+ years old may apply one patch to affected area for <8 h, maximum use of three patches/day.
  - Off-label patch (0.0375%) use: children 8+ years old may apply one patch to affected area, maximum use of three patches/day
  - Off-label patch (0.025%) use: children 8+ years old may apply one patch to affected area for <8 h, maximum use of three patches/day
  - Off-label patch (0.05%) use: Adolescents 16+ years may apply one patch to affected area, maximum use of two patches/day
- **Renal insufficiency:** No dose adjustments listed on manufacturer's labeling
- **Hepatic insufficiency:** No dose adjustments listed on manufacturer's labeling

## Monitoring

- Monitor blood pressure periodically during treatments.
- Severe irritation to the eyes, respiratory tract, skin, or mucous membranes may occur from unintended product exposure. Refer to “Adverse effects & their management” for further information.
- Sensory function (thermal, harmful stimuli) may be decreased with patch use. These are typically temporary and minor. Continue to monitor and reevaluate patients for worsening sensory deficits.
- Serious burns may occur and may need hospitalization. Discontinue use if signs of burn are present.
- Remove patches slowly and gently to decrease exposure through aerosols. Inhalation may induce coughing or sneezing.

## Contraindications and Cautions

- Use with caution in patients with a history of cardiovascular events or uncontrolled hypertension. Temporary increases in blood pressure may occur due to pain during and after product application. Monitor blood pressure throughout application period.
- Use with caution in patients with history of cerebrovascular events. Temporary increases in blood pressure may occur due to pain during and after product application.
- Contraindicated in patients with hypersensitivity to capsaicin, menthol, or any vehicles or parts of the formulation.
- Contraindicated for use on wounds, open skin, irritated skin, or into skin folds.

## Important Drug Interactions

- No known significant drug interactions

## Adverse Effects and Their Management

- Serious burns may occur and may need hospitalization. Discontinue use if signs of burns are present. Treat burn or pursue hospitalization for serious burns.
- CNS depression may occur after application; patients should be cautioned about performing activities such as operating heavy machinery or driving.
- Severe irritation to the eyes, respiratory tract, skin, or mucous membranes may occur from unintended product exposure. If irritation to eyes or mucous membranes occurs, remove the patient from the treatment area and flush affected areas with cool water. If irritation to respiratory tract occurs, remove the patient from the treatment area and provide symptomatic care if shortness of breath ensues. If irritation worsens or does not improve, do not expose patient to capsaicin. Ensure that proper protective measures (gloves, ventilation, face mask, and glasses) are used during product application. If skin not intended for the use of capsaicin is exposed to product, use cleansing gel on exposed area for 1 min and remove with dry gauze. Wash with soap and water. Pain from exposure can be treated with ice packs and analgesics.
- Sensory function (thermal, harmful stimuli) may be decreased with patch use. These are typically temporary and minor. Continue to monitor and reevaluate patients for worsening sensory deficits.
- Blood pressure should be monitored in patients with history of cardiovascular events, uncontrolled hypertension, or history of cerebrovascular events. Discontinue use if blood pressure is not maintained.
- Some forms of capsaicin include benzyl alcohol. Benzyl alcohol has been implicated in fatal neonatal toxicity known as “gasping syndrome.” Signs and symptoms include CNS dysfunction, gasping respirations, respiratory distress, hypotension, cardiovascular failure, and metabolic acidosis. Avoid use in neonates.



## **Carcinogenicity**

- No published studies on carcinogenicity

## **Patch Test Concentration**

- *N/A*

## **Essential Patient Information**

- Temporary burning may be present for several days after application.
- Qutenza® is directed for use under direct supervision and placement by a healthcare provider in-office. It should not be used by patient at home.
- Off-label cream use should not be used on wounds, open skin, damaged skin, irritated skin, or into skin folds. Do not cover area with bandage. Do not use simultaneously with other topical analgesics.
- Use caution while operating heavy machinery or driving after application.
- Do not use before or after showering, tanning, heavy exercise, swimming, or other heat/sun exposure.
- Consult your healthcare provider if you notice excessive redness, blistering, irritation, burning, or worsening symptoms.
- Seek immediate medical attention if you have difficulty breathing or swallowing. Do not touch contact lenses for 1 h after using capsaicin.

---

## **Diclofenac**

### **Classification and Mode of Action**

- Diclofenac is a topical non-steroidal anti-inflammatory drug (NSAID).

- Mechanism of action: inhibition of cyclooxygenase 1 and 2 (COX-1, COX-2), which produce prostaglandins and key inflammatory mediators. This inhibition decreases the number of circulating prostaglandins in the body and, in turn, decreases the inflammatory cascade.

## Indications and Dermatological Uses

- *Clinical indications (FDA):* Actinic Keratosis (alternate agent). Refer to Chap. 10 for topical drug treatments for actinic keratosis.
- *Off-label common uses:* Acute musculoskeletal pain

## Formulations/Presentation

- US: 3% Gel, 3% gel + 2.5% hyaluronic acid vehicle
- Canada: 3% Gel, 3% gel + 2.5% hyaluronic acid vehicle
- Europe: 3% Gel, 3% gel + 2.5% hyaluronic acid vehicle

## Dosages and Suggested Regimens

- Apply gel to affected area twice a day for 60–90 days. It is typically recommended to use a 0.5 g amount on a 5 × 5 cm surface area.

## Baseline Investigations and Considerations

### Pharmacokinetics (Percutaneous Absorption, Distribution, Metabolism, Excretion) as Relevant

- 6–10% of applied product is systemically absorbed.
- >99% of absorbed product binds to albumin.
- Undergoes hepatic first-pass metabolism with formation of several metabolites. Most are phenolic metabolites, which are subsequently converted to glucuronide conjugates. Two phenolic metabolites are biologically active but much less than diclofenac, the effect of which is recognized as negligible.

- Peak concentration noted at  $4.5 \pm 8$  h.
- Excretion through urine (~65%) and feces (~3.5%).

### **Use in Special Populations: Pregnancy (FDA Guidance), Lactation, Children, Renal Insufficiency, and Hepatic Insufficiency**

- Unknown if diclofenac is present in breast milk after topical administration. Manufacturer states that the drug's systemic availability is much less with topical administration than oral administration. Breastfeeding decision should include consideration of infant's risk, benefits of breastfeeding infant, and benefits of treatment for mother.
- Concentration of diclofenac in systemic circulation is less when used topically, compared to orally. No studies have evaluated the use of topical diclofenac in pregnancy. NSAIDs have been shown to correlate with birth defects in some studies, including constriction of the ductus arteriosus, oligohydramnios, renal dysfunction, necrotizing enterocolitis, persistent pulmonary hypertension, and intracranial hemorrhage. Prolonged maternal use of NSAIDs increases the risk of renal dysfunction leading to oligohydramnios. This may be reversed with cessation of NSAID use. Persistent ductus arteriosus may be resistant to future medical management. Collectively, NSAIDs may be used with caution during the first two trimesters but not used in the third trimester.
- Actinic keratosis is not a condition seen in the pediatric population. Diclofenac 3% gel is not recommended for use in children.
- No dosing adjustments made by manufacturer for renal insufficiency, recommend avoidance of product in advanced renal disease.
- No dosing adjustments made by manufacturer for hepatic insufficiency, recommend proceeding with caution.

## Monitoring

- Anaphylactoid reactions
- Adverse cardiovascular thrombotic events (e.g., MI and stroke)
- Adverse gastrointestinal side effects (e.g., inflammation, ulceration, bleeding, and perforation)
- DRESS syndrome
- Hematologic prolonged bleeding time
- Hyperkalemia
- Adverse skin events (e.g., Stevens-Johnsons syndrome, toxic epidermal necrolysis, and exfoliative dermatitis)

## Contraindications and Cautions

- Hypersensitivity to diclofenac or vehicles used in formulation (history of urticaria, allergic reactions, or asthma after NSAID or aspirin use)
- Coronary artery bypass graft surgery: increased post-operative risk of MI and stroke
- Advanced renal disease
- Do not use on damaged or open skin (burns, wounds, eczema, infected skin lesions, and exudative dermatitis)
- Do not use before or after cardiac surgery
- Do not use on more than two body areas at the same time

## Important Drug Interactions

### Risk C: Monitor Therapy

- Alcohol: Alcohol may increase risk of GI bleed with use of topical NSAIDs.
- Angiotensin II receptor blockers: Topical NSAIDs may decrease the intended effect of ARBs.
- Angiotensin-converting enzyme inhibitors: Topical NSAIDs may decrease the intended effect of ACE inhibitors.
- Anticoagulants: Topical NSAIDs may increase the intended effect of anticoagulants.

- Beta-blockers: Topical NSAIDs may decrease the intended effect of beta blockers.
- Corticosteroids (systemic): Topical NSAIDs may increase the adverse effects of systemic corticosteroids. Increased risk of GI bleeding, perforation, and ulceration.
- Cyclosporine (systemic): Topical NSAIDs may increase the adverse effects of systemic cyclosporine. Increased risk of nephrotoxicity.
- Deferasirox: Topical NSAIDs may increase the adverse effects of Deferasirox. Increased risk of GI bleeding and ulceration.
- Digoxin: Topical NSAIDs may increase Digoxin's circulating serum concentration.
- Herbal anticoagulant/antiplatelet products: Topical NSAIDs may increase the intended effect of herbal anticoagulants/antiplatelets
- Lithium: Topical NSAIDs may increase lithium's circulating serum concentration.
- Loop diuretics: Topical NSAIDs may decrease the intended effect of loop diuretics.
- Methotrexate: Topical NSAIDs may increase methotrexate's circulating serum concentration.
- Selective serotonin reuptake inhibitors: SSRIs may increase the antiplatelet effect of topical NSAIDs.
- Serotonin/norepinephrine reuptake inhibitors: SNRIs may increase the antiplatelet effect of topical NSAIDs.
- Tacrolimus (systemic): Topical NSAIDs may increase adverse effects of tacrolimus, particularly nephrotoxicity.
- Tenofovir and thiazide-like diuretics: topical NSAIDs may increase adverse effects of Tenofovir, particularly nephrotoxicity.
- Voriconazole: Voriconazole may increase the circulating serum concentration of topical diclofenac.

**Risk D: Consider therapy modification**

- NSAIDs: Topical NSAIDs may increase the adverse effects of other NSAIDs. Increased risk of GI toxicity. Not recommended to co-administer systemic and topical NSAIDs.
- Salicylates: Topical NSAIDs may increase the adverse effects of salicylates. Increased risk of GI toxicity. Not recommended to co-administer systemic and topical NSAIDs.

## Adverse Effects and Their Management

- Anaphylactoid reactions: Anaphylactoid reactions may occur in patients with no prior exposure. Patients with “aspirin triad” are at increased risk of anaphylactoid reaction.
- Cardiovascular effects: NSAIDs have been shown to increase risk of serious thrombotic events (e.g., MI and stroke). Patients with known CV disease or CV risk factors have a higher incidence of serious thrombotic events with the use of NSAIDs. Also linked to hypertension and exacerbation of existing hypertension. Monitor blood pressure, particularly in patients with existing hypertension. Should be used with caution in patients with edema, as NSAIDs may cause retention of sodium and fluid. Avoid use in patients with heart failure or recent MI.
- DRESS syndrome (drug reaction with eosinophilia and systemic symptoms): Monitor patients for signs and symptoms (eosinophilia, fever, lymphadenopathy, and rash). Discontinue therapy if symptoms point to DRESS.
- Gastrointestinal side effects: NSAIDs increase the risk of serious GI bleeds, ulceration, perforation, or inflammation. Greatest risk among patients with history of peptic ulcer disease, elderly patient, and patients with history of GI bleeds.

## Carcinogenicity

- No studies have been performed to evaluate the carcinogenicity of NSAIDs.

## Patch Test Concentration

- Sodium salt, 2.5% pet. (SmartPractice Canada, SmartPracticeEurope); sodium salt, 5% pet. (Chemotechnique, SmartPracticeCanada); sodium salt, 1% pet. (Chemotechnique)

## Essential Patient Information

- Diclofenac is used for the treatment of actinic keratosis. Concurrently, sun avoidance should be followed (physical clothing covers, sitting in the shade, and wearing sunscreen regularly).
- Get medical help if these side effects persist: dizziness/headache, constipation, diarrhea, upset stomach, vomiting, gas, heartburn.
- Seek immediate medical condition if these side effects (although rare) are present:
  - Vomiting or coughing up blood. Brown “coffee-ground” appearing vomit
  - Black/red/tarry stools
  - Gum bleeding
  - Abnormal vaginal bleeding
  - Unstoppable bleeding
  - High blood pressure (persistent headache, dizziness, passing out, and vision changes)
  - Kidney problems (difficulty passing urine and blood in urine)
  - High potassium (abnormal heartbeat, confusion, weak, lightheadedness, dizziness, passing out, numbness/tingling, and shortness of breath)
  - Irritation of the skin (redness, blistering, and peeling)
  - Chest pain, chest pressure, increased heartbeat
  - Abnormal increase in weight, swelling in extremities
  - Weakness on one side of the body, difficulty speaking or thinking, changes in balance, drooping face
  - Fatigue, flu-like symptoms, muscle pain
  - Liver problems (dark urine, loss of appetite, abdominal pain, change in stool color, and yellow skin/eyes)
  - Allergic reaction (rash, hives, itching, wheezing, tight chest, and difficulty breathing or swallowing)
  - Abnormal burning, numbness, or tingling

- US Boxed Warnings:
  - Serious cardiovascular thrombotic events: “Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use. Diclofenac gel is contraindicated in the setting of coronary artery bypass graft surgery [26].”
  - Serious GI bleeding, ulceration, and perforation: “NSAIDs cause an increased risk of serious GI adverse reactions, including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These reactions can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk of serious GI events [26].”

---

## References

### Capsaicin

1. FDA drug monograph Qutenza® (capsaicin) patch. Available from [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2020/022395s019lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022395s019lbl.pdf). Accessed 15 Jan 2023.
2. LexiComp drug monograph Capsaicin. Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2021 UptoDate, Inc.
3. Babbar S, Marier J-F, Mouksassi M-S, Beliveau M, Vanhove GF, Chanda S, Bley K. Pharmacokinetic analysis of capsaicin after topical administration of a high-concentration capsaicin patch to patients with peripheral neuropathic pain. *Ther Drug Monit.* 2009;31:502–10.
4. Backonja M, Wallace MS, Blonsky ER, Cutler BJ, Malan P, Rauck R, Tobias J. NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia: a randomised, double-blind study. *Lancet Neurol.* 2008;7:1106–12.
5. Bernstein JE, Korman NJ, Bickers DR, Dahl MV, Millikan LE. Topical capsaicin treatment of chronic postherpetic neuralgia. *J Am Acad Dermatol.* 1989;21:265–70.
6. Boyd K, Shea SM, Patterson JW. The role of capsaicin in dermatology. In: *Capsaicin as a therapeutic molecule*. Basel: Springer; 2014. p. 293–306.



7. Fattori V, Hohmann M, Rossaneis A, Pinho-Ribeiro F, Verri W. Capsaicin: current understanding of its mechanisms and therapy of pain and other pre-clinical and clinical uses. *Molecules*. 2016;21:844.
8. Guillet C, Steinmann S, Maul J-T, Kolm I. Primary localized cutaneous amyloidosis: a retrospective study of an uncommon skin disease in the largest tertiary care center in Switzerland. *Dermatology*. 2021;238:579–86.
9. Laude-Pagniez E, Leclerc J, Lok C, Chaby G, Arnault J-P. Capsaicin 8% patch as therapy for neuropathic chronic postsurgical pain after melanoma excision surgery: a single center case series. *JAAD Case Rep*. 2022;30:70–5.
10. Marks JG. Treatment of apocrine chromhidrosis with topical capsaicin. *J Am Acad Dermatol*. 1989;21:418–20.
11. Rumsfield JA, West DP. Topical capsaicin in dermatologic and peripheral pain disorders. *DICP*. 1991;25:381–7.
12. S; BSMC Capsaicin for acute or chronic non-cancer pain: A review of Clinical Effectiveness, safety, and cost-effectiveness [internet]. In: National Center for Biotechnology Information. <https://pubmed.ncbi.nlm.nih.gov/33284564/>. Accessed 16 Jan 2023.
13. Schäfer RC, Sohn A, Kersten A, Amr A, Held M, Wenger A. Quantification of dermal microcirculatory changes after topical administration of capsaicin: a randomized placebo-controlled study in 46 subjects. *J Investig Surg*. 2022;35:1673–8.
14. Zakaria A, Amerson E. Treatment modalities in Brachioradial pruritis: a systematic review. *Dermatol Online J*. 2022; <https://doi.org/10.5070/d328458503>.

## Diclofenac

15. FDA drug monograph Solaraze® Gel. Available from [https://www.access-data.fda.gov/drugsatfda\\_docs/label/2000/210051bl.pdf](https://www.access-data.fda.gov/drugsatfda_docs/label/2000/210051bl.pdf). Accessed 09 Jan 2023.
16. LexiComp drug monograph Diclofenac (Topical). Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2021 UptoDate, Inc.
17. De Groot AC. Patch testing. 3rd edition. Volume 3 Chapter 3.
18. Akarsu S, Aktan Ş, Atahan A, Koç P, Özkan Ş. Comparison of topical 3% diclofenac sodium gel and 5% imiquimod cream for the treatment of actinic keratoses. *Clin Exp Dermatol*. 2011;36:479–84.
19. Arisi M, Zane C, Polonioli M, et al. Effects of Mal-PDT, Ingenol Mebutate and diclofenac plus hyaluronate gel monitored by high-frequency ultrasound and digital dermoscopy in actinic keratosis – a randomized trial. *J Eur Acad Dermatol Venereol*. 2020;34:1225–32.

20. Bloor M, Paech M. Nonsteroidal anti-inflammatory drugs during pregnancy and the initiation of lactation. *Anesthesia Analg*. 2013;116:1063–75.
21. Bermas BL. Non-steroidal anti inflammatory drugs, glucocorticoids and disease modifying anti-rheumatic drugs for the management of rheumatoid arthritis before and during pregnancy. *Curr Opin Rheum*. 2014;26:334–40.
22. Cantisani C, Paolino G, Scarnò M, et al. Sequential methyl-aminolevulinate daylight photodynamic therapy and diclofenac plus hyaluronic acid gel treatment for multiple actinic keratosis evaluation. *Dermatol Ther*. 2018; <https://doi.org/10.1111/dth.12710>.
23. Çayirli M, Köse O, Demiriz M. Clinical, dermoscopic and immunohistochemical assessment of actinic keratoses and evaluation of the effectiveness of diclofenac therapy with immunohistochemical analysis. *Arch Dermatol Res*. 2013;305:389–95.
24. Dathe K, Hultzsch S, Pritchard LW, Schaefer C. Risk estimation of fetal adverse effects after short-term second trimester exposure to non-steroidal anti-inflammatory drugs: a literature review. *Eur J Clin Pharmacol*. 2019;75:1347–53.
25. Dianzani C, Conforti C, Giuffrida R, Corneli P, Meo N, Farinazzo E, Moret A, Magaton Rizzi G, Zalaudek I. Current therapies for actinic keratosis. *Int J Dermatol*. 2020;59:677–84.
26. Diclofenac gel: Package insert / prescribing information. In: [Drugs.com](https://www.drugs.com/pro/diclofenac-gel.html). <https://www.drugs.com/pro/diclofenac-gel.html>. Accessed 11 Jan 2023.
27. Koch F, Salva KA, Wirtz M, Hadaschik E, Varaljai R, Schadendorf D, Roesch A. Efficacy of cold atmospheric plasma vs. Diclofenac 3% gel in patients with actinic keratoses: a prospective, randomized and rater-blinded study (ACTICAP). *J Eur Acad Dermatol Venereol*. 2020; <https://doi.org/10.1111/jdv.16735>.
28. Pflugfelder A, Welter A-K, Leiter U, Weide B, Held L, Eigentler TK, Dirschka T, Stockfleth E, Nashan D, Garbe C. Open label randomized study comparing 3 months vs. 6 months treatment of actinic keratoses with 3% diclofenac in 2.5% hyaluronic acid gel: a trial of the German Dermatologic Cooperative Oncology Group. *J Eur Acad Dermatol Venereol*. 2011;26:48–53.
29. Sammaritano LR, Bermas BL, Chakravarty EE, et al. 2020 American College of Rheumatology guideline for the management of reproductive health in rheumatic and musculoskeletal diseases. *Arthritis Rheum*. 2020;72:529–56.
30. Zane C, Facchinetti E, Rossi MT, Specchia C, Calzavara-Pinton PG. A randomized clinical trial of photodynamic therapy with methyl aminolaevulinate vs. Diclofenac 3% plus hyaluronic acid gel for the treatment of multiple actinic keratoses of the face and scalp. *Br J Dermatol*. 2014;170:1143–50.



# Topical Antibiotics

# 12

Taylor Skinner, Parsa Abdi, Mahan Maazi,  
and Rebecca M. Law 

## Contents

|                                                   |     |
|---------------------------------------------------|-----|
| Introduction.....                                 | 242 |
| Acetic Acid and Hydrocortisone (Acetasol HC)..... | 243 |
| Bacitracin.....                                   | 247 |
| Gentamicin Sulfate.....                           | 250 |
| Gramicidin.....                                   | 255 |
| Mupirocin.....                                    | 258 |
| Neomycin Sulfate.....                             | 263 |
| Ozenoxacin.....                                   | 273 |
| Polymyxin-B Sulfate.....                          | 277 |

---

T. Skinner · P. Abdi  
Faculty of Medicine, Memorial University of Newfoundland,  
St. John's, NL, Canada  
e-mail: [pabedinzadeg@mun.ca](mailto:pabedinzadeg@mun.ca); [tcskinner@mun.ca](mailto:tcskinner@mun.ca)

M. Maazi  
Faculty of Medicine, University of British Columbia,  
Vancouver, BC, Canada  
e-mail: [maazi@student.ubc.edu](mailto:maazi@student.ubc.edu)

R. M. Law (✉)  
School of Pharmacy and Faculty of Medicine (Discipline of Family  
Medicine), Memorial University of Newfoundland, St. John's, NL, Canada  
e-mail: [rlaw@mun.ca](mailto:rlaw@mun.ca); [rlawUCSF@gmail.com](mailto:rlawUCSF@gmail.com)

© The Author(s), under exclusive license to Springer Nature  
Switzerland AG 2025

241

R. M. Law, H. I. Maibach (eds.), *Handbook of Topical Drug  
Treatment in Dermatology*,  
[https://doi.org/10.1007/978-3-031-93616-6\\_12](https://doi.org/10.1007/978-3-031-93616-6_12)

|                            |     |
|----------------------------|-----|
| Retapamulin (Altabax)..... | 281 |
| Silver Sulfadiazine.....   | 288 |
| References.....            | 292 |

---

## Introduction

Taylor Skinner and Rebecca M. Law

Topical antibiotics are used to treat localized skin infections related to minor cuts, scrapes, and burns. There is a myriad of specific indications for various topical antibiotics, including blepharitis, conjunctivitis, rosacea keratitis, scleritis, episcleritis, iridocyclitis, and otitis externa. Silver sulfadiazine is specifically indicated as an adjunct for the prevention and treatment of wound sepsis in patients with second- and third-degree burns. There are also combination products, for example, comprising an anti-infective agent plus a corticosteroid. This chapter is not meant to be a comprehensive compilation, and most monographs are single entity monographs. The product monographs included in this chapter are as follows:

|                                              |    |
|----------------------------------------------|----|
| Acetasol HC (Acetic Acid and Hydrocortisone) | 1  |
| Bacitracin                                   | 4  |
| Gentamicin                                   | 7  |
| Gramicidin                                   | 11 |
| Mupirocin                                    | 13 |
| Neomycin                                     | 16 |
| Ozenoxacin                                   | 24 |
| Polymyxin-B sulfate                          | 26 |
| Retapamulin                                  | 29 |
| Silver sulfadiazine                          | 34 |

## Acetic Acid and Hydrocortisone (Acetasol HC)

Parsa Abdi

### Classification and Mode of Action

- Acetasol HC is an otic solution, comprising a combination of a hydrocortisone and acetic acid, which is indicated for the management of otitis externa. Hydrocortisone exerts anti-inflammatory and antipruritic effects, whereas acetic acid exhibits antibacterial and antifungal properties.

### Indications and Dermatological Uses

- *Clinical indications (FDA):* Otitis externa.
- *Off-label common uses:* N/A.

### Formulations/Presentation

- US: Acetic acid 2%, propylene glycol diacetate 3%, and hydrocortisone 1% (10 mL). Solution, otic (drops).
- Canada:
- Europe:

### Dosages and Suggested Regimens

- Place a saturated cotton wick, ensuring it is thoroughly wet, and maintain its moisture for 24 h by adding three to five drops of the solution every 4–6 h. After 24 h, remove the wick and instill five drops of the solution into the affected area three to four times a day, for as long as indicated.
- *Missed Dose:* In the event that a dose of acetazol HC is missed, it is recommended to apply the solution at earliest recollection and subsequently adhere to the appropriate time interval for

the next application. Do not apply two doses or use more than the recommended amount.

- *Overdosage:* While an overdose of acetazol HC is not typically considered dangerous, it is still important to seek emergency medical attention in the event of a suspected overdose.

## Pharmacokinetics

- *Absorption:* As corticosteroids are absorbed through the aqueous humor, systemic absorption is minimal, if any, given that only low doses are administered.

## Use in Special Populations

- Currently, there are no specific dosage recommendations for Gentamicin in special populations.
- *Pediatrics:* Approved for use in children. Safety and efficacy of acetazol HC has not established in children <3 years of age.
- *Geriatrics:* No dosage change is required. Clinical experience has not identified differences in response.
- *Hepatic insufficiency:* The manufacturer's labeling does not include any recommended dosage adjustments, and the need for such adjustments is unlikely due to the low systemic absorption of the medication.
- *Renal insufficiency:* The manufacturer's labeling does not include any recommended dosage adjustments, and the need for such adjustments is unlikely due to the low systemic absorption of the medication.
- *Pregnancy:* Listed as FDA pregnancy classification C.
- *Lactation:* It is unclear whether the topical application of corticosteroids could lead to enough systemic absorption to produce detectable amounts in breast milk. Caution if used in nursing women.

## Monitoring

### Contraindications and Cautions

- Individuals who have a known hypersensitivity to hydrocortisone, other corticosteroids, or any component present in the formulation should avoid using the product.
- The use of acetazol HC is contraindicated in individuals with a confirmed or suspected viral infection, such as herpes simplex virus, vaccinia, or varicella-zoster virus, of the external ear canal.
- The presence of fungal disease in the ear structures is a contraindication for the use of acetazol HC.
- The use of this product is contraindicated in cases of acute, untreated purulent infections of the ear.
- Patients with a perforated tympanic membrane should avoid using acetazol HC.
- To prevent the development of secondary infections, this product should not be used for more than ten consecutive days. If there is no improvement in the initial infection following seven to ten days of treatment, it is advisable to obtain cultures to assist in the determination of subsequent treatment measures.

### Warnings and Precautions

- *Corticosteroid hypersensitivity:* Acetazol HC is contraindicated for individuals who have a known or suspected hypersensitivity to any of the product's ingredients, including those who are sensitive to hydrocortisone (i.e., corticosteroid hypersensitivity). If any signs of skin irritation or rash develop, discontinue the use of the product immediately.
- *Sulfite sensitivity:* Certain individuals who are susceptible may experience allergic-type reactions (such as anaphylaxis or life-threatening or mild asthmatic episodes) to sulfites, which may be present in certain otic preparations.
- *Local reaction:* When used for the first time in an inflamed ear, a temporary stinging or burning sensation may be experienced. If any signs of sensitization or irritation arise, discontinuation of the product is recommended.

## Important Drug Interactions

- *Drug-drug interactions.*
  - *Aldesleukin:* The concurrent use of corticosteroids and Aldesleukin may result in a reduced antineoplastic effect of Aldesleukin. Risk X: should be avoided.
  - *Calcipotriene:* If hydrocortisone (topical) is used with calcipotriene, the therapeutic effect of calcipotriene may be reduced. To avoid this potential interaction, monitor for reduced calcipotriene efficacy and consider separating the administration of these agents by 10–12 h.
- *Drug-food interactions:* There is currently no evidence of any interactions between acetazol HC and food.

## Adverse Effects and Their Management

- Headache, pruritus, and transient stinging or burning noticed in some patients.

## Carcinogenicity

- There are no published carcinogenicity studies on acetazol HC.

## Patch Test Concentration

- Patch testing information not available.

## Essential Patient Information

- Some side effects of acetazol HC may include burning or stinging. Contact your doctor if these or other side effects persist.
- If you experience signs of irritation at the site of application or an allergic reaction such as rash, hives, itching, blistered or



peeling skin, wheezing, tightness in chest or throat, difficulty breathing, swallowing, or speaking, unusual hoarseness, swelling of mouth, face, lips, tongue or throat, seek immediate medical attention.

- Important to inform healthcare providers about any current or planned concomitant therapies, including prescription and over-the-counter medications, as well as any concurrent illnesses.
- Patients should be informed about other significant precautionary information (see monitoring).

---

## Bacitracin

Taylor Skinner

### Classification and Mode of Action

- Bacitracin inhibits bacterial cell wall synthesis by preventing the transfer of mucopeptides into the growing cell wall and thus preventing bacterial replication. Many gram-positive bacteria are susceptible to bacitracin, such as *Staphylococcus* spp. and *Streptococcus* spp. Some gram-negative bacteria are susceptible to bacitracin; however, most are resistant.
- In comparison to placebo, bacitracin ointment has been shown to reduce the occurrence of surgical site infections.

### Indications

- *Clinical indications (FDA)*: Short-term prevention and treatment of both acute and chronic localized skin infections in minor cuts, scrapes, or burns.
- *Off-label common uses*.

## Formulations

- US: Ointment as Bacitracin Zinc (500 units/gram).
- Canada: Ointment (500 units/gram).
- Europe:

## Dosages and Suggested Regimens

- Adults: apply one to three times daily.
- Infants, children, adolescents: apply a small amount one to three times daily. It is not recommended to exceed 7 days of therapy, unless directed by a healthcare professional.
- Do not use topical ointment in the eyes or over large areas of the body. Prior to application, the affected area should be cleansed gently with mild soap and water, if possible. Ointment may be applied directly on to the implicated wound or infected area, though enough should be used to cover the entire area.
- Missed dose: In the event that a dose of bacitracin ointment is missed, it is recommended to apply at the earliest recollection and continue as intended. Do not apply two doses or use more than the recommended amount.

## Pharmacokinetics

- Absorption is limited following topical application as bacitracin displays poor absorption from mucous membranes and intact or denuded skin. A sterile dressing may be placed over the applied ointment to assist in absorption.

## Use in Special Populations

- No dosage change is required for pediatric patients.
- No dosage change is required for geriatric patients.
- There is no available information to suggest dosing changes would be required in patients with hepatic or renal dysfunction.

- Pregnancy risk category C, though no large studies have been conducted with the use of topical bacitracin during pregnancy, and, to date, there is no evidence to suggest that there is an increased risk of adverse fetal effects with the use of topical bacitracin.
- To date, no large studies have been done with the use of topical bacitracin during lactation. However, the use of bacitracin while breastfeeding has not been associated with an increased risk of adverse effects in the infant.

## **Contraindications and Cautions**

- Contraindicated in those with a hypersensitivity to bacitracin or to any component of the formulation of the available product. If signs of allergic reaction or rash occur, discontinue use immediately.
- Patients with a known hypersensitivity to neomycin may also be sensitive to bacitracin.
- Application of bacitracin on a wound from a viral or fungal infection may increase the risk of developing drug-resistant bacteria.
- There is no mention of toxicity with the use of topical bacitracin as a single agent ointment or as part of a triple therapy ointment.

## **Important Drug Interactions**

- There are no significant drug-drug interactions with bacitracin.
- There are no significant drug-food interactions with bacitracin.

## **Adverse Effects and Management**

- May cause allergic contact dermatitis upon application.

## **Carcinogenicity**

- There are no carcinogenic studies of bacitracin; however, bacitracin ointment is not considered to be a carcinogenic agent according to the IARC, ACGIH, NTP, or OSHA.

## **Patch Test Concentration**

- 5% in petrolatum or 20% in petrolatum. Patch test may become positive only at day 4.

## **Clinical Pearls**

- 1 unit of ointment is equivalent to 0.026 mg bacitracin.

## **Essential Patient Information**

- Bacitracin is available as an over the counter (OTC) medication.
- Bacitracin ointment should be stored at room temperature (15–30 °C).
- If symptoms worsen, bacitracin should be discontinued and a healthcare provider consulted.

---

## **Gentamicin Sulfate**

Parsa Abdi

## **Classification and Mode of Action**

- Gentamicin sulfate is an aminoglycoside antibiotic that blocks protein synthesis in susceptible bacteria by binding to the prokaryotic ribosome. It exhibits bactericidal activity against both

gram-positive and gram-negative bacteria in vitro. Compared to mupirocin ointment, gentamicin sulfate has similar efficacy, however, a significantly faster onset of action in the treatment of impetigo.

## Indications and Dermatological Uses

- *Clinical indications (FDA):* Skin and skin structure infections, including burn wound infection and necrotizing infections as well as minor skin infections, including impetigo, infected seborrheic dermatitis, folliculitis, furunculosis, sycosis barbae, eczema, pustular acne, pyoderma gangrenosum, infectious eczematoid dermatitis, infected contact dermatitis, pustular psoriasis, and infected excoriations.
- *Off-label common uses.*

## Formulations/Presentation

- US: 0.1% (15 g, 30 g) cream, 0.1% (15 g, 30 g) ointment.
- Canada: 0.1% (15 g, 30 g) cream, 0.1% (15 g, 30 g) ointment.
- Europe:

## Dosages and Suggested Regimens

- Apply gentamicin sulfate to the affected area three to four times per day.
- Gentamicin should only be used externally and is not indicated for ophthalmic use. Gently apply it to the affected area and consider covering it with gauze dressing. For impetigo contagiosa, remove any crust before applying.
- *Missed dose:* In the event that a dose of gentamicin sulfate is missed, it is recommended to apply the ointment/cream at earliest recollection and subsequently adhere to the appropriate time interval for the next application. Do not apply two doses or use more than the recommended amount.

- *Overdosage:* If an overdose occurs, hemodialysis may be helpful in removing the drug from the blood, particularly if renal function is impaired. Peritoneal dialysis is less effective than hemodialysis at removing gentamicin sulfate from the body.

## Pharmacokinetics

- *Absorption.*
  - Gentamicin sulfate is typically not absorbed through intact skin. However, it can be readily absorbed through denuded areas of skin, such as wounds, burns, or ulcers, as well as skin that has lost the keratin layer.
  - Gentamicin cream is more readily absorbed than gentamicin ointment.
  - Topical application to burn patients has been reported to result in systemic absorption.

## Use in Special Populations

- Currently, there are no specific dosage recommendations for Gentamicin in special populations.
- *Pediatrics:* Approved for use in children. May cause irritation or allergic reaction. Do not administer orally, topical application only. Safety and efficacy not established in children <1 year of age.
- *Geriatrics:* No dosage change is required.
- *Hepatic insufficiency:* The manufacturer's labeling does not include any recommended dosage adjustments, and the need for such adjustments is unlikely due to the low systemic absorption of the medication.
- *Renal insufficiency:* The manufacturer's labeling does not include any recommended dosage adjustments, and the need for such adjustments is unlikely due to the low systemic absorption of the medication.
- *Pregnancy:* Listed as FDA pregnancy classification C.

- *Lactation:* It is uncertain whether gentamicin sulfate is excreted in breast milk after topical application. When administered systemically, known to be excreted in small amounts in breast milk. Nevertheless, the American Academy of Pediatrics (AAP) considers gentamicin sulfate to be compatible with breastfeeding.

## Monitoring

### Contraindications and Cautions

- Patients who have a known hypersensitivity to gentamicin sulfate or any ingredients in the formulation should not use topical gentamicin sulfate. Patients who are allergic to other topical antibiotics should be closely monitored during treatment with gentamicin sulfate. If any signs of irritation or hypersensitivity appear, the medication should be discontinued immediately. It should be noted that cross-allergenicity has been demonstrated among aminoglycosides, and patients who become sensitized to topical gentamicin sulfate may also be sensitive to other topical and systemic aminoglycosides. Therefore, caution should be exercised in these patients.

### Warnings and Precautions

- *Sensitivity reactions:* Sensitization and photosensitivity have been reported in some cases following the use of topical gentamicin.
- *Superinfection:* Overgrowth and possible development of resistant bacteria or fungi. If superinfection arises, stop taking the medication and commence appropriate therapy.
- *Cross-hypersensitivity:* There is a risk of cross-allergenicity among aminoglycosides. Therefore, it's important to be aware that patients who develop sensitivity to topical gentamicin sulfate may also be sensitive to other types of topical and/or systemic aminoglycosides. If patients are known to be hypersensitive to other topical antibiotics, it is recommended to closely monitor them when using gentamicin sulfate. If any signs of irritation or hypersensitivity appear, it is advised to discontinue use.

- *Cumulative toxicity:* When topical aminoglycosides are used in combination with systemic aminoglycoside therapy and applied to large skin lesions or denuded areas, there is a risk of cumulative toxicity.

### **Important Drug Interactions**

- *Drug-drug interactions:* There are currently no known clinically significant drug interactions with gentamicin sulfate use. No interactions of Risk Level A or greater identified.
- *Drug-food interactions:* There is currently no evidence of any interactions between gentamicin sulfate and food.

### **Adverse Effects and Their Management**

- Application of gentamicin sulfate is generally considered to be relatively nontoxic, although it is possible to develop sensitization to the drug from its topical use.
- Commercially available preparations of Gentamicin often contain additional ingredients like parabens that could cause allergic contact dermatitis.
- Although infrequent, local irritation including erythema and pruritus may occur following topical administration.
- Several patients treated with topical gentamicin sulfate have reported photosensitivity reactions; however, it remains unclear whether the drug was the direct cause of these reactions.

### **Carcinogenicity, Mutagenesis, and Impairment of Fertility—If Known**

- There are no published carcinogenicity studies on gentamicin sulfate. Aminoglycoside antibiotics have been found to be non-mutagenic.

### **Patch Test Concentration**

- 20% in petrolatum. Late readings at days 6–8 are necessary to avoid possibly missing a positive patch test evolving after day 3 or 4.



---

### Essential Patient Information

- It is crucial to discontinue gentamicin and initiate appropriate treatment if superinfection occurs.
- Topical gentamicin preparations are meant for external use only and should not be ingested or used in the eyes.
- Important to inform healthcare providers about any current or planned concomitant therapies, including prescription and over-the-counter medications, as well as any concurrent illnesses.
- Patients should be informed about other significant precautionary information (see monitoring).

---

### Gramicidin

Mahan Maazi

### Classification and Mode of Action

- Gramicidin a cyclic polypeptide antibiotic is a heterogenous mixture of antimicrobial linear polypeptides that have been extracted from tyrothricin through the growth and fermentation of *Brevibacillus brevis*. It causes bacterial cell wall disruption and permeabilization and works well against most gram-positive and some gram-negative bacteria. It is used topically for infections often in combination with other antibacterials neomycin, bacitracin, nystatin, and polymyxin B and corticosteroids.

### Indications and Dermatological Uses

- *Clinical indications (FDA)*: blepharitis, eczema (eyelid), conjunctivitis (allergic, infective, rosacea), rosacea keratitis, scleritis and episcleritis, iridocyclitis, otitis externa, pruritus.
- *Off-label common uses*: other skin infections and surface wounds.

## Formulations/Presentation

- US: 0.05 mg/g cream (multi-ingredient), 0.05 mg/g ointment (multi-ingredient), 0.025 mg per 1 mL eyedrops (multi-ingredient), 0.05 mg/g nasal spray (multi-ingredient).
- Canada: 0.25 mg/g, 0.05 mg/g cream (multi-ingredient), 0.25 mg/g, 0.05 mg/g cream ointment (multi-ingredient), 0.025 mg per 1 mL eye-drops (multi-ingredient), 0.25 mg/g, 0.05 mg nasal spray (multi-ingredient).
- Europe: 0.05 mg/g cream cream (multi-ingredient), 0.05 mg cream ointment (multi-ingredient), 0.025 mg per 1 mL eye-drops (multi-ingredient), 0.05 mg nasal spray (multi-ingredient).

## Dosages and Suggested Regimens

- Cream/ointment (multi-ingredient): apply small quantity two to three times per day.
- Eyedrops (multi-ingredient): ophthalmic: one or two drops every 1–2 h for 2 or 3 days and then follow with one or two drops three to four times daily. Otic: two or three drops three or four times daily.
- Intranasal (multi-ingredient): two sprays in each nostril every 4 h for 3–5 days.
- No suggested dosage adjustment for renal or hepatic impairment due to low dose topical use only.

## Pharmacokinetics

- Only used on skin, with insignificant absorption, thus no relevant pharmacokinetics.

## Use in Special Populations

- Approved for use in children.
- Listed as FDA pregnancy classification A. (former classification system).
- Unknown whether gramicidin is present in breast milk.
- Renal insufficiency: not evaluated; dose adjustment is not expected to be needed.
- Hepatic insufficiency: not evaluated; dose adjustment is not expected to be needed.

## Monitoring

- Hypersensitivity reaction.
- Dermatologic conditions: dermatitis, pruritus, maculopapular rash, urticaria, vesicular eruption, burning sensations.

## Contraindications and Cautions

- Hypersensitivity reactions.
- Accidental ingestion may cause hemolysis and can be toxic to the liver, kidney, meninges, and olfactory system.
- Other indications would be related to other drugs in the formulation.

## Important Drug Interactions

- Risk/severity of bleeding increased when combined with Acenocoumarol.
- Risk/severity of methemoglobinemia increased with local anaesthetics (benzocaine, bupivacaine, buacaine, and chloroprocaine), capsaicin, butamben, and benzyl alcohol.

## Adverse Effects and Their Management

- Skin atrophy, striae.
- Burning, itching, erythema.
- Dryness, hypertrichosis.
- Hypopigmentation folliculitis.
- Superinfection due to prolonged use.
- Discontinue use if local irritation/sensitization occurs.

## Carcinogenicity

- Long-term studies in animals to evaluate carcinogenic or mutagenic potential with gramicidin have not been conducted.

## Patch Test Concentration

- Patch testing unavailable.

## Essential Patient Information

- Be aware of any signs of an allergic reaction and seek medical help as necessary.
- Do not use longer than indicated due to risk of second infection.
- Do not take by mouth. For use on skin only.

---

## Mupirocin

Mahan Maazi

## Classification and Mode of Action

- Also known as pseudomonic acid A. Natural crotonic acid derivative and antibiotic extracted from a strain of *Pseudomonas fluorescens*. It reversibly and selectively binds to bacterial iso-

leucyl tRNA synthase causing inhibition of bacterial protein synthesis. Most gram-positive aerobic bacteria are sensitive to mupirocin. Mupirocin is more effective than oral erythromycin, topical bacitracin, and oral cephalexin for impetigo and more effective than silver sulfadiazine, silver nitrate, mafenide acetate, and honey, for *S. aureus* acquired burn wounds.

## Indications and Dermatological Uses

- *Clinical indications (FDA)*: impetigo due to *Staphylococcus aureus* and *Streptococcus pyogenes*, secondary skin infection, *S. aureus* (including MRSA) decolonization.
- *Off-label common uses*: folliculitis, nasal vestibulitis, peritoneal dialysis catheter exit-site, or tunnel infection prophylaxis.

## Formulations/Presentation

- US: 2% cream, 2% ointment containing polyethylene glycol (PEG), 2% ointment without PEG, 2% nasal ointment.
- Canada:
- Europe:

## Dosages and Suggested Regimens

### Adult

- Impetigo: ointment—apply to affected area two to three times daily for 5 days.
- Secondary skin infection: cream/ointment—apply to affected area two to three times daily, typically for 7–14 days; re-evaluate if no response after 3–5 days.
- Folliculitis (off-label): ointment—apply to affected area three times daily for 7 days.
- Nasal vestibulitis (off-label): intranasal ointment—apply to affected nostril twice daily for 5 days.
- Peritoneal dialysis catheter exit-site or tunnel infection prophylaxis (off-label): cream—apply once daily to catheter exit site.

- Recurrent *S. aureus* infection or preoperative decolonization: ointment/intranasal ointment—apply one-half of the ointment from single-use 1 g tube into each nostril twice daily for 5–10 days.

### **Pediatric**

- Nasal MRSA decolonization: intranasal ointment—infants/children apply a small amount twice daily for 5–10 days, children 12 or older and adolescents apply 500 mg twice daily for 5–10 days.
- MRSA or impetigo; minor skin infection: cream/ointment—small amount three times daily for 5–10 days, re-evaluate for patients not showing a response after 5 days.

### **Pharmacokinetics**

- Absorption: Topical ointment and cream penetrates outer layer of skin and has minimal systemic absorption. Intranasal has 3% absorption and adults and may be significant in neonates and premature infants.
- Has a protein binding of more than 97% and is metabolized to monic acid which is its inactive form.
- The half-life is 17–36 min and is excreted in the urine as monic acid.

### **Use in Special Populations**

- Approved for use in children. Avoid high dosage use in neonates and internal use.
- Listed as FDA pregnancy classification B (former classification system).
- Unknown whether mupirocin is present in breast milk.
- Renal insufficiency: not evaluated; dose adjustment is not expected to be needed.
- Hepatic insufficiency: not evaluated; dose adjustment is not expected to be needed.

## Monitoring

- Central nervous system: headache, localized burning, stinging sensation.
- Dermatologic issues: pruritus, skin rash.
- Gastrointestinal issues: nausea, dysgeusia.
- Local pain.
- Respiratory: rhinitis, respiratory congestion, pharyngitis, cough.

## Contraindications and Cautions

- Hypersensitivity including system reactions, sensitization, or local irritation.
- Superinfection due to prolonged use.
- Polyethylene glycol from percutaneous absorption in open wounds or burns may cause toxic effects especially in large quantities.
- Benzyl alcohol may cause fatal toxicity known as “gasping syndrome” in neonates which consists of metabolic acidosis, respiratory distress, gasping respirations, CNS dysfunction, hypotension, and cardiovascular collapse. Avoid or use benzyl alcohol containing dosage forms with caution.
- Large amounts in neonates, children, and adults may cause potentially fatal toxicities (metabolic acidosis, seizures, renal failure, respiratory depression, hyperosmolality, lactic acidosis, and CNS depression) through some forms containing propylene glycol.

## Important Drug Interactions

- No known drug interactions.

## Adverse Effects and Their Management

- Hypersensitivity reactions which include systemic allergic reactions (urticaria, angioedema, and generalized rash). Discontinue use if it occurs.
- Superinfection may result in bacterial or fungal infection (*C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis).
- May cause severe burning and tearing in eyes for intranasal ointments, which resolves within days to weeks after discontinuation.

## Carcinogenicity

- Evaluation of carcinogenic potential for mupirocin in long-term studies in animals has not been conducted.

## Patch Test Concentration

- 2% in petrolatum

## Essential Patient Information

- Do not put it on skin that is damaged or has open wounds.
- Do not use in an area where drugs are given into a vein.
- Be aware of any signs of an allergic reaction, which include rash, hives, itchiness, redness, swelling, blistering, peeling skin with or without fever, wheezing, tightness in chest or throat, breathing difficulties, unusual hoarseness, or any angioedema (swelling).
- Be aware of any signs or symptoms of dizziness or fast/abnormal heartbeat.
- Be aware of any diarrhea symptoms, which can be a sign of CDAD.
- Use only on skin and keep out of mouth, nose, and eyes.
- For single use nose ointment, half into one nostril and the other half into the other nostril and spread into the nose.



## Neomycin Sulfate

Parsa Abdi

### Classification and Mode of Action

- Neomycin sulfate is classified as an aminoglycoside antibiotic and is primarily used for its bactericidal effects. Neomycin sulfate is believed to exert its antibacterial effect by binding irreversibly to the 30S ribosomal subunit of susceptible bacteria, disrupting protein synthesis. The use of neomycin sulfate has been evaluated in several clinical trials, which have demonstrated its effectiveness in treating a variety of bacterial infections. Notable trials include those examining its use in treating skin infections and urinary tract infections.

### Indications and Dermatological Uses

- *Clinical indications (FDA):*
  - *Prevention of superficial bacterial skin infections associated with minor cuts, scrapes, or burns* (neomycin sulfate fixed combination with other anti-infectives).
  - *Treatment of corticosteroid-responsive dermatoses with secondary infection* (neomycin sulfate fixed combination with a corticosteroid with or without other anti-infectives).
  - *Prevention of bacteriuria and gram-negative septicemia associated with use of indwelling catheters* (fixed combination of neomycin and polymyxin B).
- *Off-label common uses:*
  - *Treatment of minor skin infections caused by susceptible bacteria* (neomycin sulfate fixed combination with other anti-infectives).
  - *Peritoneal instillation* (no longer recommended due to potential severe toxicity).
  - *Irrigation of wounds or surgical sites* (no longer recommended due to potential severe toxicity).

## Formulations/Presentation

- US:
  - Neomycin and Polymyxin B Sulfates: Each mL contains 40 mg of neomycin sulfate and 200,000 units of polymyxin B sulfate (Urogenital—irrigation concentrate).
  - *Neomycin and polymyxin B sulfates and bacitracin zinc*: Each gram contains 3.5 mg of neomycin sulfate, 5000 units of polymyxin B sulfate, and 400 units of bacitracin zinc (topical—ointment).
  - *Neomycin and polymyxin B sulfates, bacitracin zinc, and hydrocortisone*: Each gram contains 3.5 mg of neomycin sulfate, 5000 units of polymyxin B sulfate, 400 units of bacitracin zinc, and 1% hydrocortisone (topical—ointment).
  - *Neomycin and polymyxin B sulfates and hydrocortisone acetate*: Each gram contains 3.5 mg of neomycin sulfate, 10,000 units of polymyxin B sulfate, and 5 mg of hydrocortisone acetate (topical—cream).
  - *Neomycin sulfate and fluocinolone acetonide*: Each gram contains 3.5 mg of neomycin sulfate and 0.25 mg of fluocinolone acetonide (topical—cream).
  - *Other neomycin sulfate combinations*: Each gram contains 3.5 mg of neomycin sulfate, 5000 units of polymyxin B sulfate, 400 units of bacitracin zinc, and 20 mg of lidocaine hydrochloride (topical—cream); each gram contains 3.5 mg of neomycin sulfate, 10,000 units of polymyxin B sulfate, and 10 mg of pramoxine hydrochloride (topical—cream); each gram contains 3.5 mg of neomycin sulfate, 5000 units of polymyxin B sulfate, 400 units of bacitracin zinc, and 40 mg of lidocaine (topical—ointment); each gram contains 3.5 mg of neomycin sulfate, 10,000 units of polymyxin B sulfate, 500 units of bacitracin zinc, and 10 mg of pramoxine hydrochloride (topical—ointment).

## Dosages and Suggested Regimens

- Neomycin sulfate is available in cream and ointment forms that are applied topically to the skin. The recommended frequency of use is usually one to three times a day.
- The maximum duration of use for neomycin sulfate is typically one week, unless otherwise directed by a healthcare provider. To ensure safe and effective use of the medication, it is important to follow the directions on your prescription label carefully.
- Start by thoroughly cleaning the infected area and allowing it to dry. Gently rub the medication into the skin until most of it disappears, using only enough to cover the affected area. After application, be sure to wash your hands.
- It is important not to apply neomycin to a child's diaper area, especially if the skin is raw, unless directed to do so by a doctor. If directed to apply neomycin in this area, avoid using tightly fitting diapers or plastic pants, as they can increase the absorption of the drug, leading to harmful effects.
- When using neomycin on scrapes, cuts, burns, sores, and wounds, apply only small amounts and follow the recommended frequency of use.
- May cover affected areas with a sterile bandage.
- *Missed Dose:* In the event that a dose of neomycin sulfate is missed, it is recommended to apply the solution at earliest recollection and subsequently adhere to the appropriate time interval for the next application. Do not apply two doses or use more than the recommended amount.
- *Overdosage:* It is unlikely for an acute overdose to occur with neomycin sulfate due to its low absorption rate. However, prolonged use of the medication may lead to sufficient systemic drug levels that can result in neurotoxicity, ototoxicity, and/or nephrotoxicity. If you experience any symptoms of toxicity, such as hearing difficulties, dizziness, or kidney problems, seek medical attention immediately.

## Pharmacokinetics

- *Absorption:*

- Neomycin sulfate is not significantly absorbed through intact skin, but it can be absorbed through areas of skin that have been denuded or have lost the keratin layer, such as wounds, burns, or ulcers.
- When used for bladder irrigation, systemic absorption of neomycin is not expected to be clinically significant if the bladder is intact and the duration of irrigation is less than or equal to 10 days. However, systemic absorption may occur if the bladder surface is denuded or inflamed.
- In cases where neomycin sulfate is administered into the peritoneum, drainage sinuses, wounds, or surgical sites, it is rapidly absorbed into the systemic circulation.
- When neomycin sulfate is topically applied to open wounds, burns, or granulating surfaces, the resulting plasma concentrations are similar to or greater than those achieved with oral or parenteral administration (parenteral preparation is no longer available in the US).

## Use in Special Populations

- *Pediatrics:*

- Topical: Certain manufacturers advise against using neomycin sulfate product in children under 2 years of age unless specifically instructed by a healthcare provider.
- Topical (fixed combination of neomycin and fluocinolone): The manufacturer recommends utilizing the minimum effective dose when incorporating neomycin sulfate into a therapeutic regimen. In pediatric patients, due to their higher skin surface area-to-body weight ratio, they may be more vulnerable to experiencing hypothalamic-pituitary-adrenal (HPA) axis suppression and Cushing's syndrome resulting from topical corticosteroid use compared to older patients.

- Topical (fixed combination of neomycin, polymyxin B with or without bacitracin, and hydrocortisone): There is no established evidence regarding the safety and efficacy of using neomycin sulfate in pediatric patients. However, prolonged use of topical hydrocortisone in infants and children can lead to significant absorption of the drug through the skin, which may cause growth cessation and other manifestations of hyperadrenocorticism.
- Topical (fixed combination of neomycin, polymyxin B, bacitracin, and lidocaine): According to at least one manufacturer, neomycin sulfate should not be used in children under the age of 12 years unless specifically instructed to do so by a healthcare provider.
- Bladder irrigation (fixed combination of neomycin and polymyxin B): Safety and efficacy not established in pediatric patients.
- *Geriatrics:*
  - Topical (fixed combination of neomycin, polymyxin B with or without bacitracin, and hydrocortisone): The clinical trials did not enroll a significant number of patients aged 65 years and above to ascertain whether the geriatric population has a distinct response from younger patients; however, available anecdotal evidence from other clinical experiences has not identified any significant difference in response between the two groups.
  - Bladder irrigation (fixed combination of neomycin and polymyxin B): Geriatric patients who receive high doses of neomycin sulfate for an extended period are at an increased risk of toxicity.
- *Renal insufficiency:* Patients with renal impairment are at an increased risk of toxicity when using the fixed combination of neomycin and polymyxin B for bladder irrigation.
- *Pregnancy:*
  - Aminoglycosides can be harmful to a developing fetus if absorbed systemically in pregnant women. Neomycin sulfate can cross the placenta, and some children whose mothers received parenteral streptomycin during pregnancy have reported total, irreversible, bilateral, congenital deafness.

- When used in a fixed combination with a corticosteroid, with or without other anti-infectives, during pregnancy, it should only be used if the potential benefits justify the potential risks to the fetus. Topical corticosteroids have been found to be teratogenic in animals such as mice and rabbits.
- If the fixed combination of neomycin and polymyxin B is used during pregnancy, the patient should be informed about the potential hazard to the fetus.
- Listed as FDA pregnancy classification C in the former FDA pregnancy risk classification system.
- *Lactation:*
  - It is unclear whether the topical application of corticosteroids could lead to enough systemic absorption to produce detectable amounts in breast milk. Caution if used in nursing women. Small amounts of neomycin may pass into breast milk if it is absorbed systemically, but it is not considered clinically significant.
  - Caution should be exercised when using the topical fixed combination of neomycin and a corticosteroid with or without other anti-infectives in nursing women as systemic corticosteroids can be distributed into human milk.

## Monitoring

### Contraindications

- Topical (fixed combinations of neomycin and other anti-infectives with or without a topical anesthetic): Individuals with a known hypersensitivity to neomycin or any of the components in the formulation should avoid using this product.
- Topical (fixed combinations of neomycin and a corticosteroid with or without other anti-infectives): Should not be used by individuals who have a known hypersensitivity to any of the ingredients in the formulation. Contraindicated for use on skin lesions caused by tuberculosis, fungus, or viruses such as herpes simplex or varicella zoster. Should not be used in the eyes or in the external ear canal if the eardrum is perforated.

- Bladder irrigation (fixed combination of neomycin and polymyxin B): Individuals who have a known hypersensitivity to neomycin, polymyxins, or any of the ingredients in the formulation should avoid using this product. Due to the potential for cross-sensitivity among aminoglycosides, the product may also be contraindicated in individuals who have a history of hypersensitivity or serious toxic reactions to any aminoglycoside.

## Warnings and Precautions

- *Sensitivity Reactions.*
  - Patients using topical preparations that contain neomycin sulfate should be advised to discontinue use and seek medical attention if they experience symptoms such as itching, burning, rash, or any other signs of sensitivity or allergic reaction.
  - Clinicians should consider that patients who are allergic to topical neomycin sulfate may develop cutaneous sensitivity reactions or anaphylactic reactions to the drug.
  - Cross-allergenicity can occur among aminoglycosides, and patients who become sensitized to topical neomycin may also be sensitive to other topical or systemic aminoglycosides.
  - Patients who are allergic to one fixed-combination topical preparation that contains neomycin sulfate should avoid using any products that contain any of the component drugs.
- *Topical Use.*
  - Use of this medication for more than one week should only be done under the direction of a clinician to avoid promoting bacterial resistance.
  - Prolonged use may lead to overgrowth of nonsusceptible organisms, including fungi.
  - There have been reports of ototoxicity, nephrotoxicity, and neuromuscular blockade following topical application of neomycin, particularly when used for peritoneal instilla-

tion, irrigation of wounds or surgical sites, or topical treatment of skin ulcers, granulating wounds, serious burns, or extensive areas of denuded skin, resulting in systemic absorption of the drug. Rare cases of death have also been reported.

- Risk of systemic absorption and the possibility of toxicity such as ototoxicity, nephrotoxicity, and neuromuscular blockade, caution should be exercised when using neomycin topically for extensive burns, trophic ulceration, or other extensive dermatologic conditions where rapid absorption of the drug is possible. In patients with burns covering  $\geq 20\%$  of their body surface area, especially those with impaired renal function or who are receiving other aminoglycosides concurrently, topical neomycin should be applied no more than once daily.
- *Bladder Irrigation.*
  - The fixed combination of neomycin and polymyxin B should not be used as an irrigation solution if there is a possibility of systemic absorption. This solution is intended for continuous prophylactic bladder irrigation only in patients with an intact urinary bladder. To avoid toxicity and the risk of systemic absorption, it should not be used in patients with defects in bladder mucosa or bladder wall or in conjunction with operative procedures involving bladder wall. Patients with impaired renal function, infants, dehydrated patients, geriatric patients, and those receiving prolonged treatment with high doses are especially at risk for toxicity.
  - The safety and efficacy of bladder irrigation with the fixed combination solution have not been established in patients with recent lower urinary tract surgery.
  - Overgrowth of nonsusceptible organisms, including fungi, may occur during bladder irrigation, and appropriate measures should be taken if needed.
  - Urine specimens should be collected for urinalysis, culture, and susceptibility testing. In the event of isolation of uropathogens, in vitro susceptibility testing should be performed, and systemic anti-infective therapy should be initiated if appropriate.



- *Use of Fixed Combinations.*
  - When a fixed combination of neomycin with other topical anti-infectives, topical corticosteroids, or topical anesthetics are used, caution should be taken, and contraindications associated with each drug should be considered.
  - If a fixed combination of neomycin with corticosteroid is used, it should be kept in mind that topical corticosteroids used in fixed combination with topical anti-infectives may hide clinical signs of bacterial, fungal, or viral infections or suppress hypersensitivity reactions to the anti-infectives or other ingredients in the formulation.
  - The use of topical corticosteroids can result in signs and symptoms of exogenous hyperadrenocorticism, including adrenal suppression, and if applied to extensive body surface areas or with occlusive dressing, systemic absorption of the topically applied corticosteroids can be increased. If redness, irritation, swelling, or pain persists or increases, the use should be discontinued.

## Important Drug Interactions

- *Drug-Drug Interactions.*
  - It is important to use caution when using neomycin sulfate along with other drugs that are neurotoxic or nephrotoxic as this could potentially increase the risk of nephrotoxicity or ototoxicity.
  - Similarly, caution should also be taken when using neomycin along with other aminoglycosides or polymyxins, as this may increase the risk of nephrotoxicity or ototoxicity and may also enhance neomycin's neuromuscular blocking effects.
- *Drug-Food Interactions:* There is currently no evidence of any interactions between neomycin sulfate and food.

## Adverse Effects and Their Management

- *Topical:* Allergic contact dermatitis. May result in systemic absorption of the drug, leading to ototoxicity, nephrotoxicity, and neuromuscular blockade. This risk is especially significant when neomycin is used for peritoneal instillation, irrigation of wounds or surgical sites, or topical treatment of skin ulcers, granulating wounds, serious burns, or extensive areas of denuded skin.
- *Bladder irrigation:* Irritation of urinary bladder mucosa.

## Carcinogenicity

- There have been no long-term animal studies conducted on neomycin sulfate to assess its potential for carcinogenicity or mutagenicity.

## Patch Test Concentration

- 20% in petrolatum. It is recommended to read patch test at day 7 or day 8, as late positive reactions after day 4 are frequent.

## Essential Patient Information

- Neomycin sulfate and other antibacterial medications should only be used to treat bacterial infections. They are not effective in treating viral infections.
- Neomycin-containing topical products are intended for external use only and should not be applied to the eyes. Additionally, patients should be advised to avoid using these products over large areas of the body.
- In topical preparations containing neomycin for self-medication to prevent infection in minor skin injuries like cuts, scrapes, and burns, patients should not be used for more than

one week unless directed by a clinician. Discontinue use and consult a clinician if the condition persists or worsens.

- Discontinue use of any topical preparation containing neomycin and consult a healthcare professional if any signs of sensitivity or allergic reaction, such as itching, burning, or rash, occur.
- Consult a clinician before using topical preparations containing neomycin for self-medication in cases of deep or puncture wounds, animal bites, or serious burns.
- Inform healthcare provider if you are pregnant, planning to become pregnant, or planning to breastfeed while using neomycin sulfate.

---

## Ozenoxacin

Taylor Skinner

### Classification and Mode of Action

- Ozenoxacin is a quinolone antimicrobial that inhibits the bacterial DNA replication enzymes; DNA gyrase A and topoisomerase IV.
- Ozenoxacin has been found to display potent activity against many common skin and soft tissue infections, including those displaying resistance to other common antimicrobial classes such as fusidic acid and mupirocin.

### Indications

- *Clinical indications (FDA):* Treatment of impetigo due to *Staphylococcus aureus* or *Streptococcus pyogenes* in adult and pediatric patients 2 months of age and older.
- *Off-label common uses.*

## Formulations

- US: 1% cream [brand: Xepi].
- Canada: 1% cream [brand: Ozanex].
- Europe:

## Dosages and Suggested Regimens

- Adults: apply a thin layer of cream to the affected area twice daily for 5 days.
  - The total treatment area should not exceed 100 cm<sup>2</sup> total BSA.
- Infants, children, and adolescents: apply a thin layer of cream to the affected area twice daily for 5 days.
  - The total treatment area should not exceed 2% of the total BSA for patients under 12.
  - The total treatment area should not exceed 100cm<sup>2</sup> total BSA for patients over 12.
- Wash hands after application. The treated area may be covered with a sterile bandage or gauze dressing.
- Missed dose.
- Any sign or symptom of overdose should be treated symptomatically, as no specific antidote is known.

## Pharmacokinetics

- Absorption is negligible following topical application.
- Ozenoxacin was not metabolized in the presence of human skin discs and was only minimally metabolized in human hepatocytes.
- Due to negligible systemic absorption, tissue distribution and excretion have not been investigated in humans.

## Use in Special Populations

- No dosage change is required for geriatric patients.
- There is no available information to suggest dosing changes would be required in patients with hepatic or renal dysfunction.
- To date, no large studies have been done with the use of topical ozenoxacin. However, due to negligible systemic absorption, exposure of the fetus to the drug is not expected.
- To date, no large studies have been done with the use of topical bacitracin during lactation, and it is not known if ozenoxacin is present in breastmilk. However, due to negligible systemic absorption, exposure of the infant to the drug is not expected.

## Contraindications and Cautions

- Contraindicated in those with a hypersensitivity to ozenoxacin or to any component of the formulation of the available product. If signs of allergic reaction occur, discontinue use immediately.
- Prolonged use of ozenoxacin may result in overgrowth of non-susceptible bacteria and fungi, resulting in a superinfection. Discontinue use and use alternative therapy if superinfection occurs.
- There is no mention of toxicity with the use of topical ozenoxacin.

## Important Drug Interactions

- There are no significant drug-drug interactions with ozenoxacin.
- There are no significant drug-food interactions with ozenoxacin.

## **Adverse Effects and Management**

- May cause rosacea or seborrheic dermatitis upon application.

## **Carcinogenicity**

- Long-term animal studies have not been conducted to evaluate the carcinogenicity of ozenoxacin, although ozenoxacin has not been found to induce genotoxicity when evaluated in vitro in the Ames test, mouse lymphoma cell assay, or in a rat micro-nucleus test with systemic exposure.
- Ozenoxacin has not been found to affect the fertility of male and female rats treated orally with 500 mg/kg/day, which is much greater than the maximum human plasma concentration with topical application of 1% ozenoxacin cream.

## **Patch Test Concentration**

- Patch testing information not available.

## **Essential Patient Information**

- It is recommended to use this medication for the entire duration as prescribed, even if symptoms have improved earlier.
- Ozenoxacin should be stored at room temperature (20–25 °C), though some exposure to temperatures between 15 and 30 °C are permitted.
- If symptoms worsen, ozenoxacin should be discontinued and a healthcare provider consulted.

## Polymyxin-B Sulfate

Mahan Maazi

### Classification and Mode of Action

- Polymyxin-B sulfate is a cationic, peptide antibiotic mixture of polymyxins B1 and B2 effective against gram-negative bacteria and is obtained from *Bacillus polymyxa*. It acts as a surface detergent and destroys bacterial membranes. It is usually used in combination with other antibiotics such as bacitracin or neomycin.

### Indications and Dermatological Uses

- Clinical indications (FDA): Acute infections caused by susceptible strains of *Pseudomonas aeruginosa* (urinary tract, meningitis, eyes, bloodstream).
- Serious infections (*H. influenzae*, meningitis; *E.coli*, urinary tract; *Aerobacter aerogenes*, bacteremia; and *Klebsiella pneumoniae*, bacteremia).
- Off-label common uses: inhalation for nebulization (off-label route).

### Formulations/Presentation

- US: 10,000 units = 1 mg; 500,000 units (solution injections), 100 million units (powder), 10,000 units per g (ointment), 200,000 units per 1 mL (solution; irrigation).

## Dosages and Suggested Regimens

- Topical: apply to affected area one to three times/day.
- Bladder irrigation: 1000 mL/24 h; if urine output exceeds 2000 mL/day increase to 2000 mL/24 h.
- CNS Infections (intrathecal/intraventricular): 50,000 units once daily.
- Ocular infections (ophthalmic): 10,000–25,000 units/mL as one to three drops every hour increasing the interval as response indicates. 100,000 units/day for corneal/conjunctival infections.
- Pulmonary infection (inhalation for nebulization): 500,000 units every 12 h.
- Systemic infections: 20,000–25,000 units/kg loading dose followed by a maintenance dose of 12,500–15,000 units/kg every 12 h.
- Recommended dosage reduction in kidney impairment.
- No dosage adjustments for hepatic impairment.

## Pharmacokinetics

- Not absorbed from GI tract. Insignificant absorption from intact skin or mucous membrane.
- Tissue diffusion is poor and does not cross blood brain barrier into CSF or into the eye.
- Protein binding of ~60%.
- Half-life elimination is 10.1–13.6 h.
- Excretion is in the urine with <1% as unchanged drug for first 12 h and up to 60% as therapy continues.

## Use in Special Populations

- Use in children approved, however, due to toxicity risks, systemic use should be limited to life-threatening, multidrug-resistant infection when there are no alternatives.



- Listed as FDA pregnancy classification B (former classification system).
- It is unknown whether present in breast milk.
- Kidney insufficiency: manufacturer labelling recommends dosage reduction; however, clinical data shows that clearance is not altered substantially in kidney impairment; dose adjustment is not expected to be needed.
- Hepatic insufficiency: not evaluated; dose adjustment is not expected to be needed.

## Monitoring

- Desquamation, skin hyperpigmentation, and urticaria.
- Albuminuria, hypocalcemia, hypochloremia, hypokalemia, hypomagnesemia, and hyponatremia.
- *Clostridioides difficile*-associated diarrhea (CDAD).
- Azotemia.
- Local thrombophlebitis and pain.

## Contraindications and Cautions

- Hypersensitivity reaction.
- Nephrotoxicity (mainly IM/IV use)—albuminuria, cellular casts, and azotemia.
- Neurotoxicity (mainly IM/IV use)—respiratory paralysis from neuromuscular blockade.
- Superinfection.

## Important Drug Interactions

- Enhance nephrotoxic effects (aminoglycosides, bacitracin (systemic), cefazedone, colistimethate, methoxyflurane, netilmicin (ophthalmic)).
- Enhance neuromuscular-blocking effect (capreomycin, methoxyflurane, neuromuscular-blocking agents).

- Diminish therapeutic effect of typhoid vaccine, sodium picosulfate, lactobacillus and estriol, immune checkpoint inhibitors, cholera vaccine, BCG vaccine, BCG (intravesical), bacillus clausii.
- Overall toxicity with kanamycin.

## **Adverse Effects and Their Management**

- Nephrotoxicity: avoid concurrent or sequential use of other nephrotoxic drugs, if symptoms arise, discontinue therapy with decreasing urinary output and increasing BUN.
- Neurotoxicity (respiratory paralysis): avoid concurrent or sequential use of other neurotoxic drugs.
- Superinfection with prolonged use (CDAD and pseudomembranous colitis. Avoid prolonged use.
- Toxic when given parenteral, avoid parenteral use whenever possible.

## **Carcinogenicity—If Known**

- Long-term studies to assess carcinogenicity in animals have not been conducted.

## **Patch Test Concentration**

- 3% or 5% in petrolatum

## **Essential Patient Information**

- Polymyxin-B sulfate has not been fully studied during pregnancy.
- It may cause kidney problems and/or nerve problems.
- Be aware of signs of an allergic reaction, flushing, dizziness, diarrhea, fever, headache, and stiffness.
- Wash hands before and after use and keep out moth, nose, and eyes if not indicated.

## Retapamulin (Altabax)

Parsa Abdi

### Classification and Mode of Action

- Primarily acts as a bacteriostatic agent against *Staphylococcus aureus* and *Streptococcus pyogenes* by inhibiting bacterial protein biosynthesis. It achieves this by binding to a unique site, known as protein L3, on the 50S subunit of the ribosome. This blocks peptidyl transfer and P-site interactions at this site, which prevents the formation of active 50S ribosomal subunits.

### Indications and Dermatological Uses

- For the treatment of uncomplicated bacterial skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible isolates only) or *Streptococcus pyogenes*. Primary indications include impetigo and secondarily for infected traumatic lesions (small lacerations, abrasions, and sutured wounds).
- Use in individuals who are 9 months or older, including both adults and pediatric patients. In adults, it can be used on a total area of up to 100 cm<sup>2</sup>, while in pediatric patients aged 9 months or older, it can be used on up to 2% of the total body surface area.
- The safety of Retapamulin has not been established in patients younger than 9 months.
- To maintain the effectiveness of Retapamulin and other antibacterial drugs and prevent the development of drug-resistant bacteria, it should only be used to treat or prevent infections that are known or strongly suspected to be caused by susceptible bacteria.

## Formulations/Presentation

- The ointment has a concentration of 10 mg of retapamulin per 1 gram and comes in 15 and 30 gram tubes.

## Dosages and Suggested Regimens

- To treat the affected area, apply a thin layer of retapamulin twice daily for five days. The area of application should not exceed 100 cm<sup>2</sup> in adults or 2% of the total body surface area in pediatric patients aged 9 months or older. If desired, the treated area may be covered with a sterile bandage or gauze dressing. In the event that a dose of retapamulin is skipped, it is recommended to apply the ointment at earliest recollection and subsequently adhere to the appropriate time interval for the next application. Re-evaluation of patients is advised if they don't exhibit a clinical response after 3–4 days.
- *Missed Dose:* In the event that a dose of retapamulin is skipped, it is recommended to apply the ointment at earliest recollection and subsequently adhere to the appropriate time interval for the next application.
- *Overdosage:* To date, there have been no reported incidents of overdosing on retapamulin. In the event of an overdose, whether resulting from topical application or accidental ingestion, appropriate symptom-based treatment should be administered in accordance with established clinical practices. It is important to note that there is currently no known antidote for retapamulin overdoses.

## Pharmacokinetics

- *Absorption:*
  - The absorption of retapamulin through topical application is generally low but increases when applied to abraded skin and is age-dependent, with the highest absorption observed

in younger patients. In infants and children aged 2–24 months receiving twice-daily retapamulin, a measurable serum concentration was observed in 46% of patients, compared to 7% of those aged  $\geq 2$  years. Among infants aged 2–9 months, a higher proportion had measurable serum concentrations compared to those aged 9–24 months (69% vs 32%). For children aged  $\geq 2$  years, adolescents, and adults, absorption was low but increased when applied to abraded skin.

- *Distribution:*
  - Currently, there is no available information on the tissue distribution of retapamulin in humans. However, it is known that the drug is highly bound to human plasma proteins, with an approximate binding rate of 94%.
- *Metabolism:*
  - Retapamulin is metabolized primarily by the liver through the action of the enzyme CYP 3A4. The drug undergoes extensive metabolic transformation via mono-oxygenation and di-oxygenation, resulting in the formation of multiple metabolites.
- *Excretion:*
  - There is currently no available information on the elimination of retapamulin in humans, as systemic exposure to the drug after topical application is very low. However, in pre-clinical species, elimination of  $^{14}\text{C}$ -labeled retapamulin was found to be rapid, primarily through metabolism and excretion of drug-related materials in the bile.

## Use in Special Populations

- *Pediatrics:*
  - Retapamulin has been proven to be both safe and effective for treating impetigo in pediatric patients ranging from 9 months to 17 years of age, exhibiting similar efficacy and safety profiles as those observed in adults. The safety and efficacy of retapamulin have not been established for pediatric patients below 9 months of age, thus the use of retapamulin is contraindicated in this age group.
- *Geriatrics:* No dosage change is required.

- *Hepatic Insufficiency:*
  - There is no need to adjust the dosage as low systemic exposure to retapamulin is expected following topical application in adults and pediatric patients aged 2 years and older, and hepatic impairment is unlikely to cause systemic exposure of clinical significance; however, caution should be taken for children under 2 years of age due to potential drug interactions.
- *Renal Insufficiency:*
  - There is no need to adjust the dosage as topical application of retapamulin results in low systemic exposure, hence renal impairment is not expected to cause any significant systemic exposure.
- *Pregnancy and Lactation:*
  - There is currently no data available regarding the use of retapamulin in pregnant women, and thus, there is no information about the potential drug-associated risk for fetal harm or miscarriage; however, as retapamulin is only minimally absorbed systemically after topical administration, it is unlikely to result in fetal exposure during maternal use. Additionally, no data is available on the presence of retapamulin in human milk, its impact on the nursing infant, or its effect on milk production, but given the negligible systemic absorption of retapamulin after the topical application of retapamulin, breastfeeding is not anticipated to result in drug exposure to the infant. Caution should be taken when using retapamulin in pregnant or nursing women.

## Monitoring

- Retapamulin is indicated for external use only and is intended for the treatment of impetigo that is either proven or suspected to be caused by susceptible bacteria.

## Contraindications and Cautions

- The manufacturer's labeling does not specify any contraindications.

## Warnings and Precautions

- *General:* Retapamulin should only be applied topically and should not be ingested, and it is not indicated for the management of methicillin-resistant *Staphylococcus aureus* (MRSA) or abscesses.
- *Local Irritation:* If sensitization or severe local irritation occurs with the use of retapamulin, the treatment should be discontinued immediately, the ointment should be removed, and an appropriate alternative therapy should be initiated to treat the infection.
- *Not for Mucosal or Systemic Use:* It is not recommended to use retapamulin through ingestion or oral, intranasal, ophthalmic, or intravaginal routes as it is intended only for topical use, and its efficacy and safety have not been established on mucosal surfaces. The application of retapamulin on nasal mucosa has been linked to incidents of epistaxis.
- *Potential for Microbial Overgrowth:* The utilization of antibiotics can result in the development of non-susceptible organisms. Extended usage of retapamulin may lead to fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis. It is worth noting that instances of CDAD have been reported to occur over two months after completing a course of antibiotics. Prescribing retapamulin in the absence of confirmed or highly suspected bacterial infection is improbable to provide any advantages to the patient and enhances the probability of the emergence of antibiotic-resistant bacteria.

## Important Drug Interactions

- *Drug-Drug Interactions:* There are currently no known clinically significant drug interactions in adults with retapamulin. However, co-administration of oral ketoconazole 200 mg twice daily has been shown to increase retapamulin levels in healthy adult males by 81% after topical application of retapamulin on abraded skin. The effect of co-administration of retapamulin with CYP3A4 inhibitors, such as ketoconazole, has not been studied in children. The systemic exposure of retapamulin was higher in pediatric subjects aged 2–24 months compared to those aged 2 years and older following topical application. Therefore, it is not advised to administer retapamulin concurrently with strong CYP3A4 inhibitors in patients under 24 months of age due to the higher exposure of retapamulin.
- *Drug-Food Interactions:* There is currently no evidence of any interactions between retapamulin and food.

## Adverse Effects and Their Management

- According to product labeling (unless otherwise specified), adverse drug reactions and their corresponding incidence rates for the product are reported as follows:
- In the range of 1–10%, adverse reactions include headache (1–2% incidence in the central nervous system), eczema (1% incidence in infants, children, and adolescents in the dermatologic category), diarrhea (1–2% incidence in the gastrointestinal category), nausea (1% incidence in the gastrointestinal category), application site irritation (2% incidence in adults in the local category), and application site pruritus (2% incidence in infants, children, and adolescents in the local category). Nasopharyngitis (1–2% incidence in the respiratory category) is also listed as an adverse drug reaction.
- In addition, there have been reports of several adverse drug reactions with an incidence rate of less than 1%, as well as post-marketing and/or case reports. These include angioedema,



application site burning, application site pain, contact dermatitis, epistaxis, erythema, hypersensitivity reaction, and increased creatine phosphokinase.

## **Carcinogenicity**

- There have been no long-term animal studies conducted to assess the carcinogenic potential of retapamulin. In vitro evaluations of gene mutation and chromosomal effects in the mouse lymphoma cell assay, as well as in cultured human peripheral blood lymphocytes, and in vivo testing in a rat micronucleus test, have revealed no genotoxicity associated with retapamulin. Furthermore, no indications of impaired fertility were observed in male or female rats that received oral doses of retapamulin at 50, 150, or 450 mg/kg/day.

## **Patch Test Concentration**

- 1% in petrolatum. If unavailable, may use 1% retapamulin ointment as is. It is recommended to exclude a contact allergy to butylhydroxytoluene (BHT), when indicated, as some base formulations may contain BHT.

## **Essential Patient Information**

- Patients using retapamulin should follow the instructions given by their healthcare practitioner, using the medication as directed. Hands should be washed after application, except when treating the hands. Retapamulin is for external use only, and should not be swallowed, used in the eyes, mouth, lips, inside the nose, or inside the female genital area. A sterile bandage or gauze dressing may be applied to the treated area, particularly for infants and young children who may accidentally touch or lick the lesion site, to protect the area and prevent accidental transfer of ointment to other areas. The healthcare

practitioner should be notified if symptoms do not improve within 3–4 days or if there is worsening of irritation, redness, itching, burning, swelling, blistering, or oozing at the application site.

---

## Silver Sulfadiazine

Rebecca M. Law

### Classification and Mode of Action

- Bactericidal activity for many gram-negative and gram-positive bacteria with some activity against yeast.
- Inhibits bacteria resistant to other antibiotics.
- Superior to sulfadiazine.
- Mechanism of action differs from sodium sulfadiazine and from silver nitrate.
- Acts on cell membrane and cell wall to produce its bactericidal effect.

### Indications and Dermatological Uses

- *Clinical indications (FDA)*: An adjunct for the prevention and treatment of wound sepsis in patients with second- and third-degree burns.

### Formulations/Presentation

- US: Each gram of silver sulfadiazine (SILVADENE). Cream 1% contains 10 mg of micronized silver sulfadiazine. The cream vehicle consists of white petrolatum, stearyl alcohol, isopropyl myristate, sorbitan monooleate, polyoxyl 40 stearate, propylene glycol, and water, with methylparaben 0.3% as a preservative.
- Canada:
- Europe:

## Dosages and Suggested Regimens

- The cream should be applied once to twice daily to a thickness of approximately 1/16 inch. Whenever necessary, the cream should be reapplied to any areas from which it has been removed by patient activity.
- Reapply immediately after hydrotherapy.
- Treatment should be continued until satisfactory healing has occurred, or until the burn site is ready for grafting. The drug should not be withdrawn from the therapeutic regimen while there remains the possibility of infection except if a significant adverse reaction occurs.

## Pharmacokinetics

- Absorption of silver sulfadiazine varies depending upon the percent of body surface area and the extent of the tissue damage.

## Use in Special Populations

- Should not be used on pregnant women approaching or at term, on premature infants, or on newborn infants during the first 2 months of life. Sulfonamide therapy is known to increase the possibility of kernicterus.
- It is unknown whether silver sulfadiazine is excreted in human milk.
- Safety and effectiveness in pediatric patients have not been established.
- If hepatic and renal functions become impaired and elimination of drug decreases, accumulation may occur, and drug discontinuation should be weighed against the therapeutic benefit being achieved.

## Monitoring

- In the treatment of burn wounds involving extensive areas of the body, the serum sulfa concentrations may approach adult therapeutic levels (8–12 mg%). Therefore, in these patients, it would be advisable to monitor serum sulfa concentrations. Renal function should be carefully monitored, and the urine should be checked for sulfa crystals.
- Absorption of the propylene glycol vehicle has been reported to affect serum osmolality, which may affect the interpretation of laboratory tests.

## Contraindications and Cautions

- Although few have been reported, it is possible that any adverse reaction associated with sulfonamides may occur. These include blood dyscrasias including agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, and hemolytic anemia; dermatologic and allergic reactions, including life-threatening cutaneous reactions [Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and exfoliative dermatitis]; gastrointestinal reactions; hepatitis and hepatocellular necrosis; CNS reactions; and toxic nephrosis.
- There is potential cross-sensitivity between silver sulfadiazine and other sulfonamides. If allergic reactions attributable to treatment with silver sulfadiazine occur, continuation of therapy must be weighed against the potential hazards of the particular allergic reaction.
- Fungal proliferation in and below the eschar may occur. However, the incidence of clinically reported fungal superinfection is low.
- The use of silver sulfadiazine in some cases of glucose-6-phosphate dehydrogenase-deficient individuals may be hazardous, as hemolysis may occur.

## **Important Drug Interactions**

- In considering the use of topical proteolytic enzymes in conjunction with silver sulfadiazine, there is a possibility that silver may inactivate such enzymes.

## **Adverse Effects and their Management**

- Transient leukopenia have been reported, primarily characterized by decreased neutrophil count with maximal WBC depression occurring within 2–4 days of initiation of therapy and normalized within 2–3 days. Recovery is not influenced by the continuation of silver sulfadiazine therapy.
- Other infrequently occurring events include skin necrosis, erythema multiforme, skin discoloration, burning sensation, rashes, and interstitial nephritis.

## **Carcinogenicity**

- Long-term dermal toxicity studies of 24-month duration in rats and 18 months in mice with concentrations of silver sulfadiazine three to ten times the concentration in silver sulfadiazine cream 1% revealed no evidence of carcinogenicity.

## **Patch Test Concentration**

- 5% pet.; test also silver nitrate 1% water and sulfadiazine 5% pet.; test propylene glycol

## Essential Patient Information

- The burned areas should be covered by cream at all times. Cream should be reapplied to any areas where it has been removed due to activity or other reasons such as hydrotherapy. Dressings are not required but may be used as needed.

---

## References

### Acetic Acid and Hydrocortisone (Acetasol HC)

1. LexiComp drug monograph Acetic Acid and Hydrocortisone (Topical). Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2022 UpToDate, Inc.
2. Falcon Pharmaceuticals. Neomycin and polymyxin B sulfates, and hydrocortisone otic suspension prescribing information. Fort Worth, TX; 2007 Jun.
3. Monarch Pharmaceuticals. Cortisporin® (neomycin and polymyxin B sulfates and hydrocortisone) otic solution prescribing information. Bristol, TN; 2003 Apr.
4. JHP Pharmaceuticals. Coly-Mycin® S (colistin sulfate, neomycin sulfate, thonzonium bromide, and hydrocortisone acetate) otic solution prescribing information. MI: Rochester; 2008 Feb.
5. Taro Pharmaceuticals. Hydrocortisone 1% and acetic acid 2% otic solution prescribing information. NY: Hawthorne; 2004 Jun.

### Bacitracin

6. LexiComp drug monograph. Bacitracin (Topical). Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2024 UpToDate Inc.
7. Nguyen, Rosalee, et al. "Bacitracin Topical." *StatPearls*, StatPearls Publishing, 21 November 2022.
8. Bacitracin ointment [prescribing information]. Hawthorne, NY: Taro Pharmaceuticals; Revised January 2020.
9. Antibiotic Ointment with Bacitracin Safety Data Sheet. Buffalo, NY: Safetec of America Inc; Revised February 2022.

10. Heal CF, et al. Topical antibiotics for preventing surgical site infection in wounds healing by primary intention. *Cochrane Database Syst Rev.* 2016;11(11):CD011426. <https://doi.org/10.1002/14651858.CD011426.pub2>.
11. de Groot AC. Monographs in contact allergy. In: *Topical drugs*, vol. 3. 1st ed. CRC Press; 2021. <https://doi.org/10.1201/9781003159360>.

## Gentamicin Sulfate

12. LexiComp drug monograph Gentamicin Sulfate (Topical). Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2022 UptoDate, Inc.
13. Tsai CC, Yang PS, Liu CL, Wu CJ, Hsu YC, Cheng SP. Comparison of topical mupirocin and gentamicin in the prevention of peritoneal dialysis-related infections: a systematic review and meta-analysis. *Am J Surg.* 2018;215(1):179–85. <https://doi.org/10.1016/j.amjsurg.2017.03.005>.
14. AHFS Drug Information 2007. In: McEvoy GK, editor. *Gentamicin sulfate*. Bethesda: American Society of Health-System Pharmacists; 2007. p. 3444–5.
15. Fougera. Gentamicin sulfate ointment prescribing information. Melville: From the DailyMed website. Accessed 12 Apr 2023; 1998 Mar.
16. de Groot AC. Monographs in contact allergy. In: *Topical drugs*, vol. 3. 1st ed. CRC Press; 2021. <https://doi.org/10.1201/9781003159360>.

## Gramicidin

17. FDA Drug Monograph Gramicidin. Available from <https://precision.fda.gov/uniisearch/srs/unii/5ie62321p4>. Accessed 23 Mar 2023.
18. LexiComp Drug Monograph Gramicidin. Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2022 UptoDate, Inc.
19. Sorochkina AI, Plotnikov EY, Rokitskaya TI, et al. N-terminally glutamate-substituted analogue of gramicidin as a protonophore and selective mitochondrial uncoupler. *PLoS One.* 2012;7:e41919.
20. David JM, Rajasekaran AK, Gramicidin A. A New Mission for an old antibiotic. *Journal of kidney cancer and VHL.* 2015;2:15–24.
21. DrugBank Online Monograph Gramicidin D. Available from: DrugBank Online at [go.drugbank.com/drugs/DB00027](https://go.drugbank.com/drugs/DB00027). Accessed 23 Mar 2023.
22. de Groot AC. Monographs in contact allergy. In: *Topical drugs*, vol. 3. Milton: CRC Press; 2021.

## Mupirocin

23. FDA Drug Monograph Mupirocin. Available from [https://www.access-data.fda.gov/drugsatfda\\_docs/label/2017/050591s034lbl.pdf](https://www.access-data.fda.gov/drugsatfda_docs/label/2017/050591s034lbl.pdf) Accessed 24 Mar 2023.
24. LexiComp Drug Monograph Mupirocin. Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2022 UptoDate, Inc.
25. de Groot AC. Monographs in contact allergy. In: Topical drugs, vol. 3. 1st ed. CRC Press; 2021. <https://doi.org/10.1201/9781003159360>.
26. Wolverton SE, Wu JJ, ClinicalKey Flex, Elsevier All Access Books, eBook—Specialty Medicine 2020 [EBCSM20]. Comprehensive dermatologic drug therapy. 4th ed. Philadelphia: Elsevier; 2021. p. 2019.
27. de Groot AC. Monographs in contact allergy. In: Topical drugs, vol. 3. Milton: CRC Press; 2021.
28. Katzung BG, Trevor AJ, Access Pharmacy, Access Medicine. Basic and clinical pharmacology 15e. 15th ed. Blacklick: McGraw-Hill Companies; 2021. 2020

## Neomycin Sulfate

29. LexiComp drug monograph Neomycin Sulfate (Topical). Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2022 UptoDate, Inc.
30. Johnson & Johnson. Neosporin® original (bacitracin zinc, neomycin sulfate, and polymyxin B sulfate) ointment patient information. Skillman, NJ; Undated. From Dailymed website. Accessed 2023 Apr 18.
31. Johnson & Johnson. Neosporin® Plus (bacitracin zinc, neomycin sulfate, polymyxin B sulfate, and pramoxine hydrochloride) ointment patient information. Skillman, NJ; Undated. From Dailymed website. Accessed 2023 Apr 18.
32. Actavis Pharma. Triple antibiotic (bacitracin zinc, neomycin sulfate, and polymyxin B sulfate) ointment patient information. Parsippany: Undated. From Dailymed website. Accessed; 2023 Apr 18.
33. Cell Novation Technology. Bacitracin zinc, neomycin sulfate, polymyxin B sulfate, and lidocaine hydrochloride cream patient information. Undated. From Dailymed website; 2023. Accessed 2023 Apr 18
34. Hart Health. Tribiotic LC (bacitracin zinc, neomycin sulfate, polymyxin B sulfate, and lidocaine) ointment patient information. Seattle: Undated. From Dailymed website; 2023. Accessed 2023 Apr 18
35. Pfizer. Neosporin® G.U. Irrigant sterile (neomycin sulfate-polymyxin B sulfate solution for irrigation) prescribing information. New York; 2016 Sep.



36. AHFS Drug Information 2020. In: Snow EK, editor. Neomycin sulfate. Bethesda: American Society of Health-System Pharmacists; 2020.

## Ozenoxacin

37. LexiComp Drug Monograph. Ozenoxacin (Topical). Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2024 UpToDate Inc.
38. Xepi (ozenoxacin) [Prescribing information]. Woburn: Biofontera Inc; Revised September 2023.
39. Zhanel GG, et al. In vitro activity and resistance rates of topical antimicrobials fusidic acid, mupirocin and ozenoxacin against skin and soft tissue infection pathogens obtained across Canada (CANWARD 2007-18). *J Antimicrob Chemother.* 2021;76(7):1808–14. <https://doi.org/10.1093/jac/dkab098>.

## Polymyxin-B Sulfate

40. FDA drug monograph Polymyxin B for Injection USP. Available from [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2012/060716Orig1s020Lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/060716Orig1s020Lbl.pdf). Accessed 25 Mar 2023.
41. FDA drug monograph Maxitrol. Available from [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/050023s036lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/050023s036lbl.pdf) Accessed 25 Mar 2023.
42. LexiComp drug monograph Polymyxin B. Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2022 UpToDate, Inc.
43. de Groot AC. Monographs in contact allergy. In: Topical drugs, vol. 3. 1st ed. CRC Press; 2021. <https://doi.org/10.1201/9781003159360>.
44. Wolverton SE, Wu JJ, ClinicalKey Flex, Elsevier All Access Books, eBook—Specialty Medicine 2020 [EBCSM20]. Comprehensive dermatologic drug therapy. 4th ed. Philadelphia: Elsevier; 2021. p. 2019.
45. de Groot AC. Monographs in contact allergy. In: Topical drugs, vol. 3. Milton: CRC Press; 2021.
46. Katzung BG, Trevor AJ, Access Pharmacy, Access Medicine. Basic and clinical pharmacology 15e. 15th ed. Blacklick: McGraw-Hill Companies; 2021. p. 2020.

## Retapamulin (Altabax)

47. FDA drug monograph ALTABAX® (retapamulin ointment), 1%. Available [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2012/022055s0021bl](https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022055s0021bl). Accessed 7 Apr 2023.
48. LexiComp Drug Monograph Retapamulin. Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2022 UptoDate, Inc.
49. de Groot AC. Monographs in contact allergy. In: Topical drugs, vol. 3. 1st ed. CRC Press; 2021. <https://doi.org/10.1201/9781003159360>.

## Silver Sulfadiazine

50. FDA drug monograph (silver sulfadiazine). Available from [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/017381s0501bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/017381s0501bl.pdf). Accessed 22 June 2024.
51. LexiComp drug monograph (silver sulfadiazine). Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2024 UptoDate, Inc.
52. De Groot AC. Patch testing, vol. 3. 3rd ed. Chapter 3.
53. Caffee F, Bingham H. Leukopenia and silver sulfadiazine. *J Trauma*. 1982;22:586–7.
54. Jarret F, Ellerbe S, Demling R. Acute leukopenia during topical burn therapy with silver sulfadiazine. *Amer J Surg*. 1978;135:818–9.
55. Kiker RG, Carvajal HF, Micak RP, Larson DL. A controlled study of the effects of silver sulfadiazine on white blood cell counts in burned children. *J Trauma*. 1977;17:835–6.



# Topical Antifungals

# 13

Laurie A. Temiz, Austinn C. Miller,  
Susuana Adjei, and Stephen K. Tyring

## Contents

|                   |     |
|-------------------|-----|
| Introduction..... | 297 |
| Allylamines.....  | 299 |
| Azoles.....       | 306 |
| References.....   | 355 |

## Introduction

Topical antifungal drugs are used to treat a variety of yeast and dermatophyte infections. Topical formulations are often only effective in treating superficial and localized infections of the

---

L. A. Temiz

Department of Dermatology and Cutaneous Surgery, University of South  
Florida, Tampa, FL, USA

Center for Clinical Studies, Webster, TX, USA

e-mail: [Itemiz@ccstexas.com](mailto:Itemiz@ccstexas.com)

A. C. Miller · S. Adjei

Center for Clinical Studies, Webster, TX, USA

e-mail: [fellowwebster@ccstexas.com](mailto:fellowwebster@ccstexas.com); [fellowtmc@ccstexas.com](mailto:fellowtmc@ccstexas.com)

S. K. Tyring (✉)

Center for Clinical Studies, Webster, TX, USA

Department of Dermatology, University of Texas Health Science Center,  
Houston, TX, USA

e-mail: [styring@ccstexas.com](mailto:styring@ccstexas.com)

© The Author(s), under exclusive license to Springer Nature  
Switzerland AG 2025

297

R. M. Law, H. I. Maibach (eds.), *Handbook of Topical Drug  
Treatment in Dermatology*,

[https://doi.org/10.1007/978-3-031-93616-6\\_13](https://doi.org/10.1007/978-3-031-93616-6_13)

skin, hair, and nails, whereas systemic medications are reserved for more severe disease.

Fungi of medical importance are capable of causing an array of diseases, ranging from asymptomatic superficial skin infections to fatal systemic infections. Fungi are a group of eukaryotic microorganisms often divided into yeasts and molds. Yeasts are single-celled, oval-shaped microorganisms that reproduce primarily through budding. Molds are multicellular microorganisms formed from elongated multinucleate filaments (hyphae) that reproduce by apical extension. While most fungi exist as either a yeast or a mold, dimorphic fungi can switch between each form depending on environmental factors, such as temperature. Regardless of the form, all fungi share common properties: absorptive nutrition (food digestion occurs externally via expulsion of hydrolytic enzymes and absorption of the resulting product), lysine synthesis, chitinous cell wall (rather than peptidoglycan found in mammalian walls), and plasma membranes containing ergosterol (rather than cholesterol found in mammalian membranes).

Many antifungals target steps in the fungal plasma membrane synthesis pathway with high affinity, given that fungi utilize ergosterol, rather than cholesterol as occurs in mammalian sterol synthesis. Most topical antifungals are fungistatic, inhibiting cell growth; however, a few are fungicidal resulting in cell death (amphotericin, echinocandins, and nystatin).

Superficial fungal infections are most likely to be seen in immunocompromised individuals. This includes infants without full immune maturity, elderly with waning immune responses, and those who are immunosuppressed for any other reason. However, anyone can be infected. Other high-risk populations include those who are in frequent contact with people who may be infected (athletes), come in contact with spores in the environment (digging, gardening, contact with animals, and caving), and recent use of antibiotics (vulvovaginal candidiasis).

Like other antimicrobials, resistance to antifungals is increasing, and several factors contribute to this issue. Resistance is defined as persistent fungal infections despite the use of appropriate fungal therapy. These factors range from mutations, biofilm

formation, poor medication adherence, and host immunosuppression.

Fungi of medical importance can cause an array of diseases, ranging from asymptomatic superficial skin infections to fatal systemic infections. While immunocompromised individuals are at greatest risk of fungal infections, they may occur in anyone. Topical antifungal drugs are commonly used to treat a superficial yeast and dermatophyte infections. Most antifungals function by taking advantage of cellular processes unique to fungi, allowing for limited cross reactivity with human cells and thus less side effects. However, like other antimicrobials, resistance to antifungals is increasing. When faced with recalcitrant or severe fungal infections, systemic antifungals are typically the treatment of choice.

---

## Allylamines

### Naftifine

#### Classification and Mode of Action

- Synthetic allylamine derivative. Naftifine is a topical, broad-spectrum antifungal agent that works via dose-dependent selective inhibition of squalene-2,3-epoxidase. As this enzyme is crucial to fungal cells' ability to synthesize ergosterol, the result is a buildup of intracellular squalene and the loss of the fungal membrane's primary sterol. Thus, naftifine has both fungicidal and fungistatic activity.

#### Indications and Dermatological Uses

- *Clinical indications:* Topical treatment of interdigital tinea pedis (athlete's foot), tinea corporis (ringworm), and tinea cruris (jock itch) caused by *Trichophyton rubrum*.
- *Off-label common uses:* Tinea manuum (Level of evidence: C).

#### Formulations/Presentation

- US: 1% cream, 2% cream, 1% gel, 2% gel.
- Canada: Not on Lexicomp.
- Europe: Not on Lexicomp.

### **Dosages and Suggested Regimens**

- *Cream (1%, 2%)*: A thin layer of cream should be applied to clean, dry skin on the affected area(s), plus a ½-inch margin of surrounding tissue once daily until clinical resolution. For tinea pedis and tinea manuum infections, treatment should be continued for 1 week after clinical resolution.
- *Gel (1%, 2%)*: A thin layer of gel should be applied to clean, dry skin on the affected area(s), plus a ½-inch margin of surrounding tissue twice daily until clinical resolution. For tinea pedis and tinea manuum, treatment should be continued for 1 week after clinical resolution.
- The selected treatment regimen should be maintained for a minimum of 2 weeks. Clinical effects may take 1–4 weeks to become apparent.
- No suggested dosage adjustment for renal or hepatic impairment due to low systemic absorption.

### **Baseline Investigations and Considerations**

- Culture and KOH exams.

### **Pharmacokinetics (Percutaneous Absorption, Distribution, Metabolism, Excretion: As Relevant for the Drug)**

- When applied topically, naftifine hydrochloride penetrates the stratum corneum but has a low systemic bioavailability. The cream formulation has more systemic penetration, reaching 6% systemic absorption as compared to 4% in the gel form.
- The plasma elimination half-life of naftifine and its metabolites is 2–3 days.
- Unchanged naftifine, as well as its metabolites, is excreted in both the feces and urine.

### **Use in Special Populations: Pregnancy (FDA Guidance), Lactation, Children, Renal Insufficiency, Hepatic Insufficiency**

- The treatment of tinea corporis is approved in children  $\geq 2$  years of age and for the treatment of tinea cruris and pedis in children  $\geq 12$  years of age. No pediatric dose adjustment is required.

- Naftifine may be present in breast milk. Lactating patients should not apply this product to the nipples or breasts.
- Human studies of naftifine in pregnant or lactating patients have not been performed; however, due to its low systemic bioavailability, application over a limited area is acceptable in these patients.

### Monitoring

- Culture and KOH exams (*repeat if no signs of clinical improvement after 4 weeks*).
- Application-site reactions (*exfoliation, erythema, or dermatitis*).

### Contraindications and Cautions

- Naftifine is contraindicated in patients with a hypersensitivity to either the drug product or any component of the formulation.
- Naftifine is indicated for topical use only and contact with the eyes, nose, mouth, or mucous membranes should be avoided.
- This medication should not be used with occlusive dressings.

### Important Drug Interactions

- This drug has no significant drug interactions.

### Adverse Effects and Their Management

- Contact dermatitis is the most commonly reported adverse event seen with the use of naftifine. Other common cutaneous reactions include a burning or stinging sensation of the skin, xeroderma, skin irritation, erythema, and pruritus. Approximately 2% of patients reported local application site reactions. If sensitivity or irritation occurs, naftifine should be discontinued and replaced with an alternative therapy.
- In rare cases, more severe cutaneous and systemic reactions have been reported. Systemic manifestations include agranulocytosis, leukopenia, inflammatory reactions, dizziness, and headache. Rare cutaneous reactions reported were maceration, rash, serous drainage, blistering of the skin, and tenderness and swelling of the skin.

- Despite the structural and mechanistic similarities between naftifine and terbinafine, there is no evidence of cross-reactivity or sensitization to active ingredients across the class of allylamine antifungals.

### **Patch Test Concentration**

- 1% and 5% in alcohol

### **Essential Patient Information**

- This drug is used to treat fungal infections of the skin.
- Hands should be washed before and after use.
- Naftifine should be applied to the affected area and approximately ½ inch of surrounding healthy skin in all directions.
- This drug should only be applied to clean, dry skin. Contact with the eyes, nose, mouth, or intravaginal tissue should be avoided.
- Occlusive dressings should not be used.
- If irritation, redness, peeling, other skin sensitivity, or worsening of condition occurs, a physician should be contacted immediately, and the use of the medication should be discontinued.
- If any signs of an allergic reaction (*rash; hives; itching; red, swollen, blistered, or peeling skin; wheezing; chest or throat tightness; difficulty breathing, swallowing or talking; unusual hoarseness; or swelling of the mouth, face, lips, tongue, or throat*) are noticed, appropriate medical help should be sought immediately. Use of the medication should be discontinued, and any side effects should be reported to the physician.

## **Terbinafine**

### **Classification and Mode of Action**

- Synthetic allylamine derivative. Terbinafine inhibits the enzyme squalene-2,3-epoxidase, limiting fungal cells' ability to synthesize ergosterol, a key component of the fungal cell membrane. Without this sterol, the integrity of the fungal cell membrane is severely compromised, leading to fungal cell death.



## Indications and Dermatological Uses

- **Clinical indications:** Treatment of tinea pedis (athlete's foot), tinea cruris (jock itch), tinea corporis (ringworm), and tinea versicolor (*in Canada only*).
  - **\*\*Note:** In the United States, the above indications are approved for OTC management\*\*
- **Off-label common uses:** Topical treatment of tinea manuum (Level of evidence: C).

## Formulations/Presentation

- US: 1% cream, 1% gel, 1% solution.
- Canada: 1% cream, 1% solution.
- Europe: Not on Lexicomp.

## Dosages and Suggested Regimens

- *Tinea corporis:* The cream or gel should be applied to the affected and surrounding area(s) once daily for at least 1 week. Treatment should be continued until clinical resolution.
- *Tinea cruris:* Cream, gel, or spray should be applied to the affected and surrounding area(s) once daily for at least 1 week. Treatment should be continued until clinical resolution.
- *Tinea pedis/manuum:* This drug should be applied to the affected and surrounding area(s) once daily (gel) or twice daily (cream) until 1 week after clinical resolution.
- *Tinea versicolor (Canada only):* This drug should be applied to the affected area once daily (pediatric) or twice daily (adult).
  - The gel formulation should be used for 1 week, while the cream formulation should be used for 2 weeks.
  - Terbinafine spray is approved for pediatric use only.

## Baseline Investigations and Considerations

- There is no specific requirement for baseline investigations.

**Pharmacokinetics (Percutaneous Absorption, Distribution, Metabolism, Excretion: As Relevant for the Drug)**

- When applied topically, less than 5% of a given dose of terbinafine reaches the systemic circulation. The drug is primarily distributed to the sebum and skin with an elimination half-life of 14–35 h.

**Use in Special Populations: Pregnancy (FDA Guidance), Lactation, Children, Renal Insufficiency, and Hepatic Insufficiency**

- Terbinafine is present in breast milk following oral administration, but systemic absorption is limited following topical application. This drug should be used with caution and should avoid being applied on or near the nipples in lactating patients.
- Infants should not be allowed to come into contact with treated skin.
- Due to low systemic absorption, topical terbinafine may be considered for use in a pregnant population if needed.

**Monitoring**

- There is no specific requirement for monitoring.

**Contraindications and Cautions**

- Terbinafine is contraindicated in patients with a hypersensitivity to either the drug product or any component of the formulation.
- If irritation or sensitivity occurs, the medication should be discontinued, and appropriate alternative therapy should be instituted.
- Some dosage forms may be formulated with propylene glycol. Exposure to large amounts of propylene glycol has been associated with potentially fatal neonatal toxicity and may present with metabolic acidosis, renal failure, CNS depression, and seizures. Similar propylene glycol toxicity has also been reported in children and adults and may present with these

findings, in addition to hyperosmolality and respiratory depression.

- Some dosage forms may be formulated with benzyl alcohol; some studies have implicated benzoate in the displacement of bilirubin from protein binding sites. Exposure to benzyl alcohol in doses exceeding 99 mg/kg/day has been associated with a potentially fatal neonatal toxicity known as gasping syndrome. Gasping syndrome presents with metabolic acidosis, hypotension, cardiovascular collapse, seizures, intracranial hemorrhage, other CNS dysfunction, gasping respirations, and respiratory distress. The use of products containing benzyl alcohol should be avoided in this patient population.

### **Important Drug Interactions**

- There are no known significant drug interactions.

### **Adverse Effects and Their Management**

- The most commonly reported adverse reactions are localized skin irritation, contact dermatitis, burning or stinging sensations of the skin, skin dryness, exfoliation, pruritus, and skin rash.
- A wider range of cutaneous reactions have been reported with the use of terbinafine as opposed to naftifine. These reactions are relatively common, occurring in approximately 2.7% of patients. Severity of reactions can vary; however, severe reactions may necessitate the discontinuation of therapy.
- Such reactions may include instances of erythema multiforme, erythroderma, pityriasis rosea, or worsening of the initial skin condition.
- Other reported cutaneous reactions include lichenoid drug eruption, de novo inductions of cutaneous lupus, exacerbations of systemic lupus erythematosus, and symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), acute generalized exanthematous cutaneous pustulosis (AGEP), and drug rash with eosinophilic systemic symptoms (DRESS) syndrome.

### Patch Test Concentration

- No data available

### Essential Patient Information

- This drug is used to treat fungal infections of the skin.
- For external use only. Contact with the eyes, nose, mouth, or intravaginal tissue should be avoided.
- This drug should not be used on the nails, scalp, or for vaginal yeast infections.
- The affected area should be washed with soap and water and dried completely prior to application. This drug should only be applied to clean, dry skin, in sufficient amounts to cover the affected area. Hands should be washed before and after use.
- If any signs of an allergic reaction (*rash; hives; itching; red, swollen, blistered, or peeling skin; wheezing; chest or throat tightness; difficulty breathing, swallowing, or talking; unusual hoarseness; or swelling of the mouth, face, lips, tongue, or throat*) are noticed, appropriate medical help should be sought immediately. This medication should be discontinued and any side effects should be reported to a physician.

---

## Azoles

### Clotrimazole

#### Classification and Mode of Action

- Imidazole antifungal. By binding to phospholipids within the fungal cell membrane, clotrimazole significantly alters cell wall permeability, resulting in the loss of essential intracellular elements.
- Clotrimazole is not effective in infections caused by *Candida glabrata*.

## Indications and Dermatological Uses

- *Clinical indications:* Topical treatment of candidiasis due to *Candida albicans*, tinea versicolor due to *Malassezia furfur*, vulvovaginal candidiasis, and relief of external vulvar itching and irritation.
- *OTC indications:* Topical treatment of tinea cruris, *Candida albicans*, tinea corporis, and tinea pedis.
- *Off-label common uses:* Otomycosis (level of evidence: C) and tinea manuum (level of evidence: C).

## Formulations/Presentation

- US: External cream (1%), intravaginal cream (1% and 2%), external ointment (1%), external solution (1%).
- Canada: External cream (1%), intravaginal cream (1% and 2%), 100 mg, 150 mg, 200 mg, 500 mg vaginal tablet/insert.
- Europe: Not on Lexicomp.

## Dosages and Suggested Regimens

- *Vulvovaginal candidiasis:* One applicator of vaginal cream should be inserted once daily (preferably at bedtime). Duration of treatment is based on the strength of the product selected with the 1%, 2%, and 10% formulations requiring treatment for 7 days, 3 days, and 1 day, respectively. Cream may also be applied externally twice daily for up to 7 days as needed for itching and irritation.
- *Cutaneous candidiasis:* Cream should be applied to the affected area twice daily for 4 weeks. Alternatively, OTC ointment may be applied twice daily for 2 weeks.
- *Otomycosis:* Four to five drops of topical solution should be instilled into the affected ear(s) twice daily for 10–14 days.
- *Tinea corporis/cruris:* An appropriate amount of cream, ointment, or solution should be applied to the affected and surrounding area(s) twice daily for 4 weeks or until clinical resolution of infection. If treating tinea cruris in a pediatric patient, the duration of therapy should be limited to 2 weeks.

- *Tinea pedis*: An appropriate amount of cream, ointment, or solution should be applied to the affected and surrounding area(s) twice daily until 1 week after clinical resolution.
- *Tinea versicolor*: An appropriate amount of cream or solution should be applied to the affected area(s) twice daily.

### **Baseline Investigations and Considerations**

- In patients with otomycosis, the provider should perform a thorough cleansing of the ear canal prior to initiating pharmacotherapy.

### **Pharmacokinetics (Percutaneous Absorption, Distribution, Metabolism, Excretion: As Relevant for the Drug)**

- When applied to intact skin, clotrimazole exhibits negligible systemic absorption. When applied intravaginally, 3–10% of the applied dose is absorbed, reaching peak serum concentration in approximately 24 h.

### **Use in Special Populations: Pregnancy (FDA Guidance), Lactation, Children, Renal Insufficiency, and Hepatic Insufficiency**

- It is not known if clotrimazole is excreted in breast milk. Use with caution in lactating patients.
- Approved for the treatment of cutaneous candidiasis in pediatric patients  $\geq 2$  years of age and for the treatment of vulvovaginal candidiasis in patients  $\geq 12$  years of age.

### **Monitoring**

- This drug should be monitored for both signs of clinical improvement and severe skin irritation.
- In patients with otomycosis, the presence of fungal elements in the ear canal should be assessed following completion of therapy. Several cycles of ear cleansing, pharmacotherapeutic treatment, and reassessment may be necessary to achieve complete resolution. If otomycosis persists after multiple cycles of treatment, the patient should be managed by an otolaryngologist.

- If there is no improvement in clinical signs of cutaneous candidiasis or tinea versicolor after 4 weeks of treatment, the diagnosis should be reassessed.

### Contraindications and Cautions

- This drug is contraindicated in patients with a hypersensitivity to either the drug product or any component of the formulation.
- Some cases may require an extended course of therapy for effective management. Up to 14 days of treatment may be indicated for patients with severe or recurrent infections, infections with candida species other than *C. albicans*, or immunocompromised states.
- While rare, there have been reports of severe toxicity and allergic reaction associated with the use of azole antifungals. Allergic reactions have been reported in up to 2% of patients and usually present as a rash or pruritus. More severe dermal reactions, including epidermal necrolysis, serum sickness, and anaphylaxis have been reported with the use of oral formulations. In most cases, allergic reactions may become apparent several days or weeks after starting therapy. In sensitized patients, symptoms may occur within minutes or hours. Allergic reactions to azole antifungals have been found to respond well to corticosteroids and antihistamine.
- Clinical data regarding incidences of cross-reaction is limited; however, there are numerous case reports of significant occurrences. While there is potential for cross-reactivity between all types of azole antifungals, the possibility is greatest in patients who have taken other imidazoles due to the high degree of structural similarity.
- Some dosage forms may be formulated with benzyl alcohol; some studies have implicated benzoate in the displacement of bilirubin from protein binding sites. Exposure to benzyl alcohol in doses exceeding 99 mg/kg/day has been associated with a potentially fatal neonatal toxicity known as gasping syndrome. Gasping syndrome presents with metabolic acidosis, hypotension, cardiovascular collapse, seizures, intracranial hemorrhage, other CNS dysfunction, gasping respirations, and

respiratory distress. The use of products containing benzyl alcohol should be avoided in this patient population.

### **Important Drug Interactions**

- Progesterone (*Risk X*): Clotrimazole may decrease the efficacy of progesterone. Combinations with these products should be avoided.

### **Adverse Effects and Their Management**

- Vulvovaginal burning associated with the use of vaginal preparations is relatively common and has been reported in up to 10% of patients.
- In addition, burning sensations of the penis (of the sexual partner), polyuria, pruritus vulvae, vaginal discharge, and vulvar pain and swelling have been reported in <1% of patients.
- Hepatotoxicity is a rare adverse event associated with the use of azole antifungals and may represent either direct toxicity or immune system involvement. If cholestatic jaundice or other signs of liver toxicity occur, immediately discontinue medication and initiate appropriate therapy.

### **Patch Test Concentration**

- 1% pet. (SmartPracticeCanada & Europe); generally, alcohol or methyl ethyl ketone (MEK) may be more suitable for patch testing imidazoles.

### **Essential Patient Information**

- This drug is used to treat fungal infections of the skin and vaginal yeast infections.
- Hands should be washed before and after use.
- Medication use should be supervised in children under the age of 12.
- If a patient develops severe skin irritation; sensitivity; burning; or blisters that ooze, drain, or crust over, or if nausea, vomiting, abdominal pain, or foul-smelling vaginal discharge occurs, this medication should immediately be discontinued and a physician should be informed.



- If any signs of an allergic reaction (*rash; hives; itching; red, swollen, blistered, or peeling skin; wheezing; chest or throat tightness; difficulty breathing, swallowing or talking; unusual hoarseness; or swelling of the mouth, face, lips, tongue, or throat*) are noticed, appropriate medical help should be sought immediately. This medication should be discontinued, and any side effects should be reported to a physician.
- Topical formulations are intended for external use only. Contact with the eyes should be avoided.
- Clotrimazole is not effective for the treatment of infections impacting the scalp or nails.
- If a patient has not previously had a vaginal yeast infection diagnosed by a doctor, experienced 3 or more yeast infections within 3 months, or had an exposure to HIV, a physician should be consulted prior to using any formulation of vaginal cream for OTC self-medication.
- If treating vaginal yeast infection, vaginal intercourse and the use of tampons, douches, spermicides, or other vaginal products should be refrained from for the duration of treatment.
- Vaginal preparations may weaken latex condoms and diaphragms, decreasing their efficacy in preventing unwanted pregnancy and sexually transmitted diseases.
- If treating athlete's foot, special attention should be paid to the spaces between the toes and wear well-fitting, ventilated shoes. Patients should change shoes and socks at least once daily.

## Econazole

### Classification and Mode of Action

- Imidazole antifungal. Econazole inhibits the synthesis of ergosterol, a primary sterol of the fungal cell membrane. By decreasing the availability of ergosterol, this drug fundamentally alters cell wall permeability, causing an accumulation of 14 $\alpha$ -methyl sterols and leakage of cellular contents. Econazole may also interfere with lipid metabolism and the synthesis of RNA and proteins.

- In clinical trials, econazole was found to effectively treat interdigital tinea pedis in approximately 48% of cases, achieving mycological cure in 67–68.3% of patients and complete cure in 23.2 = 25.3% of cases. In comparison, luliconazole and sertaconazole were considered to provide effective treatment in 33–48% and 32.3–50.5% of cases, respectively.

### Indications and Dermatological Uses

- *Clinical indications:* Topical treatment of cutaneous candidiasis; tinea versicolor; and tinea pedis, tinea cruris, and/or tinea corporis caused by *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Trichophyton tonsurans*, *Microsporum canis*, *Microsporum audouinii*, *Microsporum gypseum*, and/or *Epidermophyton floccosum*.
- *Off-label common uses:* Tinea manuum (level of evidence: C).

### Formulations/Presentation

- US: 1% cream, 1% foam.
- Canada: 1% cream, 150 mg vaginal ovule.
- Europe: Not on Lexicomp.

### Dosages and Suggested Regimens

- *Cutaneous candidiasis:* Affected area(s) should be applied with treatment twice daily.
- *Tinea versicolor:* The affected and surrounding area(s) should be applied with this drug once daily for 2 weeks (adults) or 4 weeks (pediatric).
- *Other tinea infection:* The affected and surrounding area(s) should be applied with treatment once daily for 4 weeks, or until condition resolves.
- If treating tinea pedis, treatment should be continued for 1 week after clinical resolution.

### Baseline Investigations and Considerations

- There is no specific requirement for baseline investigations.

**Pharmacokinetics (Percutaneous Absorption, Distribution, Metabolism, Excretion: As Relevant for the Drug)**

- Following topical administration, econazole exhibits expansive penetration of the skin, with concentrations exceeding those necessary to achieve minimum inhibitory concentration in the stratum corneum, epidermis, and mid-dermis. Less than 10% of an applied dose reaches the systemic circulation; peak serum concentration is reached in  $6.8 \pm 5.1$  h.
- Econazole undergoes extensive hepatic metabolism, producing more than 20 distinct metabolites. Less than 1% of a given dose is excreted as unchanged drug in the feces and urine.

**Use in Special Populations: Pregnancy (FDA Guidance), Lactation, Children, Renal Insufficiency, and Hepatic Insufficiency**

- It is not known if econazole is present in breast milk. Use with caution in lactating patients.
- There is little data available regarding the use of econazole in pregnant patients. It is recommended to avoid the use of this drug in this population during the first trimester and use sparingly for the remainder of pregnancy only when necessary.
- Approved for use in pediatric patients  $\geq 12$  years of age.

**Monitoring**

- Signs of clinical improvement should be monitored.
- If there is no improvement after completing the course of therapy, diagnosis should be reassessed.

**Contraindications and Cautions**

- Econazole cream is contraindicated in patients with a hypersensitivity to either the drug product or any component of the formulation.

- Occlusion, application to the genitals, or use over a large body surface area may increase systemic absorption and subsequent risk for adverse events or drug interaction.
- If sensitivity or irritation occurs, the use of this drug should be discontinued.
- While rare, there have been reports of severe toxicity and allergic reaction associated with the use of azole antifungals. Allergic reactions have been reported in up to 2% of patients and usually present as a rash or pruritus. More severe dermal reactions, including epidermal necrolysis, serum sickness, and anaphylaxis have been reported with the use of oral formulations. In most cases, allergic reactions may become apparent several days or weeks after starting therapy. In sensitized patients, symptoms may occur within minutes or hours. Allergic reactions to azole antifungals have been found to respond well to corticosteroids and antihistamine.
- Clinical data regarding incidences of cross-reaction is limited; however, there are numerous case reports of significant occurrences. While there is potential for cross-reactivity between all types of azole antifungals, the possibility is greatest in patients who have taken other imidazoles due to the high degree of structural similarity.
- Some dosage forms may be formulated with propylene glycol. Exposure to large amounts of propylene glycol has been associated with potentially fatal neonatal toxicity and may present with metabolic acidosis, renal failure, CNS depression, and seizures. Similar propylene glycol toxicity has also been reported in children and adults and may present with these findings, in addition to hyperosmolality and respiratory depression.

### **Important Drug Interactions**

- Vitamin K Antagonists (*Risk: C*): Econazole may increase the serum concentration of vitamin K antagonist drugs, resulting in an increased anticoagulant effect. Monitor therapy.

## Adverse Effects and Their Management

- Adverse events have been noted to occur in approximately 3% of patients and include burning or stinging sensations of the skin, pruritus, and erythema.
- Hepatotoxicity is a rare adverse event associated with the use of azole antifungals and may represent either direct toxicity or immune system involvement. If cholestatic jaundice or other signs of liver toxicity occur, immediately discontinue medication and initiate appropriate therapy.

## Patch Test Concentration

- Nitrate, 1.0% alc. (Chemotechnique).

## Essential Patient Information

- This drug is used to treat fungal infections of the skin.
- For external use only. Contact with the eyes, nose, mouth, vagina, and other mucous membranes should be avoided.
- The foam canister should be shaken for ~5 s before use.
- Topical foam is flammable. Exposure to heat, flame, and smoking should be avoided during and immediately after foam application.
- Containers should not be punctured, incinerated, or stored at high temperatures (>120 °F/49 °C) or in direct sunlight, even when empty.
- If any signs of an allergic reaction (*rash; hives; itching; red, swollen, blistered, or peeling skin; wheezing; chest or throat tightness; difficulty breathing, swallowing, or talking; unusual hoarseness; or swelling of the mouth, face, lips, tongue, or throat*) are noticed, appropriate medical help should be sought immediately. This medication should be discontinued and any side effects should be reported to a physician.

## Ketoconazole

### Classification and Mode of Action

- Imidazole antifungal. Ketoconazole inhibits fungal cytochrome P450 and multiple other enzymes, blocking the synthesis of triglycerides and phospholipids, altering the permeability of the cell wall, inhibiting androgen synthesis, and causing accumulation of hydrogen peroxide to detrimental levels in fungi.

### Indications and Dermatological Uses

- *Clinical indications:* Topical treatment of tinea (pityriasis) versicolor due to *Pityrosporum orbiculare* also termed *Malassezia furfur*. Topical treatment of tinea corporis (ringworm), tinea cruris (jock itch), and tinea pedis (athlete's foot) due to *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum*. Treatment of cutaneous candidiasis due to *Candida* sp. Treatment of seborrheic dermatitis. Please see Chap. 24: *Seborrheic Dermatitis* for additional discussion.
- *OTC indications:* Control of flaking, scaling, and itching associated with dandruff.
- *Off-label common uses:* Tinea manuum (Level of evidence: C).

### Formulations/Presentation

- US: 2% foam, 2% cream, 2% gel, 1% shampoo, 2% shampoo.
- Canada: 2% cream, 2% shampoo.
- Europe: Not on Lexicomp.

### Dosages and Suggested Regimens

- *Cutaneous candidiasis:* Topical cream is applied over the entire affected area plus the surrounding area once a day for 2 weeks (2–3 weeks according to Canadian label).

- *Tinea corporis* and *Tinea cruris*: Topical cream is applied over the entire affected area(s) plus surrounding area once a day for 1–3 weeks or until clinical resolution of the infection.
- *Tinea pedis*: Topical cream is applied over the entire affected area(s) plus surrounding area once a day for 4–6 weeks, or 1 week after clinical resolution.
- *Tinea versicolor*: Topical cream is applied over the entire affected plus the surrounding area for 2 weeks (Canadian label recommends 2–3 weeks).
- *Seborrheic dermatitis*: Topical cream is applied to the entire affected area twice a day for 4 weeks or until clinical resolution.
- *Dandruff*: 5–10 mL of 2% ketoconazole shampoo is applied to the wet scalp. It should be lathered and allowed to sit for 3–5 min before rinsing. This drug is used twice weekly for 2–4 weeks, then once every 1–2 weeks for ongoing control. If self-treating dandruff, 1% ketoconazole shampoo can be used once every 3–4 days for up to 8 weeks, then as needed to control condition.

### **Baseline Investigations and Considerations**

- There is no specific requirement for baseline investigations.

### **Pharmacokinetics (Percutaneous Absorption, Distribution, Metabolism, and Excretion: As Relevant for the Drug)**

- Systemic absorption of ketoconazole following topical application is limited. In patients using ketoconazole shampoo, serum drug levels are undetectable, even after chronic use. Use of the cream, gel, and foam products results in minimal systemic absorption, with observed serum levels 250 times lower than seen with an equivalent oral dose.

### **Use in Special Populations: Pregnancy (FDA Guidance), Lactation, Children, Renal Insufficiency, and Hepatic Insufficiency**

- Topical ketoconazole is approved for use in the treatment of complications secondary to infectious atopic dermatitis in pregnant patients.
- While topically administered ketoconazole demonstrates low systemic absorption, it may be present in breast milk. Use with caution in patients desiring to breastfeed. Do not allow the medication to come into contact with the nipple, surrounding breast, or infant.

### **Monitoring**

- There is no specific requirement for monitoring.

### **Contraindications and Cautions**

- Ketoconazole is contraindicated in patients with a hypersensitivity to either the drug product or any component of the formulation.
- When used for self-medication, do not apply if the scalp is broken or inflamed.
- If sensitivity or irritation occurs, the use of this medication should be discontinued.
- While rare, there have been reports of severe toxicity and allergic reaction associated with the use of azole antifungals. Allergic reactions have been reported in up to 2% of patients and usually present as a rash or pruritus. More severe dermal reactions, including epidermal necrolysis, serum sickness, and anaphylaxis have been reported with the use of oral formulations. In most cases, allergic reactions may become apparent several days or weeks after starting therapy. In sensitized patients, symptoms may occur within minutes or hours. Allergic reactions to azole antifungals have been found to respond well to corticosteroids and antihistamine.
- Some formulations of this product may contain sulfites, posing a risk for severe or life-threatening asthmatic episodes, allergic reactions, and anaphylaxis in patients with a sensitivity.



- Clinical data regarding incidences of cross-reaction is limited; however, there are numerous case reports of significant occurrences. While there is potential for cross-reactivity between all types of azole antifungals, the possibility is greatest in patients who have taken other imidazoles due to the high degree of structural similarity.
- Some dosage forms may be formulated with propylene glycol. Exposure to large amounts of propylene glycol has been associated with potentially fatal neonatal toxicity and may present with metabolic acidosis, renal failure, CNS depression, and seizures. Similar propylene glycol toxicity has also been reported in children and adults and may present with these findings, in addition to hyperosmolality and respiratory depression.

### **Important Drug Interactions**

- There are no known significant drug interactions.

### **Adverse Effects and Their Management**

- Hepatotoxicity is a rare adverse event associated with the use of azole antifungals and may represent either direct toxicity or immune system involvement. If cholestatic jaundice or other signs of liver toxicity occur, immediately discontinue medication and initiate appropriate therapy.
- The shampoo may cause burning, itchy, or dry scalp; changes in hair texture, including straight hair, or discoloration; loss of hair.
- Adverse reactions from dermatologic administration include application-site pruritus from cream in <5% of patients, from shampoo in up to 3% of patients, from foam and gel in <1% of patients; Xeroderma from shampoo in up to 3% of patients, from foam and gel in <1% of patients; stinging from cream in <5% of patients.
- Adverse reactions from local administration include: application-site reactions from cream in <6% of patients, from shampoo in up to 3% of patients, from foam gel in <1% of patients; burning from gel in 4% of patients, from foam and shampoo in

<1% of patients; local irritation from cream in <5% of patients, from foam and shampoo in less than 1% of patients.

- Other reported adverse events include: urticaria, anaphylaxis, angioedema, application-site dermatitis and/or discharge, erythema, pain, contact dermatitis, skin irritation, skin rash; cheilitis; dizziness; eye irritation, swelling of the eye, dry eye syndrome, eye irritation; swelling of the face; headache; hypersensitivity reaction; impetigo; nail discoloration; localized warm feeling; paresthesia; pustules; pyogenic granuloma; acne vulgaris.

### **Patch Test Concentration**

- 1% alcohol

### **Essential Patient Information**

- For external use only. Contact with the eyes, nose, mouth, vagina, and other mucous membranes should be avoided.
- Topical gel and foam preparations are flammable. Exposure to heat, flame, and smoking should be avoided during and immediately after application.
- Foam canister contains alcohol and propane/butane. Containers should not be punctured or incinerated.
- If any signs of an allergic reaction (*rash; hives; itching; red, swollen, blistered, or peeling skin; wheezing; chest or throat tightness; difficulty breathing, swallowing, or talking; unusual hoarseness; or swelling of the mouth, face, lips, tongue, or throat*) are noticed, appropriate medical help should be sought immediately. This medication should be discontinued, and any side effects should be reported to a physician.
- Foam application is best performed when the foam is kept in cool temperatures. Warm surfaces, including hands and fingers, will cause the foam to melt prematurely. Utilizing the cap or hands previously rinsed in cool water prior to application is preferable. After obtaining a small amount in the fingers, application of the foam to the affected area will cause it to disappear. It should be ensured that hair is parted away from the application site in order to apply to skin in hair-bearing areas.

- For gel application, the entire affected area should be treated. Application of products such as sunscreen or makeup should be delayed for 20 min. Washing of the affected area after gel application should be delayed for 3 h.

## Luliconazole

### Classification and Mode of Action

- Imidazole antifungal: By inhibiting the CYP450-dependent enzyme 14 $\alpha$ -lanosterol demethylase, luliconazole interferes with the conversion of lanosterol to ergosterol, the primary sterol of the fungal cell wall. This results in decreased availability of ergosterol and a subsequent buildup of the precursor component.
- In clinical trials, luliconazole was found to effectively treat interdigital tinea pedis in between 33% and 48% of cases, achieving mycological cure in 56–62% of patients and complete cure in 14–26% of cases. In comparison, econazole and sertaconazole were considered to provide effective treatment in 48.4–48.8% and 32.3–50.5% of cases, respectively.

### Indications and Dermatological Uses

- *Clinical indications:* Topical treatment of interdigital tinea pedis, tinea cruris, and/or tinea corporis secondary to infection with *Trichophyton rubrum* or *Epidermophyton floccosum*.
- *Off-label common uses:* Tinea manuum (level of evidence: C).

### Formulations/Presentation

- US: 1% cream.
- Canada: Not in Health Canada Drug Product Database.
- Europe: Not on Lexicomp.

**Dosages and Suggested Regimens**

- Luliconazole should be applied to affected area(s) and 1 inch of surrounding healthy tissue once daily until condition resolves.
- For the treatment of tinea pedis or tinea manuum, treatment should be continued for 1 week following clinical resolution.
- Clinical efficacy may take up to 3 weeks to become evident.

**Baseline Investigations and Considerations**

- There is no specific requirement for baseline investigations.

**Pharmacokinetics (Percutaneous Absorption, Distribution, Metabolism, and Excretion: As Relevant for the Drug)**

- Luliconazole demonstrates limited systemic absorption following topical application.
- Within the serum, luliconazole exhibits >99% binding to plasma proteins.
- This drug is a weak-to-moderate inhibitor of CYP2C19. It also inhibits the activity of CYP2B6, CYP2C8, CYP2C19, and CYP3A4.

**Use in Special Populations: Pregnancy (FDA Guidance), Lactation, Children, Renal Insufficiency, and Hepatic Insufficiency**

- It is not known if luliconazole is present in the breast milk; however, small amounts of drug can be found in the serum following topical administration. Use with caution in lactating patients.
- There are no studies evaluating the use of luliconazole in pregnant or lactating patients; however, animal reproduction studies have demonstrated an increased risk for adverse outcomes. Extrapolated risks of birth defect and miscarriage within the United States population reach up to 4% and 20%, respectively.
- This product is approved for use in pediatric patients  $\geq 2$  years of age.

**Monitoring**

- Luliconazole should be monitored for localized dermatitis, cellulitis, application site reactions, and irritation during use.

**Contraindications and Cautions**

- There are no known contraindications.
- While rare, there have been reports of severe toxicity and allergic reaction associated with the use of azole antifungals. Allergic reactions have been reported in up to 2% of patients and usually present as a rash or pruritus. More severe dermal reactions, including epidermal necrolysis, serum sickness, and anaphylaxis have been reported with the use of oral formulations. In most cases, allergic reactions may become apparent several days or weeks after starting therapy. In sensitized patients, symptoms may occur within minutes or hours. Allergic reactions to azole antifungals have been found to respond well to corticosteroids and antihistamine.
- Clinical data regarding incidences of cross-reaction is limited; however, there are numerous case reports of significant occurrences. While there is potential for cross-reactivity between all types of azole antifungals, the possibility is greatest in patients who have taken other imidazoles due to the high degree of structural similarity.

**Important Drug Interactions**

- Clobazam; Fosphenytoin; Phenytoin (*Risk C*): Luliconazole is a weak inhibitor of CYP2C19, though some studies have reported moderate enzyme inhibition. Concurrent use may result in increased serum concentrations of fosphenytoin, phenytoin, or clobazam and its active metabolites. Therapy should be monitored.
- CYP Interactions: May inhibit the breakdown of drugs metabolized by CYP2B6, 2C8, 2C19, and 3A4.

**Adverse Effects and Their Management**

- Reports of adverse events with the use of luliconazole are rare. Post-marketing reports of adverse drug effects include application site reactions, contact dermatitis, and cellulitis; however, these occurred in <1% of patients.
- Hepatotoxicity is a rare adverse event associated with the use of azole antifungals and may represent either direct toxicity or immune system involvement. If cholestatic jaundice or other signs of liver toxicity occur, medication should be discontinued immediately, and appropriate therapy should be initiated.

**Patch Test Concentration**

- 2% pet.

**Essential Patient Information**

- This drug is used to treat fungal infections of the skin.
- Hands should be washed after use.

**Miconazole Nitrate****Classification and Mode of Action**

- Imidazole Antifungal: The exact mechanism by which miconazole exerts its fungicidal action is not fully understood; however, azole antifungals as a group are known to inhibit the synthesis of ergosterol, a key component of the fungal cell membrane, resulting in a toxic accumulation of methylated sterols.
- Clinical studies of miconazole have demonstrated interference with triglyceride and fatty acid synthesis, damage to actin cables, and inhibition of fungal oxidative and peroxidase enzymes. It has been postulated that the cumulative result of these actions is increased accumulation of reactive oxygen species (ROS), mitochondrial dysregulation, and, ultimately, the induction of cellular apoptosis.

## Indications and Dermatological Uses

- *Clinical indications:* Topical treatment of cutaneous and mucocutaneous fungal infections, vulvovaginal candidiasis, and adjunctive treatment of diaper dermatitis complicated by documented evidence of comorbid candidiasis in immunocompetent patient  $\geq 4$  weeks of age.
- *Off-label common uses:* Tinea manuum.

## Formulations/Presentation

- US: Aerosol powder (2%), non-aerosol powder (2%), cream (2%), fungoid tincture/solution (2%), ointment (2%).
- Canada: Spray (2%), cream (2%), vaginal cream (2%).
- Europe: Not on Lexicomp.

## Dosages and Suggested Regimens

- *Diaper dermatitis:* A thin layer of ointment should be applied to clean, dry skin of the affected area using the tips of the fingers at each diaper change for 7 days. The ointment should not be rubbed in.
- *Other dermatologic infection:* This drug should be applied to the affected area twice daily for up to 4 weeks or clinical resolution. If treating tinea pedis or tinea manuum, treatment should be continued for 1 week following clinical resolution.

## Baseline Investigations and Considerations

- Prior to initiating treatment for diaper dermatitis, confirmation of candidal infection should be obtained with microscopic evidence of pseudohyphae and/or budding yeast.
- KOH Prep.

## Pharmacokinetics (Percutaneous Absorption, Distribution, Metabolism, Excretion: As Relevant for the Drug)

- Although topical miconazole is negligibly absorbed into the systemic circulation, it is widely distributed and highly protein bound (91–93%) with detectable concentrations in the body

tissues, joint spaces, and fluid spaces. There is very little evidence of penetration into the saliva, urine, sputum, and CSF. Absorption is slightly increased when applied vaginally but is still low. Miconazole is primarily metabolized in the liver and exhibits multiphasic degradation; its alpha, beta, and terminal half-lives are 40 min, 126 min, and 24 h, respectively. Excretion occurs mostly via the feces; 50% of absorbed miconazole is excreted unchanged in the feces, as opposed to <1%, which appears in the urine.

### **Use in Special Populations: Pregnancy (FDA Guidance), Lactation, Children, Renal Insufficiency, and Hepatic Insufficiency**

- Miconazole has not been evaluated for use in pregnant, lactating, or geriatric patients.
- In animal studies, miconazole given at high doses was found to be associated with prolonged gestation and a decreased rate of live births.
- It is not known if miconazole is expressed in breast milk. Only the cream formulation is approved for treatment of candidiasis affecting the breasts or nipples. Miconazole gel should not be applied to these areas and prolonged administration of any dosage form should be avoided.
- This drug is not approved for OTC use in children <2 years of age.
- Clinical efficacy has not been demonstrated in infants <4 weeks of age. Safety and efficacy have not been evaluated in very-low-birthweight or premature infants.
- Some dosage forms may be formulated with propylene glycol. Exposure to large amounts of propylene glycol has been associated with potentially fatal neonatal toxicity and may present with metabolic acidosis, renal failure, CNS depression, and seizures. Similar propylene glycol toxicity has also been reported in children and adults and may present with these findings, in addition to hyperosmolality and respiratory depression.
- Some dosage forms may be formulated with benzyl alcohol; some studies have implicated benzoate in the displacement of



bilirubin from protein binding sites. Exposure to benzyl alcohol in doses exceeding 99 mg/kg/day has been associated with a potentially fatal neonatal toxicity known as gasping syndrome. Gasping syndrome presents with metabolic acidosis, hypotension, cardiovascular collapse, seizures, intracranial hemorrhage, other CNS dysfunction, gasping respirations, and respiratory distress. The use of products containing benzyl alcohol should be avoided in this patient population.

### **Monitoring**

- There is no specific requirement for monitoring.

### **Contraindications and Cautions**

- Miconazole is contraindicated in patients with a hypersensitivity to either the drug product or any component of the formulation.
- If skin sensitivity, irritation, or worsening of condition occurs, use of this medication should be discontinued, and a healthcare provider should be contacted.
- While rare, there have been reports of severe toxicity and allergic reaction associated with the use of azole antifungals. Allergic reactions have been reported in up to 2% of patients and usually present as a rash or pruritus. More severe dermal reactions, including epidermal necrolysis, serum sickness, and anaphylaxis have been reported with the use of oral formulations. In most cases, allergic reactions may become apparent several days or weeks after starting therapy. In sensitized patients, symptoms may occur within minutes or hours. Allergic reactions to azole antifungals have been found to respond well to corticosteroids and antihistamine.
- Clinical data regarding incidences of cross-reaction is limited; however, there are numerous case reports of significant occurrences. While there is potential for cross-reactivity between all types of azole antifungals, the possibility is greatest in patients who have taken other imidazoles due to the high degree of structural similarity.

- May inhibit the metabolism of oral sulfonylureas. Caution should be used in diabetic patients and counseling should be provided on appropriate blood glucose testing procedures.

### **Important Drug Interactions**

- Progesterone (*Risk X*): Miconazole may decrease the efficacy of progesterone. Combinations should be avoided with these products.
- Vitamin K Antagonists (*Risk: D*): Miconazole may increase the serum concentration of vitamin K antagonist drugs, resulting in an increased anticoagulant effect. Coadministration with warfarin may lead to elevations in INR, prothrombin time, and bleeding risk. The use of miconazole-containing drug products should be avoided in patients treated with warfarin. If use of both agents is unavoidable, therapy modification should be strongly considered. The anticoagulant dose can be decreased by 10–20%; close monitoring for signs of excessive anticoagulant activity should be performed for the duration of therapy.
- Miconazole may inhibit the metabolism of orally administered sulfonylureas. Patients should monitor blood glucose regularly.

### **Adverse Effects and Their Management**

- The primary adverse event for this drug is allergic contact dermatitis, a burning sensation of the skin, and skin maceration. Notably, clinical trials have evidenced similar incidences of adverse events in patients treated with either miconazole preparations or the inactive vehicle alone.
- The following adverse events have been reported in <1% of patients: blistering and exfoliation of the skin, skin dryness, diaper dermatitis, pruritus, erythema, vomiting, pain, and inflammation.
- Hepatotoxicity is a rare adverse event associated with the use of azole antifungals and may represent either direct toxicity or immune system involvement. If cholestatic jaundice or other signs of liver toxicity occur, medication should be immediately discontinued, and appropriate therapy should be initiated.

- If any signs of an allergic reaction (*rash; hives; itching; red, swollen, blistered, or peeling skin; wheezing; chest or throat tightness; difficulty breathing, swallowing or talking; hoarseness; or swelling of the mouth, face, lips, tongue, or throat*) are noticed, appropriate medical help should be sought immediately. This medication should be discontinued, and any side effects should be reported to a physician.

### **Patch Test Concentration**

- 1% alc. (Chemotechnique)

### **Essential Patient Information**

- This product is indicated for topical use only. Contact with the eyes and mouth should be avoided.
- Miconazole preparations (e.g., *ointment, cream, and powder*) should not be used for intravaginal treatment unless specifically directed by either the package labeling or a physician.
- Prior to application, skin should be washed with lukewarm water and patted dry with a towel.
- The safety of long-term treatment with miconazole ointment has not been evaluated. Miconazole should not be used for longer than 7 days.
- Diapers should be changed frequently to minimize the occurrence of diaper dermatitis. This medication is not a substitute for routine diaper changes, and it should not be used as prophylactic therapy. Diaper dermatitis should be treated for the full recommended 7 days, even if symptoms resolve.
- Inappropriate, preventive, or extended use of this medication may lead to the development of drug resistance.

## **Oxiconazole Nitrate**

### **Classification and Mode of Action**

- Imidazole antifungal: Oxiconazole inhibits the synthesis of ergosterol, a key component of the fungal cell membrane, resulting in the loss of cytoplasmic membrane integrity.

- Oxiconazole has fungicidal activity and is known to be active against *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Epidermophyton floccosum*, and *Malassezia furfur*.
- Clinical studies have found that oxiconazole reaches a minimum inhibitory concentration (MIC) sufficient to inhibit growth for several other fungal species, however its safety and efficacy in the treatment of these infections has not been established. These include most strains of *Candida albicans*, *Trichophyton violaceum*, *Trichophyton tonsurans*, *Microsporum canis*, *Microsporum audouinii*, and *Microsporum gypsum*.

### Indications and Dermatological Uses

- *Clinical indications:* Topical treatment of tinea (pityriasis) versicolor due to *Malassezia furfur*. Topical treatment of tinea pedis (athlete's foot), tinea cruris (jock itch), and/or tinea corporis (ringworm) due to *Trichophyton rubrum*, *Trichophyton mentagrophytes*, or *Epidermophyton floccosum*.
- *Off-label common uses:* Tinea manuum (level of evidence: C).

### Formulations/Presentation

- US: 1% cream, 1% lotion.
- Canada: Cancelled Post Market (Health Canada).
- Europe: Not on Lexicomp.

### Dosages and Suggested Regimens

- Oxiconazole should be applied to clean, dry skin on the affected area(s), plus a 1/2-inch margin of surrounding tissue one to two times daily for 2 weeks or until clinical resolution.
- For tinea pedis and tinea manuum infections, treatment should be for a minimum of 4 weeks and continued until 1 week after clinical resolution.

### Baseline Investigations and Considerations

- Culture and KOH preparation.
- Clinical signs of infection.

**Pharmacokinetics (Percutaneous Absorption, Distribution, Metabolism, and Excretion: As Relevant for the Drug)**

- A topical dose can penetrate the epidermis, upper corium, and deeper corium within 5 h of application.
- Oxiconazole exhibits low systemic absorption with <0.3% of an administered dose reaching the urine 5 days after application.

**Use in Special Populations: Pregnancy (FDA Guidance), Lactation, Children, Renal Insufficiency, and Hepatic Insufficiency**

- Although systemic absorption of oxiconazole is very limited, it has been found to be excreted in breast milk. Caution should be used in patients desiring to breastfeed.
- There are insufficient human trials of oxiconazole in geriatric patients to effectively establish safety and efficacy.
- Animal studies and Phase IV marketing have not evidenced any notable teratogenic effects; however, due to the lack of human trial data, this drug should only be used in pregnant patients if clearly needed.
- This product is approved for use in children  $\geq 12$  years of age.

**Monitoring**

- Signs of clinical resolution should be monitored.
- Culture and KOH preparation can be used to evaluate for mycological cure (no evidence of baseline pathogen) 2 weeks after completion of treatment.
- Treatment is considered successful if both mycological cure and a 90% improvement in clinical signs are achieved.
- If there is no improvement within 3 weeks of initiation, the diagnosis should be reassessed.

## **Contraindications and Cautions**

- Hypersensitivity to oxiconazole or any component of the formulation.
- If sensitivity or irritation occurs, this medication should be discontinued.
- While there are no reports of topical oxiconazole overdose in humans, clinical trials have evidenced dermal reactions due to drug toxicity in animal models.
- While rare, there have been reports of severe toxicity and allergic reaction associated with the use of azole antifungals. Allergic reactions have been reported in up to 2% of patients and usually present as a rash or pruritus. More severe dermal reactions, including epidermal necrolysis, serum sickness, and anaphylaxis have been reported with the use of oral formulations. In most cases, allergic reactions may become apparent several days or weeks after starting therapy. In sensitized patients, symptoms may occur within minutes or hours. Allergic reactions to azole antifungals have been found to respond well to corticosteroids and antihistamine.
- Clinical data regarding incidences of cross-reaction is limited; however, there are numerous case reports of significant occurrences. While there is potential for cross-reactivity between all types of azole antifungals, the possibility is greatest in patients who have taken other imidazoles due to the high degree of structural similarity.

## **Important Drug Interactions**

- There are no known significant drug interactions.

## **Adverse Effects and Their Management**

- The most commonly reported adverse events for this medication are pruritus and localized burning; however, these have been reported in <2% of patients.
- Other reported adverse events include allergic contact dermatitis; dyshidrotic eczema; erythema; pain; stinging or tingling sensations of the skin; maceration, folliculitis, or exfoliation of

the skin; development of skin fissures, papules, and nodules; erythema; pain; and rashes and irritation.

- If sensitivity, irritation, or worsening of condition occurs, the drug should be discontinued.
- Hepatotoxicity is a rare adverse event associated with the use of azole antifungals and may represent either direct toxicity or immune system involvement. If cholestatic jaundice or other signs of liver toxicity occur, the medication should be immediately discontinued, and appropriate therapy should be initiated.

### **Patch Test Concentration**

- 1% alcohol or MEK (methyl ethyl ketone)

### **Essential Patient Information**

- This medication is not intended for ophthalmic or intravaginal use. For external use only on clean, dry, intact skin as directed by a physician.
- Contact with the eyes, nose, mouth, vagina, and other mucous membranes should be avoided.
- The use of occlusive dressings should be avoided, unless otherwise directed.
- Hands should be washed before and after use. This drug should be shaken well before using.
- If there is no improvement after 2–4 weeks of therapy, or if the condition gets worse, a physician should be contacted.
- Tinea (pityriasis) versicolor may present with patches of skin discoloration on the trunk, neck, arms, and upper thighs. The timing for pigment normalization is highly variable and depends on such factors as individual skin type and incidental sun exposure. Restoration of normal or consistent skin tone may not occur for several months following successful treatment. Further, although tinea versicolor is not contagious, the causative organism is part of the normal skin flora. Therefore, it is possible for this condition to recur even after successful treatment.

- The use of this medication should be continued for the full duration of the prescribed treatment, even if symptoms have improved.
- If a patient experiences a severe skin reaction at the application site such as blistering, swelling, burning, oozing, or bleeding, immediate medical help should be sought.

## Sertaconazole Nitrate

### Classification and Mode of Action

- Imidazole antifungal: By inhibiting the CYP450-dependent enzyme 14 $\alpha$ -lanosterol demethylase, sertaconazole interferes with the conversion of lanosterol to ergosterol, the primary sterol of the fungal cell wall. This results in increased permeability of the fungal cell membrane and cellular injury secondary to leakage of cytoplasmic contents from the cell.
- Sertaconazole is active against most strains of *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum*.

### Indications and Dermatological Uses

- *Clinical indications:* Topical treatment of interdigital tinea pedis caused by *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum*.
- *Off-label common uses:* Cutaneous candidiasis (level of evidence: B), seborrheic dermatitis (level of evidence: B), tinea corporis/cruris (level of evidence: B), tinea manuum (level of evidence: C), tinea versicolor (level of evidence: C).

### Formulations/Presentation

- US: 2% cream.
- Canada: Not on Health Canada Drug Product Database.
- Europe: Not on Lexicomp.



**Dosages and Suggested Regimens**

- Sertaconazole should be applied to clean, dry skin on the affected area(s), plus a 1/2-inch margin of surrounding tissue twice daily for 4 weeks. If treating tinea pedis or tinea manuum, regimen should be continued for 1 week after clinical resolution of infection.
- For the treatment of tinea corporis or tinea cruris, this drug should be applied one to two times daily until clinical resolution of infection. It may take 1–3 weeks for clinical effect to become apparent.

**Baseline Investigations and Considerations**

- There is no specific requirement for baseline investigations.

**Pharmacokinetics (Percutaneous Absorption, Distribution, Metabolism, Excretion: As Relevant for the Drug)**

- The systemic bioavailability of sertaconazole is negligible. Following the application of a topical dose, serum drug concentrations are undetectable.

**Use in Special Populations: Pregnancy (FDA Guidance), Lactation, Children, Renal Insufficiency, and Hepatic Insufficiency**

- This drug is only approved for use in immunocompetent patients  $\geq 12$  years of age.
- Animal studies and Phase IV marketing have not evidenced any notable teratogenic effects. It is not known if sertaconazole is present in breast milk, however, systemic absorption is very low. Use with caution in lactating women.
- Due to the low systemic bioavailability of this product, no dosage adjustments are required for patients with hepatic or renal dysfunction.

**Monitoring**

- Clinical improvement should be monitored. If there is no improvement after 2 weeks of treatment, diagnosis and therapy should be reevaluated.

**Contraindications and Cautions**

- There are no known contraindications to the use of this medication.
- While rare, there have been reports of severe toxicity and allergic reaction associated with the use of azole antifungals. Allergic reactions have been reported in up to 2% of patients and usually present as a rash or pruritus. More severe dermal reactions, including epidermal necrolysis, serum sickness, and anaphylaxis have been reported with the use of oral formulations. In most cases, allergic reactions may become apparent several days or weeks after starting therapy. In sensitized patients, symptoms may occur within minutes or hours. Allergic reactions to azole antifungals have been found to respond well to corticosteroids and antihistamine.
- Clinical data regarding incidences of cross-reaction is limited; however, there are numerous case reports of significant occurrences. While there is potential for cross-reactivity between all types of azole antifungals, the possibility is greatest in patients who have taken other imidazoles due to the high degree of structural similarity.

**Important Drug Interactions**

- Progesterone (*Risk X*): Sulconazole may decrease the efficacy of progesterone. Combinations with these products should be avoided.

**Adverse Effects and Their Management**

- The most commonly reported adverse events are skin dryness, contact dermatitis, skin tenderness, and a burning sensation of the skin.

- Phase IV reports have noted desquamation, erythema, hyperpigmentation, pruritus, and vesicular eruptions in <1% of patients.
- Hepatotoxicity is a rare adverse event associated with the use of azole antifungals and may represent either direct toxicity or immune system involvement. If cholestatic jaundice or other signs of liver toxicity occur, immediately discontinue medication and initiate appropriate therapy.

### **Patch Test Concentration**

- 1% and 5% pet.; imidazoles are usually tested 1% alcohol or MEK (methyl ethyl ketone)

### **Essential Patient Information**

- This drug is used to treat fungal infections of the skin.
- This product is for external use only and contact with the eyes, nose, mouth, or mucous membranes should be avoided.
- Sertaconazole should be applied only to skin which has been thoroughly cleansed and dried. Hands should be washed before and after application. Contact with the eyes, nose, mouth, vagina, and other mucous membranes should be avoided.
- This medication should be used for the entire duration of treatment recommended by a physician, even if symptoms improve.
- This medication should not be used with occlusive dressings.
- If irritation, redness, peeling, change in skin color, other skin sensitivity, or worsening of condition occurs, a physician should be contacted immediately, and the use of this medication should be discontinued.
- If any signs of an allergic reaction (*rash; hives; itching; red, swollen, blistered, or peeling skin; wheezing; chest or throat tightness; difficulty breathing, swallowing, or talking; unusual hoarseness; or swelling of the mouth, face, lips, tongue, or throat*) are noticed, appropriate medical help should be sought immediately. This medication should be discontinued, and any side effects should be reported to a physician.

## Sulconazole

### Classification and Mode of Action

- Imidazole antifungal. Sulconazole inhibits the synthesis of ergosterol, a key component of the fungal cell membrane, resulting in decreased growth of dermatophytes and other fungal organisms. In most cases, the drug effect is primarily fungistatic; however, in the treatment of some *Candida albicans* and *Candida parapsilosis* infections, its activity is actually fungicidal.

### Indications and Dermatological Uses

- *Clinical indications:* Topical treatment of tinea pedis (athlete's foot), tinea corporis (ringworm), and tinea cruris (jock itch) caused by *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Epidermophyton floccosum*, and *Microsporum canis*. Topical treatment of tinea versicolor.
- *Off-label common uses:* Topical treatment of tinea manuum (level of evidence: C).

### Formulations/Presentation

- US: 1% cream, 1% solution.
- Canada: Not on Health Canada Drug Product Database.
- Europe: Not on Lexicomp.

### Dosages and Suggested Regimens

- A small amount of sulconazole should be applied to the affected and surrounding area(s) and gently rubbed in one to two times daily for at least 3 weeks, or until clinical resolution.
- For tinea pedis infections, this medication should be used twice daily and continue treatment for 1 week after clinical resolution.

### Baseline Investigations and Considerations

- There are no known significant drug interactions.

**Pharmacokinetics (Percutaneous Absorption, Distribution, Metabolism, Excretion: As Relevant for the Drug)**

- Following topical administration, sulconazole exhibits between 8.7% and 11% percutaneous absorption. The drug is primarily excreted in the urine.

**Use in Special Populations: Pregnancy (FDA Guidance), Lactation, Children, Renal Insufficiency, and Hepatic Insufficiency**

- There are insufficient human studies concerning the use of this drug in pediatric, geriatric, pregnant, or lactating patients. In animal studies, sulconazole given at high doses was found to be embryotoxic, but not teratogenic. High-dose sulconazole was also found to cause prolonged gestation and dystocia, resulting in maternal death in several animal models.
- It is not known if sulconazole is present in breast milk. This drug should be used with caution and should not be applied on or near the nipples in lactating patients.

**Monitoring**

- Signs of clinical improvement should be monitored. If the condition does not improve following 4–6 weeks of appropriate therapy, the diagnosis should be reevaluated.

**Contraindications and Cautions**

- This drug is contraindicated in patients with a hypersensitivity to either the drug product or any component of the formulation.
- Effectiveness has not been proven in the treatment of tinea pedis; tinea pedis infections should be treated for a minimum of 4 weeks.
- If sensitivity or irritation occurs, this medication should be discontinued,

- While rare, there have been reports of severe toxicity and allergic reaction associated with the use of azole antifungals. Allergic reactions have been reported in up to 2% of patients and usually present as a rash or pruritus. More severe dermal reactions, including epidermal necrolysis, serum sickness, and anaphylaxis have been reported with the use of oral formulations. In most cases, allergic reactions may become apparent several days or weeks after starting therapy. In sensitized patients, symptoms may occur within minutes or hours. Allergic reactions to azole antifungals have been found to respond well to corticosteroids and antihistamine.
- Clinical data regarding incidences of cross-reaction is limited; however, there are numerous case reports of significant occurrences. While there is potential for cross-reactivity between all types of azole antifungals, the possibility is greatest in patients who have taken other imidazoles due to the high degree of structural similarity.

### **Important Drug Interactions**

- There are no known significant drug interactions.

### **Adverse Effects and Their Management**

- The most commonly reported adverse events are localized burning, erythema, pruritus, and stinging of the skin.
- Hepatotoxicity is a rare adverse event associated with the use of azole antifungals and may represent either direct toxicity or immune system involvement. If cholestatic jaundice or other signs of liver toxicity occur, immediately discontinue medication and initiate appropriate therapy.

### **Patch Test Concentration**

- 1% alcohol or MEK (methyl ethyl ketone)

### **Essential Patient Information**

- This drug is used to treat fungal infections of the skin.
- Symptomatic relief typically occurs within the first few days of treatment; however, it may take a full week for signs of clinical improvement to become apparent.

- This product is intended for external use only. Contact with the eyes and mucous membranes should be avoided.
- Exposing solution to light or excessive heat ( $> 104^{\circ}\text{F}/40^{\circ}\text{C}$ ) should be avoided.
- If any signs of an allergic reaction (*rash; hives; itching; red, swollen, blistered, or peeling skin; wheezing; chest or throat tightness; difficulty breathing, swallowing, or talking; unusual hoarseness; or swelling of the mouth, face, lips, tongue, or throat*) are noticed, appropriate medical help should be sought immediately. This medication should be discontinued, and any side effects should be reported to a physician.

## Butenafine HCl

### Classification and Mode of Action

- Benzylamine antifungal. Butenafine inhibits the enzyme squalene-2,3-epoxidase, limiting fungal cells' ability to synthesize ergosterol, a key component of the fungal cell membrane.

### Indications and Dermatological Uses

- *Clinical indications:* Topical treatment of tinea (pityriasis) versicolor due to *Malassezia furfur*.
- *OTC indications:* Topical treatment of interdigital tinea pedis (athlete's foot), tinea corporis (ringworm), and tinea cruris (jock itch) and relief of burning, itching, scaling, or cracking associated with these infections.
- *Off-label common uses:* Topical treatment of tinea manuum.

### Formulations/Presentation

- US: 1% cream.
- Canada: 1% cream.
- Europe: Not on Lexicomp.

### Dosages and Suggested Regimens

- *Tinea versicolor:* A thin layer should be applied to clean, dry skin on the affected area(s), plus a 1/2-inch margin of surrounding tissue once daily for 2 weeks.

- *Tinea corporis and cruris*: A thin layer should be applied to clean, dry skin on the affected area(s), plus a ½-inch margin of surrounding tissue once daily for 2 weeks. Treatment should be continued until clinical resolution of infection.
- *Tinea pedis and manuum*: A thin layer should be applied to clean, dry skin on the affected area(s), plus a ½-inch margin of surrounding tissue twice daily for 2 weeks or once daily for 4 weeks. Treatment should be continued until 1 week after clinical resolution of infection.
- Clinical effects may take 1–3 weeks to become apparent.

### **Baseline Investigations and Considerations**

- There are no known significant drug interactions.

### **Pharmacokinetics (Percutaneous Absorption, Distribution, Metabolism, Excretion: As Relevant for the Drug)**

- Following topical application, butenafine demonstrates minimal systemic bioavailability. Absorbed drug undergoes hepatic metabolism via hydroxylation, reaching its peak serum concentration in 6–15 h. Butenafine undergoes biphasic elimination with the alpha phase having a  $t_{1/2}$  of 35 h, and the beta phase having a  $t_{1/2}$  of over 150 h.

### **Use in Special Populations: Pregnancy (FDA Guidance), Lactation, Children, Renal Insufficiency, and Hepatic Insufficiency**

- This product is approved for use in children  $\geq 12$  years of age.
- Human studies of naftifine in pregnant or lactating patients have not been performed; however, animal studies have not evidenced any notable adverse events. Butenafine should be used with caution in patients desiring to breastfeed.

### **Monitoring**

- Patients should be monitored for signs of clinical efficacy using fungal cultures and a KOH exam. Tinea pedis can also be monitored by its clinical signs.



**Contraindications and Cautions**

- Butenafine is contraindicated in patients with a hypersensitivity to either the drug product or any component of the formulation.
- When used for OTC self-medication, butenafine should not be used for any treatment of the nails, scalp, or mucous membranes, or for intravaginal yeast infections. This drug should not be used in or near the mouth and/or eyes.
- Butenafine should not be used with occlusive dressings.
- This drug should be used with caution in patients with sensitivities to allylamine antifungals. Cross sensitivity may occur due to the structural similarity between benzylamines and allylamines.

**Important Drug Interactions**

- This drug has no known significant drug interactions.

**Adverse Effects and Their Management**

- Primary adverse events are contact dermatitis, application site irritation, and burning and stinging of the skin. This medication should be discontinued if sensitivity or irritation occurs.

**Patch Test Concentration**

- No data available

**Essential Patient Information**

- The area of skin to be treated can be washed with soap and water and dried completely before application.
- If treating athlete's foot, well-fitting, ventilated shoes should be worn, and shoes and socks should be changed at least once per day.
- Hands should be washed after each use.
- If skin irritation occurs or worsens, this medication should be discontinued, and a physician should be notified.
- In case of contact with the eye(s), a patient should rinse thoroughly with water. If swallowed, a patient should seek immediate medical help or contact a Poison Control Center.

## Ciclopirox Olamine

### Classification and Mode of Action

- Hydroxypyridinone derivative. Ciclopirox is a hydroxypyridone that chelates trivalent cations, thereby inhibiting metal dependent enzymes. Its broad mechanism of action targets fungi in a variety of ways: inhibition of cytochromes, oxidative damage, affects nutrient uptake, synthesis of proteins, and nucleic acids.
- Less effective than Efinaconazole and Tavaborole solutions in complete clearance of onychomycosis.

### Indications and Dermatological Uses

- *Clinical indications:* Tinea (pedis, cruris, corporis, versicolor), onychomycosis, candidiasis, and seborrheic dermatitis.
- *Off-label common uses:* Tinea manuum (level of evidence: D).

### Formulations/Presentation

- US: 0.77% gel, 0.77% cream, 0.77% solution, 1% shampoo, 8% nail lacquer.
- Canada: 1% cream, 1% lotion, 1.5% shampoo, 8% nail lacquer.
- Europe: Not on LexiComp.

### Dosages and Suggested Regimens

- Tinea: Application is once to twice daily, reassess after 4 weeks.
- Onychomycosis: Application is once daily for 24 weeks (fingernails) to 48 weeks (toenails).
- Candidiasis: Application is twice daily, reassess after 4 weeks.
- Seborrheic dermatitis: Application is twice daily (gel) or twice weekly (shampoo).
- No suggested dosage adjustment for renal or hepatic impairment due to low systemic absorption.

### Baseline Investigations and Considerations

- There are no known significant drug interactions.

**Pharmacokinetics (Percutaneous Absorption, Distribution, Metabolism, Excretion: As Relevant for the Drug)**

- Minimal topical absorption. Elimination half-life is between 1.7 h (cream), 5.5 h (gel). Excreted in urine, feces.
- Onset of effect: < 4 weeks (gel, cream).

**Use in Special Populations: Pregnancy (FDA Guidance), Lactation, Children, Renal Insufficiency, and Hepatic Insufficiency**

- Approved for use in children. Internal use should be avoided.
- Listed as FDA pregnancy classification B (former classification system).
- Unknown whether ciclopirox is present in breast milk.
- Renal insufficiency: not evaluated; dose adjustment is not expected to be needed.
- Hepatic insufficiency: not evaluated; dose adjustment is not expected to be needed.

**Monitoring**

- Skin irritation (dryness, itching, erythema, pain/burning, blistering, swelling, oozing) at the application site.
- Allergy (angioedema, lip swelling, facial edema, tachycardia—reported with shampoo).

**Contraindications and Cautions**

- Contraindication: Hypersensitivity to ciclopirox or any component of the formulation.
- Ophthalmic, oral, and intravaginal use should be avoided.
- Occlusive dressings should not be placed over treated areas.

**Important Drug Interactions**

- There are no known significant drug interactions.

### **Adverse Effects and Their Management**

- Skin irritation can occur. Erythema, stinging/burning, dryness, or pruritus may occur especially during the initial 2–4 weeks of use. These may lessen with continued use.
- May cause headaches.
- Hypersensitivity reactions including facial edema and tachycardia have been reported with shampoo. Use must be discontinued immediately as anaphylactoid/anaphylactic reactions may occur.

### **Patch Test Concentration**

- 1% pet.

### **Essential Patient Information**

- Contact with broken, sunburned, eczematous or abraded skin should be avoided.
- Contact with eyes, lips, or other mucous membranes (e.g., inside nose) should be avoided.
- For external use only. This drug should not be ingested.
- Occlusive dressings should be avoided.
- Nail polish should not be used during the treatment of onychomycosis.

## **Nystatin**

### **Classification and Mode of Action**

- Polyene antifungal derived from *Streptomyces noursei*. Nystatin binds to sterols in fungal cell membranes, fundamentally altering permeability across the cell wall and allowing for leakage of cellular contents.
- Active against a wide variety of yeasts and yeast-like fungi, including *Candida albicans*, *C. parapsilosis*, *C. tropicalis*, *C. guilliermondii*, *C. pseudotropicalis*, *C. krusei*, *Torulopsis glabrata*, *Trichophyton rubrum*, and *T. mentagrophytes*.

- *Candida albicans* does not develop resistance to nystatin. Other *Candida* species (*C. tropicalis*, *C. guilliermondii*, *C. krusei*, and *C. stellatoidea*) develop significant resistance to nystatin and can simultaneously become cross-resistant to amphotericin. Resistance is lost following removal of the antibiotic.

### Indications and Dermatological Uses

- *Clinical indications:* Treatment of cutaneous and mucocutaneous fungal infections caused by *Candida albicans* or other susceptible *Candida* species.

### Formulations/Presentation

- US: 100,000 units/g cream, 100,000 units/g ointment, 100,000 units/g powder.
- Canada: 100,000 units/g cream, 100,000 units/g ointment.
- Europe: Not on Lexicomp.

### Dosages and Suggested Regimens

- When using cream or ointment, this drug can be applied liberally and gently massaged into the affected area(s) of skin twice daily until condition resolves. For treatment of candidal diaper dermatitis, medication can be applied up to four times daily.
- When using powder, the affected area(s) should be applied two to three times daily until condition resolves.
- For application to particularly moist areas, nystatin powder is the preferred dosage form. The cream formulation is preferred over ointment for intertriginous areas.

### Baseline Investigations and Considerations

- Confirm fungal origin of infection and diagnosis of cutaneous or mucocutaneous candidiasis via KOH smears, cultures, or other appropriate diagnostic methods.

**Pharmacokinetics (Percutaneous Absorption, Distribution, Metabolism, Excretion: As Relevant for the Drug)**

- Nystatin is not absorbed systemically from the skin or mucous membranes.
- Symptomatic relief from candidiasis is typically achieved within 24–72 h after initiation of therapy.

**Use in Special Populations: Pregnancy (FDA Guidance), Lactation, Children, Renal Insufficiency, and Hepatic Insufficiency**

- This drug has not been evaluated in human or animal models for use in pregnant or lactating patients; however, due to the lack of systemic absorption, nystatin may be used with caution in such patients.
- It is not known whether nystatin is excreted in human milk.
- Safe for use in pediatric patients of all ages.

**Monitoring**

- Clinical response should be monitored.
- If condition does not improve with treatment, a repeat assessment of KOH smears, cultures, or other diagnostic methodology may be used to confirm diagnosis.

**Contraindications and Cautions**

- Nystatin is contraindicated in patients with a hypersensitivity to either the drug product or any component of the formulation.
- Hypersensitivity or skin irritation may occur. This medication should be discontinued if a hypersensitivity reaction occurs.
- This product is approved for external use only. Contact with the eyes, nose, mouth, or intravaginal tissue should be avoided.
- Some dosage forms may be formulated with propylene glycol. Exposure to large amounts of propylene glycol has been associated with potentially fatal neonatal toxicity and may present with metabolic acidosis, renal failure, CNS depression, and seizures. Similar propylene glycol toxicity has also been

reported in children and adults and may present with these findings, in addition to hyperosmolality and respiratory depression.

### **Important Drug Interactions**

- Progesterone (*Risk X*): Nystatin may decrease the efficacy of progesterone. Combinations with these products should be avoided.

### **Adverse Effects and Their Management**

- Contact dermatitis, Stevens-Johnson Syndrome, and hypersensitivity reactions are the most commonly reported adverse events seen with the use of nystatin; however, the overall incidence of adverse events in patients treated with Nystatin is <0.1%.

### **Patch Test Concentration**

- 2% pet. (SmartPractice Canada, Smart Practice Europe); testing in polyethylene glycol 400 (100,000 IU nystatin/gr) may be preferable over petrolatum

### **Essential Patient Information**

- This drug is used to treat fungal infections of the skin.
- For external use only. Contact with the eyes, nose, mouth, vagina, and other mucous membranes should be avoided.
- Nystatin powder should be stored at room temperature. Exposures to excessive heat ( $\geq 104^{\circ}\text{F}/40^{\circ}\text{C}$ ) should be avoided.
- This medication should be used for the full duration of treatment as prescribed by a physician, even if a patient's condition appears to have resolved.
- If severe skin irritation occurs or condition worsens, this medication should be discontinued, and a physician should be notified.

- If using the powder formulation for the treatment of tinea pedis, the powder can be dusted in all footwear in addition to being applied to the feet as directed by a physician.
- If any signs of an allergic reaction (*rash; hives; itching; red, swollen, blistered, or peeling skin; wheezing; chest or throat tightness; difficulty breathing, swallowing, or talking; unusual hoarseness; or swelling of the mouth, face, lips, tongue, or throat*) are noticed, appropriate medical help should be sought immediately. This medication should be discontinued and any side effects should be reported to a physician.

## **Tavaborole**

### **Classification and Mode of Action**

- Benzoxaborole derivative. Tavaborole is a benzoxaborole that prevents fungal synthesis through inhibition of fungal aminoacyl-transfer RNA (tRNA) synthetase. It has broad-spectrum antifungal activity against dermatophytes, non-dermatophyte molds, and yeasts.
- More effective than Ciclopirox but less effective than Efinaconazole in complete clearance of onychomycosis.

### **Indications and Dermatological Uses**

- *Clinical indications:* Onychomycosis (toenails).
- *Off-label common uses:* None.

### **Formulations/Presentation**

- US: 5% solution.
- Canada: Not on Health Canada Drug Product Database.
- Europe: Not on Lexicomp.

### **Dosages and Suggested Regimens**

- Onychomycosis: Application is once daily for 48 weeks (toenails).
- No suggested dosage adjustment for renal or hepatic impairment due to low systemic absorption.



**Baseline Investigations and Considerations**

- There are no known significant drug interactions.

**Pharmacokinetics (Percutaneous Absorption, Distribution, Metabolism, Excretion: As Relevant for the Drug)**

- Minimal topical absorption. Elimination half-life 28.5 h. Excreted in urine.
- Onset of effect: 2–3 months.

**Use in Special Populations: Pregnancy (FDA Guidance), Lactation, Children, Renal Insufficiency, and Hepatic Insufficiency**

- Safety and efficacy have not been determined in children. Internal use should be avoided.
- Listed as FDA pregnancy classification C (former classification system).
- Unknown whether tavaborole is present in breast milk.
- Renal insufficiency: not evaluated; dose adjustment is not expected to be needed.
- Hepatic insufficiency: not evaluated; dose adjustment is not expected to be needed.

**Monitoring**

- Skin irritation (erythema, exfoliation, and dermatitis) at the application site.

**Contraindications and Cautions**

- There are no contraindications listed in the manufacturer's labeling.
- Ophthalmic and mucous membrane use should be avoided.

**Important Drug Interactions**

- There are no known significant drug interactions.

### **Adverse Effects and Their Management**

- Skin irritation can occur at the application site. Exfoliation, erythema, and dermatitis are most common.
- Ingrown nails may occur.
- Hypersensitivity reactions such as allergic contact dermatitis may occur.

### **Patch Test Concentration**

- No data available

### **Essential Patient Information**

- This drug should be applied to the entire toenail surface including underside near the hyponychium.
- Nail polish should not be used during the treatment of onychomycosis.
- Contact with skin should be avoided. Excess solution from surrounding skin can be wiped.
- Tavaborole is flammable. Heat and flame should be avoided when applied.
- Contact with eyes, lips, or other mucous membranes should be avoided (e.g. inside nose).
- For external use only. This drug should not be ingested.

## **Tolnaftate**

### **Classification and Mode of Action**

Synthetic thiocarbamate. Tolnaftate works by distorting susceptible fungi hyphae and thereby stunting mycelial growth.

### **Indications and Dermatological Uses**

- *Clinical indications:* Tinea corporis, tinea cruris, tinea pedis treatment and prevention.
- *Off-label common uses:* Tinea manuum (level of evidence: D).

**Formulations/Presentation**

- US: 1% aerosol, 1% aerosol powder, 1% cream, 1% powder, 1% solution.
- Canada: 1% w/w spray, 1% cream, 1% tincture, 1% powder.

**Dosages and Suggested Regimens**

- This drug should be applied to the affected and surrounding area(s) twice a day until resolution in tinea corporis and tinea cruris but until 1 week after resolution for tinea pedis and tinea manuum.
- There is no suggested dosage adjustment for renal or hepatic impairment due to low systemic absorption.

**Baseline Investigations and Considerations**

- There are no known significant drug interactions.

**Pharmacokinetics (Percutaneous Absorption, Distribution, Metabolism, Excretion: As Relevant for the Drug)**

- Data on pharmacokinetics is unknown.
- Onset of effect: 24–72 h.

**Use in Special Populations: Pregnancy (FDA Guidance), Lactation, Children, Renal Insufficiency, Hepatic Insufficiency**

- Approved for use in children but not for self-medication for children under 2 years of age.
- There are no known effects of tolnaftate use in pregnancy or during lactation.
- There are no dosage adjustments recommended for use in hepatic or renal insufficiency.

**Monitoring**

- Skin irritation.
- Contact dermatitis.
- Pruritus.

**Contraindications and Cautions**

- Some dosage forms may be formulated with propylene glycol. Exposure to large amounts of propylene glycol has been associated with potentially fatal neonatal toxicity and may present with metabolic acidosis, renal failure, CNS depression, and seizures. Similar propylene glycol toxicity has also been reported in children and adults and may present with these findings, in addition to hyperosmolality and respiratory depression.

**Important Drug Interactions**

- There are no known significant drug interactions.

**Adverse Effects and Their Management**

- Skin irritation, stinging, and pruritus may occur and will improve when use is reduced.
- Contact dermatitis. Will improve when use is reduced. Topical steroids can improve symptoms.

**Patch Test Concentration**

- 1% pet.

**Essential Patient Information**

- Does not work for nail or scalp infections.
- May cause skin irritation.
- Affected area should be cleaned before use.
- The treated area should be dried well and should not be covered unless specified by healthcare provider.
- Hands should be washed before and after use.
- Contact with eyes should be avoided.
- This drug should not be used for diaper rash.

**Summary**

Fungi of medical importance are capable of causing an array of diseases, ranging from asymptomatic superficial skin infections to fatal systemic infections. While immunocompromised individ-

uals are at greatest risk of fungal infections, they may occur in anyone. Topical antifungal drugs are commonly used to treat a superficial yeast and dermatophyte infections. Most antifungals function by taking advantage of cellular processes unique to fungi, allowing for limited cross reactivity with human cells and thus less side effects. However, like other antimicrobials, resistance to antifungals is increasing. When faced with recalcitrant or severe fungal infections, systemic antifungals are typically the treatment of choice.

---

## References

### Allylamines

1. FDA drug monograph. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/019356s008,019599s014,204286s0031bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/019356s008,019599s014,204286s0031bl.pdf). Accessed: 15 Dec 2021.
2. Naftifine monograph from LexiComp Online at [online.lexi.com](https://online.lexi.com). Copyright 2021 UpToDate, Inc.

### Terbinafine

3. FDA drug monograph. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/1999/20846s0011bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/1999/20846s0011bl.pdf). Accessed: December 16, 2021.
4. Terbinafine monograph from LexiComp Online at [online.lexi.com](https://online.lexi.com). Copyright 2021 UpToDate, Inc.

### Azoles: Clotrimazole

5. FDA drug monograph. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2009/020010s0211bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020010s0211bl.pdf). Accessed: 17 Dec 2021.
6. <https://nctr-crs.fda.gov/fdalabel/services/spl/set-ids/78d792a0-15d5-4c71-a63b-91c24e469df1/spl-doc?hl=Clotrimazole>. Accessed 17 Dec 2021.
7. Clotrimazole monograph from LexiComp Online at [online.lexi.com](https://online.lexi.com). Copyright 2024 UpToDate, Inc.
8. Health Canada Drug & Health Products Register—Clotrimazole: <https://hpr-rps.hres.ca/query.php?drugquery=clotrimazole>. Accessed 28 Feb 2024.

## Econazole

9. FDA drug monograph. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/205175s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/205175s000lbl.pdf). Accessed 18 Dec 2021.
10. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/018751s024lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/018751s024lbl.pdf). Accessed 18 Dec 2021.
11. <https://fda.report/DailyMed/3ACC5E03-0339-4B23-945D-641746E81923.pdf>. Accessed 18 Dec 2021.
12. Econazole monograph from LexiComp Online at [online.lexi.com](https://online.lexi.com). Copyright 2021 UpToDate, Inc.

## Ketoconazole

13. FDA drug monograph. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/019927s032lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/019927s032lbl.pdf). Accessed 20 Dec 2021.
14. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/021946s007lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021946s007lbl.pdf). Accessed 20 Dec 2021.
15. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2007/021738lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021738lbl.pdf). Accessed 20 Dec 2021.
16. Ketoconazole monograph from LexiComp Online at [online.lexi.com](https://online.lexi.com). Copyright 2021 UpToDate, Inc.
17. Health Canada Drug & Health Products Register—Ketoconazole: <https://hpr-rps.hres.ca/query.php?drugquery=ketoconazole>. Accessed 28 Feb 2024.

## Luliconazole

18. FDA drug monograph. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/204153s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204153s000lbl.pdf). Accessed 22 Dec 2021.
19. <https://fda.report/DailyMed/7CCDA3BA-9C98-468D-83C6-7F0CC7C88C33.pdf>. Accessed 22 Dec 2021.
20. Luliconazole monograph from LexiComp Online at [online.lexi.com](https://online.lexi.com). Copyright 2021 UpToDate, Inc.

## Miconazole Nitrate

21. FDA drug monograph. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/021026s013lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021026s013lbl.pdf). Accessed 27 Dec 2021.
22. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2006/021026s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/021026s000lbl.pdf). Accessed 27 Dec 2021.
23. Miconazole Nitrate monograph from LexiComp Online at [online.lexi.com](https://online.lexi.com). Copyright 2021 UpToDate, Inc.

24. Health Canada Drug & Health Products Register—Miconazole: <https://hpr-rps.hres.ca/query.php?drugquery=miconazole>. Accessed 28 Feb 2024.
25. Barasch A, Griffin AV. Miconazole revisited: new evidence of antifungal efficacy from laboratory and clinical trials. *Future Microbiol.* 2008;3(3):265–9. <https://doi.org/10.2217/17460913.3.3.265>.

## Oxiconazole Nitrate

26. FDA drug monograph. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2004/19828slr009,20209slr005\\_oxistat\\_lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/19828slr009,20209slr005_oxistat_lbl.pdf). Accessed 29 Dec 2021.
27. <https://nctr-crs.fda.gov/fdalabel/services/spl/set-ids/b87a89d2-6e45-4eb8-be2c-7f55f34d61e5/spl-doc?hl=oxiconazole%20nitrate>. Accessed 29 Dec 2021.
28. Oxiconazole Nitrate monograph from LexiComp Online at [online.lexi.com](https://online.lexi.com). Copyright 2021 UpToDate, Inc.
29. Health Canada Drug & Health Products Register—Oxiconazole: <https://hpr-rps.hres.ca/query.php?drugquery=oxiconazole>. Accessed 19 Apr 2024.

## Sertaconazole Nitrate

30. FDA drug monograph. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2020/021385s006lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021385s006lbl.pdf). Accessed 1 Jan 2021.
31. Sertaconazole Nitrate monograph from LexiComp Online at [online.lexi.com](https://online.lexi.com). Copyright 2021 UpToDate, Inc.

## Sulconazole

32. FDA drug monograph. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2003/18737slr003\\_exelderm\\_lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2003/18737slr003_exelderm_lbl.pdf). Accessed 3 Jan 2021.
33. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2009/018738s009lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/018738s009lbl.pdf). Accessed 3 Jan 2021.
34. <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=cf6f4340-940c-4a61-b675-456e3297d810&type=display>. Accessed 3 Jan 2021.
35. <https://nctr-crs.fda.gov/fdalabel/services/spl/set-ids/cf6f4340-940c-4a61-b675-456e3297d810/spl-doc?hl=sulconazole%20nitrate>. Accessed 3 Jan 2021.

36. <https://nctr-crs.fda.gov/fdalabel/services/spl/set-ids/5b731aa0-fb3f-4a96-9034-636138cbca03/spl-doc?hl=sulconazole%20nitrate>. Accessed 3 Jan 2021.
37. Sulconazole monograph from LexiComp Online at [online.lexi.com](https://online.lexi.com). Copyright 2021 UpToDate, Inc.

## Butenafine HCl

38. FDA drug monograph. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2002/214081bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2002/214081bl.pdf). Accessed 4 Jan 2021.
39. Butenafine HCl monograph from LexiComp Online at [online.lexi.com](https://online.lexi.com). Copyright 2021 UpToDate, Inc.
40. Health Canada Drug & Health Products Register—Butenafine: <https://hpr-rps.hres.ca/query.php?drugquery=butenafine>. Accessed 19 Apr 2024.

## Ciclopirox Olamine

41. FDA drug monographs. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/018748s024,019824s023,020519s0161bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/018748s024,019824s023,020519s0161bl.pdf). Accessed 11 Nov 2021.
42. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2004/21022s0041bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/21022s0041bl.pdf). Accessed 11 Nov 2021.
43. Ciclopirox olamine monograph from LexiComp Online at [online.lexi.com](https://online.lexi.com). Copyright 2021 UpToDate, Inc.
44. Lipner SR, Scher RK. Onychomycosis: treatment and prevention of recurrence. *J Am Acad Dermatol*. 2019;80(4):853–67.

## Nystatin

45. FDA drug monograph. <https://nctr-crs.fda.gov/fdalabel/services/spl/set-ids/629d2b7e-a5b8-4b6d-ba59-46e1c51da5bf/spl-doc?hl=nystatin>. Accessed: 5 Jan 2021.
46. <https://nctr-crs.fda.gov/fdalabel/services/spl/set-ids/e1b4622c-0f9f-4c00-b42c-2aa85a5e3d4f/spl-doc?hl=nystatin>. Accessed 5 Jan 2021.
47. <https://nctr-crs.fda.gov/fdalabel/services/spl/set-ids/6a3bb3da-adf9-46d2-a5ff-f796e7aae7a1/spl-doc?hl=nystatin>. Accessed 5 Jan 2021.
48. Nystatin monograph from LexiComp Online at [online.lexi.com](https://online.lexi.com). Copyright 2021 UpToDate, Inc.
49. Health Canada Drug & Health Products Register—Nystatin: <https://hpr-rps.hres.ca/query.php?drugquery=nystatin>. Accessed 28 Feb 2024.



## Tavaborole

50. FDA drug monograph. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2014/204427s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/204427s000lbl.pdf). Accessed 11 Nov 2021.
51. Tavaborole monograph from LexiComp Online at [online.lexi.com](https://online.lexi.com). Copyright 2021 UpToDate, Inc.
52. Elewski BE, Aly R, Baldwin SL, Soto RF, Rich P, Weisfeld M, Wiltz H, Zane LT, Pollak R. Efficacy and safety of tavaborole topical solution, 5%, a novel boron-based antifungal agent, for the treatment of toenail onychomycosis: results from 2 randomized phase-III studies. *J Am Acad Dermatol*. 2015;73(1):62–9.

## Tolnaftate

53. FDA drug monograph. <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=333.210>. Accessed 3 Jan 2021.
54. Tolnaftate monograph from LexiComp Online at [online.lexi.com](https://online.lexi.com). Copyright 2021 UpToDate, Inc.
55. Health Canada Drug & Health Products Register—Tolnaftate: <https://hpr-rps.hres.ca/query.php?drugquery=tolnaftate>. Accessed 19 Apr 2024.



# Topical Antineoplastics in Dermatology

# 14

Christina Huang, Paola A. Baker,  
Chavy Chiang, Anuk Burli,  
Enzo Berardesca, Bradley D. Kwinta,  
Larisa J. Geskin, and Jack L. Arbiser

## Contents

|                               |     |
|-------------------------------|-----|
| Introduction.....             | 362 |
| Antineoplastic Retinoids..... | 363 |
| Fluorouracil (5-FU).....      | 364 |
| Mechlorethamine Gel.....      | 364 |
| Romidepsin.....               | 368 |
| Vorinostat.....               | 373 |
| References.....               | 378 |

---

C. Huang  
Sidney Kimmel Medical College, Thomas Jefferson University,  
Philadelphia, PA, USA  
e-mail: [christina.huang@students.jefferson.edu](mailto:christina.huang@students.jefferson.edu)

P. A. Baker  
Department of Dermatology, Emory University School of Medicine,  
Atlanta, GA, USA  
e-mail: [pao-olaya@hotmail.com](mailto:pao-olaya@hotmail.com)

C. Chiang  
Department of Dermatology, University of Rochester Medical Center,  
Rochester, NY, USA  
e-mail: [chavyz@gmail.com](mailto:chavyz@gmail.com)

© The Author(s), under exclusive license to Springer Nature  
Switzerland AG 2025  
R. M. Law, H. I. Maibach (eds.), *Handbook of Topical Drug  
Treatment in Dermatology*,  
[https://doi.org/10.1007/978-3-031-93616-6\\_14](https://doi.org/10.1007/978-3-031-93616-6_14)

361

## Introduction

Topical antineoplastic agents have been effective against various cutaneous lesions for multiple decades and serve as useful therapeutic tools in clinical dermatology [1]. Of note, efficacy of topical antineoplastics against basal cell carcinoma and actinic keratosis has been well acknowledged [2, 3]. Beyond these applications, certain antineoplastic agents have shown utility in treating multiple skin conditions outside of their FDA-approved indications. For instance, imiquimod has been used to treat various cutaneous conditions such as mycosis fungoides and Kaposi's sarcoma, despite it being only FDA approved for perianal warts, basal cell carcinoma, and actinic keratosis [4]. Topical antineoplastics also have various mechanisms of action, from 5-fluorouracil, which inhibits metabolism, to imiquimod, which modulates the immune system [1, 5, 6]. With diversity in clinical applications and mechanism of action, topical antineoplastics have significant potential for future research regarding clinical efficacy or new compounds under development [7].

The use of topical antineoplastics is clinically beneficial in multiple ways. Topical antineoplastics serve as a valuable alternative

---

A. Burli

Department of Dermatology, Stanford University School of Medicine,  
Redwood City, CA, USA

e-mail: [anukb@stanford.edu](mailto:anukb@stanford.edu)

E. Berardesca

Dr. Phillip Frost Department of Dermatology and Cutaneous Surgery,  
Miller School of Medicine, University of Miami, Miami, FL, USA

e-mail: [Berardesca@berardesca.it](mailto:Berardesca@berardesca.it)

B. D. Kwintā · K. L. Geskin

Department of Dermatology at Columbia University Irving Medical  
Center, New York, NY, USA

e-mail: [bdk2123@cumc.columbia.edu](mailto:bdk2123@cumc.columbia.edu); [ljk2145@cumc.columbia.edu](mailto:ljk2145@cumc.columbia.edu)

J. L. Arbiser (✉)

Department of Dermatology, Emory University School of Medicine,  
Winship Cancer Institute, Atlanta Veterans Administration Health Center,  
Atlanta, GA, USA

e-mail: [jarbise@emory.edu](mailto:jarbise@emory.edu)

to surgical treatment in conditions such as basal cell carcinoma, especially if the presentation or preferences of the individual patient disfavor surgery [8]. One study found that patients with low-risk nodular and superficial basal cell carcinoma valued 5% imiquimod cream more highly than excisional surgery, with patients considering cosmetic outcome and potential adverse effects [9]. Another study found that although surgical outcomes were superior to topical imiquimod in low-risk nodular or superficial basal cell carcinoma, there is still sustained treatment benefit for lesions that respond to topical antineoplastics [10]. When compared to systemic therapies, topical antineoplastic agents have less systemic absorption, limiting potential adverse effects [11, 12]. Topical administration also increases the local concentration of a drug, resulting in higher efficacy in the area of administration, which is particularly useful for localized cutaneous tumors [7]. Overall, topical antineoplastics serve as an important option in the individualized clinical treatment of cutaneous tumors.

---

## Antineoplastic Retinoids

Enzo Beradesca

There are two retinoids which are used topically as antineoplastic agents.

*Alitretinoin* is a retinoic acid derivative used as an antineoplastic (topical) and anti-inflammatory (oral) agent. It is a naturally occurring endogenous retinoid that binds to and activates intracellular retinoid receptors (RAR and RXR subtypes); this results in altered expression of the genes controlling cellular differentiation and proliferation in normal and neoplastic cells, inhibiting the growth of Kaposi sarcoma.

*Bexarotene* binds to and activates retinoid X receptor subtypes. Once activated, these receptors function as transcription factors that regulate the expression of genes which control cellular differentiation and proliferation, resulting in decreased cell proliferation, apoptosis of some cancer cell types, and tumor regression. It is indicated for treatment of cutaneous T-cell lymphoma.

See Chap. 23: Retinoids for the alitretinoin and bexarotene drug monographs.

---

## Fluorouracil (5-FU)

Chavy Chiang and Anuk Burli

Fluorouracil prevents methylation of deoxyuridylic acid to thymidylic acid to block DNA and, to a lesser extent, RNA synthesis, particularly so in rapidly growing cells.

It is indicated for the treatment of actinic keratosis and basal cell carcinoma (superficial). There are off-label uses for other neoplasms as well.

See Chap.10: Drug Treatment for Actinic Keratosis for the Drug Monograph.

---

## Mechlorethamine Gel

B. Kwinta and L. Geskin

### Classification and Mode of Action

- Mechlorethamine, known as nitrogen mustard, is an alkylating agent. When used systemically, it forms DNA cross-links and inhibits DNA synthesis in rapidly dividing cells. Topically, the mechanism of action is not fully understood but may be immune mediated [22, 23].
- Mechlorethamine HCl 0.016% gel (equivalent to 0.02% chlor-methine/mechlorethamine ointment) was shown to be non-inferior to Aquaphor®-based mechlorethamine HCl 0.02% ointment in a pivotal 2013, phase 2, randomized controlled trial in patients with persistent or recurrent stage IA, IB, and IIA mycosis fungoides who had received at least one skin directed therapy [24].

## Indications and Dermatological Uses

- *Clinical indications (FDA)*: Topical treatment of stage IA and IB mycosis fungoides in adult patients who have received prior skin-directed therapy.
- *Off-label common uses*: Not applicable.

## Formulations/Presentation

- USA: Brand name Valchlor. 60 g tube of Valchlor 0.016% gel (equivalent to 0.02% mechlorethamine HCl). No generic.
- Canada: Brand name Legada. 60 g tube of Legada 0.016% gel (equivalent to 0.02% mechlorethamine HCl).
- Europe: Brand name Legada. 60 g tube of Legada 0.016% gel (equivalent to 0.02% mechlorethamine HCl).

## Dosages and Suggested Regimens

- Mechlorethamine gel should be stored in a refrigerator, at a temperature between 36 °F and 46 °F (2 °C–8 °C).
- Apply within 30 min of removal from the refrigerator.
- Apply to dry skin at least 4 h before or 30 min after showering or washing.
- Using disposable nitrile gloves, apply a thin film once daily to affected areas of the skin. Safely dispose of gloves after application.
- Wash hands after application, and let skin dry for 5–10 min before covering area with clothing.
- Avoid open flames as the gel is alcohol-based and flammable.
- Moisturizer can be applied within 2 h of application.
- Do not apply water or air-tight dressings to the area.
- The pivotal randomized trial prohibited topical corticosteroid use. Some studies suggest that dose frequency modifications and concomitant therapy use (primarily corticosteroids, phototherapy, systemic retinoids) are generally well tolerated [25, 26].

- Experts generally recommend concurrent intermittent use of topical corticosteroids to minimize skin irritation and avoid dose modifications [26].

## **Baseline Investigations and Considerations**

### **Pharmacokinetics**

- No systemic absorption was detected in the pivotal trial.

### **Use in Special Populations: Pregnancy**

- Women should avoid becoming pregnant while using this medication.
- It is unknown whether mechlorethamine passes into breast-milk. Nursing mothers should discontinue drug or nursing.
- Not approved for use in children.
- No special considerations are needed for renal or hepatic insufficiency.

### **Monitoring**

- Dermatitis.
- Non-melanoma skin cancers.

### **Contraindications and Cautions**

- Patients with known severe hypersensitivity reactions to this medication, including anaphylaxis, should avoid using it. Patients who experience a severe hypersensitivity reaction should seek immediate medical help.

## Important Drug Interactions

- Drug interaction studies have not been conducted, though are unlikely due to lack of systemic absorption.

## Adverse Effects and Their Management

- May cause dermatitis. Patients should be monitored and report any redness, swelling, inflammation, itchiness, blisters, ulceration, or secondary skin infections. Treatment should be stopped or dose frequency reduced.
- May increase risk of developing non-melanoma skin cancers. Patients should undergo full body skin examinations during and after treatment. Patients should report new skin lesions to their healthcare provider.

## Carcinogenicity

- Painting studies in mice at a dose of 4 mg/kg weekly for up to 33 weeks resulted in squamous cell tumors in 9 of 33 mice—however, at maximum, over the total body surface, patients use 0.034 mg/kg daily, 100 times less. More recent studies show no increased risk of secondary malignancies [27].

## Patch Test Concentration

- 0.02% water; perform an open test first.

## Essential Patient Information

- For use on the skin only.
- Avoid contact with the eyes, lips, or other mucous membranes (e.g., inside the nose). Exposure can cause permanent damage or blindness. If exposure occurs, irrigate the area for 15 min with water and then seek immediate medical help.



Caregivers and individuals other than the patient should avoid direct skin contact. Risks of exposure are the same as in the patient including dermatitis, non-melanoma skin cancers, and eye/mucosa injury. If contact occurs, wash the area with soap and water for at least 15 min and remove contacted clothing.

---

## Romidepsin

C. Huang, P. Baker, and J. Arbiser

### Classification and Mode of Action

- Romidepsin is a histone deacetylase (HDAC) inhibitor. By inhibiting histone deacetylation, romidepsin causes accumulation of acetylated histones. This leads to a wide profile of epigenetic modifications and gene expression. This is thought to result in arrest cell cycle at G1 and G2/M phase and induce apoptosis [30].
- Romidepsin may also have other effects that target survival of malignant T cells, including activation of stress signal pathways and DNA hypomethylation [31].
- A Phase II clinical trial showed romidepsin had a relatively high response rate in the treatment of cutaneous T-cell lymphoma (CTCL), leading to its approval as a monotherapy for CTCL patients who had failed at least one prior systemic therapy [32].
- A Phase III clinical trial showed the addition of romidepsin to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) therapy did not significantly improve outcomes as a first-line treatment for peripheral T-cell lymphoma (PTCL) [33].

## Indications and Dermatological Uses

- *Clinical indications (FDA)*: Romidepsin is indicated for the treatment of CTCL in patients who had received at least one prior systemic therapy.
- *Off-label common uses*: Evidence previously supported romidepsin use to treat PTCL that has either relapsed or been refractory to treatment. However, after Phase III clinical trial results of romidepsin and CHOP, the indication for romidepsin in PTCL has been withdrawn [34].

## Formulations/Presentation

- USA: Brand name Istodax. 10 mg of romidepsin in lyophilized powder and 20 mg of povidone with a 20-mL dilutant (80% propylene glycol, USP, and 20% dehydrated alcohol, USP). Generic: 27.5 mg/5.5 mL IV solution or 10 mg powder.
- Canada: Brand name Istodax. 10 mg of romidepsin in lyophilized powder and 20 mg of povidone with a 20-mL dilutant (80% propylene glycol, USP, and 20% dehydrated alcohol, USP).
- Europe: Not approved for use in Europe.

## Dosages and Suggested Regimens

- Romidepsin should be administered intravenously (IV) at a dose of 14 mg/m<sup>2</sup> over a 4-hour period on days 1, 8, and 15 of a 28-day cycle.
- Repeat this treatment cycle every 28 days as long as the patient benefits from and tolerates romidepsin.
- Romidepsin powder, romidepsin solution, and provided dilutant should be stored at 20 °C to 25 °C.
- Once romidepsin powder is reconstituted, the solution is stable for 8 h at room temperature.

- If romidepsin powder or romidepsin solution is diluted for infusion in normal saline, the solution can be stable for up to 24 h at room temperature. However, manufacturer instructions recommend infusing as soon as possible.

## **Baseline Investigations and Considerations**

- Antiemetics are recommended as romidepsin has a moderate emetic potential.
- Electrolyte imbalances either before or during treatment should be corrected.
- Antiviral prophylaxis should be considered in patients with a history of hepatitis B infection.
- Romidepsin binds to estrogen receptors and may reduce effectiveness of estrogen-containing contraceptives.

## **Pharmacokinetics**

- Romidepsin has linear pharmacokinetics at the recommended dose.
- Distribution: Romidepsin is 92–94% bound to plasma protein (mostly  $\alpha$ 1-acid-glycoprotein).
- Metabolism: Romidepsin is primarily metabolized hepatically by CYP3A4, with minor CYP3A5, CYP1A1, CYP2B6, and CYP2C19 activity.
- Excretion: The terminal half-life of romidepsin is approximately 3 h.

## **Use in Special Populations**

- Pregnancy: FDA former Category D. Not to be used in pregnancy.
- Lactation: No information.
- Children: No information about safety and efficacy of romidepsin in children.

- Renal insufficiency: Renal function is not expected to affect safety of romidepsin; however, patients with end-stage renal disease should be treated with caution.
- Hepatic insufficiency: Mild hepatic impairment does not impair romidepsin metabolism; patients with moderate to severe hepatic impairment should be treated with caution.

## Monitoring

- Monitor potassium and magnesium levels to avoid QT prolongation.
- Monitor hematological parameters to avoid thrombocytopenia, leukopenia, and/or anemia.
- Monitor for prolonged prothrombin time (PT) and International Normalized Ratio. (INR) in patients receiving romidepsin and coumadin derivatives.
- Monitor for tumor lysis syndrome.
- Monitor for toxicity in patients with moderate or severe hepatic impairment.

## Contraindications

- Hypersensitivity reaction to romidepsin.

## Cautions

- QT interval prolongation, especially in patients with congenital long QT syndrome, patients taking medications that may increase QT length, or patients with current or previous cardiac disease.
- Thrombocytopenia, leukopenia, anemia—note that serious infections may occur because of leukopenia.
- Tumor lysis syndrome, especially in patients with advanced disease/high tumor burden.

## Important Drug Interactions

- CYP3A4 inhibitors/inducers might increase/decrease concentrations of romidepsin, respectively.
- Coumadin with romidepsin may excessively increase PT/INR.
- Drugs that inhibit P-glycoprotein, an efflux transporter, may increase concentrations of romidepsin.

## Adverse Effects and Their Management

- Nausea/vomiting—antiemetics are recommended as romidepsin is associated with moderate emetic potential.
- Fatigue—patients can seek medical help if fatigue is persistent or bothersome.
- Infections—patients should seek medical advice for more severe adverse effects such as infections.
- Anorexia—patients can seek medical help if fatigue is persistent or bothersome.
- Anemia—patients should have hematologic parameters monitored.
- Thrombocytopenia—patients should have hematologic parameters monitored.
- ECG T-wave changes—patient electrolyte levels (especially sodium and potassium) should be monitored and corrected as needed to prevent cardiologic adverse effects.
- Neutropenia—patients should have hematologic parameters monitored.
- Lymphopenia—patients should have hematologic parameters monitored.

## Carcinogenicity

- No studies done.

## Patch Test Concentration

- Not available.

## Essential Patient Information

- Patients should be cautioned that romidepsin could prolong the QT interval, potentially leading to torsades de pointes if given with other medications that prolong the QT interval.

---

## Vorinostat

P. Baker, C. Huang, and J. L. Arbiser

## Classification and Mode of Action

- Vorinostat, known as suberoylanilide hydroxamic acid or SAHA, is a histone deacetylase (HDAC) class I and II inhibitor. Vorinostat induces cell cycle arrest, differentiation, or apoptosis of transformed cells. Vorinostat inhibits HDAC activity by binding to the active site and inducing accumulation of acetylated proteins. The antiproliferative effects of vorinostat are believed to be due to a drug-induced accumulation of acetylated proteins, including the core nucleosomal histones and other proteins such as BCL6, p53, and Hsp90. These effects include an alteration in the transcription of genes via acetylation of histones and transcription factors, and non-transcriptional effects such as inhibition of mitosis. Vorinostat has shown to impact the expression of several genes, some of which are induced such as p21<sup>WAF1</sup>, histone H2B, metallothionein 1 L, TBP-2, and gelsolin, while others are repressed including cyclin D1, thymidylate synthase, ErbB2, and importin b [37, 38].

- Vorinostat has shown to be active against hematologic malignancies and solid tumors as oral and intravenous preparations in Phase I development trial. In two Phase II clinical trials, vorinostat shown to be safe and effective at an oral dose of 400 mg/day with an overall response rate of 24–30% in refractory advanced patients with cutaneous T-cell lymphoma (CTCL) including large cell transformation and Sezary syndrome [39]. One of these trials led vorinostat's approval as treatment of cutaneous manifestation of CTCL in refractory patients [40, 41].

## Indications and Dermatological Uses

- *Clinical indications (FDA)*: Oral systemic therapy of cutaneous manifestation of CTCL in patients with progressive, persistent, or recurrent disease on or following two systemic therapies.
- *Off-label common uses*: No data available.

## Formulations/Presentation

- USA: Brand name Zolinza. Capsules 100 mg. No generic.
- Canada: Brand name Zolinza. Capsules 100 mg.
- Europe: Not approved for use in the EU.

## Dosages and Suggested Regimens

- Zolinza capsules should be stored at 68 °F to 77 °F (20 °C to 25 °C); excursions are permitted to 59 °F to 86 °F (15 °C to 30 °C).
- The recommended dose is 400 mg orally once daily with food. It's important to maintain adequate hydration ( $\geq 2$  L/day fluids) during treatment. The treatment may be continued until disease progression or unacceptable toxicity.
- The capsules shouldn't be opened, broken, or chewed.

## Baseline Investigations and Considerations

- If patient is intolerant to therapy, the dose may be reduced to 300 mg orally once daily with food. The dose may be further reduced to 300 mg orally once daily with food for 5 consecutive days each week.

## Pharmacokinetics

- Time to peak plasma with high-fat meal is 4 h (range 2–10 h).
- Distribution: Vorinostat is approximately 71% bound to human plasma proteins.
- Metabolism: Vorinostat is glucuronidated and hydrolyzed followed by beta-oxidation to inactive metabolites. Vorinostat has negligible biotransformation by cytochromes P450.
- Excretion: Vorinostat is eliminated predominantly through metabolism. Renal excretion is ~52 as inactive metabolites and <1% as unchanged drug in urine.
- Vorinostat half-life elimination is ~2 h.

## Use in Special Populations

- Pregnancy: FDA former category D. Not to be used in pregnancy.
- Lactation: It is not known whether vorinostat is excreted in human milk. Due to the potential for serious adverse reactions, breastfeeding is not recommended during therapy and for at least 7 days after the last dose.
- Children: Safety and effectiveness in pediatric patients have not been established.
- Renal insufficiency: Vorinostat was not evaluated in patients with renal impairment. However, renal excretion does not play a role in the elimination of vorinostat, patients with preexisting renal impairment should be treated with caution.
- Hepatic insufficiency: Vorinostat is contraindicated in patients with severe hepatic impairment and should be used with caution in patients with mild and moderate hepatic impairment.



Mild to moderate hepatic impairment (total bilirubin one to three times ULN or AST > ULN): Initial dose 300 mg once daily.

## Monitoring

- Monitor CBC Classification and (with differential) and serum chemistry including potassium, calcium, magnesium, glucose, and creatinine at baseline, then every 2 weeks during the first 2 months of therapy, and monthly thereafter, or as clinically necessary.
- Monitor hepatic function to avoid hepatic toxicity.
- Monitor INR if on concomitant warfarin therapy.
- Monitor fluid status.
- Monitor for signs/symptoms of thromboembolism.

## Contraindications and Cautions

- Patients with severe hepatic impairment (total bilirubin  $\geq 3$  times ULN) should avoid use.
- Patients with known hypersensitivity to vorinostat should avoid use.
- Patients with mild and moderate hepatic impairment should be treated with caution.
- Screening for hepatitis B virus should be performed prior to starting therapy.
- Correct electrolyte abnormalities prior to starting therapy.
- Use vorinostat with caution in patients with a history of QT prolongation or with medications known to prolong the QT interval.

## Important Drug Interactions

- Coumarin-derivate anticoagulants might increase PT/INR.
- Other HDAC inhibitors might increase risk of thrombocytopenia and gastrointestinal bleeding.
- 5-Aminosalicylic acid derivatives might enhance myelosuppressive effect.

## Adverse Effects and Their Management

- Gastrointestinal symptoms: diarrhea/constipation, nausea, dry mouth, and dysgeusia. Vorinostat is associated with low emetic potential (<30%): Patients can seek medical help if symptoms are persistent or bothersome. Patient fluid status and electrolyte levels should be monitored and corrected as needed.
- Constitutional symptoms: fatigue, anorexia, and weight decrease: Patients can seek medical help if fatigue/anorexia is persistent or bothersome.
- Hematologic abnormalities: thrombocytopenia and anemia: Patients should have hematologic parameters monitored. If toxicity, consider dose reduction.
- Cardiopulmonary: pulmonary embolism: Monitor for signs/symptoms especially in patients with a history of thrombotic events. Patients should seek immediate medical help if symptoms of thromboembolism occur. Prolonged QT interval on ECG: Monitor and correct potassium, calcium, and magnesium levels during therapy.
- Signs of an allergic reaction/anaphylaxis: Patients should seek immediate medical help if symptoms of allergy occur.
- Laboratory abnormalities: hyperglycemia and increased serum creatinine: Patients should have metabolic parameters monitored.

## Carcinogenicity

- Carcinogenicity studies have not been performed with vorinostat.

## Patch Test Concentration

- Not available.

## Essential Patient Information

- Avoid pregnancy: pregnancy testing should be conducted within 7 days prior to treatment in females of reproductive potential, and use an effective contraceptive during therapy and for at least 6 months after the last vorinostat dose.

---

## References

1. Ceilley RI. Mechanisms of action of topical 5-fluorouracil: review and implications for the treatment of dermatological disorders. *J Dermatolog Treat.* 2012;23:83–9. <https://doi.org/10.3109/09546634.2010.507704>.
2. Micali G, Lacarrubba F, Nasca MR, Schwartz RA. Topical pharmacotherapy for skin cancer: part I. pharmacology. *J Am Acad Dermatol.* 2014;70(965):e961–965.e912. <https://doi.org/10.1016/j.jaad.2013.12.045>.
3. Micali G, Lacarrubba F, Nasca MR, Ferraro S, Schwartz RA. Topical pharmacotherapy for skin cancer: part II. Clinical applications. *J Am Acad Dermatol.* 2014;70(979):e971–979.e912. <https://doi.org/10.1016/j.jaad.2013.12.037>.
4. Hanna E, Abadi R, Abbas O. Imiquimod in dermatology: an overview. *Int J Dermatol.* 2016;55:831–44. <https://doi.org/10.1111/ijd.13235>.
5. Rhodes J. Discovery of immunopotentiatory drugs: current and future strategies. *Clin Exp Immunol.* 2002;130:363–9. <https://doi.org/10.1046/j.1365-2249.2002.02016.x>.
6. Grossberg AL, Gaspari AA. Topical antineoplastic agents in the treatment of mucocutaneous diseases. *Curr Probl Dermatol.* 2011;40:71–82.
7. Cullen JK, Simmons JL, Parsons PG, Boyle GM. Topical treatments for skin cancer. *Adv Drug Deliv Rev.* 2020;153:54–64. <https://doi.org/10.1016/j.addr.2019.11.002>.

8. Kash N, Silapunt S. A review of emerging and non-US FDA-approved topical agents for the treatment of basal cell carcinoma. *Future Oncol.* 2021;17:3111–32. <https://doi.org/10.2217/fon-2020-1147>.
9. Tinelli M, Ozolins M, Bath-Hextall F, Williams HC. What determines patient preferences for treating low risk basal cell carcinoma when comparing surgery vs imiquimod? A discrete choice experiment survey from the SINS trial. *BMC Dermatol.* 2012;12:19. <https://doi.org/10.1186/1471-5945-12-19>.
10. Williams HC, et al. Surgery versus 5% imiquimod for nodular and superficial basal cell carcinoma: 5-year results of the SINS randomized controlled trial. *J Invest Dermatol.* 2017;137:614–9. <https://doi.org/10.1016/j.jid.2016.10.019>.
11. Dillaha CJ, Jansen GT, Honeycutt WM, Holt GA. Further studies with topical 5-fluorouracil. *Arch Dermatol.* 1965;92:410–7. <https://doi.org/10.1001/archderm.1965.01600160066015>.
12. Bubna AK. Imiquimod—its role in the treatment of cutaneous malignancies. *Ind J Pharmacol.* 2015;47:354–9. <https://doi.org/10.4103/0253-7613.161249>.

## Antineoplastic Retinoids: Alitretinoin

13. Panretin (alitretinoin) [prescribing information]. Concordia Pharmaceuticals; May 2020.
14. Walmsley S, Northfelt DW, Melosky B, Conant M, Friedman-Kien AE, Wagner B. Treatment of AIDS-related cutaneous Kaposi's sarcoma with topical alitretinoin (9-cis-retinoic acid) gel. Panretin Gel North American Study Group. *J Acquir Immune Defic Syndr.* 1999;22(3):235–46. [PubMed 10770343]

## Antineoplastic Retinoids: Bexarotene

15. Breneman D, Duvic M, Kuzel T, Yocum R, Truglia J, Stevens VJ. Phase 1 and 2 trial of bexarotene gel for skin-directed treatment of patients with cutaneous T-cell lymphoma [published correction appears in *Arch Dermatol.* 2002;138(10):1386]. *Arch Dermatol.* 2002;138(3):325–32. <https://doi.org/10.1001/archderm.138.3.325>. [PubMed 11902983]
16. Heald P, Mehlmauer M, Martin AG, Crowley CA, Yocum RC, Reich SD, Worldwide Bexarotene Study Group. Topical bexarotene therapy for patients with refractory or persistent early-stage cutaneous T-cell lymphoma: results of the phase III clinical trial. *J Am Acad Dermatol.* 2003;49(5):801–15. [https://doi.org/10.1016/s0190-9622\(03\)01475-0](https://doi.org/10.1016/s0190-9622(03)01475-0). [PubMed 14576658]
17. Targretin (bexarotene) [prescribing information]. Bridgewater, NJ: Valeant; October 2016.

## Fluorouracil (5-FU)

18. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/012209s0401bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/012209s0401bl.pdf)
19. LexiComp drug monograph Fluorouracil. Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2024 UpToDate, Inc.

## Mechlorethamine Gel

20. FDA drug monograph VALCHLOR (mechlorethamine) gel, for topical use. Available from: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/2023171bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/2023171bl.pdf). Accessed 5 Jan 2022.
21. LexiComp drug monograph Mechlorethamine (nitrogen mustard) topical gel. Available from: LexiComp Online at [online.lexi.com](https://online.lexi.com) Copyright 2021 UpToDate, Inc.
22. Kim YH, Martinez G, Varghese A, Hoppe RT. Topical nitrogen mustard in the management of mycosis fungoides: update of the Stanford experience. *Arch Dermatol*. 2003;139:165–73.
23. Tang L, Cao L, Bernardo O, Chen Y, Sundberg JP, Lui H, et al. Topical mechlorethamine restores autoimmune-arrested follicular activity in mice with an alopecia areata-like disease by targeting infiltrated lymphocytes. *J Invest Dermatol*. 2003;120:400–6.
24. Lessin SR, Duvic M, Guitart J, Pandya AG, Strober BE, Olsen EA, et al. Topical chemotherapy in cutaneous T-cell lymphoma: positive results of a randomized, controlled, multi-center trial testing the efficacy and safety of a novel mechlorethamine, 0.02%, gel in mycosis fungoides. *JAMA Dermatol*. 2013;149:25–32.
25. Kim EJ, Guitart J, Querfeld C, Girardi M, Musiek A, Akilov OE, Angello JT, Bailey WL, Geskin LJ. The PROVe study: US real-world experience with chlormethine/mechlorethamine gel in combination with other therapies for patients with mycosis Fungoides cutaneous T-cell lymphoma. *Am J Clin Dermatol*. 2021 May;22(3):407–14. <https://doi.org/10.1007/s40257-021-00591-x>. Epub 2021 Mar 3. PMID: 33656660; PMCID: PMC8068681
26. Garcia-Saleem TJ, Stonesifer CJ, Khaleel AE, Geskin LJ. Management of mycosis fungoides with topical Chlormethine/Mechlorethamine Gel: a Columbia University cutaneous lymphoma center experience. *Acta Derm Venereol*. 2021;101(9):adv00544. <https://doi.org/10.2340/00015555-3911>. PMID: 34436621
27. Lindahl LM, Fenger-Grøn M, Iversen L. Secondary cancers, comorbidities and mortality associated with nitrogen mustard therapy in patients with mycosis fungoides: a 30-year population-based cohort study. *Br J Dermatol*. 2014 Mar;170(3):699–704. <https://doi.org/10.1111/bjd.12620>. PMID: 24024659

## Romidepsin

28. FDA drug monograph ISTODAX (romidepsin) for injection. Available from: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2009/022393lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022393lbl.pdf). Accessed 17 Dec 2022.
29. LexiComp drug monograph RomiDEPsin. Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2022 UptoDate, Inc.
30. Jain S, Zain J. Romidepsin in the treatment of cutaneous T-cell lymphoma. *J Blood Med*. 2:37–47. <https://doi.org/10.2147/jbm.S9649>.
31. Valdez BC, et al. Romidepsin targets multiple survival signaling pathways in malignant T cells. *Blood Cancer J*. 5:e357–7. <https://doi.org/10.1038/bcj.2015.83>.
32. Whittaker SJ, et al. Final results from a multicenter, international, pivotal study of romidepsin in refractory cutaneous T-cell lymphoma. *J Clin Oncol*. 28:4485–91. <https://doi.org/10.1200/jco.2010.28.9066>.
33. Bachy E, et al. Romidepsin plus CHOP versus CHOP in patients with previously untreated peripheral T-Cell lymphoma: results of the Ro-CHOP Phase III study (conducted by LYSA). *J Clin Oncol*. 40:242–51. <https://doi.org/10.1200/jco.21.01815>.
34. Bristol Myers Squibb Statement on Istodax® (romidepsin) Relapsed/Refractory Peripheral T-cell Lymphoma U.S. Indication. Available from: <https://news.bms.com/news/details/2021/Bristol-Myers-Squibb-Statement-on-Istodax-romidepsin-Relapsed-Refractory-Peripheral-T-cell-Lymphoma-U.S.-Indication/default.aspx>. Accessed 17 Dec 2022.

## Vorinostat

35. FDA drug monograph (name of monograph). Available from (FDA web-link). Accessed (date).
36. LexiComp drug monograph (name of monograph). Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2022 UptoDate, Inc.
37. Eckschlagner T, Plch J, Stiborova M, Hrabeta J. Histone deacetylase inhibitors as anticancer drugs. *Int J Mol Sci*. 2017;18(7)
38. Richon VM. Cancer biology: mechanism of antitumour action of vorinostat (suberoylanilide hydroxamic acid), a novel histone deacetylase inhibitor. *Br J Cancer*. 2006;95(1):S2–6.
39. Duvic M, Vu J. Update on the treatment of cutaneous T-cell lymphoma (CTCL): focus on vorinostat. *Biologics*. 2007;1(4):377–92.
40. Mann BS, Johnson JR, Cohen MH, Justice R, Pazdur R. FDA approval summary: Vorinostat for treatment of advanced primary cutaneous T-cell lymphoma. *Oncologist*. 2007;12(10):1247–52.
41. Olsen EA, Kim YH, Kuzel TM, Pacheco TR, Foss FM, Parker S, et al. Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma. *J Clin Oncol*. 2007;25(21):3109–15.



Nadia Kashetsky and Aileen Feschuk

## Contents

|                                 |     |
|---------------------------------|-----|
| Doxepin 5% Cream (Zonalon)..... | 384 |
| Pramoxine.....                  | 403 |
| Topical Anesthetics.....        | 411 |
| References.....                 | 411 |

## Note

*Other topical agents with antipruritic properties are discussed elsewhere. See Chap. 17 for Calcineurin Inhibitors. See Chap. 18 for topical corticosteroids.*

Other topical anesthetics, e.g., lidocaine benzocaine creams, etc., are not included in this textbook as they are sensitizing and should not be used.

---

N. Kashetsky (✉)

Department of Dermatology and Skin Science, Faculty of Medicine,  
University of British Columbia, Vancouver, BC, Canada  
e-mail: [nkashetsky@mun.ca](mailto:nkashetsky@mun.ca)

A. Feschuk

Faculty of Medicine, Memorial University of Newfoundland,  
St. John's, NL, Canada  
e-mail: [afeschuk@mun.ca](mailto:afeschuk@mun.ca)

## Doxepin 5% Cream (Zonalon)

### Classification and Mode of Action

- Zonalon (doxepin hydrochloride) cream, 5%, is a topical drug approved by the FDA in 1994 [1, 2]. Each gram contains that active ingredient: 50 mg of doxepin hydrochloride (equivalent to 44.3 mg of doxepin) [1]. Zonalon cream also contains the following ingredients: sorbitol, cetyl alcohol, isopropyl myristate, glyceryl stearate, PEG-100 stearate, petrolatum, benzyl alcohol, titanium dioxide, and purified water [1].
- Doxepin hydrochloride is part of the classification of agents called dibenzoxepin tricyclic antidepressant compounds [1].
- The exact mechanism of action of the active ingredient doxepin is unknown [1]. Doxepin HCl does have H1 and H2 histamine receptor blocking actions; however, it is suggested that the drowsiness produced by Zonalon cream may reduce awareness of pruritis [1].

### Indications and Dermatological Uses

- Clinical indications recommended by the FDA include short-term management (up to 8 days) of moderate pruritus in atopic dermatitis or lichen simplex chronicus in adult patients [1].
- Off-label common uses include neuropathic pain [2].

### Formulations/Presentation

- *United States:* Available in the United States as Zonalon cream in 30-g (NDC 62436-523-30) and 45-g (NDC 62436-523-45) tubes [1]. Store at or below 27 °C (80 °F) [2].
- *Canada:* Available in Canada as Zonalon cream, doxepin HCL cream 5%, in 30-g aluminum tubes [3].



## Dosages and Suggested Regimens

- Application and dosing: Apply a thin film of Zonalon Cream, four times daily, with at least a 3-to-4-hour interval between applications, for up to 8 days [1]. Data does not exist establishing safety and efficacy for more than 8 days [1]. Use beyond 8 days may result in increased systemic levels and risk of contact sensitization [1].
- Greater body surface area application (>10%) may increase the risk of sedation and drowsiness [1]. Patients treating more than 10% of their body surface area should therefore be cautious to monitor for drowsiness and other systemic adverse effects of doxepin [1]. If sedation occurs, it is suggested that patients decrease the body surface area treated, number of applications per day, amount of cream applied, or discontinue Zonalon cream [1].
- Absorption of topical drugs are increased by occlusive dressings and thus should not be used with Zonalon cream [1].

## Baseline Investigations and Considerations

- No baseline investigations are recommended. Review contraindications, warnings, precautions, and drug interactions and special populations before commencing the drug.

## Pharmacokinetics

- Plasma concentrations of doxepin from topical application of Zonalon cream ranges from undetectable 47 ng/mL from percutaneous absorption, which may affect the central nervous system and result in other systemic side effects [1]. After systemic absorption, hepatic metabolism converts digoxin to pharmacologically active desmethyldoxepin [1].

- Urinary excretion of the drug and its metabolites follows subsequent glucuronidation [1].
- The half-life of desmethyldoxepin is not affected by multiple dosing and ranges from 28 to 52 hours [1].
- Doxepin and desmethyldoxepin plasma levels are variable and poorly correlated with dosing [1].
- Distribution occurs widely across the body including the liver, brain, lungs, and heart [1].
- Metabolism and elimination of doxepin are impacted by the following variables: renal disease, genetic factors, age, and other medications [1].

## Use in Special Populations

- *Pregnancy (FDA Guidance)*
  - Studies evaluating doxepin hydrochloride carcinogenesis, mutagenesis, and impairment of fertility have not been completed [1].
  - In vivo animal studies with rats and rabbits exposed to oral doxepin have revealed no evidence of harm to rat or rabbit fetuses due to doxepin [1]. However, as in vivo animal studies are not always predictive of human clinical response, Zonalon should be used only if necessary and with caution in pregnant women [1].
- *Lactation*
  - Following oral administration, doxepin is excreted in human milk, and thus following topical application, it is possible that doxepin may also be excreted in human milk [1]. Clinically, one case of apnea and drowsiness in a nursing infant has been reported where the mother was taking oral doxepin HCl [1]. Thus, a decision should be made to discontinue nursing versus discontinuing the drug based on the importance of Zonalon cream to the mother [1].

- *Children*

- Zonalon cream is not recommended in pediatrics, as safe use has not been established [1]. Additionally, a 2.5-year-old pediatric patient receiving treatment with Zonalon cream, 27 grams had been applied over 3 days for eczema, was reported to developed somnolence, grand mal seizure, respiratory depression, ECG abnormalities, and coma [1]. He had complete resolution with supportive care, activated charcoal, and systemic alkalization [1].

- *Geriatrics*

- Studies do not have large enough sample sizes of geriatric patients to determine whether they respond differently from younger adults [1]. However, reported clinical data has not identified differences in responses between these two groups [1].
- As discussed above, monitoring for confusion and over sedation in the geriatric population is advised [1]. Caution should be used when determining dosing, starting at lower levels of the dosing range due to greater frequency in the geriatric population of decreased hepatic, renal or cardiac function, and of concomitant drug treatment or disease [1]. Of note, clinically a geriatric patient has been reported to develop probable systemic anticholinergic toxicity (urinary retention and delirium) after the application of Zonalon cream to their arms, legs, and back three times daily over 2 days [1].

- *Renal Insufficiency*

- Renal excretion of doxepin extent has not been determined [1], and thus there are no dosage adjustments provided [2].

- *Hepatic Insufficiency*

- Be cautious in dose selection for hepatic insufficiency, because once absorbed into the systemic circulation, doxepin undergoes hepatic metabolism [1]; however there are no dosage adjustments provided [2].

## Monitoring

- Monitor for drowsiness, other systemic effects, and anticholinergic effects [2]. Monitor sites of application for pruritus, redness, and irritation [2]. Monitor for efficacy [2].

## Contraindications and Warnings and Precautions

- *Contraindications:* Patients with previous sensitivity to any of Zonalon's components or untreated narrow angle glaucoma or a tendency to urinary retention, due to the anticholinergic effects of doxepin HCl [1].
- *Warnings*
  - Deaths may occur with overdosage of this drug (see Management of Overdose section) [1].
  - Drowsiness and sedation occur in over one fifth of patients, especially in patients receiving Zonalon on greater than 10% of their body surface area. Patients should be cautioned regarding driving or operating hazardous machinery while receiving Zonalon treatment [1].
  - Excessive drowsiness may warrant reduced frequency of applications, amount of dose applied, or amount of body surface area treated or discontinuation of Zonalon [1].
  - Potentiating of alcohol, antihistamine, and other central nervous system depressant sedating effects while being treated with Zonalon [1].
  - Keep Zonalon away from the eyes [1].
- *Precautions*
  - Drowsiness: As described under warnings, patients should be cautioned regarding driving or operating hazardous machinery while receiving Zonalon treatment due to potential drowsiness. Similarly, as described above, patients should also be cautioned that alcohol, antihistamine, and other central nervous system depressant sedating effects

may be potentiated. Additionally, geriatric patients should be monitored closely as Zonalon may cause confusion or oversedation in this population [1].

- Occlusive dressings should not be used with Zonalon as this may increase absorption [1].
- Contact sensitization, or a type IV hypersensitivity reaction, may be caused by doxepin [1].

## Important Drug Interactions

There are many significant potential drug interactions, even for the topical use of doxepin (c.f. LexiComp drug monograph). Please check for drug interactions with the patient's list of medications using drug interaction checkers or other methods of verification prior to using doxepin.

The following table (Table 15.1) provides potential drug interactions with the topical use of doxepin.

For more details about each of the listed drugs, please visit LexiComp drug monograph [2].

Although most drug interactions with Zonalon cream have not been investigated by studies [1], topical application of Zonalon leads to plasma levels of doxepin that can reach levels obtained with oral doxepin HCl therapy [1]. Thus, the following interactions are possible with topical Zonalon cream [1].

## Drugs Metabolized by P450 2D6

Poor metabolizers or people with reduced biochemical activity of the drug-metabolizing isozyme cytochrome P450 2D6 have increased plasma concentrations of tricyclic antidepressants (TCAs). Approximately 7–10% of Caucasians are poor metabolizers. Unfortunately, prevalence estimates of reduced P450 2D6 isozyme activity among Asian, African, and other populations are not yet available.

**Table 15.1** Topical doxepin drug interactions and associated action to be taken

| Drugs that should concomitantly be avoided | Drugs that should be considered for modification | Drugs that should be monitored  | Drugs that require no action                       |
|--------------------------------------------|--------------------------------------------------|---------------------------------|----------------------------------------------------|
| Aciclinium                                 | Alpha- $\beta$ -agonists                         | Acetylcholinesterase Inhibitors | Hydrocortisone (ophthalmic)                        |
| Azelastine (nasal)                         | Alpha2-agonists                                  | Alcohol (ethyl)                 | Levodropropizine                                   |
| Bromopride                                 | Barbiturates                                     | Alizapride                      | Procabazine                                        |
| Bromperidol                                | Blonanserine                                     | Almotriptan                     | QT-prolonging agents (indeterminate risk: avoid)   |
| Cimetropium                                | Buprenorphine                                    | Alosetron                       | QT-prolonging agents (indeterminate risk: caution) |
| Dapoxetine                                 | Chlormethiazole                                  | Alpha1-agonists                 | Hydrocortisone (ophthalmic)                        |
| Dronedarone                                | Clozapine                                        | Alpha2-agonists (ophthalmic)    | Levodropropizine                                   |
| Eluxadoline                                | Domperidone                                      | Altretamine                     | Procabazine                                        |
| Glycopyrrrolate (oral inhalation)          | Droperidol                                       | Amantadine                      |                                                    |

|                                               |                                   |                                            |
|-----------------------------------------------|-----------------------------------|--------------------------------------------|
| Glycopyrronium (topical)                      | Flunitrazepam                     | Amifampridine                              |
| Iobenguane radiopharmaceutical products       | Fluoxetine                        | Amisulpride (oral)                         |
| Ipratropium (oral inhalation)                 | Iohexol <i>depends on route</i>   | Amphetamines                               |
| Kratom                                        | Ioproprol <i>depends on route</i> | Anticholinergic agents                     |
| Levosulpiride                                 | Iopamidol <i>depends on route</i> | Antiemetics (5HT <sub>3</sub> antagonists) |
| Linezolid                                     | Lemborexant                       | Antipsychotic agents                       |
| Methylene blue                                | Lofexidine                        | Aspirin                                    |
| Monoamine oxidase inhibitors (antidepressant) | Methadone                         | Baclofen                                   |
| Orphenadrine                                  | Methotrimeprazine                 | Beta <sub>2</sub> -agonists                |
| Oxatamide                                     | Opioid agonists                   | Botulinum toxin-containing products        |
| Oxomemazine                                   | Oxybate salt products             | Brexanolone                                |

(continued)

**Table 15.1** (continued)

| Drugs that should concomitantly be avoided          | Drugs that should be considered for modification                                                                                                                                                     | Drugs that should be monitored  | Drugs that require no action |
|-----------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|------------------------------|
| Paraldehyde                                         | Oxodone                                                                                                                                                                                              | Brimonidine (topical)           |                              |
| Pimozide                                            | Paroxetine                                                                                                                                                                                           | Bupropion                       |                              |
| Pitolisant <i>depends on international labeling</i> | QT-prolonging agents (highest risk: consider alternatives. Patients with other risk factors: (older age, female, bradycardia, hypokalemia, hypomagnesemia, and heart disease are at increased risk)) | Buspirone                       |                              |
| Potassium chloride <i>depends on dosage form</i>    | Ropeginterferon Alfa-2b                                                                                                                                                                              | Cannabinoid-containing products |                              |
| Potassium citrate                                   | Secretin                                                                                                                                                                                             | Carbamazepine                   |                              |
| Pramlintide                                         | Serotonergic opioids (high risk)                                                                                                                                                                     | Chloral betaine                 |                              |
| Rasagiline                                          | Suvorexant                                                                                                                                                                                           | Chlorphenesin carbamate         |                              |
| Revefenacin                                         | Zolpidem <i>depends on brand name</i>                                                                                                                                                                | Cimetidine                      |                              |
| Safinamide                                          |                                                                                                                                                                                                      | Citalopram                      |                              |
| Selegiline                                          |                                                                                                                                                                                                      | CNS depressants                 |                              |
| Thalidomide                                         |                                                                                                                                                                                                      | Cocaine (topical)               |                              |
| Tiotropium                                          |                                                                                                                                                                                                      | Cyclobenzaprine                 |                              |
| Umeclidinium                                        |                                                                                                                                                                                                      | CYP2D6 inhibitors (moderate)    |                              |



|  |  |                                                   |  |
|--|--|---------------------------------------------------|--|
|  |  | CYP2D6 inhibitors (strong)                        |  |
|  |  | Desmopressin                                      |  |
|  |  | Dexmethy/phenidate-methylphenidate                |  |
|  |  | Dextromethorphan                                  |  |
|  |  | Difelikefalin                                     |  |
|  |  | Dimethindene (topical)<br><i>depends on route</i> |  |
|  |  | Doxylamine <i>depends on brand name</i>           |  |
|  |  | Duloxetine                                        |  |
|  |  | Eletriptan                                        |  |
|  |  | CNS depressants                                   |  |
|  |  | Ergot derivatives                                 |  |
|  |  | Escitalopram                                      |  |
|  |  | Esketamine                                        |  |
|  |  | Fenfluramine                                      |  |
|  |  | Fexinidazole                                      |  |

(continued)

**Table 15.1** (continued)

| Drugs that should concomitantly be avoided | Drugs that should be considered for modification | Drugs that should be monitored            | Drugs that require no action |
|--------------------------------------------|--------------------------------------------------|-------------------------------------------|------------------------------|
|                                            |                                                  | Fluvoxamine                               |                              |
|                                            |                                                  | Gastrointestinal agents (prokinetic)      |                              |
|                                            |                                                  | Gilteritinib                              |                              |
|                                            |                                                  | Glucagon <i>depends on indication</i>     |                              |
|                                            |                                                  | Guanethidine                              |                              |
|                                            |                                                  | Haloperidol <i>depends on route</i>       |                              |
|                                            |                                                  | Hydroxyzine                               |                              |
|                                            |                                                  | Itopride                                  |                              |
|                                            |                                                  | Kava kava                                 |                              |
|                                            |                                                  | Lasmiditan                                |                              |
|                                            |                                                  | Levodopa-containing products              |                              |
|                                            |                                                  | Lisuride                                  |                              |
|                                            |                                                  | Lorcaserin (withdrawn from the US market) |                              |

|  |                                                         |  |
|--|---------------------------------------------------------|--|
|  | Magnesium sulfate <i>depends on dose</i>                |  |
|  | Metaxalone                                              |  |
|  | Metoclopramide                                          |  |
|  | Metyrosine                                              |  |
|  | Mianserin                                               |  |
|  | Minocycline (systemic) <i>depends on route</i>          |  |
|  | Mirabegron                                              |  |
|  | Nefazodone                                              |  |
|  | Nicorandil                                              |  |
|  | Nitroglycerin <i>depends on dosage form</i>             |  |
|  | Nonsteroidal anti-inflammatory agents (COX-2 selective) |  |
|  | Nonsteroidal anti-inflammatory agents (nonselective)    |  |
|  | Ondansetron <i>depends on route</i>                     |  |

(continued)

**Table 15.1** (continued)

| Drugs that should concomitantly be avoided | Drugs that should be considered for modification | Drugs that should be monitored                         | Drugs that require no action |
|--------------------------------------------|--------------------------------------------------|--------------------------------------------------------|------------------------------|
|                                            |                                                  | Oxtripitan                                             |                              |
|                                            |                                                  | Ozanimod                                               |                              |
|                                            |                                                  | Pentamidine (systemic)<br><i>depends on route</i>      |                              |
|                                            |                                                  | Perampanel                                             |                              |
|                                            |                                                  | Piribedil                                              |                              |
|                                            |                                                  | Pramipexole                                            |                              |
|                                            |                                                  | QT-prolonging antipsychotics (moderate risk)           |                              |
|                                            |                                                  | QT-prolonging class IC antiarrhythmics (moderate risk) |                              |
|                                            |                                                  | QT-prolonging kinase inhibitors (moderate risk)        |                              |
|                                            |                                                  | QT-prolonging miscellaneous agents (moderate risk)     |                              |

|  |                                                                |  |
|--|----------------------------------------------------------------|--|
|  | QT-prolonging moderate<br>CYP3A4 inhibitors<br>(moderate risk) |  |
|  | QT-prolonging quinolone<br>antibiotics (moderate risk)         |  |
|  | QT-prolonging strong<br>CYP3A4 inhibitors<br>(moderate risk)   |  |
|  | Ramosetron                                                     |  |
|  | Ropinirole                                                     |  |
|  | Rotigotine                                                     |  |
|  | Rufinamide                                                     |  |
|  | Serotonergic agents (high<br>risk, miscellaneous)              |  |
|  | Serotonergic non-opioid<br>CNS depressants                     |  |
|  | Serotonin 5-HT <sub>1D</sub> receptor<br>agonists (triptans)   |  |

(continued)

**Table 15.1** (continued)

| Drugs that should concomitantly be avoided | Drugs that should be considered for modification | Drugs that should be monitored               | Drugs that require no action |
|--------------------------------------------|--------------------------------------------------|----------------------------------------------|------------------------------|
|                                            |                                                  | Serotonin/norepinephrine reuptake inhibitors |                              |
|                                            |                                                  | Sertraline                                   |                              |
|                                            |                                                  | Sodium phosphates <i>depends on dose</i>     |                              |
|                                            |                                                  | St. John's wort                              |                              |
|                                            |                                                  | Sulfonyleureas                               |                              |
|                                            |                                                  | Syrian rue                                   |                              |
|                                            |                                                  | Thiazide and thiazide-like diuretics         |                              |
|                                            |                                                  | Thyroid products                             |                              |
|                                            |                                                  | Topiramate                                   |                              |
|                                            |                                                  | Tricyclic antidepressants                    |                              |
|                                            |                                                  | Trimeprazine                                 |                              |
|                                            |                                                  | Valerian                                     |                              |
|                                            |                                                  | Valproate products                           |                              |
|                                            |                                                  | Vasopressin                                  |                              |
|                                            |                                                  | Vilazodone                                   |                              |
|                                            |                                                  | Vortioxetine                                 |                              |

Normal metabolizers can act as poor metabolizers with the addition of drugs that inhibit isozyme cytochrome P450 2D6 activity. These drugs include medications not metabolized by the enzyme (quinidine; cimetidine) and substrates (many other antidepressants, phenothiazines, and the type 1C antiarrhythmics propafenone and flecainide).

Selective serotonin reuptake inhibitors (SSRIs) also inhibit P450 2D6, but vary in their extent of inhibition. Thus, caution is advised for concomitant TCAs with any SSRIs, and sufficient time must elapse before initiating a TCA in a patient previously on an SSRI (at least 5 weeks may be necessary).

For these reasons, TCAs used concomitantly with drugs that can inhibit cytochrome P450 2D6 activity may require lower doses for either drug. Additionally, monitoring plasma levels of TCA whenever it will be co-administered with a P450 2D6 inhibitor is advised.

## **MAO Inhibitors**

MAO inhibitors should be discontinued at least 2 weeks prior to initiation of Zonalon cream as serious adverse events, and death have been reported with concomitant use of certain drugs with MAO inhibitors.

## **Cimetidine**

Concomitant use of TCA and cimetidine have produced serious anticholinergic symptoms including severe dry mouth, urinary retention, and blurred vision. Additionally, higher TCA plasma levels have been observed in patients already taking cimetidine.

## **Alcohol**

As discussed above, alcohol ingestion may exacerbate the potential sedative effects of Zonalon cream.

## Tolazamide

Severe hypoglycemia has been reported in a type two diabetic patient on tolazamide (1 gm/day) 11 days after the addition of oral doxepin (75 mg/day).

## Adverse Effects and Overdose

### Adverse Reactions

Adverse events from clinical trials are reported in Table 15.2 [1]. The most common systematic side effect was drowsiness occurring in 22% ( $n = 71/330$ ) patients with Zonalon cream versus 2% ( $n = 7/334$ ) patients with vehicle cream [1]. In these controlled trials, drowsiness lead to discontinuation of Zonalon cream prematurely in approximately 5% of patients [1]. The most common local site adverse reaction was stinging and/or burning in 23% (76/330) of patients with Zonalon cream versus 16% (54/334) using vehicle cream [1]. Approximately 1% of patients treated

**Table 15.2** Adverse events during clinical trials at incidence  $\geq 1\%$  while using vehicle cream versus Zonalon cream<sup>a</sup>

| Adverse reaction                   | Vehicle cream, %<br>(n/N) | Zonalon cream, %<br>(n/N) |
|------------------------------------|---------------------------|---------------------------|
| Burning/stinging                   | 16% (54/334)              | 23% (76/330)              |
| Drowsiness                         | 2% (7/334)                | 22% (71/330)              |
| Dry mouth                          | 1% (4/334)                | 10% (32/330)              |
| Pruritus                           | 6% (20/334)               | 4% (13/330)               |
| Fatigue                            | 2% (5/334)                | 3% (10/330)               |
| Eczema exacerbation                | 2% (8/334)                | 3% (10/330)               |
| Other reaction at application site | 5% (16/334)               | 3% (10/330)               |
| Dizziness                          | 1% (3/334)                | 2% (7/330)                |
| Emotional changes                  | 0.5% (1/334)              | 2% (6/330)                |
| Taste changes                      | 0.5% (1/334)              | 2% (5/330)                |
| Edema                              | 0.5% (1/334)              | 1% (4/330)                |
| Headache                           | 4% (14/334)               | 1% (3/330)                |

<sup>a</sup>Table is adapted from FDA Zonalon Drug Label [1]



with Zonalon cream finished the study prematurely second to stinging and/or burning [1].

Additionally, nervousness/anxiety, tongue numbness, fever, and nausea occurred in less than 1% of participants [1].

## Overdosage and Management

As previously stated, overdosage with this class of drugs may cause death [1]. Physicians should recognize signs and symptoms of overdosage and contact their local poison control center for current information on treatment [1].

Signs and symptoms of tricyclic antidepressant toxicity develop rapidly and include the following:

- Cardiac dysrhythmias
- Severe hypotension
- Convulsions
- CNS depression (including coma)
- Electrocardiogram changes (QRS axis or width)
- Confusion
- Disturbed concentration
- Transient visual hallucinations
- Dilated pupils
- Agitation
- Hyperactive reflexes
- Stupor
- Drowsiness
- Muscle rigidity
- Vomiting
- Hypothermia
- Hyperpyrexia
- Any of the symptoms listed under section “Adverse Reactions” [1]

A general guide to the management of overdosage is outlined as follows. Hospital monitoring is required immediately [1]. Patient’s

airway should be protected, electrocardiogram obtained, and cardiac monitoring should be commenced immediately [1]. Intravenous access should be established, and then gastric decontamination should be initiated [1]. The time of observation for the central nervous system of respiration depression should be a minimum of 6 hours [1]. During these 6 hours, patients should also be closely monitored for hypotension, cardiac dysrhythmias and/or conduction blocks, and seizures [1]. Any signs of toxicity within the 6-hour time period suggest an extended period of monitoring [1]. Management should not be guided by plasma levels of drug [1]. Early intubation is recommendation for patients with central nervous system depression second to the potential for abrupt deterioration [1]. Seizures should be controlled with benzodiazepines which are recommended as first line to control seizures, with other anticonvulsants including phenobarbital or phenytoin if benzodiazepines are ineffective [1]. Physostigmine is reserved for life-threatening symptoms that are unresponsive to other therapies, and only after consultation with a poison control center [1]. The best indication of overdose severity may be a maximal limb-lead QRS duration of  $\geq 0.10$  seconds [1]. Serum pH should be maintained with intravenous sodium bicarbonate, with hyperventilation being used if response is inadequate [1]. Their concomitant use should be done with extreme caution and monitoring [1]. Lidocaine, bretylium, or phenytoin are third line if response is inadequate [1]. Hemoperfusion may be beneficial in rare cases of acute toxicity leading acute refractory cardiovascular instability [1].

## Patch Test Concentration

- One percent and 5% pet.
- There have been at least 20 cases documented that have had a positive patch test to doxepin 5% cream [1, 4].

---

## Essential Patient Information

- Patients should be provided the following information:
  - This drug is used for itching [2]. It may also be given for other reasons, and if this is the case for you, please talk to your doctor [2]. Speak with your physician if you have dry mouth, burning, stinging, and increased thirst that bothers you or does not go away [2]. Although very rare, it is possible that some people have severe or deadly side effects; when taking this drug, tell your doctor or seek medical care if you have severe fatigue; confusion; severe skin irritation; signs of an allergic reaction, including rash, hives, itching, red, swollen, blistered, or peeling skin with or without fever; wheezing; tightness in the chest or throat, trouble breathing, swallowing, or talking; unusual hoarseness; or swelling of the mouth, face, lips, tongue, or throat [2].

---

## Pramoxine

### Classification and Mechanism of Action

- Pramoxine is classified as a local anesthetic agent [4].
- The mechanism of action is identical to other anesthetics: decreasing neurons' membrane permeability to sodium ions, leading to blockage of both initiation and conduction nerve impulses, and inhibition of neuron depolarization [4].

### Indications and Dermatological Uses

- Clinical indications (FDA) include the following:
  - Perianal pruritus, hemorrhoidal irritations, and anorectal cleaning;
  - Minor skin irritations (pain and pruritus) including rashes, sunburns, hives, minor burns, minor cuts and scrapes, insect bites, poison ivy, oak, and sumac

- Mouth irritations (pain and pruritus) including fever blisters and cold sores
- Vaginal irritations (pruritus and burning) including minor vaginal skin irritations

## Off-Label Common Uses

- No off-label common uses are reported [4].

## Formulations/Presentation

- Pramoxine can be administered alone or in combination with hydrocortisone or other ingredients in several forms including gel, lotion, solution, aerosol foam, cream, ointment, or pledget [4].
- Typical formulation for pramoxine is 1% concentration [4].

Formulations in the United States are as follows:

As hydrochloride

### Foams

- Proctofoam: 1% (15 g) (steroid free; contains cetyl alcohol, methylparaben, propylene glycol, propylparaben, trolamine (triethanolamine))
- Generic: 1% (15 g)

### Gels

- Itch-X: 1% (35.4 g)
- PrameGel: 1% (118 mL)
- Pramox: 1% (113 g) (contains methylparaben, propylene glycol, propylparaben)

### Lotions

- Calaclear: Pramoxine hydrochloride 1% and zinc acetate 0.1% (177 mL) (contains alcohol, usp, methylparaben, polysorbate 80, propylene glycol, propylparaben)
- Caladryl Clear: Pramoxine hydrochloride 1% and zinc acetate 0.1% (177 mL) (contains methylparaben, propylene glycol, propylparaben, sd alcohol)
- Caldyphe Clear: Pramoxine hydrochloride 1% and zinc acetate 0.1% (177 mL) (contains alcohol, usp, methylparaben, polysorbate 80, propylene glycol, propylparaben)
- Callergy Clear: Pramoxine hydrochloride 1% and zinc acetate 0.1% (177 mL) (contains alcohol, usp, methylparaben, propylene glycol, propylparaben)
- DerMend Moisturizing Anti-Itch: 1% (237 mL) (fragrance free, paraben free, steroid free; contains cetyl alcohol, coconut oil (copra/cocos nucifera oil), trolamine (triethanolamine))
- GoodSense Clear Anti-Itch: Pramoxine hydrochloride 1% and zinc acetate 0.1% (177 mL) (contains alcohol, usp, methylparaben, propylene glycol, propylparaben)
- Ivy Wash Poison Ivy Cleanser: 1% (177 mL) (contains disodium edta, methylparaben, propylene glycol, propylparaben)
- Prax: 1% (118 mL, 237 mL) (contains cetyl alcohol, trolamine (triethanolamine))
- Sarna Sensitive: 1% (222 mL) (fragrance free, steroid free; contains benzyl alcohol, cetyl alcohol)

Approved drugs in Canada containing pramoxine include the following [5]:

### Foams

- Proctofoam-HC (hydrocortisone acetate 1%, pramoxine hydrochloride 1%): Each application delivers approximately 375 mg of foam containing approximately 1% hydrocortisone acetate (3.75 mg/dose) and 1% pramoxine hydrochloride (3.75 mg/dose).

### Ointment

- Anusol Plus (pramoxine HCl-zinc sulfate monohydrate): Each tube of smooth, colorless, translucent ointment contains pramoxine HCl 1% w/w and zinc sulfate monohydrate 0.5% w/w. Nonmedicinal ingredients: calcium phosphate, mineral oil, oleth-2, parabens, and petrolatum. Tubes of 30 g with applicator. Store between 15 and 30 °C.
- Proctodan-HC (pramoxine HCl-hydrocortisone acetate-zinc sulfate monohydrate): Each g of ointment contains pramoxine HCl 1%, hydrocortisone acetate 0.5%, and zinc sulfate monohydrate 0.5%. Nonmedicinal ingredients: methylparaben, propylparaben, and petrolatum. Tubes of 15 and 30 g with rectal applicator.

### Suppositories

- Anusol Plus (pramoxine HCl-zinc sulfate monohydrate): Each white, opaque suppository contains pramoxine HCl 20 mg and zinc sulfate monohydrate 10 mg. Nonmedicinal ingredients: calcium phosphate, magnesium stearate, parabens, and vegetable oil. Boxes of 12 and 24. Store between 15 and 30 °C.
- Proctodan-HC (pramoxine HCl-hydrocortisone acetate-zinc sulfate monohydrate): Each suppository contains pramoxine HCl 20 mg, zinc sulfate monohydrate 10 mg, and hydrocortisone acetate 10 mg in a triglyceride base. Nonmedicinal ingredients: dibasic calcium phosphate, magnesium stearate, methylparaben, propylparaben, and triglyceride. Boxes of 12. Store between 15 and 30 °C. Avoid freezing.

Europe: Not listed in LexiComp monograph

## Dosages and Suggested Regimens

As described above pramoxine can be administered topically alone or in combination with other ingredients in several forms summarized below [4].

- Anorectal cleaning wipes: use topically up to five times daily.
- For hemorrhoidal irritations and/or perianal itching: gel can be applied topically to the affected local area three to four times daily, or foam, wipes, or lotion can be applied topically to the affected area up to five times daily [4].
- For minor skin irritations: cream, gel, lotion, or spray can be applied to the affected local area up to three to four times daily [4].
- For mouth irritations: liquid can be topically applied up to three to four times daily, beginning at the first sign of a fever blister or cold sore [4].
- For vaginal irritation: wipes should be applied topically—applied externally to vaginal area as needed (Luvena) or applied to affected area up to three to four times daily (Vagisil) [4].

## Baseline Investigations and Considerations

No baseline investigations are recommended. Review contraindications, warnings, precautions, and drug interactions and special populations before commencing the drug.

## Pharmacokinetics

A study by Lewis and Wingold in 1985 concluded that pramoxine was not systemically absorbed [6].

## Use in Special Populations

- *Pregnancy*
  - Pramoxine has been suggested to be compatible and safe with pregnancy. A study by Lewis and Wingold in 1985 concluded that pramoxine was not systemically absorbed [6]. Accordingly, insignificant systemic absorption results in negligible risk to the embryo or fetus [4]. Although, theoretically the low molecular weight of the drug would allow it to cross the placenta and reach the fetus, the amount, if any of the mother's plasma concentration, is negligible [4].
  - A second study by Ebrahimi et al. in 2011 studied the effects of using pramoxine during the third trimester of pregnancy in 204 women and found no adverse effects on fetal gestational age, birth weight, prematurity rates, or perinatal complications. Insignificant systemic absorption results in negligible risk to the embryo or fetus [7].
- *Lactation*
  - There are no human studies that describe the use of pramoxine during lactation [4]. Theoretically, it is suggested that the risk to a nursing infant is negligible [4]. Although the molecular weight of the drug's free base is low enough that excretion into the breast milk is possible, the drug is thought not to be systemically absorbed [4].
- *Children*
  - Pramoxine should not be used in patients younger than 2 for minor skin irritations [4].
  - Pramoxine should not be used in patients younger than 12 years for hemorrhoidal/anorectal itching [4].
- *Geriatrics*
  - There are no dosage adjustments provided for the geriatric population [4].



- *Renal Insufficiency*
  - There are no dosage adjustments provided.
- *Hepatic Insufficiency*
  - There are no dosage adjustments provided.

## Monitoring

- None recommended

## Contraindications and Cautions

- *Contraindications*
  - Use is contraindicated in patients with known hypersensitivity to pramoxine or any ingredient in the formulation [4].
- *Warnings/Cautions*
  - This drug is for external use only; do not ingest this drug [4]. Keep away from the eyes and nose [4]. If condition does not improve within a week, worsens, resolves, and then reoccurs again within a few days, or additional symptoms arise including edema, rash, and irritation, contact a health care provider [4]. This drug is not to be used over open wounds or large body surface areas [4]. When using the foam or gel anorectal products, do not put the foam or gel into the rectum [4].

## Important Drug Interactions

- Pramoxine has two important drug interactions.
  - The first is bupivacaine as pramoxine may enhance adverse effects and toxicity of this drug [4]. Thus, pramoxine should be avoided within 96 hours of a bupivacaine implant insertion or bupivacaine and meloxicam periarticular solution, and pramoxine should be avoided within 168 hours after subacromial infiltration [4].

- The second drug interaction is methemoglobinemia-associated agents, as these drugs may enhance the adverse effects and toxicity of pramoxine, specifically they may increase the risk of methemoglobinemia [4].

## **Adverse Effects and Their Management**

- Local effects after topical application of the drug, including burning or stinging [4].
- Pramoxine has a low index of sensitization and a low index of cross-sensitization with other local anesthetics [4].

## **Patch Test Concentration**

- Hydrochloride 2% pet. (Chemotechnique)

## **Essential Patient Information**

- This drug is used for several conditions including hemorrhoids or rectal irritation, itching, and pain from insect bites, skin irritation, poison oak, ivy, and sumac rashes [4].
- Although very rare, it is possible that some people have severe or deadly side effects when taking this drug; tell your doctor or seek medical care if you have irritation; swelling, warmth, or redness of the skin; signs of an allergic reaction, like rash; hives; itching; red, swollen, blistered, or peeling skin with or without fever; wheezing; tightness in the chest or throat; trouble breathing, swallowing, or talking; unusual hoarseness; or swelling of the mouth, face, lips, tongue, or throat; or bleeding from the rectum or rectal pain [4].

## Topical Anesthetics

Topical Anesthetics such as benzocaine and lidocaine are numbing; thus, they have antipruritic properties. However, they are not recommended due to the risk of sensitization. (Intradermal lidocaine is often used prior to skin biopsies which is an appropriate use of the injectable lidocaine formulation.)

---

## References

### Topical Antipruritic Agents

1. ZONALON® (doxepin hydrochloride) CREAM, 5%.
2. Lexicomp. [http://online.lexi.com.qe2a-proxy.mun.ca/lco/action/doc/retrieve/docid/patch\\_f/1827022?cesid=9NQ6ESUDebI&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3Dzonalon%26t%3Dname%26va%3Dzonalon](http://online.lexi.com.qe2a-proxy.mun.ca/lco/action/doc/retrieve/docid/patch_f/1827022?cesid=9NQ6ESUDebI&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3Dzonalon%26t%3Dname%26va%3Dzonalon). Accessed 7 Jan 2022.
3. Unknown. Zonalon (doxepin hydrochloride) 5% cream [product monograph]. 2013.
4. Lexicomp. [http://online.lexi.com.qe2a-proxy.mun.ca/lco/action/doc/retrieve/docid/patch\\_f/7540?cesid=5sA13gVckA5&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3Dpramoxine%26t%3Dname%26va%3Dpramoxine#thelist](http://online.lexi.com.qe2a-proxy.mun.ca/lco/action/doc/retrieve/docid/patch_f/7540?cesid=5sA13gVckA5&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3Dpramoxine%26t%3Dname%26va%3Dpramoxine#thelist). Accessed 7 Jan 2022.
5. Woodby R. Compendium of Pharmaceuticals and Specialties (CPS) Database: Canadian Standard for Drug Monographs. <https://library.rrc.ca/RxTx/drug>. Accessed 8 Jan 2022.
6. Lewis JH, Weingold AB. The use of gastrointestinal drugs during pregnancy and lactation. *Am J Gastroenterol*. 1985;80(11):912–23.
7. Ebrahimi N, Vohra S, Gedeon C, et al. The fetal safety of hydrocortisone-pramoxine (Proctofoam-HC) for the treatment of hemorrhoids in late pregnancy. *J Obstet Gynaecol Can*. 2011;33:153. [https://doi.org/10.1016/S1701-2163\(16\)34802-2](https://doi.org/10.1016/S1701-2163(16)34802-2).



Rebecca M. Law , Drake Carter,  
Sean Mangion, and Howard I. Maibach

## Contents

|                             |     |
|-----------------------------|-----|
| Introduction.....           | 414 |
| Acyclovir (Zovirax).....    | 415 |
| Berdazimer.....             | 418 |
| Famciclovir.....            | 422 |
| Penciclovir (Denavir).....  | 426 |
| Valacyclovir (Valtrex)..... | 430 |
| References.....             | 436 |

---

R. M. Law (✉)

School of Pharmacy and Faculty of Medicine (Discipline of Family  
Medicine), Memorial University of Newfoundland, St. John's, NL, Canada  
e-mail: [rlaw@mun.ca](mailto:rlaw@mun.ca); [rlawUCSF@gmail.com](mailto:rlawUCSF@gmail.com)

D. Carter

Chicago Medical School, Rosalind Franklin University of Medicine &  
Science, North Chicago, IL, USA  
e-mail: [drake.carter@my.rfums.org](mailto:drake.carter@my.rfums.org)

© The Author(s), under exclusive license to Springer Nature  
Switzerland AG 2025

413

R. M. Law, H. I. Maibach (eds.), *Handbook of Topical Drug  
Treatment in Dermatology*,  
[https://doi.org/10.1007/978-3-031-93616-6\\_16](https://doi.org/10.1007/978-3-031-93616-6_16)

## Introduction

Rebecca M. Law

Antiviral agents discussed in this chapter are those non-HIV anti-viral agents which have topical formulations. Some of the agents are precursors/prodrugs for others, and both agents have been included as separate monographs. The clinical uses discussed in the monographs include herpes simplex virus (HSV) infections such as recurrent herpes labialis (HSV-1) and genital infections (HSV-2), varicella-zoster virus (VZV) infections such as shingles, and molluscum contagiosum.

The drug monographs included are the following:

Acyclovir  
Berdazimer  
Famciclovir  
Penciclovir  
Valaciclovir

---

S. Mangion

UniSA: Clinical and Health Sciences, University of South Australia,  
Adelaide, SA, Australia

Therapeutics Research Centre, Basil Hetzel Institute of Translational  
Health Research, The Queen Elizabeth Hospital,  
Woodville, SA, Australia

Sydney Medical School, The University of Sydney,  
Camperdown, NSW, Australia  
e-mail: [sean.mangion@hotmail.com](mailto:sean.mangion@hotmail.com)

H. I. Maibach

Department of Dermatology, University of California San Francisco  
(UCSF), San Francisco, CA, USA  
e-mail: [howard.maibach@ucsf.edu](mailto:howard.maibach@ucsf.edu)

## Acyclovir (Zovirax)

Rebecca M. Law

### Classification and Mode of Action

- Acyclovir is a synthetic purine nucleoside analogue with cell culture and in vivo inhibitory activity against herpes simplex virus (HSV) types 1 (HSV-1) and 2 (HSV-2).
- The inhibitory activity of acyclovir is highly selective due to its affinity for the enzyme thymidine kinase (TK) encoded by HSV. This viral enzyme converts acyclovir into acyclovir monophosphate, a nucleotide analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes.
- In cell culture, acyclovir triphosphate stops the replication of herpes viral DNA. This inhibition is accomplished in three ways: (1) competitive inhibition of viral DNA polymerase, (2) incorporation into and termination of the growing viral DNA chain, and (3) inactivation of the viral DNA polymerase.

### Indications and Dermatological Uses

- *Clinical indications (FDA)*: Indicated for the treatment of recurrent herpes labialis (cold sores) in immunocompetent adults and adolescents 12 years of age and older

### Formulations/Presentation

- USA: Acyclovir 5% cream
- Canada: Acyclovir 5% cream

## Dosages and Suggested Regimens

- Apply five times per day for 4 days.
- Initiate therapy as soon as possible after onset of signs or symptoms.

## Pharmacokinetics

- Absorption: In one study, the average daily urinary excretion of acyclovir was approximately 0.04% of the daily applied topical dose. Plasma acyclovir concentrations were below the limit of detection (0.01  $\mu\text{M}$ ) in five subjects and barely detectable (0.014  $\mu\text{M}$ ) in one subject. Systemic absorption of acyclovir from 5% cream is minimal in adults.

## Use in Special Populations

- Pregnancy: No adequate and well-controlled studies of acyclovir cream in pregnant women. Acyclovir cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (formerly FDA pregnancy category B).
- Lactation: Unknown whether topically applied acyclovir is excreted in breast milk. However, after oral administration, acyclovir concentrations have been seen in breast milk (0.6–4.1 times the corresponding plasma levels). Thus nursing mothers with active herpetic lesions near or on the breast should avoid breastfeeding.
- Pediatrics: Safety profile in children 12–17 years was similar to that observed in adults. Safety in children under 12 years is not established.
- Geriatrics: Systemic absorption after topical administration is minimal. Clinical experience have shown no differences in responses between the elderly and younger adults.

## Monitoring

- Monitor for adverse effects including irritant skin reactions (cumulative) and hypersensitivity reactions.

## Contraindications and Cautions

- Contraindicated in patients with known hypersensitivity to acyclovir, valacyclovir.
- Cream should only be applied on the affected external aspects of the lips and face in patients with herpes labialis. Because no data are available, application to human mucous membranes is not recommended. Zovirax cream is intended for cutaneous use only and should not be used in the eye or inside the mouth or nose.

## Important Drug Interactions

- None known

## Adverse Effects and Their Management

- There is a potential for irritation and contact sensitization. In particular, there is a high and cumulative irritation potential.
- The most common adverse reactions at the site of topical application were dry lips, desquamation, dryness of the skin, cracked lips, burning skin, pruritus, flakiness of the skin, and stinging on the skin (each adverse reaction occurred in less than 1% of patients receiving Zovirax cream).
- Postmarketing adverse events included angioedema, anaphylaxis, contact dermatitis, and eczema.

## Carcinogenicity

- Unknown



## Patch Test Concentration

- Ten percent pet (Chemotechnique); scratch-patch tests may be performed in the case of a? + reaction or a negative reaction to acyclovir with highly suspected history for allergy.

## Essential Patient Information

- Should be used for cold sores on the lips and around the mouth only. It should not be used in the eyes, mouth, nose, or on the genitals.
- Acyclovir cream is not a cure for cold sores.
- Acyclovir cream should be used as soon as the first symptoms of a cold sore occur, such as itching, redness, burning or tingling, or when the cold sore appears.
- Apply to the affected area five times daily for 4 days, including the outer edge.
- Do not apply other skin products to the affected area during treatment with acyclovir cream.
- Do not rub the cold sore, since this may cause spread to other areas around the mouth or make the cold sore worse.

---

## Berdazimer

Sean Mangion

## Classification and Mode of Action

- First-in-class nitric oxide (NO)-releasing topical agent for molluscum contagiosum.
- NO has antimicrobial activity related to protein nitrosylation that influences immunomodulation, apoptosis, cytokine production, and inflammation. It may also affect viral replication through cytotoxic reactive oxygen and nitrogen species.

- In a 12-week pivotal Phase 3 trial (B-SIMPLE4), 891 patients with a mean age of 6.6 years (range, 0.9–47.5 years) were randomly assigned to treatment with berdazimer gel 10.3% or a vehicle gel applied in a thin layer to all lesions once daily. At 12 weeks, 32.4% of patients in the berdazimer group achieved complete clearance of lesions compared with 19.7% in the vehicle group ( $P < 0.001$ ).
- It is also being explored for use in acne (phase 3 trial currently underway for a 3.4% containing gel).

## Indications and Dermatological Uses

- *Clinical indications (FDA)*: Molluscum contagiosum: adults and pediatric patients  $\geq 1$  year of age
- *Off-label common uses*: None

## Formulations/Presentation

- USA: Berdazimer sodium (Zelsuvmi®), 10.3% gel

## Dosages and Suggested Regimens

- Apply to lesions once daily.
- The product comes with two tubes of gel that must be mixed according to the dosing guide before application. The drug should be applied immediately after mixing, by thin layer on the affected lesion/s. The drug should dry for at least 10 minutes before occlusion with clothes or gloves.
- Bathing, showering, or swimming should not occur for 1 hour after application.

## Baseline Investigations and Considerations

- None

## Pharmacokinetics

- Measurement of NO metabolite hMAP3 during the Phase I study showed that once-daily application of berdazimer resulted in minimal systemic absorption in children aged 2–12 years old. Efficacy and safety data for use in molluscum contagiosum is so far limited to a maximum of 12 weeks of use.

## Use in Special Populations

### Pediatrics

- Approved for use in children aged over 1 year.

### Pregnancy and Lactation

- Not currently classified as limited human data available.

### Renal insufficiency

- Not evaluated; dose adjustment is not expected to be needed.

### Hepatic insufficiency

- Not evaluated; dose adjustment is not expected to be needed.

## Monitoring

- Signs of an allergic reaction, like rash; hives; itching; red, swollen, blistered, or peeling skin with or without fever; wheezing; tightness in the chest or throat; trouble breathing, swallowing, or talking; unusual hoarseness; or swelling of the mouth, face, lips, tongue, or throat.

## Contraindications and Cautions

- None reported.

## Important Drug Interactions

- None reported.

## **Adverse Effects and their Management**

- Signs of skin infection like oozing, heat, swelling, redness, or pain.
- Skin breakdown where this drug is used.
- Dry skin, blisters, peeling, flaking, or change in the color of the skin.
- Pain, burning, stinging, itching, swelling, or redness.
- Product should be discontinued, and medical advice should be sought on management.

## **Carcinogenicity (if Known, Including Mouse Painting Studies)**

- The carcinogenic potential of berdazimer gel was assessed in a 2-year dermal mouse carcinogenicity study. There were no drug-related tumor findings associated with daily topical administration of berdazimer gel to mice at doses up to 4% berdazimer gel. Berdazimer was mutagenic in a bacterial mutagenicity assay (Ames assay) but was not clastogenic in an in vitro chromosomal aberration assay in human peripheral blood lymphocytes or in an in vivo micronucleus assay in rats.

## **Patch Test Concentration**

- Not available

## **Essential Patient Information**

- Not to be taken orally, ophthalmologically, or intravaginally.
- Not to be mixed until ready for use.
- Not to be applied on healthy skin or on open wounds.
- Wash hands after application unless the hand is the affected site.

## Famciclovir

Drake Carter

### Classification and Mode of Action

- Famciclovir is a prodrug that undergoes biotransformation into its active metabolite, penciclovir. This metabolite is phosphorylated by HSV-1, HSV-2, and VZV thymidine kinase into penciclovir monophosphate. Cellular enzymes then convert this into penciclovir triphosphate, which competes with deoxyguanosine triphosphate to inhibit viral DNA polymerase by chain termination.
- Famciclovir was found to be less effective than valacyclovir for suppression of genital HSV infections and the resolution and pain management of acute herpes zoster (VZV).

### Indications and Dermatological Uses

- *Clinical indications (FDA):* HSV (orolabial and genital infections), varicella-zoster (shingles)
- *Off-label common uses:* Varicella (chickenpox) infection in patients with uncomplicated HIV (level of evidence: G); HSV prevention in solid organ transplant recipients (level of evidence: G)

### Formulations/Presentation

- USA: 125-mg, 250-mg, and 500-mg tablets
- Canada: 125-mg, 250-mg, and 500-mg tablets

## Dosages and Suggested Regimens

- Genital HSV infections (immunocompetent patients)
  - Initial episode: 250 mg three times daily for 7–10 days
  - Recurrent episodes: 1 g twice daily for 1 day; 500 mg as single dose followed by 250 mg twice a day for 5 days
- Orolabial HSV infections (immunocompetent patients)
  - Initial episode (gingivostomatitis): 250 mg three times daily for 1 day; 500 mg twice daily for 7–10 days
  - Recurrent episodes: 1.5 g as a single dose
- HSV infections (immunocompromised patients, including those with HIV)
  - 500 mg twice daily for 5–10 days
- Herpes zoster (shingles)
  - Dermatomal lesions: 500 mg three times daily for 7–10 days

## Baseline Investigations and Considerations

### Pharmacokinetics

- Famciclovir undergoes deacetylation and oxidation by the liver to turn into penciclovir.
- Oral bioavailability is  $77 \pm 8\%$ .
- Half-life is  $2.8 \pm 1.0$  hour following a 500-mg dose in patients with herpes zoster.
- Time to maximum plasma concentration is 0.9 hour.
- Excreted primarily in urine. Active tubular secretion contributes to renal clearance.

### Use in Special Populations

- Listed as FDA pregnancy classification B (former classification scheme).
- Unknown whether famciclovir is excreted in breast milk.
- The efficacy and safety of famciclovir has not been determined in children due to limited data available.
- Dosage adjustments due to renal impairment should be made based on the patient's measured creatinine clearance (CrCl).

- For recurrent HSV infections (genital-immunocompetent)
  - When CrCl is 40–59 mL/minute: 500 mg every 12 hours for 1 day
  - When CrCl is 20–39 mL/minute: 500 mg as single dose
  - When CrCl is <20 mL/minute: 250 mg as single dose
- For recurrent HSV infections (oral-immunocompetent)
  - When CrCl is 40–59 mL/minute: 750 mg as single dose
  - When CrCl is 20–39 mL/minute: 500 mg as single dose
  - When CrCl is <20 mL/minute: 250 mg as single dose
- For HSV infections in immunocompromised (including those with HIV)
  - When CrCl is 20–39 mL/minute: 500 mg every 24 hours
  - When CrCl is <20 mL/minute: 250 mg every 24 hours
- For herpes zoster dermatomal lesions
  - When CrCl is 40–59 mL/minute: 500 mg every 12 hours
  - When CrCl is 20–39 mL/minute: 500 mg every 24 hours
  - When CrCl is <20 mL/minute: 250 mg every 24 hours
- No suggested dose adjustment for hepatic impairment as it has not been studied.

## Monitoring

- Renal impairment. Change dosing as indicated above, as needed

## Contraindications and Cautions

- Contraindicated in patients with known allergy to famciclovir or its active metabolite, penciclovir.
- Tablets contain lactose; use with caution in cases of lactase deficiency, galactose intolerance, or glucose-galactose malabsorption syndromes.

## Important Drug Interactions

- Concurrent use of other drugs eliminated by active renal tubular secretion may increase the plasma concentrations of famciclovir (e.g., probenecid).
- Famciclovir may decrease the efficacy of other drugs that undergo intracellular phosphorylation (e.g., cladribine).
- Famciclovir may diminish the efficacy of other antitherpetic antivirals (e.g., talimogene laherparepvec).
- Famciclovir may reduce the efficacy of both varicella virus and zoster vaccinations.

## Adverse Effects and Their Management

- The most commonly reported adverse effects are headache and nausea (>10%).
- Other adverse reactions include fatigue (5%), migraine (3%), paresthesia (3%), pruritus (2–4%), rash (3%), diarrhea (2–8%), flatulence (5%), vomiting (5%), dysmenorrhea (8%), neutropenia (3%), leukopenia (1%), increased serum ALT (3%), increased serum AST (2%), and increased serum bilirubin (2%).
- Cases of acute renal failure have occurred in patients with underlying renal impairment; dose adjustment is needed in patients with renal impairment to avoid giving an inappropriately high dose.

## Carcinogenicity (if Known, Including Mouse Painting Studies)

- A 2-year carcinogenicity study found a higher incidence of mammary adenocarcinoma in female rats receiving famciclovir in high doses of 600 mg/kg/day (1.1 to 4.5x the human systemic exposure at the recommended dose range of 500–2000 mg daily).



- No increases in tumor incidence were found in male rats receiving doses up to 240 mg/kg/day.
- No increases in tumor incidence were seen in male and female mice receiving high doses of 600 mg/kg/day.

### **Patch Test Concentration**

- Not available

### **Essential Patient Information**

- Famciclovir can be taken with or without food.
- Alert medical provider if there is a known history of renal impairment.
- Use with caution if there is a known history of lactose intolerance.

---

### **Penciclovir (Denavir)**

Drake Carter

### **Classification and Mode of Action**

- Penciclovir is phosphorylated by viral thymidine kinases in HSV-1 and HSV-2 infected cells into a monophosphate form. This form is then converted to penciclovir triphosphate by cellular kinases, which then competitively inhibits HSV DNA polymerase via competing with deoxyguanosine triphosphate.

## Indications and Dermatological Uses

- *Clinical indications (FDA):* herpes labialis (cold sores)
- *Off-label common uses:*

## Formulations/Presentation

- USA: 1% cream
- Canada:
- Europe:

## Dosages and Suggested Regimens

- Apply (topically) at the first indication of cold sore (during prodrome or when symptoms appear). During waking hours, apply every 2 hours for 4 days.

## Baseline Investigations and Considerations

### Pharmacokinetics

- No systemic percutaneous absorption has been reported.
- Concentrations of penciclovir were not detected in urine or plasma of healthy male volunteers (n = 12) following single or repeat topical application of 1% penciclovir cream in doses of 180 g daily (about 67 times the usual dose).

### Use in Special Populations

- Listed as FDA pregnancy classification B. No well-controlled studies have been conducted in pregnant women.
- There is no data on whether topically applied penciclovir is excreted in breast milk. However, penciclovir has been shown to be excreted in breast milk following oral administration of famciclovir, a prodrug that is converted into penciclovir.

- The frequency of adverse effects in children aged 12–17 was similar to adult patients. However, safety and efficacy in patients <12 has not been established.
- No dosage adjustment required in patients with impaired renal function.
- No dosage adjustment required in patients with impaired hepatic function.

## **Monitoring**

- Skin irritation following application
- Taste distortion
- Local anesthesia
- Erythematous rash

## **Contraindications and Cautions**

- Penciclovir is contraindicated in patients with known hypersensitivity to the product or any of its components.

## **Important Drug Interactions**

- No drug interaction studies have been performed. Since penciclovir is minimally absorbed percutaneously, systemic drug interactions are unlikely.

## **Adverse Effects and Their Management**

- Application site reaction
- Hypesthesia/local anesthesia
- Taste perversion
- Erythematous rash

## **Carcinogenicity (if Known, Including Mouse Painting Studies)**

- Two-year carcinogenicity studies were conducted with the pro-drug of penciclovir, famciclovir. After oral doses of 600 mg/kg/day (395 times the maximum theoretical human exposure following topical penciclovir application), an increase in the incidence of mammary adenocarcinoma was seen in female rats. No increases in tumor incidence were seen in male rats treated with 240 mg/kg/day (190 times the maximum theoretical exposure to penciclovir) or in male and female mice receiving doses of 600 mg/kg/day (100 times the maximum theoretical exposure to penciclovir).
- Testicular toxicity was observed in rats and dogs following repeated intravenous administration of penciclovir following doses of 160 mg/kg/day (1155x the maximum theoretical human AUC) in rats and 100 mg/kg/day (3255x the maximum theoretical human AUC) in dogs. Adverse reactions reported include atrophy of the seminiferous tubules, reduced sperm count, and increased incidence of sperm with altered morphology that affected motility.

## **Patch Test Concentration**

- Not available

## **Essential Patient Information**

- Wash your hands before applying to a clean, dry skin.
- Only apply over affected areas. Rub in the cream until it disappears.
- Do not ingest. For topical use only.

## Valacyclovir (Valtrex)

Drake Carter

### Classification and Mode of Action

- Valacyclovir is a nucleoside analog viral DNA polymerase inhibitor. It is converted to its active metabolite, acyclovir, via intestinal and hepatic metabolism. Acyclovir is then converted to acyclovir monophosphate by viral thymidine kinase and then further converted to acyclovir triphosphate by cellular enzymes. Acyclovir triphosphate competes with deoxyguanosine triphosphate in order to be incorporated into viral DNA and act as a terminator of the growing DNA chain.
- Valacyclovir was found to be better than famciclovir for suppression of genital herpes in a comparative study.
- Valacyclovir showed to accelerate the resolution of herpes zoster-associated pain compared to acyclovir, while maintaining a simpler dosing and favorable safety profile.

### Indications and Dermatological Uses

- *Clinical Indications (FDA)*
  - Cold sores (herpes labialis) in both pediatric and adult patients
  - Genital herpes in adults
  - Herpes zoster (shingles) in adults
  - Chickenpox (varicella) in pediatric patients
- *Off-Label Common Uses*
  - VZV prevention in immunocompromised patients (level of evidence: G)

## Formulations/Presentation

- USA: 500-mg tablet, 1-g tablet
- Canada: 500-mg tablet, 1-g tablet

## Dosages and Suggested Regimens

- *Genital Herpes: Adult*
  - Initial episode (immunocompetent): Take 1 g twice daily for 7–10 days; extend duration of treatment if lesion is not healed after 10 days.
  - Initial episode (immunocompromised): Take 1 g twice daily for 5–10 days; extend duration of treatment if lesion is not healed after 10 days.
  - Initial episode (pregnant): Take 1 g daily for 7–10 days; extend duration of treatment if lesion is not healed after 10 days.
  - Recurrent episode (immunocompetent): Take 500 mg twice daily for 3 days *or* 1 g once daily for 5 days; most effective when initiated either during prodrome phase or within 1 day of onset of lesion.
  - Recurrent episode (pregnant): Take 500 mg twice daily for 3 days *or* 1 g once daily for 5 days.
  - Suppressive therapy (immunocompetent): Take 500 mg *or* 1 g once daily. Reassess the need for continued treatment annually.
  - Suppressive therapy (immunocompromised): Take 500 mg twice daily. Reassess the need for continued treatment annually.
  - Suppressive therapy (pregnant): Take 500 mg twice daily beginning at 36 weeks of gestation until delivery; for patients with primary infection during the third trimester, suppressive therapy may be considered before 36 weeks of gestation.

- *Genital Herpes: Pediatric*
  - First episode: Take 20 mg/kg/dose orally every 12 hours, with a maximum dose of 1 g/dose. Treat for 7–10 days. Some patients may need extension of treatment duration if lesion has not healed by 10 days.
  - Recurrent episode: Take 20 mg/kg/dose orally every 12 hours, with a maximum dose of 1 g/dose. Treat for 5–10 days. Adolescents without HIV may receive 500 mg every 12 hours for 3 days alternatively.
  - Suppressive therapy (patients without HIV): Take 20 mg/kg/dose orally once daily, with a maximum dose of 500 mg/dose. Doses of 1 g/day may be more effective in patients with  $\geq 10$  occurrences per year. Reassess the need for continued treatment annually.
  - Suppressive therapy (patients with HIV: take 500 mg orally every 12 hours). Reassess the need for continued treatment annually.
- *Orolabial HSV (Gingivostomatitis, Cold Sores): Adult*
  - Initial infection (immunocompetent): Take 1 gram twice daily for 7–10 days.
  - Initial infection (immunocompromised): Take 1 g twice daily for 5–10 days until complete resolution of lesion.
  - Recurrent infection (immunocompetent): Take 2 g twice daily for 1 day.
  - Recurrent infection (immunocompromised): Take 1 g twice daily for 5–10 days until complete resolution of lesion.
  - Suppressive therapy (immunocompetent): Take 500 mg once daily *or* 1 g once daily.
  - Suppressive therapy (immunocompromised): Take 500 mg twice daily.
- *Orolabial HSV (Gingivostomatitis, Cold Sores): Pediatric*
  - Patients without HIV treatment
    - Infants  $\geq 3$  months, children, and adolescents: Dose is 20 mg/kg/dose orally every 12 hours. Maximum dose of 1000 mg/dose. Treat immunocompromised patients for 5–7 days and immunocompromised patients 10–14 days.

Patients  $\geq 12$  years old: Take 2 g orally every 12 hours for 1 day.

- Patients with HIV  
Treatment (adolescents): Take 1 g orally every 12 hours for 5–10 days  
Suppressive therapy (adolescents): Take 500 mg orally every 12 hours
- *Herpes Zoster (Shingles): Adults*
  - Acute localized dermatomal lesions: Take 1 g three times a day for 7–10 days. Initiate at the earliest sign of lesion. Treatment is most effective within 72 hours of rash onset.
  - Disseminated zoster: Take 1 g three times daily for 10–14 days after receiving initial therapy with IV acyclovir and the formation of new lesions has ceased.
- *Chickenpox (Varicella): Pediatric*
  - Infants  $\geq 3$  months, children, adolescents: Take 20 mg/kg/dose orally every 8 hours for 5 days with a maximum dose of 1 g/dose. Initiate treatment within 24 hours of rash onset for best results. Immunocompromised patients should be treated for 7–14 days depending upon clinical response. Patients with HIV may require 4–6 weeks of treatment.
- *VZV Prevention in Hematopoietic Cell Transplant (HCT) Recipients (off-label): Adult*
  - *Post-exposure prophylaxis*: Take 1 g orally three times daily within 96 hours of exposure. Continue for 22 days after exposure.
  - *Prevention of VZV reactivation in seropositive patients*: Take 500 mg orally twice daily for 1 year following transplantation.
- *VZV Prevention in Hematopoietic Cell Transplant (HCT) Recipients (Off-Label): Pediatric*
  - *Post-exposure prophylaxis*: Take 500 mg (if  $<40$  kg) or 1 g (if  $\geq 40$  kg) orally three times daily within 48 hours of exposure. Continue for 22 days after exposure.
  - *Prevention of VZV reactivation in seropositive patients*: Take 250 (if  $<40$  kg) or 500 mg (if  $\geq 40$  kg) orally twice daily.



- *VZV Prevention in Solid Organ Transplant Recipients (Off-Label): Adult*
  - *Solid organ transplant recipients* (VZV-seropositive patients not requiring CMV prophylaxis): Take 500 mg orally twice daily for 3–6 months after transplantation and during periods of lymphodepletion.

## Baseline Investigations and Considerations

### Pharmacokinetics

- Valacyclovir is converted to acyclovir and *L*-valine by first-pass metabolism.
- Bioavailability is  $54.5\% \pm 9.1\%$  and is not altered by administration with food.
- Half-life ranges from 2.5 to 3.3 hours.
- Excretion is primarily excreted through urine.

### Use in Special Populations

- Approved for use in children. Dosing adjustments based on weight may need to be done.
- Listed as FDA pregnancy category B (former FDA classification).
- Caution should be exercised when prescribing to lactating women. A 500-mg dose of valacyclovir to a lactating mother provides a nursing infant with less than 2% of the exposure obtained after a standard neonatal dose of 30 mg/kg/day. The decision to continue or discontinue breastfeeding while a mother is on valacyclovir should consider the risk of infant virus exposure, the benefits of breastfeeding to the infant, and the benefits of valacyclovir to the mother. Valacyclovir is considered compatible with breastfeeding.
- Dosage adjustments are required in patients with renal impairment, with lower doses indicated as the patient's creatinine clearance decreases

- Dosage modification is not necessary for those with hepatic impairment. Data shows that the rate but not the extent of conversion to active acyclovir is decreased in patients with hepatic impairment.

## Monitoring

- Kidney function (especially in elderly patients)
- CNS function (altered mental status, mood changes, seizures, hallucinations)
- CBC (risk of thrombotic thrombocytopenic purpura and hemolytic uremic syndrome)

## Contraindications and Cautions

- Valacyclovir is contraindicated in patients with known hypersensitivity to valacyclovir, acyclovir, or other components in the formulation.

## Important Drug Interactions

- *No significant drug or food interactions with valacyclovir are known.*

## Adverse Effects and Their Management

- Acute kidney injury, including obstructive nephropathy
- Neurotoxicity: including confusion, agitation, lethargy, hallucination, impaired consciousness, aphasia, ataxia, myoclonus, tremor, and seizures
- Thrombotic thrombocytopenic purpura (TTP)
- Hemolytic uremic syndrome (HUS)
- Gastrointestinal: abdominal pain and nausea
- Headache

- Nasopharyngitis
- Skin rash
- Dysmenorrhea

### **Carcinogenicity (if Known, Including Mouse Painting Studies)**

- No studies have shown that valacyclovir was carcinogenic.

### **Patch Test Concentration**

- Not available

### **Essential Patient Information**

- Take medications as directed at the first sign of lesion onset.
- Alert your provider if your lesions are not healed after finishing the medication.
- Monitor for signs of altered CNS function (confusion, headaches, hallucinations, seizures).
- Monitor for signs of kidney injury (pain with urination, blood in urine, back pain).
- Monitor for excess bruising, rash, or yellowing of the skin.

---

## **References**

### **Acyclovir (Zovirax)**

1. FDA drug monograph (acyclovir). Available from ([https://www.access-data.fda.gov/drugsatfda\\_docs/label/2014/021478s0071bl.pdf](https://www.access-data.fda.gov/drugsatfda_docs/label/2014/021478s0071bl.pdf) ). Accessed 27 June 2024.
2. De Groot AC. Patch testing. 3rd ed. Volume 3 Chapter 3.

## Berdazimer

3. FDA drug monograph (Berdazimer). Available from ([https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2024/217424s0001bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/217424s0001bl.pdf)). Accessed 9 Feb 2024.
4. LexiComp drug monograph (Berdazimer). Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2024 UptoDate, Inc.
5. Browning JC, Cartwright M, Thorla I, et al. A patient-centered perspective of molluscum contagiosum as reported by B-SIMPLE4 clinical trial patients and caregivers: global impression of change and exit interview substudy results. *Am J Clin Dermatol*. 2023;24:119–33. <https://doi.org/10.1007/s40257-022-00733-9>.
6. Browning JC, Enloe C, Cartwright M, et al. Efficacy and safety of topical nitric oxide–releasing berdazimer gel in patients with molluscum contagiosum. *JAMA Dermatol*. 2022;158(8):871–8. <https://doi.org/10.1001/jamadermatol.2022.2721>.
7. Cartwright M, Enloe C, Stripling S, Maeda-Chubachi T. Pharmacokinetic profile, safety, and tolerability of topical Berdazimer gel, 10.3% in patients with molluscum contagiosum. *J Drugs Dermatol*. 2022;21(10):1104–10. <https://doi.org/10.36849/jdd.6938>.
8. Hebert AA, Siegfried EC, Durham T, et al. Efficacy and tolerability of an investigational nitric oxide–releasing topical gel in patients with molluscum contagiosum: a randomized clinical trial. *J Am Acad Dermatol*. 2020;82(4):887–94. <https://doi.org/10.1016/j.jaad.2019.09.064>.

## Famciclovir

9. FDA drug monograph (FAMVIR). Available from [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2011/020363s0371bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020363s0371bl.pdf). Accessed 04/12/2023.
10. LexiComp drug monograph (Famciclovir). Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2022 UptoDate, Inc.
11. Wald A, Selke S, Warren T, Aoki FY, Sacks S, Diaz-Mitoma F, Corey L. Comparative efficacy of famciclovir and valacyclovir for suppression of recurrent genital herpes and viral shedding. *Sex Transm Dis*. 2006;33(9):529–33. <https://doi.org/10.1097/01.olq.0000204723.15765.91>. PMID: 16540883.
12. Bist A, Savitha A, Gumma KM. Efficacy of valacyclovir and famciclovir in herpes zoster: a comparative study. *Indian J Pharmacol*.

2020;52(6):472–5. [https://doi.org/10.4103/ijp.IJP\\_555\\_18](https://doi.org/10.4103/ijp.IJP_555_18). PMID: 33666187; PMCID: PMC8092181.

## Penciclovir (Denavir)

13. FDA drug monograph (DENA VIR). Available from [https://www.access-data.fda.gov/drugsatfda\\_docs/label/2013/020629s0161bl.pdf](https://www.access-data.fda.gov/drugsatfda_docs/label/2013/020629s0161bl.pdf). Accessed 04/14/2023.
14. LexiComp drug monograph (Penciclovir). Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2022 UptoDate, Inc.

## Valacyclovir (Valtrex)

15. FDA drug monograph (VALTrex – valacyclovir hydrochloride). Available from [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2008/020487s0141bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/020487s0141bl.pdf). Accessed 04/17/2023.
16. LexiComp drug monograph (Valacyclovir). Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2022 UptoDate, Inc.
17. Wald A, Selke S, Warren T, Aoki FY, Sacks S, Diaz-Mitoma F, Corey L. Comparative efficacy of famciclovir and valacyclovir for suppression of recurrent genital herpes and viral shedding. *Sex Transm Dis*. 2006;33(9):529–33. <https://doi.org/10.1097/01.olq.0000204723.15765.91>. PMID: 16540883.
18. Lin WR, Lin HH, Lee SS, Tsai HC, Huang CK, Wann SR, Chen YS, Chiang SC, Yen MY, Liu YC. Comparative study of the efficacy and safety of valaciclovir versus acyclovir in the treatment of herpes zoster. *J Microbiol Immunol Infect*. 2001;34(2):138–42. PMID: 11456360.



# Atopic Dermatitis: Topical Therapy

# 17

Rebecca M. Law 

## Contents

|                      |     |
|----------------------|-----|
| Introduction.....    | 439 |
| Drug Monographs..... | 441 |
| References.....      | 451 |

## Introduction

Atopic dermatitis is primarily a disease seen in infants and young children. Treatment with topical therapies is the standard of care, although for severe cases systemic therapies such as biologic agents are effective. Topical pharmacologic therapies include the use of topical corticosteroids (TCS), topical calcineurin inhibitors (TCI), and phosphodiesterase (PDE)-4 inhibitors. Topical non-pharmacologic treatment modalities include the copious use of moisturizers, wet wrap therapy, etc. which are not discussed in this chapter.

---

R. M. Law (✉)

School of Pharmacy and Faculty of Medicine (Discipline of Family Medicine), Memorial University of Newfoundland, St. John's, NL, Canada  
e-mail: [rlaw@mun.ca](mailto:rlaw@mun.ca); [rlawUCSF@gmail.com](mailto:rlawUCSF@gmail.com)

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2025

439

R. M. Law, H. I. Maibach (eds.), *Handbook of Topical Drug Treatment in Dermatology*,  
[https://doi.org/10.1007/978-3-031-93616-6\\_17](https://doi.org/10.1007/978-3-031-93616-6_17)

## **Topical Corticosteroids (TCS)**

Topical corticosteroids (TCS) are first-line treatments for atopic dermatitis. They remain the standard of care. See Chap. 18: Topical Corticosteroids for a discussion of TCS and the monographs for individual TCS. Not all TCS have been FDA approved for use in infants and children.

## **Topical Calcineurin Inhibitors (TCI)**

Topical calcineurin inhibitors (TCI) are usually considered second-line treatments for atopic dermatitis. They are efficacious but have potential side effects including a carcinogenicity concern. They are not FDA approved for use in children <2 years of age. There are two calcineurin inhibitors used topically for atopic dermatitis: tacrolimus (Protopic) and pimecrolimus (Elidel). Tacrolimus 0.03% ointment is approved for children 2–15 years and adults, whereas the 0.1% ointment is approved only for adults. Pimecrolimus 1% cream is not FDA approved for use in children <2 years of age. The drug monographs for tacrolimus and pimecrolimus are provided below.

## **Phosphodiesterase (PDE)-4 Inhibitors**

Crisaborole and apremilast are small-molecule phosphodiesterase (PDE)-4 inhibitors. Cyclic nucleotide PDEs break down cAMP and cGMP into inactive metabolites, and there is increased PDE activity in AD, creating a proinflammatory state that may result in the stimulation of Th<sub>2</sub> cells to release inflammatory mediators. PDE-4 inhibitors inhibit the increased PDE activity; and crisaborole ointment is FDA approved for the treatment of mild-to-moderate AD in adults and children 2 years of age or older [1]. Crisaborole is applied topically, whereas apremilast is an oral medication. Thus, only the drug monograph for crisaborole is provided below.

---

## Janus Kinase (JAK) Inhibitors

Janus kinase (JAK) inhibitors target JAK/STAT and signal transducers and activators of transcription. JAK inhibitors inhibit this signal pathway, thus blocking the transcription of proinflammatory cytokines that play a central role in the pathogenesis of many inflammatory and autoimmune diseases, including atopic dermatitis, psoriasis, and vitiligo [2]. There are topical and systemic JAK inhibitors—systemic JAK inhibitors are also useful as treatment of steroid refractory graft-versus-host disease, myelofibrosis, and polycythemia vera [3]. Ruxolitinib (topical) is a JAK inhibitor approved for atopic dermatitis and vitiligo and investigated for psoriasis. See Chap. 21: Psoriasis for the ruxolitinib (topical) drug monograph.

---

## Drug Monographs

### Topical Corticosteroids (TCS)

See Chap. 18: Topical Corticosteroids

### Ruxolitinib

See Chap. 21: Psoriasis

### Tacrolimus (Topical) [4, 5, 6]

#### Classification and Mode of Action

- Tacrolimus is a topical calcineurin inhibitor (TCI). Tacrolimus inhibits T-cell activation by first binding to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin is then formed, and the calcineurin phosphatase activity is inhibited.



## Indications and Dermatological Uses

- *Clinical indications (FDA)*: Atopic dermatitis (moderate to severe) in immunocompetent patients not responsive to conventional therapy or when conventional therapy (i.e., corticosteroids) is not appropriate.
- *Off-label common uses*: Oral lichen planus, psoriasis (intertriginous and facial), pyoderma gangrenosum, vitiligo.
- Not approved for <2 years of age. 0.03% ointment is approved for 2–15 years old.

## Formulations/Presentation

- USA: 0.03% and 0.1% ointment
- Canada: 0.03% and 0.1% ointment

## Dosages and Suggested Regimens

- For atopic dermatitis: Apply a thin layer twice daily. Duration of use: Either discontinue use when symptoms have cleared or (off-label use) go to maintenance therapy using 0.03% or 0.1% ointment twice daily twice a week.
- For oral lichen planus (off-label use): Apply 0.1% ointment up to four times daily. Treatment period in clinical trials ranged from 4 to 6 weeks.
- For psoriasis (intertriginous and facial) (off-label use): 0.1% ointment twice daily for 6–8 weeks.
- For pyoderma gangrenosum (off-label use): 0.1% ointment once daily and may taper to 0.03% once daily after improvement is seen.
- For vitiligo (off-label use): 0.1% ointment twice daily and reassess every 3–6 months for adequate response.

## Pharmacokinetics

- Minimally absorbed. Serum concentration is about 2 ng/mL in the majority of adult patients studied (range: undetectable to 20 ng/mL) using the 0.1% ointment.
- Bioavailability about 0.5%.

**Use in Special Populations**

- Children 2–15 years should use 0.03% ointment only (FDA approved).
- Not for use in children <2 years of age.
- Tacrolimus is transferred across the placenta. The use of systemically administered tacrolimus during pregnancy has been associated with neonatal hyperkalemia and renal dysfunction. Tacrolimus should be used during pregnancy only if the potential benefit to the mother justifies a potential risk to the fetus.
- Although systemic absorption of tacrolimus following topical applications of tacrolimus is minimal relative to systemic administration, it is known that tacrolimus is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from tacrolimus, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
- No manufacturer recommendations for dosage adjustments in renal or hepatic failure.
- Adverse profile in the elderly (>65) was consistent with other adult patients. No manufacturer recommendations for dosage adjustments in the elderly.

**Contraindications and Cautions**

- Should not be used in patients with Netherton's syndrome or skin diseases with a potential for increased systemic absorption.
- Avoid treatment on malignant or premalignant skin conditions, as these can present as dermatitis.

**Important Drug Interactions**

- Formal topical drug interaction studies with Protopic ointment have not been conducted. Based on its minimal extent of absorption, interactions of Protopic ointment with systemically administered drugs are unlikely to occur but cannot be ruled out.

- The concomitant administration of known CYP3A4 inhibitors in patients with widespread and/or erythrodermic disease should be done with caution.

### **Adverse Effects and Their Management**

- Local symptoms such as skin burning (burning sensation, stinging, soreness) or pruritus, most commonly during the first few days of use and typically improve as the lesions of atopic dermatitis heal.
- Use in patients with Netherton's syndrome is not recommended due to the potential for increased systemic absorption of tacrolimus.
- Safety has not been established in patients with generalized erythroderma.
- No phototoxicity and no photoallergenicity was detected in clinical studies of 12 and 216 normal volunteers, respectively.
- One out of 198 normal volunteers showed evidence of sensitization in a contact sensitization study.

### **Carcinogenicity**

- Although a causal relationship has not been established, rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with TCIs.
- The enhancement of ultraviolet carcinogenicity is not necessarily dependent on phototoxic mechanisms. Despite the absence of observed phototoxicity in humans, Protopic ointment shortened the time to skin tumor formation in an animal photocarcinogenicity study. Therefore, it is prudent for patients to minimize or avoid natural or artificial sunlight exposure.
- No evidence of genotoxicity was seen in bacterial (*Salmonella* and *E. coli*) or mammalian (Chinese hamster lung-derived cells) in vitro assays of mutagenicity, the in vitro CHO/HGPRT assay of mutagenicity, or in vivo clastogenicity assays performed in mice. Tacrolimus did not cause unscheduled DNA synthesis in rodent hepatocytes.
- In a 52-week photocarcinogenicity study, the median time to the onset of skin tumor formation was decreased in hairless

mice following chronic topical dosing with concurrent exposure to UV radiation (40 weeks of treatment followed by 12 weeks of observation) with tacrolimus ointment at  $\geq 0.1\%$  tacrolimus.

### Patch Test Concentration

- 5% alcohol

### Essential Patient Information

- Use sun protection. Limit sun exposure even when the medication is not on the skin.
- Minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment).
- Do not use sun lamps, tanning beds, or get treatment with ultraviolet light therapy during treatment with tacrolimus.
- Tacrolimus ointment is not for oral use. Oral ingestion may lead to adverse effects associated with systemic administration of tacrolimus. If oral ingestion occurs, seek medical advice.

### Pimecrolimus [6, 7, 8]

#### Classification and Mode of Action

- Pimecrolimus is a topical calcineurin inhibitor indicated as second-line therapy for the short-term and noncontinuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised adults and children 2 years of age and older, who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable
- See tacrolimus for the mode of action.

#### Indications and Dermatological Uses

- *Clinical indications (FDA):* Atopic dermatitis.
- *Off-label common uses:* Oral lichen planus, psoriasis (intertriginous and facial), rosacea, and vitiligo.
- Not FDA approved for children <2 years of age.

- FDA black box warning: Although a causal relationship has not been established, rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors, including Elidel cream, 1%.
  - Therefore: Continuous long-term use of topical calcineurin inhibitors, including Elidel cream, 1%, in any age group should be avoided, and application limited to areas of involvement with atopic dermatitis.

### **Formulations/Presentation**

- USA: 1% cream (Elidel)
- Canada: 1% cream (Elidel)

### **Dosages and Suggested Regimens**

- Atopic dermatitis: Apply a thin layer twice daily. Limit application to affected area. Discontinue use when symptoms resolve, and re-evaluate if symptoms persist >6 weeks.
- Oral lichen planus (off-label use): Apply twice daily for 1 month.
- Psoriasis (intertriginous and facial) (off-label use): Apply twice daily.
- Vitiligo (off-label use): Apply twice daily for 6 months. Treatment beyond 12 months may be useful.
- Rosacea (off-label use): Apply twice daily.

### **Pharmacokinetics**

- Low systemic concentrations after topical use. Usually <2 ng/mL
- Protein binding 99.5% primarily to various lipoproteins
- Metabolized in the liver via CYP 3A4. Elimination half-life 30–40 hours. Excreted by fecal route (78% as metabolites, <1% as unchanged drug)

### **Use in Special Populations**

- Not recommended for use in children <2 years of age.
- Pregnancy: No adverse effects seen in animal reproduction studies after topical application.

- Breastfeeding: Unknown whether pimecrolimus is excreted in breast milk. Manufacturer recommends deciding whether to discontinue the drug or discontinue nursing, taking into account the importance of treatment to the mother.
- No manufacturer recommendations for dosage adjustments in renal or hepatic failure, or in the elderly.

### **Contraindications and Cautions**

- Continuous long-term use should be avoided. Safety of intermittent use for >1 year has not been established.
- Avoid treatment on malignant or premalignant skin conditions, as these can present as dermatitis.
- Should not be used in patients with Netherton's syndrome or skin diseases with a potential for increased systemic absorption.
- Should not be used in immunocompromised adults and children, including patients on systemic immunosuppressive medications.
- Safety has not been established in patients with generalized erythroderma.
- Before commencing treatment, bacterial or viral infections at treatment sites should be resolved. Trials have not evaluated the safety and efficacy of Elidel cream 1% in the treatment of clinically infected atopic dermatitis.

### **Important Drug Interactions**

- Avoid combination with systemic corticosteroids or other immunosuppressive agents, as pimecrolimus may enhance the immunosuppressive effect.
- Due to low blood levels of pimecrolimus detected in some patients after topical application, systemic drug interactions are not expected, but cannot be ruled out. Since pimecrolimus is metabolized by CYP 3A4, CYP 3A4 inhibitors may reduce its metabolism. Monitoring is recommended.
- Alcohol may enhance the dermatologic adverse effects of pimecrolimus. Monitoring is recommended.

## **Adverse Effects and Their Management**

- The most commonly reported adverse reactions ( $\geq 1\%$ ) were application site burning, headache, nasopharyngitis, cough, influenza, pyrexia, and viral infection.
- While patients with atopic dermatitis are predisposed to superficial skin infections including eczema herpeticum (Kaposi's varicelliform eruption), treatment with Elidel cream 1% may be independently associated with an increased risk of varicella zoster virus infection (chicken pox or shingles), herpes simplex virus infection, or eczema herpeticum.
- In clinical trials, 15/1544 (1%) cases of skin papilloma (warts) were observed in subjects using Elidel cream 1%. The youngest subject was age 2 and the oldest was age 12. In cases where there is worsening of skin papillomas or they do not respond to conventional therapy, discontinuation of pimecrolimus should be considered until complete resolution of the warts is achieved.
- From clinical trial experience, no phototoxicity or photoallergenicity were detected. Also, there was no contact sensitization or cumulative irritation.
- From post-marketing experience (causal relationship to pimecrolimus use not established), the following have been reported: anaphylactic reactions, ocular irritation after application of the cream to the eye lids or near the eyes, angioneurotic edema, facial edema, skin flushing associated with alcohol use, skin discoloration, lymphomas, basal cell carcinoma, malignant melanoma, and squamous cell carcinoma.

## **Carcinogenicity**

- Although a causal relationship has not been established, rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors

## **Patch Test Concentration**

- 1% pet. If not available, test 1% pimecrolimus cream and its base.

**Essential Patient Information**

- Use sun protection. Limit sun exposure even when the medication is not on the skin. Do not use sun lamps, tanning beds, or get treatment with ultraviolet light therapy during treatment with pimecrolimus.
- Not for prolonged continuous use.

**Crisaborole [9, 10]****Classification and Mode of Action**

- Crisaborole is a phosphodiesterase 4 (PDE-4) inhibitor. PDE-4 inhibition results in increased intracellular cyclic adenosine monophosphate (cAMP) levels.

**Indications and Dermatological Uses**

- *Clinical indications (FDA)*: Treatment of mild to moderate atopic dermatitis in adults and pediatric patients >3 months of age

**Formulations/Presentation**

- USA: 2% ointment
- Canada: 2% ointment

**Dosages and Suggested Regimens**

- Apply thin film to affected area(s) twice daily. Consider reducing to once daily once clinical response is achieved.

**Pharmacokinetics**

- Crisaborole is absorbed systemically after topical application.
- Crisaborole is 97% protein bound.
- Crisaborole is metabolized by the liver.



**Use in Special Populations**

- Pregnancy: adverse effects not seen in animal reproduction studies, except with high oral doses that also produced maternal toxicity.
- Breastfeeding: Unknown whether excreted in breast milk.
- There are no dosage adjustments provided in the manufacturer's labeling for patients with altered kidney or liver function.
- There are no dosage adjustments provided in the manufacturer's labeling for use in pediatrics.

**Contraindications and Cautions**

- Riociguat (see below)

**Important Drug Interactions**

- Riociguat: Crisaborole may enhance the hypotensive effect of riociguat. This is a contraindication.

**Adverse Effects and Their Management**

- Pain at application site, including burning and stinging of the skin (1–10%), urticaria (<1%). Post marketing: allergic contact dermatitis and other hypersensitivity reactions have been reported.

**Carcinogenicity**

- No information yet available

**Patch Test Concentration**

- Not available

**Essential Patient Information**

- If there is severe application site irritation or if signs of an allergic reaction are seen (rash, hives), contact a medical professional.

## References

1. Law RM, Gulliver W. Chapter 119: atopic dermatitis. In: Dippiro's pharmacotherapy: a pathophysiologic approach. 12th ed. NY: McGraw-Hill Medical; 2023. p. 1661–72.
2. Sluczanowska-Glabowska S, Ziegler-Krawczyk A, Szumilas K, Pawlik A. Role of Janus kinase inhibitors in therapy of psoriasis. *J Clin Med*. 2021;10(19):4307.
3. LexiComp drug monograph (Ruxolitinib). Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2024 UptoDate Inc.
4. FDA drug monograph (tacrolimus). Available from [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2000/507771bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2000/507771bl.pdf). Accessed 1 Aug 2024.
5. LexiComp drug monograph (Tacrolimus). Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2024 UptoDate, Inc.
6. De Groot AC. Patch testing. 3rd ed. Volume 3 Chapter 3.
7. FDA drug monograph (pimecrolimus). Available from [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2014/021302s0181bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021302s0181bl.pdf). Accessed 3 Aug 2024.
8. LexiComp drug monograph (pimecrolimus). Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2024 UptoDate, Inc.
9. FDA drug monograph (crisaborole). Available from [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2020/207695s007s009s0101bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/207695s007s009s0101bl.pdf). Accessed 3 Aug 2024.
10. LexiComp drug monograph (crisaborole). Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2024 UptoDate, Inc.



Kiha Kim, Taylor Skinner,  
and Rebecca M. Law 

## Contents

|                                                           |     |
|-----------------------------------------------------------|-----|
| Introduction.....                                         | 454 |
| High to Super High Potency.....                           | 463 |
| Mid-High to Mid-Low Potency (Class 3 to 5).....           | 481 |
| Least Potent Class 7.....                                 | 505 |
| Appendix A: Topical Corticosteroid Potency Table [2]..... | 514 |
| References.....                                           | 517 |

---

K. Kim  
Faculty of Medicine, Memorial University of Newfoundland,  
St. John's, NL, Canada  
e-mail: [kihak@mun.ca](mailto:kihak@mun.ca)

T. Skinner (✉)  
Faculty of Medicine, Memorial University of Newfoundland,  
St. John's, NL, Canada  
e-mail: [tcskinner@mun.ca](mailto:tcskinner@mun.ca)

R. M. Law  
School of Pharmacy and Faculty of Medicine (Discipline of Family  
Medicine), Memorial University of Newfoundland, St. John's, NL, Canada  
e-mail: [rlaw@mun.ca](mailto:rlaw@mun.ca); [rlawUCSF@gmail.com](mailto:rlawUCSF@gmail.com)

## **Introduction**

### **Indications for Use**

Topical corticosteroids (TCS) are a classification of anti-inflammatory drugs applied directly on the skin to treat various skin-related inflammatory diseases. They are effective in providing relief for ailments such as psoriasis, atopic dermatitis (eczema), rash, and multiple other miscellaneous skin conditions. TCS are first-line therapies for atopic dermatitis and psoriasis. Some TCS are also indicated for vitiligo (e.g., some of the fluorinated/higher potency TCS have this indication).

Although systemic corticosteroids can be an alternative effective method of combating severe or urgent/life-threatening inflammatory disease, they are not routinely used for atopic dermatitis or psoriasis—the TCS are. TCS provide more localized/focused areas of treatment with fewer adverse systemic effects.

### **Mechanisms of Action**

TCS have anti-inflammatory, immunosuppressive, and vasoconstrictive properties. TCS induce phospholipase A2 inhibitory proteins which suppress the production of arachidonic acid and interleukin-1 that are responsible for inducing inflammation, thus reducing endogenous inflammation mediators. TCS have anti-inflammatory properties that aim to suppress the immune response at the site of application.

During the inflammatory process, blood vessels become dilated around the site of inflammation. TCS also work to reduce skin inflammation by constricting the blood vessels around the site of inflammation and reducing capillary wall permeability for leukocytes to enter.

These drugs also decrease the complement components and histamine activity, while inhibiting macrophage recruitment into the site of inflammation.

### **Formulations**

TCS can be delivered in various dosage forms such as creams, ointments, gels, lotions, sprays, and foams. The mode of delivery

varies based on the site of application and the severity of disease. For example, lotions and gels are commonly used in hairy areas (e.g. scalp), while ointments are used for dry scaly lesions or more severe cases (e.g. psoriasis on the palms), as ointments provide better occlusion and hence increased potency. Formulation bases in decreasing occlusion order are ointment > creams > lotions. Specific formulations available for each TCS are discussed in the drug monographs.

## **Suggested Regimens and Usage Guidance**

Apply TCS sparingly. For hydrocortisone (the lowest potency corticosteroid), the frequency of use is up to three times daily for atopic dermatitis or 2–4 times daily for other corticosteroid-responsive dermatoses. Hair should be moved to allow direct application of the topical agent to the skin for a hairy skin. For betamethasone valerate (a medium potency corticosteroid), the frequency of use is once to twice daily depending on the formulation. Augmented ointment formulations of betamethasone dipropionate (a high potency corticosteroid) are often used once daily for conditions such as plaque psoriasis, and can be used twice daily if needed. Reassessment at two weeks for efficacy is essential, and duration of use should be limited to minimize the risk of adverse effects, including systemic side effects. If continuing TCS use is needed, step down to a lower potency TCS as soon as possible.

TCS is for external use only, not for oral, ophthalmic, or intravaginal use; wash hands after use unless hands are part of the treatment area. Avoid contact with eyes; wash eyes thoroughly with water if contact occurs.

Do not use occlusive dressing unless otherwise stated, including the diaper area for pediatric populations, as they can significantly increase percutaneous absorption; occlusive dressings may be used for some TCS in some situations (e.g., for managing psoriasis or recalcitrant conditions) if their use is deemed necessary.

Therapy should usually be stopped once control has been met unless otherwise directed by a healthcare professional. If no improvements is seen, reassessment of diagnosis should be done.

## Anti-inflammatory Potency Classifications

As mentioned above, the potency of TCS can vary greatly based on the innate anti-inflammatory potency of the drug, the vehicle/formulation, and whether the drug has been augmented or not. A drug in a tape, due to its occlusive properties, may be very potent (e.g., flurandrenolide tape). An ointment base provides more occlusion than a cream or lotion, and the same TCS in an ointment base may be more potent than in a cream or lotion. Augmented betamethasone dipropionate 0.05% ointment is one of the most potent TCS. Furthermore, the salt form of the drug may affect potency—for example, betamethasone dipropionate is more potent than betamethasone valerate. In addition, the site of application, the individual patient, and whether an occlusive dressing used may affect potency.

TCS have been classified from Groups 1 to 7, with Group 1 being the most potent and Group 7 being the least potent. The Topical Corticosteroid Potency Table in this chapter (Appendix A) is an updated table from a reference textbook chapter (Law and Gulliver 2023) using a seven-group classification [1]. This was collated from several classification systems and is currently a classification system used in the USA. There are other classification systems from different countries where TCS potencies are sorted into three, four, or five groups. We recently published an updated seven-group topical corticosteroid potency classification system [2].

## Pharmacokinetic Considerations

Topical corticosteroids need to have sufficient percutaneous absorption on the skin for topical efficacy. Topical corticosteroids have low bioavailability in systemic circulation, as most is retained in the epidermal and dermal layers of the skin. There is a general consensus that most TCS are not significantly absorbed into the systemic circulation; however, this varies based on the innate characteristics of the particular TCS. Fluorinated TCS are

more potent than non-fluorinated TCS, for example. See monographs for specific pharmacokinetics relating to a particular TCS.

## **Sites and Methods of Application Affecting Potency**

When topical corticosteroids are applied onto the skin, only a small amount of the drug is percutaneously absorbed into the inner layer of the dermis and into the systemic circulation. This percutaneous absorption of the drug can be increased by using occlusive dressings, by using different vehicles, by increasing the dose concentration, or when a layer of the skin has been damaged due to skin conditions such as psoriasis and eczema. Hence, these drugs have higher rates of absorption when applied to the face, scalp, eyelid, axilla, or scrotum, compared to thicker surfaces of the skin with a stratum corneum layer such as the elbow, palm, or sole.

## **Adverse Effects**

Common side effects include mild sensations of burning and stinging that occur within the first few application cycles of TCS, which is transient. However, prolonged uses of TCS at high doses can cause skin thinning or reddening (erythema) which in turn makes the skin more susceptible to bruises and stretching. Therefore, people with sensitive skin, including young infants and elders, are more likely to experience these side effects. Other dermatologic adverse effects of TCS include acne vulgaris, alopecia, pruritus, xeroderma, dermatitis, folliculitis, skin discoloration, skin rashes, and telangiectasia.

Non-dermatologic adverse effects of TCS include the following:

Ophthalmic: conjunctivitis  
Endocrine: hyperglycemia  
Gastrointestinal: dysgeusia

Nervous system: paresthesia.

Adverse systemic effects can occur especially from prolonged use of TCS and especially if used on large areas of the skin, and in particular with the high potency TCS groups (classified in Groups 1 and 2 of the TCS Potency Table included as Appendix A). Transient manifestations of Cushing's syndrome, hyperglycemia, and reversible hypothalamic-pituitary-adrenal axis suppression have occurred for certain patients.

Although rare, some patients have had very negative side effects that require drug discontinuation. The possible side effects that should be monitored are Cushing syndrome-like symptoms, adrenal gland problems, vision changes, high blood pressure, excessive skin changes including stretching, irritation, and thinning.

### **Adverse Effects in Special Populations, Pregnancy, and Lactation Concerns**

- Although the use of TCS is not associated with a significant risk of adverse pregnancy outcomes, however, newborn infants have an increased risk of being low weight and birth, though the risk is shown to be low.
- Pregnant populations should avoid application of the drug to high absorptive areas such as the arm pit, skin folds, and vulva; extra precaution should be taken for application to abdomen, breast, and thighs, as they are more prone to developing striae. In general, medium potency TCS should be used with avoidance of very-high-potency agents.
- Pregnant women should use low- to medium-potency TCS and avoid using very-high-potency agents; rectal corticosteroids may be used for flares in pregnant patients with inflammatory bowel disease, but maintenance therapy should be avoided.
- Regular doses of rectal corticosteroids are not expected to suppress lactation.
- For many TCS, no specific human data can be found for breast-feeding populations, although it is speculative to be probably



compatible; however, for some TCS traces of drug can be detected in breastmilk. The decision to breastfeed during TCS use should be considered based on the benefits provided to the mother versus the potential drug exposure to the infant. If the decision is to breastfeed, avoid application of TCS to the nipple and areola when breastfeeding.

- Topical corticosteroids can be used for parents who are planning a pregnancy; although the use of rectal corticosteroid for ulcerative colitis does not decrease fertility, patients with inflammatory bowel disease may have decreased fertility and should plan pregnancy after a 3–6-month remission.
- Children are more prone to systemic effects and may absorb proportionally higher amounts of TCS (due to larger body surface area to body mass ratio in comparison to adults). When used in children, HPA suppression, intracranial hypertension, and Cushing syndrome have been reported; growth of the child should be monitored routinely as prolonged use may stunt growth velocity. Use with caution in pediatric patients; generally, TCS should not be used in neonates and infants under 1 year of age. Use of augmented formulations in children <13 years of age is generally not recommended. (Refer to Chaps. 4 and 5 for further discussion.)
- Topical corticosteroids should be used cautiously for older populations in the smallest possible effective dose for the shortest duration possible.

## Contraindications

TCS should not be used in combination with calcipotriene or with clotrimazole. Do not use if the patient is hypersensitive to corticosteroids.

## Monitoring Considerations

### Ocular Effects

TCS may increase the risk of cataracts and glaucoma. Monitor for ocular symptoms and avoid contact with eyes.

### Skin Reactions

Discontinue if skin rashes, contact dermatitis, or other dermatologic reactions occur (as described above). As noted, mild stinging or burning may be transient and do not require drug discontinuation. Prolonged use of TCS may lead to steroid atrophy, and striae may be seen.

### Systemic Effects

TCS may be absorbed percutaneously. Absorption of TCS may cause manifestations of Cushing syndrome, hyperglycemia, or glycosuria. Absorption can be increased by using occlusive dressings, application to denuded skin, application to large surface areas, or prolonged use.

HPA axis suppression and adrenal insufficiency can occur, especially in children or with augmented formulation use: foam, gel, lotion (augmented), and ointment (augmented):

- ACTH stimulation test, morning plasma cortisol test, and urinary free-cortisol test can be obtained when signs of adrenal suppression have been detected; reassess again after 2 weeks.

Monitor and assess for hyperglycemia (showing confusion, fatigue, increased thirst, hunger, polyuria).

Some TCS formulations may contain benzyl alcohol and other derivatives; large amounts of benzyl alcohol (e.g.  $\geq 99$  mg/kg/day) have been associated with a potentially fatal toxicity; avoid benzyl alcohol-containing formulations for newborn patients; monitor for signs and symptoms of hypotension, respiratory distress, gasping respirations, CNS dysfunction, and cardiovascular collapse. Some TCS formulations may contain propylene glycol; in neonates large amounts of propylene glycol even topically may be associated with metabolic acidosis, seizures, renal failure, and CNS depressions potentially resulting in fatalities. Toxicities of propylene glycol reported in children and adults have included lactic acidosis, seizures and respiratory depression.

## Patch Test Concentration

In general, TCS may be tested at 0.1% and 1% in alcohol; late readings (6–10 days) are strongly recommended [3]. Other patch test formulations for specific TCS listed in deGroots have been included with each monograph, as available.

## Drug Interactions

- General contraindications within TCS applies. TCS may suppress the wheal and flare reactions to skin test antigens.
- Aldesleukin: Corticosteroids may diminish the antineoplastic effect of aldesleukin; combination should be avoided.
- CYP3A4 inhibitors may increase the serum concentration of betamethasone (topical).
- Nirmatrelvir and ritonavir may increase the serum concentration of topical corticosteroids.

## Use in Special Populations

- See Under Adverse Effects Above
- Pregnancy and Breastfeeding
  - The systemic bioavailability of topical corticosteroids may be variable (see Chap. 1). In general, the use of topical corticosteroids is not associated with a significant risk of adverse pregnancy outcomes. However, there may be an increased risk of low birth weight infants following maternal use of very potent topical products especially in high doses. In general, the use of the least potent product in limited amounts for the shortest time period is recommended during pregnancy.
  - Not adequate data – may be teratogenic in certain animal populations.
  - Use only if necessary; do not used in large amounts for prolonged time periods.
  - Extra caution for nursing women, as TCS (and systemic corticosteroids) can be distributed in milk.

- Avoid application of TCS to the nipple and areola when breastfeeding. If needed, apply TCS immediately after breastfeeding, then clean nipples prior to the next feeding.
- Pediatrics
  - Extra precaution should be used for young children, as adrenal suppression may be increased with decreasing age. Other adverse effects as described above under Systemic Effects.
  - Example: Seventy-three percent of children 6–12 years old and 32% of children 3 months–12 years for betamethasone dipropionate-augmented ointment or cream experienced adrenal suppression. Thus this product is not recommended for patients younger than 13 years old for augmented ointment or cream.
- Renal or Hepatic Insufficiency
  - In general, there are no dosage adjustments needed for patients with altered renal or hepatic insufficiency. Any specific concerns will be discussed in the individual monographs.

## Essential Patient Information

- Apply TCS sparingly to a clean, dry skin. Clean the hands before and after application.
- Do not use occlusive dressing unless otherwise stated, including in the diaper area.
- Do not apply very-high-potency agents to the face, groin, axillae, or diaper area—not for oral, ophthalmic, or intravaginal use.
- TCS are not generally subject to restriction in sporting activities, but competitors should check with the appropriate sports authorities; furthermore, care may be advisable with TCS if conditions liable to promote systemic absorption are present.

*Individual drug monographs follow. These are arranged in order of potency, as per Appendix A. Where potency changes*

*based on drug augmentation, formulation, or concentration, the drug monograph is placed at the first occurrence of the drug, i.e., the highest drug potency.*

*If part of a monograph is similar to what has been discussed in the Introduction to TCS (e.g., mechanisms of action or adverse effects), that section will be omitted.*

---

## High to Super High Potency

### Betamethasone Dipropionate (Augmented and Nonaugmented)

(not augmented is included in this monograph)

#### Classification and Mode of Action

- Class of betamethasone dipropionate augmented to become more potent.
  - Betamethasone dipropionate not augmented (classic) is also available.
- A synthetic fluorinated corticosteroid.
- *Potency varies with the formulation as follows:*
  - Betamethasone dipropionate (augmented) ointment 0.05% and gel 0.05% are Class 1: super potent.
  - Betamethasone dipropionate (not augmented) ointment 0.05% and gel 0.05% are Class 2: highly potent.
  - Betamethasone dipropionate (augmented) cream 0.05% and lotion 0.05% are Class 2: highly potent.
  - Betamethasone dipropionate (not augmented) cream 0.05% is Class 3: mid-high potent.
  - Betamethasone dipropionate (not augmented) lotion 0.05%, emulsion 0.05% (Sernivo), and spray 0.05% (Sernivo) are Class 4 or 5: mid- to mid-low potent.
- See under Introduction for other details.

## Formulations/Presentation

- USA: 0.05% ointment, gel, lotion.
- Canada: Ointment, as dipropionate augmented: diprolene: 0.05% (50 g), generic: 0.05% (15 g, 50 g)

## Dosages and Suggested Regimens

Cream 0.05% and ointment 0.05%: adolescents (topical): Apply a thin film to affected area once or twice daily; maximum dose: 50 g/week; evaluate continuation of therapy if no improvement within 2 weeks of treatment.

Gel 0.05%: children  $\geq 12$  years and adolescents (topical): Apply a thin layer to the affected area once or twice daily; rub in gently; maximum dose: 50 g/week; not recommended for use longer than 2 weeks.

Lotion 0.05%: adolescents (topical): Apply a few drops to the affected area once or twice daily; rub in gently; maximum dose: 50 mL/week; not recommended for use for longer than 2 weeks.

## Pharmacokinetics

- Percutaneous absorption.
  - Can be increased by increasing concentration and using occlusive dressings.
  - Percutaneous absorption using occlusive dressings increased notably for up to 96 hours, but no real differences for the first 24 hours vs regular topical application.
  - Up to 30–90% absorption when administered rectally.
- Metabolized by liver.
- Excreted by the kidneys or sometimes in the bile.
- Half-life is 8.5 days, while the drug was completely eliminated 48 days after withdrawal.

## Use in Special Populations

- See under Introduction.

- Studies: Seventy-three percent of children 6–12 years old and 32% of children 3 months–12 years using augmented ointment or cream experienced adrenal suppression.
- Thus, augmented ointment or creams are not recommended for patients younger than 13 years old.

## Contraindications

- Contraindications associated when used in combination with calcipotriene or with clotrimazole
- Not to use if hypersensitive to corticosteroids

## Drug Interaction

- General contraindications within the topical corticosteroids applies.
- Aldesleukin: Corticosteroids may diminish the antineoplastic effect of aldesleukin; combination should be avoided.
- CYP3A4 inhibitors May increase the serum concentration of betamethasone (topical).
- Nirmatrelvir and ritonavir may increase the serum concentration of topical corticosteroids.

## Patch Test Concentration

- 1.0% pet. (Chemotechnique); 0.5% pet., 0.1% pet. (SmartPracticeCanada)

## Essential Patient Information

- Apply topical sparingly to affected areas.
- Do not use if atrophy is present at the treatment site.
- Do not cover with occlusive dressing unless directed otherwise by a healthcare provider.
- Do not apply very-high-potency agents to the face, groin, axillae, or diaper area—not for oral, ophthalmic, or intravaginal use.
- Wash the hands after use.
- Product use should be stopped if irritation or allergic reactions occur; consult your doctor immediately.

## **Clobetasol Propionate**

### **Classification and Mode of Action**

- Clobetasol is a synthetic fluorinated corticosteroid.
- Indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in patients 12 years of age and older.
- See Introduction.

### **Formulation/Presentation**

- US: 0.05% as cream, ointment, shampoo, lotion, solution, foam, and gel
- Canada: 0.05% as cream, ointment, shampoo, solution, foam, and liquid

### **Dosages and Suggested Regimens**

- Clobetasol propionate cream, foam gel, lotion, and ointment use should not exceed 14 days, while the shampoo formulas should not exceed 4 consecutive weeks—due to a possibility of HPA-axis suppression.
- The total dosage should not exceed 50 grams per week.
- Topical clobetasol propionate should be applied sparingly in thin films and applied gently onto the skin twice daily; shampoo and solutions are applied to the scalp once and twice daily, respectively.
- Do not use occlusion.

### **Pharmacokinetics**

- Follows pharmacokinetic elimination of general topical corticosteroids.
- However, systemic metabolism not fully characterized.
- Excreted in the bile and in urine.



- Percutaneous absorption varies among individuals; absorption with gel is greater than cream; absorption increased with occlusive dressings and with an inflamed skin.
- Peak plasma concentration occurred after 3 hours of a single application.
- Mean peak plasma of 0.63 ng/mL of clobetasol propionate concentrations occurred 8 hours after a second 30-g dose (applied 13 hours after first dose) of 0.05% ointment for healthy individuals with normal skin; mean peak plasma was slightly higher when using the 0.05% cream; another study showed mean peak plasma concentration of 2.3 or 4.6 ng/mL which occurred 3 hours after a single application of a 25-g dose of 0.05% ointment for subjects with psoriasis or eczema, respectively.

### Use in Special Populations

- Not recommended for children under the age of 12
  - Can lead to HPA axis suppression, intracranial hypertension, and Cushing syndrome for children who received the topical
- Clobex and Clodan shampoo not recommended for patients under the age of 17
- Adverse effects reported in geriatric patients over 65 years of age similar to pediatric patients, although clinical studies are insufficient
- Pregnancy
  - Teratogenic properties for pregnant women are not known; however, clinical studies in mice and rabbits have shown harm to the fetus (cleft palate, skeletal abnormalities, cranioschisis).
  - Clinical studies in rats demonstrated decrease in viable fetuses from increased fetal resorptions when the dose was higher than 50 mcg/kg daily.
- No human data for breastfeeding patients

## Contraindications and Cautions

- See Introduction.
- This is also contraindicated for individuals with primary infections of the scalp.
- Canadian labelling: The product should not be used children under 2 years of age (for shampoo and spray formulas) and under 1 year of age (for cream, ointment, scalp formulas); avoid application to eyes and eyelids; should be careful for treatment of rosacea, acne vulgaris, perioral dermatitis, or perianal and genital pruritus, viral (herpes or varicella) lesions of the skin, bacterial or fungal skin infections, parasitic infections, skin manifestations relating to tuberculosis or syphilis, and eruptions following vaccinations.

## Carcinogenicity

- No evidence of clobetasol-induced mutagenesis for in vitro studies

## Patch Test Concentration

- 1% pet. (Chemotechnique, SmartPracticeCanada, SmartPracticeEurope), 0.25% pet. (SmartPracticeCanada, SmartPracticeEurope), 0.1% alc. (SmartPracticeCanada)

## Essential Patient Information

- Applied sparingly in thin films and applied gently to the skin. Do not use for longer than 2 weeks (4 weeks for shampoos).
- Cream, ointment, gel, lotion, foam, and shampoo for vehicles should not be applied to the face and intertriginous areas (axilla and groin).
- Dosage of the drug should not exceed 50 g/week in a 0.05% cream, ointment, foam, or shampoo.
- Clobetasol propionate cream, foam, gel, lotion, ointment, solution, or shampoo should *not* be used with occlusive dressings or be covered with bandages.

## Desoximetasone

### Classification, Mechanism of Action, and Clinical Uses

- Desoximetasone is a synthetic fluorinated corticosteroid.
- *Potency varies with formulation.* See Appendix A.
  - Has intermediate potency to high potency, dependent on the dosage form and concentration
    - 0.25% spray. *Class 1: super potent*
    - 0.25% ointment, 0.25% cream. *Class 2: highly potent*
    - 0.05% gel, 0.05% ointment. *Class 3: mid-high potent*
    - 0.05% cream. *Class 4: mid potent*
- See Introduction for other information.

### Indications and Dermatological Uses

- Clinical Indications (FDA)
  - See Introduction.
- Off-Label Common Uses
  - Used for short-term relief of inflammation and corticosteroid-responsive dermatosis for dental purposes

### Formulations/Presentation

- USA: Desoximetasone cream, ointment, spray (0.25%), desoximetasone gel (0.05%, Topicort and Topicort LP (0.05%))
- Canada: Desoxi cream and gel (0.05%), desoximetasone, Topicort gel and ointment

### Use in Special Populations

- No dosing adjustments for patients with altered renal or hepatic impairments,
- Pediatric populations are more prone to develop systemic side effects (e.g. HPA suppression) due to a larger skin surface area to body mass ratio; use with caution in pediatric patients.

## **Contraindications and Cautions**

- In Canadian labelling, contraindications for untreated bacterial, tubercular, fungal, and most viral lesions of the skin (including herpes simplex, vaccinia, and varicella); not for ophthalmic use.
- Not recommended for use in infants and neonates less than 1 year of age due to a possibility of adrenal suppression.
- See Introduction for other information.

## **Adverse Effects and Their Management**

- Greater than 10% of patients experienced HPA-axis suppression (especially with the 0.25% formulations).
- If skin infections occur, use appropriate antibacterial or antifungal agents to treat the skin; discontinue use of the desoximetasone topical if the infection persists.
- The use of the topical may increase the risk of posterior subcapsular cataracts and glaucoma; consult an ophthalmologist if visual abnormalities persist with the use of the drug.

## **Carcinogenicity**

- No mention on the drug's carcinogenicity

## **Patch Test Concentration**

- 1.0% pet. (Chemotechnique, SmartPracticeCanada)

## **Essential Patient Information**

- Not to use with occlusive dressing unless otherwise stated.
- Spray: Avoid contact with eyes; avoid using on the face, axilla, groin, or in the presence of atrophy at the treatment site; avoid heat, flame, or smoking when applying topical.
- Cream, gel, and ointment: Avoid contact with eyes.
- Desoximetasone preparations should be stored in well-closed containers at 15–30 °C.

## **Difflocortolone Valerate**

### **Formulations/Presentation**

- Cream and ointment: 0.1% and 0.3%

### **Dosages and Suggested Regimens**

- Cream and ointment: 0.1% and 0.3%
  - Apply a thin layer using only enough to cover affected area one to two times daily. The drug can be used for a maximum of 4 weeks, where a lack of improvement or worsening of condition after 2 weeks of application should be assessed for further evaluation.

### **Contraindications and Cautions**

- Do not use for infants under 1 year of age.
- Do not use for viral lesions of the skin; discontinue use if bacterial, fungal, or parasitic skin infections; eruptions following vaccinations; or skin manifestations relating to tuberculosis or syphilis occur.
- This should not be used with occlusive dressings.
- Application to chronic leg ulcers induce increased chance of hypersensitivity.
- See under Introduction.

### **Adverse Effects and Their Management**

- See under Introduction. Since this is a high-potency TCS, adverse reactions have included adrenal suppression, immunosuppression, Cushing syndrome, and hyperglycemia.
- Special caution should be used for patients with psoriasis as systemic toxicity due to impaired skin have been previously observed.
- Other side effects have included folliculitis, contact dermatitis, and hypersensitivity.
- Skin infections (fungal, bacterial) have been observed after prolonged or repeated use.

## **Carcinogenicity**

- Kaposi sarcoma has been reported as being associated.

## **Patch Test Concentration**

- In general, TCS may be tested at 0.1% and 1% in alcohol; late readings (6–10 days) are strongly recommended.

## **Essential Patient Information**

- For topical use only; apply a thin layer of the topical to cover the affected area.
- Clean hands and affected skin area before use.
- Do not use occlusive dressings or apply nearby eye or mucous membranes.
- Diflucortolone valerate is restricted for certain sports as a prohibited agent; patients should check with the sporting officials to see if the drug is suitable for use in competition.

## **Fluocinonide**

### **Classification and Mechanism of Action and Clinical Uses**

- Fluocinonide is a fluorinated TCS considered to be of high potency.
- See under Introduction.
- *Please note that this is a different TCS than fluocinolone acetate, in structure and in potency.* (See fluocinolone acetate for its drug monograph.)

### **Formulations/Presentation**

- Cream, gel, ointment, and solution (0.05%)
- Cream (0.1%)

## Dosages and Suggested Regimens

- Cream, gel, ointment, and solution (0.05%): Apply a thin layer to affected area two to four times daily.
- Cream (0.1%): Apply a thin layer to affected areas once daily. Seek consultation with a physician if no improvement is seen within 2 weeks; not recommended for use of over 2 weeks or a dose higher than 60 g per week.
- Lower strength 0.05% formulations may be used carefully on the face and areas of the skin folds around the groin, axilla, and breasts; higher strength 0.1% formulas should not be used on these surfaces.

## Pharmacokinetics

- No specified differences in pharmacokinetics compared to other TCS

## Use in Special Populations

- Fluocinonide can be used for atopic dermatitis for patients planning pregnancy. A milder version of the drug should be used and refrained from using in highly absorptive areas (armpit, skin folds, vulva) during pregnancy.
- Avoid 0.1% fluocinonide concentration for patients who are breastfeeding.
- Due to skin changes related to old age, older adults should limit the use of TCS.
- See under Introduction for other considerations.

## Monitoring

- HPA axis suppression test (ACTH stimulation test, AM plasma cortisol test, urinary free cortisol test) should be administered, especially for children.
- Signs of fungal and bacterial infections should be monitored for.

## **Contraindications, Cautions, and Important Drug Interactions**

- See Introduction.

## **Adverse Effects and Their Management**

- See under Introduction.
- Higher strength formulas (0.1%) should not be used on the face, groin, and axilla.
- When using lower strength formulas (0.05%), special care should be taken so the opposing skin surfaces do not rub or touch.
- Children are more prone to systemic effects and may absorb proportionally higher amounts; growth signs of adrenal suppression should be regularly monitored for.

## **Patch Test Concentration**

- In general, TCS may be tested at 0.1% and 1% in alcohol; late readings (6–10 days) are strongly recommended.

## **Carcinogenicity**

- No data available

## **Essential Patient Information**

- See under Introduction.
- Do not use occlusive dressing unless otherwise stated, including the diaper area for pediatric populations, as they significantly increase percutaneous absorption; occlusive dressings may be used with 0.05% fluocinonide for managing psoriasis or recalcitrant conditions if they are deemed necessary by a healthcare professional.
- Store cream, gel, ointment, solution, and shampoo between 15 and 30 °C, and discard shampoo after 3 months of use; do not freeze or heat above 40 °C.



## Flurandrenolide: Tape, Cream, and Lotion

### Classification, Mechanism of Action, and Clinical Use

- Flurandrenolide is a synthetic fluorinated corticosteroid.
- *Potency varies with the formulation as follows:*
  - *Ultra-high to high:* Flurandrenolide tape 4 ug/cm<sup>2</sup> (Cordran)
  - *Mid to mid-low:* Flurandrenolide 0.025%, 0.05% cream, and 0.05% lotion
  - See TCS Potency Table (Appendix A)
- See Introduction for other details.

### Formulations/Presentation

#### USA

- Cream: 0.025%, 0.05%
- Lotion: 0.05%
- Ointment: 0.05%
- Tape: 4 mcg/cm<sup>2</sup>

### Dosages and Suggested Regimens

- See Introduction for cream, lotion, and ointment.
- For tape (4 mcg/cm<sup>2</sup>): Apply every 12 hours. Measure the appropriate amount of tape to be used. If used on the face, apply carefully and avoid contact with eyes. Do not use in intertriginous areas. Tape application is most effective for dry, scaling, localized lesions.

### Contraindications and Cautions

- Do not use in intertriginous areas for drug administered via tape.

### Patch Test Concentration

- In general, TCS may be tested at 0.1% and 1% in alcohol; late readings (6–10 days) are strongly recommended.

## **Carcinogenicity**

- No animal studies for carcinogenicity, mutagenicity, or fertility are reported. See introduction for TCS.

## **Essential Patient Information**

- Flurandrenolide cream, lotion, and ointment should be protected from light and stored in tight containers at a temperature less than 40 °C, preferably between 15 and 30 °C; freezing should be avoided. Flurandrenolide tape should be stored at 15–30 °C.

## **Halobetasol Propionate**

### **Indications and Dermatological Uses**

- Clinical Indications (FDA)
  - For treating plaque psoriasis in patients older than 18 years of age with the generic foam and 0.01% lotion, or with patients greater than 12 years of age with the 0.05% foam (Lexette).
  - See Introduction.

### **Formulations/Presentation**

- USA: Cream (0.05%), foam (0.05%), lotion (0.01%, 0.05%), and ointment (0.05%)
- Canada: cream (0.05%), lotion (0.01%), and ointment (0.05%)

### **Dosages and Suggested Regimens**

- See Introduction.
- Apply a thin layer to the affected skin once daily for up to 8 weeks (lotion 0.01%) or 2 weeks (foam, lotion 0.05%). Total dosage should not exceed 50 g/week.

## Pharmacokinetics

- See Introduction.
- Study: Less than 6% of the topical dose enters the systemic circulation within 96 hours of application.

## Use in Special Populations

- No human data on pregnant populations using the drug; animal data suggests moderate risk due to the high potency of the drug.
- In animal data, rats which were exposed with 13–33 times the human topical dose resulted in cleft lip and omphalocele.
- See Introduction.

## Contraindications and Cautions

- Contraindications for Canadian labelling includes untreated bacterial, tubercular, and fungal skin infections and viral diseases (such as herpes simplex, chicken pox, vaccinia).
- See Introduction.

## Patch Test Concentration

- No data available

## Carcinogenicity

- No data available

## Amcinonide

### Classification, Mechanism of Action, and Clinical Uses

- Amcinonide is a synthetic fluorinated corticosteroid.
- *Potency varies with the formulation as follows:*

- *Ointment*: 0.1% (Class 2 high potency)
- *Cream & lotion*: 0.1% (Class 3 mid-high potency)
- See Introduction.

## **Formulations/Presentation**

- USA: Cream (0.1%), ointment (0.1%), and lotion (0.1%)
- Canada: Cream (0.1%)

## **Patch Test Concentration**

- 0.1% pet. (SmartPracticeCanada; SmartPraxticeEurope)

## **Carcinogenicity**

- No indications of its carcinogenicity

## **Essential Patient Information**

- Store in well-closed containers at a temperature less than 40 °C, preferably between 15 and 30 °C; freezing should be avoided. Amcinonide lotion and ointment should be stored at 15–30 °C; freezing of the lotion should be avoided.
- Should not be used in neonates and infants under 1 year of age due to higher risk of adrenal suppression.
- See Introduction.

## **Diflorasone Diacetate**

### **Classification, Mechanism of Action, and Clinical Use**

- Diflorasone diacetate is a synthetic fluorinated corticosteroid.
- See Introduction.

## Formulations/Presentation

- USA: Cream (0.05%) and ointment (0.05%)
- Appears white or a buff-colored powder and is insoluble in water.

## Use in Special Populations

- Follows similar precautions for special populations compared to other topical corticosteroids. See Introduction.
- Pediatric populations are prone to develop HPA suppression due to larger skin surface to body mass ratio; use with caution in pediatric patients; should not be used in neonates and infants under 1 year of age.

## Important Drug Interactions

- Does fall under the category of corticosteroids, which may diminish antineoplastic effect of aldesleukin.
- Concurrent use of diflorasone may result in false-negative results for the nitroblue tetrazolium test for bacterial infection.

## Adverse Effects and Their Management

- See Introduction.
- Very few (less than 1%) of cases reported the following adverse effects: Acne rosacea, aggravation reaction (cutaneous candidiasis, herpes, demodex, cataract, dermal ulcer, glaucoma, hirsutism, hyperpigmentation, Kaposi's sarcoma, nonthrombocytopenic purpura, ocular hypertension, psoriasis flare, purpura, skin photosensitivity, spontaneous star-shaped scar-like lesions, telangiectasia, and tinea).

## Carcinogenicity

- No mention on the drug's carcinogenicity

## **Patch Test Concentration**

- In general, corticosteroids may be tested at 0.1% and 1% in alcohol; late readings (6–10 days) are strongly recommended.

## **Halcinonide**

### **Classification, Mechanism of Action, and Clinical Use**

- Halcinonide is a synthetic fluorinated corticosteroid.
- Halcinonide's potency varies with formulation: 0.1% ointment is Class 1: super potent, and 0.1% cream and solution are Class 2: highly potent.
- See Introduction.

### **Formulations/Presentation**

- USA
  - Cream: Halog, generic at 0.1%
  - Ointment: Halog 0.1% (60 g)
  - Solution: Halog 0.1%

### **Use in Special Populations**

- Follows similar precautions for special populations compared to other topical corticosteroids
- No dosing adjustments for patients with altered renal or hepatic impairments

### **Adverse Effects and Their Management**

- Some formulations may contain propylene glycol, where large amounts can be toxic and be associated with hyperosmolarity, lactic acidosis, seizures, and respiratory depression.
- See Introduction for other adverse effects.

## **Patch Test Concentration**

- In general, corticosteroids may be tested at 0.1% and 1% in alcohol; late readings (6–10 days) are strongly recommended.

## **Carcinogenicity**

- No mention on the drug's carcinogenicity

## **Essential Patient Information**

- Topical cream, ointment, and solution should be stored in closed containers at room temperature; freezing or refrigeration should be avoided; excess heat should be avoided.
- Apply to affected area externally two to three times daily; administration of drug should be discontinued when control is achieved.
- If no improvement is seen, reassessment of diagnosis may be necessary.
- For pediatric populations, experts suggest once or twice daily application.
- Occlusive dressings may be used for managing and treating psoriasis; apply a small amount of topical onto the affected area, and cover with nonporous film to seal the edges; a damp cloth may be applied before occlusive dressing is used; topical should be reapplied for each dressing change; discontinue occlusive dressings if infections arise.

---

## **Mid-High to Mid-Low Potency (Class 3 to 5)**

### **Betamethasone Valerate**

- See betamethasone dipropionate monograph for further information; mechanism of action and clinical indications; etc. are similar as both are classified as betamethasone topicals. However, there are structural differences: betamethasone

dipropionate contains two esters—this makes it more fat soluble and increases its ability to penetrate skin. This makes betamethasone dipropionate more potent than betamethasone valerate, which only contains one ester. This is a clinically significant potency difference: betamethasone dipropionate formulations, especially when augmented, are TCS potency Class 1 and Class 2, in comparison to *betamethasone valerate formulations being TCS potency Class 3 to Class 5*. Thus, betamethasone dipropionate has greater efficacy and greater risk for adverse effects *than betamethasone valerate*. *For details of potency classification differences for the various formulations, see Appendix A.*

## Formulations/Presentation

- USA: Foam 0.12%, lotion 0.1%, cream 0.1%, and ointment 0.1%
- Canada: Lotion 0.1%, cream 0.1%, ointment 0.1%, and patch 2.25 mg (Beteflam)

## Patch Test Concentration

- 1.0% pet. (Chemotechnique, SmartPracticeCanada); 0.12% pet. (SmartPracticeCanada, SmartPracticeEurope); 0.1% alc. (SmartPracticeCanada)

## Fluticasone Propionate

### Classification and Mechanism of Action

- Fluticasone propionate is a mid-range potency TCS with the ointment more potent than the cream, even at 1/10th the concentration. Fluticasone propionate 0.005% ointment is considered Class 3: mid-high potent, whereas fluticasone propionate 0.05% cream is Class 4: mid-potent. See Appendix A.



## Indications and Dermatological Uses

- Clinical Indications (FDA)
  - Used for the relief of various skin rashes, irritation, and steroid-responsive dermatosis
  - Used for the treatment and management of psoriasis and vitiligo
  - Used for the treatment of atopic dermatitis for infants

## Formulations/Presentation

- US: Ointment (0.005%) and cream (0.05%)
- Canada: Ointment (0.005%)

## Patch Test Concentration

- In general, corticosteroids may be tested at 0.1% and 1% in alcohol; late readings (6–10 days) are strongly recommended.

## Carcinogenicity

- No mention of the drug's carcinogenicity

## Essential Patient Information

- For pediatric patients, do not apply topical to diaper area; safety and efficacy in cream have not been established for use in children beyond 4 weeks; children may absorb proportionally higher amounts of topical and may be prone to more systemic side effects.
- Cream and ointment should be stored between 2 and 30 °C (36 and 86 °F).
- Cream may be used for corticosteroid-responsive dermatoses in patients 3 months of age or older. Ointment is for adult use only.
- Avoid contact with eyes; not recommended for routine use around the face, underarms, and groin.

## **Mometasone Furoate**

### **Classification, Mechanism of Action, and Clinical Use**

- See Introduction.

### **Formulations/Presentation**

- USA: Cream (0.1%), ointment (0.1%), and solution (0.1%)
- Canada: Cream (0.1%), ointment (0.1%), and lotion (0.1%)

### **Pharmacokinetics**

- Percutaneous absorption of cream is 0.4%; lotion, ointment, and solution have an absorption rate of 0.7%; both absorptions can be increased with skin inflammation.
- No mention on the drug's metabolism or excretion.

### **Adverse Effects and Their Management**

- Do not use with occlusive dressing or on weeping/exudative lesions.
- 1–10% of the population may experience the following adverse reactions:
  - Central nervous system: paresthesia (1–3%)
  - Dermatologic: dyschromia (loss of normal skin markings:  $\leq 6\%$ ), taut and shiny skin ( $\leq 6\%$ ), folliculitis (lotion: 3%; cream, children:  $< 1\%$ ), telangiectasia ( $\leq 3\%$ ), dermatologic disorders (2%), bacterial skin infection (infants and children:  $\leq 2\%$ ), and epidermal thinning ( $\leq 2\%$ )
  - Endocrine and metabolic: decreased cortisol (infants and children: lotion:  $\leq 6\%$ , cream and ointment:  $\leq 2\%$ ), and endocrine disease (lotion: 2%)
  - Gastrointestinal: xerostomia (infants and children: 2%)
  - Hematologic and oncologic: bruise (1%)
  - Local: application site burning (2%) and application site pruritus ( $\leq 2\%$ )

- Less than 1% or an undefined frequency of the population may experience the following adverse reactions:
  - Tingling of the skin, furunculosis, skin atrophy, stinging of the skin at site of application, acneiform eruption, cataract, cutaneous candidiasis, glaucoma, skin and depigmentation
- Not for treatment of diaper dermatitis for pediatric populations; discontinue therapy when control is met for pediatric patients and reassess from a physician if no improvements is seen in 2 weeks.

### **Patch Test Concentration**

- 0.1% alc. (SmartPracticeCanada); late readings (6–10 days) are strongly recommended.

### **Carcinogenicity**

- No mention of the carcinogenicity of the drug

### **Essential Patient Information**

- Store at 25 °C.
- Reassess diagnosis if no improvements is seen after 2 weeks of use for pediatric populations.

## **Triamcinolone Acetonide**

### **Classification and Mechanism of Action**

- Triamcinolone has intermediate to mid-high-range potency dependent on dosage, concentration, and what type of vehicles are used (Class 3 to 5); more information listed on the table below and in Appendix A.

## Indications and Dermatological Uses

- Clinical Indications (FDA)
  - Used for relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses, such as atopic dermatitis, contact/vulvar/seborrheic dermatitis, and psoriasis)
  - Can provide temporary relief of symptoms associated with oral inflammation and oral ulcers resulting from trauma in a form of oral paste, such as Aphthous stomatitis
- Off-Label Common Uses
  - Used for stasis dermatitis, where the use of topical triamcinolone showed evidence of management; the evidence is derived from observational studies, unsystematic clinical experience, or potentially controlled and flawed randomized trials; the estimate of effect is uncertain.

## Formulations/Presentation

- USA
  - Aerosol (0.147 mg/g)
  - Cream (0.1%, 0.025%)
  - Lotion (0.025%)
  - Ointment (0.05%, 0.025%)
  - Oral paste (0.1%)
  - Therapy pack (0.1%)
- Canada
  - Cream (0.5%, 0.1%, 0.025%)
  - Ointment (0.1%)
  - Oral paste (0.1%)

## Potencies Related to Formulation Differences

- Potency of topical triamcinolone varies depending on the dosage, concentration, and vehicle used; it is best to start with the lowest potency agent.
- The various potency of topical triamcinolone is listed on the table below.

| Vehicle                      | Strength                                | Potency (according to the US classification system) |
|------------------------------|-----------------------------------------|-----------------------------------------------------|
| Ointment                     | 0.5%                                    | High (Class 3)                                      |
| Cream                        | 0.5%                                    | Medium (Class 4)                                    |
| Aerosol spray                | (delivering ~0.2 mg per 2-second spray) | Medium-low (Class 5)                                |
| Ointment                     | 0.1%                                    | Medium (Class 4)                                    |
| Cream, oral/<br>dental paste | 0.1%                                    | Medium-low (Class 5)                                |
| Ointment                     | 0.05%                                   | Medium-low (Class 5)                                |
| Lotion                       | 0.1%                                    | Medium-low (Class 5)                                |
| Ointment                     | 0.025%                                  | Medium-low (Class 5)                                |
| Cream, lotion                | 0.025%                                  | Low (Class 6)                                       |

Goldstein 2019; Tadicherla 2009, DiPiro 12th ed

## Pharmacokinetics

- Triamcinolone acetonide is percutaneously absorbed; epidermal integrity, formulation used, and use of occlusive dressings may affect absorption rates.
- The drug is metabolized in the liver.
- The drug is excreted mostly by feces (60%) and urine (40%).
- The drug has a biologic half-life of 18–36 hours.

## Use in Special Populations

- See Introduction.

## Contraindications and Cautions

- Fungal, viral, or bacterial infections within the oral cavity and throat when using oral topical formulations.

## Important Drug Interactions

- Triamcinolone is a class of corticosteroid that may diminish the antineoplastic effects of Aldesleukin; recommended to avoid the combination of both drugs.

- CYP3A4 inhibitors may strongly increase the serum concentration of mometasone, and therapy should be monitored when used in conjunction.
- Nirmatrelvir and ritonavir may increase the serum concentration of corticosteroids, and therapy should be monitored when used in conjunction.

## **Adverse Effects and Their Management**

- The following adverse reactions may occur when using triamcinolone:
  - Dermatologic: acneiform eruption, allergic contact dermatitis, atrophic striae, desquamation, folliculitis, hypertrichosis, hypopigmentation, local dryness, maceration of the skin, miliaria, perioral dermatitis, skin atrophy, and skin blister
  - Endocrine and metabolic: Cushing syndrome, glycosuria, HPA-axis suppression, and hyperglycemia
  - Gastrointestinal: Oral mucosa changes (paste; atrophy or maceration)
  - Local: application site burning, application site irritation, and application site pruritus
- Minor side effects such as burning, itching, or dry skin may occur.
- See Introduction for other adverse effects and cautions.

## **Patch Test Concentration**

- 1% pet. (Chemotechnique, SmartPracticeCanada, SmartPracticeEurope); 0.1% pet. (SmartPracticeCanada); the lower concentration may be preferable; late readings (6–10 days) are strongly recommended

## **Carcinogenicity**

- No mention on drug's carcinogenicity

## Essential Patient Information

- See Introduction.
- When using oral paste, do not apply the same paste onto skin or eyes; if noticeable improvement around oral cavity is not seen after a week of use, reassessment of the etiology of oral lesion is recommended.
- Store cream, ointment, lotion, and oral paste at 20–25 °C; do not freeze oral paste.
- Store aerosol spray at room temperature; avoid excessive heat and puncturing the spray.

## Clocortolone Pivalate

### Classification, Mechanism of Action, and Clinical Use

- Clocortolone is a mid-potent TCS (Class 4).
- See under Introduction for sections not listed below.

### Formulations/Presentation

- USA: Cream (0.1%) (Cloderm and generic)

### Carcinogenicity

- No mention on the drug's carcinogenicity

## Essential Patient Information

- Store drug between 15 and 30 °C and do not freeze.
- See Introduction.

## Fluocinolone Acetonide

### Classification, Mechanism of Action, and Clinical Use

- Fluocinolone acetonide is a fluorinated corticosteroid. Fluocinolone acetonide and fluocinonide are both synthetic fluorinated corticosteroids that share the action of other TCS *but differ significantly in potency*. Fluocinolone acetonide is low-mid potency depending on the dosage formulation and concentration. Fluocinolone acetonide 0.025% ointment is considered mid-potency; 0.025% cream is considered mid-low potency; 0.01% cream, shampoo, solution and oil are considered low potency (weakly potent).
- *Please note that this is a different TCS than fluocinonide, in structure and in potency.* Refer to fluocinonide monograph for info relating to fluocinonide.
- Fluocinolone acetonide is generally most effective in acute or chronic dermatoses such as seborrheic or atopic dermatitis, localized neurodermatitis, anogenital pruritus, psoriasis, late phase of allergic contact dermatitis, and inflammatory phase of xerosis.

### Formulations/Presentation

- USA
  - Cream (0.025%, 0.01%)
  - Ointment (0.025%)
  - Oil (0.01%)
  - Shampoo (0.01%)
  - Solution (0.01%)
- Canada
  - Cream (0.025%, 0.01%) (discontinued)
  - Ointment (0.025%, 0.01%)
  - Oil (0.01%)
  - Solution (0.01%) (discontinued)



## **Formulations, Packaging, and Manufacturer (Included for Clarification)**

- Cream as acetoneide
  - Synalar: 0.025% (120 g) (contains cetyl alcohol, edetate (edta) disodium, methylparaben, propylene glycol, propylparaben)
  - Generic: 0.01% (15 g, 60 g); 0.025% (15 g, 60 g)
- Kit as acetoneide
  - Synalar (cream): 0.025% (contains cetyl alcohol, edetate (edta) disodium, methylparaben, propylene glycol, propylparaben)
  - Synalar (ointment): 0.025%
  - Synalar TS: 0.01% (contains propylene glycol)
  - Xilapak: 0.01% (discontinued) (contains butylparaben, cetyl alcohol, methylparaben, propylene glycol, propylparaben)
- Oil as acetoneide
  - Derma-Smoothe/FS Body: 0.01% (118.28 mL) (contains isopropyl alcohol, peanut oil)
  - Derma-Smoothe/FS Scalp: 0.01% (118.28 mL) (contains isopropyl alcohol, peanut oil)
  - Generic: 0.01% (118.28 mL)
- Ointment as acetoneide
  - Synalar: 0.025% (120 g)
  - Generic: 0.025% (15 g, 60 g)
- Shampoo, external, as acetoneide
  - Capex: 0.01% (120 mL)
- Solution, external, as acetoneide
  - Synalar: 0.01% (60 mL) (contains propylene glycol)
  - Generic: 0.01% (60 mL)

For further clarification, below are two tables outlining the various forms of fluocinolone acetoneide and fluocinonide that are available:

| Fluocinolone acetonide |              |           |                                 |              |
|------------------------|--------------|-----------|---------------------------------|--------------|
| Routes                 | Dosage forms | Strengths | Brand names                     | Manufacturer |
| Topical                | Cream        | 0.01%*    |                                 |              |
|                        |              | 0.025%*   |                                 |              |
|                        |              |           | Synalar®                        | Medicis      |
|                        |              |           | Synemol® emollient cream        | Medicis      |
|                        | For shampoo  | 0.01%     | Capex® shampoo                  | Galderma     |
|                        | Oil          | 0.01%     | Derma-Smoothe/FS®               | Hill         |
|                        | Ointment     | 0.025%*   | Fluocinolone acetonide ointment |              |
|                        |              |           | Synalar®                        | Medicis      |
|                        | Solution     | 0.01%*    |                                 |              |
|                        |              |           | Synalar®                        | Medicis      |
| Fluocinonide           |              |           |                                 |              |
| Routes                 | Dosage forms | Strengths | Brand names                     | Manufacturer |
| Topical                | Cream        | 0.05%*    | Fluocinonide E emollient cream  |              |
|                        |              |           | Lidex®                          | Medicis      |
|                        |              |           | Lidex®-E emollient cream        | Medicis      |
|                        | Gel          | 0.05%*    | Fluocinonide gel                |              |
|                        |              |           | Lidex® gel                      | Medicis      |
|                        | Ointment     | 0.05%*    |                                 |              |
|                        |              |           | Lidex®                          | Medicis      |
|                        | Solution     | 0.05%*    |                                 |              |
|                        |              |           | Lidex®                          | Medicis      |

## Pharmacokinetics

- Metabolized in the liver
- Excreted primarily by urine, and the rest by bile

## Contraindications and Cautions

- See Introduction.
- For Canadian labelling, additional contraindications state as following:
  - Viral lesions of the skin
  - Bacterial/fungal/parasitic infections
  - Skin manifestations relating to tuberculosis or syphilis
  - Eruptions after vaccinations
  - Application to the eye or surrounding areas
- Certain fluocinolone acetonide 0.01% topical is made with 48% refined peanut oil; as peanut protein is undetected at 2.5 ppm, this formulation should be used with caution for patients with hypersensitivity to peanuts; discontinue use if wheal and flare-type hypersensitivity reactions occur.

## Patch Test Concentration

- In general, TCS may be tested at 0.1% and 1% in alcohol; late readings (6–10 days) are strongly recommended.

## Carcinogenicity

- Although some corticosteroids have exhibited mutagenic activity in some in vivo and in vitro microbial/mammalian tests, no studies have been performed to evaluate the carcinogenicity of fluocinolone acetonide (or the similar fluocinonide formula).

## Essential Patient Information

- For scalp psoriasis, apply a thin layer of oil or topical onto scalp and massage thoroughly on wet hair; leave overnight or for at least 4 hours before washing hair with shampoo.
- For seborrheic dermatitis of the scalp, apply no more than 1 ounce of shampoo onto the scalp once daily; leave for at least 5 minutes before washing hair with shampoo.

- If no improvements is seen, reassessment of diagnosis should be met.
- May use occlusive dressings for the management of psoriasis or recalcitrant conditions; if skin infection occurs, discontinue use and seek appropriate antimicrobial therapy.
- Store oil and shampoo between 20 and 25 °C, and discard shampoo after 2 months of use; store cream, ointment, and topical solution between 15 and 25 °C, and avoid freezing or exposing it to excessive heat above 40 °C.
- Only use shampoo solution for seborrheic dermatitis of the scalp, as this formulation has not been proven to be effective in other corticosteroid responsive dermatoses.
- See Introduction.

## **Flurandrenolide**

- Cordran 0.05% Ointment is mid-potency.
- See flurandrenolide above for further details.

## **Hydrocortisone Salts (Valerate, Butyrate, Acetate, Probutate, Etc.)**

### **Classification, Mechanism of Action, and Clinical Uses**

- *Hydrocortisone salts differs from hydrocortisone (base)* and has low to intermediate range potency depending on the salt form, dosage form and formulation, and concentration. In general, salt forms are more potent than hydrocortisone base (Class 7: lowest potency). See table below for comparisons, and Appendix A Potency table.

|                |                                               |                        | Potency (according to the US classification system) |
|----------------|-----------------------------------------------|------------------------|-----------------------------------------------------|
| Hydrocortisone | Vehicle                                       | Strength               |                                                     |
| Valerate       | Ointment                                      | 0.2%                   | Medium (Class 4)                                    |
| Butyrate       | Ointment                                      | 0.1%                   | Medium (Class 4)                                    |
| Butyrate       | Cream, lotion, and solution                   | 0.1%                   | Lower-mid (Class 5)                                 |
| Probutate      | Cream                                         | 0.1%                   | Lower-mid (Class 5)                                 |
| Valerate       | Cream                                         | 0.2%                   | Lower-mid (Class 5)                                 |
| Acetate        | Ointment                                      | 1%                     | Weakly potent (Class 6)                             |
| Acetate        | Cream, lotion                                 | 1%, 2%, and 2.5%       | Least potent (Class 7)                              |
| Base           | Cream, gel, lotion, ointment, solution, spray | 0.5%, 1%, 2%, and 2.5% | Least potent (Class 7)                              |

Goldstein (2021), Tadicherla (2009)

- See Introduction for Clinical Uses
  - For OTC hydrocortisone products, the drug can be used for temporary relief of itching associated with minor skin irritations, inflammation, and rashes (such as eczema, psoriasis, poison ivy or insect bites, seborrheic dermatitis) and temporary relief of external anal and genital itching.
- Off-Label Common Uses
  - For the management of stasis dermatitis.
  - The 10% hydrocortisone (base) cream, but not the valerate derivative, has been used for desquamative inflammatory vaginitis.

## Use in Special Populations

- See Introduction.
- Pregnant woman have been prescribed hydrocortisone products and gave birth to infants with congenital malformations, but the relationship between the drug and the outcome could not be determined for human data.

- Although hydrocortisone may cross the placenta to the fetus for pregnant populations, there is a low transfer to the fetus as the placenta is rich with enzymes called 11 $\beta$ -ol-dehydrogenase that metabolize the hydrocortisone into an inactive 11-ketosteroid compound.
- Some formulations of the drug may contain propylene glycol, which can cause fatal toxicities in neonates when delivered orally, topically, or intravenously (over 3000 mg/day); symptoms include metabolic acidosis, seizures, renal failure, and CNS depression; symptoms such as hyperosmolality, lactic acidosis, respiratory depression, and seizures have been observed in adults and children when exposed to high amounts of this substance.

### **Contraindications and Cautions**

- Do not use for the treatment of diaper dermatitis when treating it as an OTC self-medication.
- See Introduction.

### **Important Drug Interactions**

- Topical hydrocortisone may diminish the therapeutic effects of calcipotriene; combined use should be monitored by detecting if there is a reduced efficacy of calcipotriene when used with hydrocortisone; separating the administration of both drugs by 10–12 hours may minimize the risk of this interaction.
- See Introduction.

### **Adverse Effects and Their Management**

- See Introduction.

### **Patch Test Concentration**

- Hydrocortisone (base): 1.0% pet. (SmartPracticeCanada, SmartPracticeEurope): late readings (6–10 days) are strongly recommended. Testing with this preparation probably results

in many false-negative reactions. In general, corticosteroids can be tested 0.1% and 1% alcohol.

- Hydrocortisone acetate: 1.0% pet. (Chemotechnique; SmartPracticeCanada); late readings (6–10 days) are strongly recommended. Hydrocortisone acetate 1% in alc./DMSO is irritant.
- Hydrocortisone butyrate: 1.0% pet. (Chemotechnique, SmartPracticeCanada); 1% alc. (Chemotechnique, SmartPracticeCanada); 0.1% pet. (SmartPracticeCanada, SmartPracticeEurope); alcohol may be a better vehicle for testing hydrocortisone butyrate than petrolatum. Late readings (6–10 days) are strongly recommended.
- Hydrocortisone hemisuccinate/hydrocortisone probutate/hydrocortisone valerate: In general, corticosteroids may be tested at 0.1% and 1% in alcohol; late readings (6–10 days) are strongly recommended.

## **Carcinogenicity**

- No available information

## **Essential Patient Information**

- Store at 20–25 °C; do not freeze or heat the medication.
- For topical products, apply topical corticosteroids to moist skin immediately after bathing for optimal absorption.
- Clean and dry the skin at the site of topical application, removing offending agents surrounding the skin; do not use on scars or damaged skin.
- Occlusive dressings may be used when instructed by health-care professional; the use of occlusive dressings may increase absorption of the drug by a factor of 10.
- Shake lotion well before use.
- Hydrocortisone is a larger class of corticosteroids with different derivatives. Instructions for hydrocortisone valerate use for certain corticosteroid-responsive dermatoses are listed below, but may not be a comprehensive list.

- Atopic dermatitis: Apply hydrocortisone valerate cream once or twice daily to affected areas for 2 to 4 weeks; apply valerate ointment for moderate to severe cases once or twice daily to affected areas for 2 to 4 weeks, with intermittent application once daily for 2 consecutive days per week for patients seeing improvement; lower-potency preparations are recommended for areas affecting the groin, face, and areas of skin folds.
- Contact dermatitis: Apply valerate cream or ointment once or twice daily for 1–2 weeks for allergic dermatitis; apply valerate cream once or twice daily for 1–2 weeks for irritant dermatitis.
- Genital pruritus: Apply valerate ointment once daily for 2–4 weeks; therapy can be continued indefinitely at minimum frequency until pruritus is effectively controlled.
- Seborrheic dermatitis: Apply valerate cream once or twice daily until symptoms subside for chest and upper back symptoms, usually lasting 1–2 weeks
- Stasis dermatitis: Apply valerate ointment once or twice daily for 1–2 weeks; avoid prolonged use due to a risk of ulceration and skin atrophy at site of application.

## Hydrocortisone (Topical) (Geriatric Lexi-Drugs)

*Hydrocortisone valerate* (Martindale: The Complete Drug Reference)

*Hydrocortisone, hydrocortisone acetate, hydrocortisone butyrate, hydrocortisone butyrate, hydrocortisone valerate (topical)* (AHFS Essentials (adult and pediatric))

*Hydrocortisone, hydrocortisone acetate, hydrocortisone butyrate, hydrocortisone butyrate, hydrocortisone valerate (topical)* (AHFS DI (adult and pediatric))

*Hydrocortisone (topical)* (Pediatric and Neonatal Lexi-Drugs)

*Hydrocortisone* (Briggs Drugs in Pregnancy and Lactation)



## Alclometasone Dipropionate

### Classification, Mechanism of Action, and Clinical Use

- Alclometasone dipropionate is a synthetic corticosteroid.
- Unlike other topical corticosteroids, alclometasone dipropionate should not be used for the treatment of acne, rosacea, or perioral dermatitis.
- *Potency varies with formulation.* Alclometasone dipropionate 0.05% ointment is Class 5: mid-low potency, and other formulations (0.05% cream) are Class 6: weakly potent.
- Cream as alclometasone dipropionate is as follows:
  - Generic: 0.05% (15 g, 45 g, 60 g)
  - Aclovate: 0.05%
- Ointment as alclometasone dipropionate is as follows:
  - Generic: 0.05% (15 g, 45 g, 60 g)
  - Aclovate: 0.05% (with propylene glycol)
- Indicated for patients more than 1 year of age.

### Pharmacokinetics

- About 3% of the drug is reportedly absorbed into the systemic circulation during an 8-hour period of a single application of a 0.05% ointment; systemic absorption may be increased with skin disease and inflammation.
- Onset of initial response occurs after 5.3 days of drug use for eczema and 6.7 days after for psoriasis.
- There is a peak response of the drug 13.9 days after for eczema and 14.8 days after for psoriasis.
- Metabolism of drug is not fully characterized; in animal testing, topical drug did not accumulate in tissues and is thought to be completely metabolized to unidentifiable metabolites.
- Drug and its metabolites are excreted in feces by biliary elimination and by urine.

## Use in Special Populations

- Although teratogenic properties of alclometasone dipropionate is unknown, some potent corticosteroid have shown to be teratogenic in animals after topical application; reproduction studies in rabbit with dosages of 1.2 g/kg oral or 0.75 mg/kg topical application has shown maternal toxicity, inability to maintain pregnancy, increased resorption, inhibition of weight gain, decreased litter size, and death; evidence of fetal harm (such as cleft palate, developmental problems, increased malformations) as a secondary effect from the mother's toxicity was been shown in this animal study.
- See Introduction.

## Contraindications and Cautions

- Unlike other topical corticosteroids, alclometasone dipropionate should not be used for the treatment of acne, rosacea, or perioral dermatitis.
- Alclometasone shares toxic properties with other topical corticosteroids and precautions should be taken; no evidence of local irritation, anesthetic effect, phototoxicity/photosensitization, or local antigenic/immunogenic effects when 0.1% of alclometasone dipropionate ointment was applied in animal studies.
- Alclometasone dipropionate does not appear to suppress the HPA axis with usual doses; no effect on plasma cortisol levels in patients with psoriasis or atopic dermatitis after 15 g of 0.05% ointment applied to 30% of body twice daily for 7 days with 12/24-hour occlusive dressings on certain patients; essentially unchanged levels of plasma cortisol concentrations before and after the drug use for children 3 months to 12 years old using drug therapy for various dermatosis such as atopic eczema, seborrheic eczema, diaper dermatitis or psoriasis; slightly decreased cortisol, urinary-free cortisol, and 17-hydroxysteroid concentration for healthy individuals using

30 g of 0.05% cream covering 80% of body twice daily for 21 days with daily 12 hour occlusive dressing use—however, the treatment values were within normal ranges, and the application was higher than usual dosages.

- Efficacy and safety of drug has not been established for pediatric use over 3 weeks of duration or for children under 1 year of age.

### **Patch Test Concentration**

- 1.0% pet. (Chemotechnique)

### **Carcinogenicity**

- No evidence of alclometasone-induced mutagenesis in the Ames microbial mutagen test and in in vitro mammalian cell systems; studies have also shown certain other topical corticosteroids such as hydrocortisone or prednisolone to be mutagenic.
- Long-term studies determining carcinogenicity has not been performed to date.

### **Essential Patient Information**

- Generally not for use on the face, underarms, or groin area unless specifically directed to do so.
- Store cream and ointment between 2 and 30 °C.

## **Desonide**

### **Classification, Mechanism of Action, and Clinical Use**

- Desonide is Class 5: mid-low potent and Class 6: weakly potent. *Potency is formulation dependent.* See Appendix A.
- Can be used for atopic dermatitis in infants greater than 3 months old.

## Formulations/Presentation

- USA
  - Cream (0.05%)
  - Foam (0.05%)
  - Gel (0.05%)
  - Lotion (0.05%)
  - Ointment (0.05%)
- Canada
  - Cream (0.05%)
  - Ointment (0.05%)

## Contraindications and Cautions

- Some dosages of the drug may contain propylene glycol, which can cause fatal toxicities in neonates when delivered orally, topically, or intravenously (over 3000 mg/day); symptoms include metabolic acidosis, seizures, renal failure, and CNS depression; symptoms such as hyperosmolality, lactic acidosis, respiratory depression, and seizures have been observed in adults and children when exposed to high amounts of this substance.

## Adverse Effects and Their Management

- 1–10% of patients using this drug may experience the following adverse reactions:
  - Cardiovascular: increased blood pressure (2%)
  - Central nervous system: headache (2%) and irritability (1%)
  - Dermatologic: stinging of the skin ( $\leq 3\%$ ), atopic dermatitis ( $< 2\%$ ; exacerbation), contact dermatitis ( $< 2\%$ ), exfoliation of skin ( $< 2\%$ ), pruritus ( $< 2\%$ ), skin irritation ( $< 2\%$ ), xeroderma ( $< 2\%$ ), and skin rash ( $\leq 1\%$ )
  - Endocrine and metabolic: hyperglycemia (2%) and HPA-axis suppression (more common in pediatric patients)

- Hepatic: abnormal liver function (1%)
- Infection: viral infection (2%)
- Local: application site reaction (1% to 6%), application site burning ( $\leq 3\%$ ), and application site atrophy (1%)
- Respiratory: Upper respiratory tract infection (10%), cough (4%), asthma (1%), and pharyngitis (1%)

### **Patch Test Concentration**

- In general, corticosteroids may be tested at 0.1% and 1% in alcohol; late readings (6–10 days) are strongly recommended.

### **Carcinogenicity**

- No mention on the drug's carcinogenicity

### **Essential Patient Information**

- When applying onto the face, apply desonide first into hands, and gently massage into affected areas of the face.
- Desonide may be directly applied onto the affected area if not applied onto the face.
- Wash hands after use unless hands are part of the treatment area .
- Do not use on open wounds, cuts, or damaged skin.
- Not recommended for use with occlusive dressings unless told otherwise.
- Do not use for diaper dermatitis for pediatric populations.
- When using foam or lotion solution, shake well before use.
- Foam solution is flammable; patients should not smoke during or immediately following application.
- Store cream, lotion, and ointment between 2 and 30 °C (tridesilon cream at 20–25 °C); store foam between 20 and 25 °C, and keep away from excessive heat and refrain from puncturing container; store gel at 15–30 °C but 25 °C is optimal.

## **Prednicarbate**

### **Classification, Mechanism of Action, and Clinical Use**

- Prednicarbate is a synthetic corticosteroid
- Prednicarbate is Class 5: mid-low potent

### **Formulations/Presentation**

- USA: Cream (0.1%) and ointment (0.1%).
- Canada: Cream (0.1%) and ointment (0.1%).
- In Canada, similar formulas can be found as the name “Dermatop” Canadian Labelling:
  - Cream, external  
Dermatop: 0.1% (20 g, 60 g) (contains benzyl alcohol, edetate, sodium (tetrasodium))
  - Ointment, external  
Dermatop: 0.1% (60 g) (contains propylene glycol)

### **Contraindications and Cautions**

- See Introduction.
- Do not use for diaper dermatitis for pediatric populations.
- For Canadian labelling, additional contraindications are as follows:
  - Hypersensitivity to wool or lanolin
  - Treatment of bacterial/fungal/viral skin infections
  - Diseases such as tuberculosis, syphilis, and chicken pox
  - Eruptions after vaccination

### **Patch Test Concentration**

- 1.0% alc. (SmartPracticeCanada); late readings (6–10 days) are strongly recommended.

## Carcinogenicity

- No mention on the carcinogenic properties of prednicarbate

## Essential Patient Information

- Store cream at 5–25 °C and ointment at 20–25 °C.

---

## Least Potent Class 7

### Hydrocortisone (Base $\geq 2\%$ )

- *Refer back to “hydrocortisone salts” monograph for further details.*

## Indications and Dermatological Uses

- Clinical Indications (FDA)
  - Hydrocortisone topical is used for relief and treatment of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses such as atopic dermatitis, contact dermatitis, vulvar dermatitis, psoriasis, and seborrheic dermatitis.
  - Can be used for the treatment and relief of psoriasis and vitiligo.
  - Can be used for anal and genital pruritus for genital and anal itching.
  - Hydrocortisone is often used in combination with another agent such as a hemorrhoidal agent (e.g., Anusol-HC). Some of these combination products are listed here.
- Off-Label Common Uses
  - Topical hydrocortisone can be used for the management of stasis dermatitis and desquamative inflammatory vaginitis when administered intravaginally.
  - Both treatments for off-label uses have a “Level of Evidence C” which shows evidence from observational studies, unsystematic clinical experience, or potentially flawed randomized, or controlled trials, where the estimate of effect is uncertain.

## Formulations/Presentation

- USA
  - Ointment (2.5%), cream (2.5%), lotion (2%, 2.5%), and solution (2.5%)
- Canada
- Europe

The following hydrocortisone products have a base equal to or greater than 2%:

- Cream as hydrocortisone base
  - Ala-Cort: 2.5% (30 g) (contains cetyl alcohol, propylene glycol)
  - Anusol-HC: 2.5% (30 g)
  - Procto-Med HC: 2.5% (28 g, 30 g) (contains cetearyl alcohol, methylparaben, propylene glycol, propylparaben)
  - Proctosol HC: 2.5% (28.35 g)
  - Proctozone-HC: 2.5% (30 g)
  - Proctozone-HC: 2.5% (30 g) (contains cetearyl alcohol, methylparaben, propylene glycol, propylparaben)
  - Hytone (with propylene glycol): 2.5% (volume not available)
  - Generic: 2.5% (20 g, 28 g, 28.35 g, 30 g, 453.6 g, 454 g)
- Kit as hydrocortisone base
  - Advanced allergy collection: 2.5% (contains cetyl alcohol, methylparaben, propylene glycol, propylparaben)
  - Dermasorb HC: 2% (discontinued) (contains menthol, methylparaben, propylene glycol, propylparaben)
  - Scalacort DK: hydrocortisone lotion 2% and salicylic acid 2% and sulfur 2% (contains benzalkonium chloride, isopropyl alcohol, methylparaben, propylene glycol, propylparaben, soybean lecithin)
- Lotion as hydrocortisone base
  - Ala Scalp: 2% (29.6 mL, 59.2 mL) (contains benzalkonium chloride, isopropyl alcohol, propylene glycol)
  - Hytone (with propylene glycol): 2.5% (volume not available)
- Ointment as hydrocortisone base



- Hytone (with propylene glycol): 2.5% (volume not available)
- Generic: 0.5% (28 g (discontinued), 30 g); 2.5% (20 g, 28.35 g, 453.6 g, 454 g)
- Solution, external, as base
  - Texacort: 2.5% (30 mL) (lipid free, paraben free; contains alcohol, usp)

## Use in Special Populations

- Pregnant women prescribed hydrocortisone produced infants with congenital malformations, but the relationship between the drug and the outcome could not be determined for human data.
- Although hydrocortisone may cross the placenta to the fetus for pregnant populations, there is a low transfer to the fetus as the placenta is rich with enzymes called 11 $\beta$ -ol-dehydrogenase that metabolize the hydrocortisone into an inactive 11-ketosteroid compound.
- Some dosages of the drug may contain propylene glycol, which can cause fatal toxicities in neonates when delivered orally, topically, or intravenously (over 3000 mg/day); symptoms include metabolic acidosis, seizures, renal failure, and CNS depression; symptoms such as hyperosmolality, lactic acidosis, respiratory depression, and seizures have been observed in adults and children when exposed to high amounts of this substance.
- See Introduction.

## Monitoring

- Signs of HPA axis suppression should be monitored via ACTH stimulation test, morning plasma cortisol test, or urinary free cortisol test.
- Signs of skin atrophy should be noted and monitored.
- As topical absorption may be minimal due to the low potency of this product, there is no additional monitoring for healthcare professionals.

## **Contraindications and Cautions**

- Hypersensitivity to hydrocortisone or other components of the drug.
- Systemic fungal infections and ileocolostomy during the immediate or early postoperative period.
- Cases such as obstruction, abscess, perforation, peritonitis, fresh intestinal anastomoses, and extensive fistulas.
- Possibility of allergenic cross-sensitivity cannot be ruled out for certainty, as documentation of allergenic cross-reactivity is limited.
- Do not use for the treatment of diaper dermatitis when treating it as an OTC self-medication.

## **Important Drug Interactions**

- Hydrocortisone is a class of corticosteroid that may diminish the antineoplastic effects of aldesleukin; recommended to avoid the combination of both drugs.
- Topical hydrocortisone may diminish the therapeutic effects of calcipotriene; combined use should be monitored by detecting if there is a reduced efficacy of calcipotriene when used with hydrocortisone; separating the administration of both drugs by 10–12 hours may minimize the risk of this interaction.

## **Patch Test Concentration**

- Hydrocortisone (base): 1.0% pet. (SmartPracticeCanada, SmartPracticeEurope): late readings (6–10 days) are strongly recommended. Testing with this preparation probably results in many false-negative reactions. In general, corticosteroids can be tested 0.1% and 1% alcohol.

## **Carcinogenicity**

- No available information

## Essential Patient Information

- Store at 20–25 °C; do not freeze or heat the medication.
- For topical products, apply topical corticosteroids to moist skin immediately after bathing for optimal absorption.
- Clean and dry the skin at the site of topical application, removing offending agents surrounding the skin; do not use on scars or damaged skin.
- Occlusive dressings may be used when instructed by health-care professional; the use of occlusive dressings may increase absorption of the drug by a factor of 10.
- Shake lotion well before use.
- Hydrocortisone is a larger class of corticosteroids with different derivatives. Instructions for hydrocortisone use for certain corticosteroid-responsive dermatoses are listed below, but may not be a comprehensive list; also, some of the conditions not listed here may have directions to treat with other hydrocortisone derivatives, for example, contact dermatitis treated with hydrocortisone butyrate or probutate.
  - Atopic dermatitis: Apply 2.5% hydrocortisone base cream or ointment once or twice daily to affected areas for 2 to 4 weeks for mild cases; lower-potency preparations are recommended for areas affecting groin, face, and areas of skin folds.
  - Genital pruritus: Apply 0.5–2.5% hydrocortisone base ointment once daily for 2–4 weeks for vulvar dermatitis; therapy can be continued indefinitely at minimum frequency until pruritus is effectively controlled.
  - Hemorrhoids: Apply 1% or 2.5% hydrocortisone base cream up to twice daily
  - Psoriasis: Apply 1–2.5% hydrocortisone base ointment or cream twice daily until lesions resolve, typically for 2 weeks.
  - Seborrheic dermatitis: Apply 0.5–2.5% hydrocortisone base (cream, ointment, lotion) once or twice daily until signs subside for symptoms on the face or intertriginous areas.

- Vaginitis (off-label): Apply 3–5 g of 10% hydrocortisone cream intravaginally once daily at bedtime for 4–6 weeks; as this is not commercially available, it must be prepared at a compounding facility or substituted for a 0.5% base hydrocortisone cream.
- For pediatric populations: Hydrocortisone base can be used for dermatologic irritation for up to 3–4 times daily for children over 2 years of age; children over 12 years of age can use hydrocortisone base for anal and genital itching; hydrocortisone base can be used for corticosteroid-responsive dermatosis including psoriasis up to 2–4 times daily.

## Hydrocortisone (Base <2%)

See above hydrocortisone base  $\geq 2\%$ , and the hydrocortisone salts monograph for further details.

## Dosages and Suggested Regimens

The following hydrocortisone products have a base less than 2%:

- Cream as base
  - Ala-Cort: 1% (28.4 g) (contains cetyl alcohol, propylene glycol)
  - Cortaid Maximum Strength: 1% (28 g (discontinued)) (contains cetyl alcohol, disodium edta, ethylparaben, methylparaben, propylparaben)
  - Cortizone-10 (with parabens and propylene glycol): 1%
  - Curad hydrocortisone: 1% (1.5 g (DSC), 28.4 g (discontinued)) (latex free; contains methylparaben, polysorbate 80, propylene glycol, propylparaben)
  - Hydrocortisone anti-itch: 1% (28 g) (contains cetyl alcohol, chlorocresol (chloro-m-cresol), propylene glycol)
  - Hydrocortisone Max St: 1% (28.4 g)
  - Hydrocortisone Max St/12 Moist: 1% (28.4 g) (contains cetearyl alcohol, methylparaben, propylene glycol, propylparaben)

- Hydrocortisone/Aloe Max Str: 1% (28 g) (contains cetyl alcohol, edetate (edta) trisodium, isopropyl alcohol, methylparaben, propylparaben, trolamine (triethanolamine))
- Hytone (with propylene glycol): 1%
- Instacort 5: 0.5% (28.4 g)
- Medpura hydrocortisone: 1% (28 g) (contains benzyl alcohol, cetyl alcohol)
- Preparation H: 1% (26 g) (contains cetyl alcohol, edetate (edta) disodium, methylparaben, propylene glycol, propylparaben, sodium benzoate)
- Procto-Pak: 1% (28.4 g)
- Proctocort: 1% (28.4 g) (contains cetyl alcohol, propylene glycol)
- Recort Plus: 1% (30 g)
- Generic: 0.5% (15 g, 28.35 g (discontinued), 28.4 g); 1% (1 g, 1.5 g (discontinued), 14.2 g, 20 g, 28 g, 28.35 g, 28.4 g, 30 g, 453.6 g, 454 g)
- Lotion as base
  - Aquanil HC: 1% (120 mL)
  - Beta HC: 1% (60 mL)
  - Nutracort (with parabens): 1%
  - Sarnol-HC: 1% (59 mL)
  - Generic: 1% (114 g, 120 mL)
- Ointment as base
  - Hydrocortisone in Absorbase: 1% (110 g (discontinued))
  - Hydrocortisone Max St: 1% (28 g (discontinued))
  - Generic: 0.5% (28 g (discontinued), 30 g); 2.5% (20 g, 28.35 g, 453.6 g, 454 g); 1% (28 g, 28.35 g, 28.4 g, 30 g, 453.6 g)
- Ointment as base (preservative free)
  - Hydrocortisone in Absorbase: 1% (110 g (discontinued))
- Solution as base:
  - Scalpicin Maximum Strength: 1% (44 mL (discontinued)) (contains disodium edta, menthol, propylene glycol)
  - Cortaid® FastStick® Maximum Strength (with alcohol and methylparaben): 1%

- Cortaid® Spray Maximum Strength (with alcohol and methylparaben): 1%
- Cortizone-10® Scalp Itch Formula Liquid (with alcohol SD 40–2 60% v/v, benzyl alcohol, and propylene glycol): 1%
- Penecort® (with alcohol SD 40–2 57%, benzyl alcohol, and propylene glycol): 1%
- Texacort® (with SD alcohol 33% and propylene glycol): 1%

## Essential Patient Information

- Store at 20–25 °C; do not freeze or heat the medication.
- For topical products, apply topical corticosteroids to the moist skin immediately after bathing for optimal absorption.
- Clean and dry the skin at the site of topical application, removing offending agents surrounding the skin; do not use on scars or damaged skin.
- Occlusive dressings may be used when instructed by health-care professional; the use of occlusive dressings may increase absorption of the drug by a factor of 10.
- Shake lotion or cream well before use.
- Hydrocortisone is a larger class of corticosteroids with different derivatives. Instructions for hydrocortisone use for certain corticosteroid-responsive dermatoses are listed below, but may not be a comprehensive list; also, some of the symptoms not listed here may have directions to treat for other hydrocortisone derivatives, for example, contact dermatitis treated with hydrocortisone butyrate or probutate.
  - Genital pruritus: Apply 0.5–2.5% hydrocortisone base ointment once daily for 2–4 weeks for vulvar dermatitis; therapy can be continued indefinitely at minimum frequency until pruritus is effectively controlled; apply 1% hydrocortisone base cream or ointment for balanitis twice daily for 1–2 weeks.
  - Hemorrhoids: Apply 1% or 2.5% hydrocortisone base cream up to twice daily.

- Psoriasis: Apply 1–2.5% hydrocortisone base ointment or cream twice daily until lesions resolve, typically for 2 weeks.
- Seborrheic dermatitis: Apply 0.5–2.5% hydrocortisone base (cream, ointment, lotion) once or twice daily until signs subside for symptoms on the face or intertriginous areas.
- Vaginitis (off-label): Apply 3–5 g of 10% hydrocortisone cream intravaginally once daily at bedtime for 4–6 weeks; as this is not commercially available, it must be prepared at a compounding facility or substituted for a 0.5% base hydrocortisone cream.
- For pediatric populations: Hydrocortisone base can be used for dermatologic irritation for up to 3–4 times daily for children over 2 years of age; children over 12 years of age can use hydrocortisone base for anal and genital itching; Hydrocortisone base can be used for corticosteroid-responsive dermatosis including psoriasis up to 2–4 times daily.

## Appendix A: Topical Corticosteroid Potency Table [2]

| Potency rating               | Topical corticosteroid                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Class 1:<br>super<br>potent  | Betamethasone dipropionate (augmented) 0.05%<br>Ointment (Diprolene)<br>Gel (generic only)<br>Clobetasol propionate 0.05%<br>Cream, ointment (Dermovate [cr, ung])<br>Lotion, spray, shampoo (Clobex [ltn, sp., shmp], Clodan [shmp])<br>Foam (Olux-E, Tovet)<br>Gel (generic only)<br>Desoximetasone 0.25%<br>Spray (Topicort, generic)<br>Diflucortolone valerate 0.3%<br>Ointment, oily cream (Nerisone Forte, Temetex Forte)<br>Fluocinonide 0.1%<br>Cream (Vanos)<br>Flurandrenolide tape 4ug/cm <sup>2</sup><br>Tape roll (Cordran)<br>Halcinonide 0.1%<br>Ointment (Halog)<br>Halobetasol propionate 0.05%<br>Cream, lotion, ointment (Ultravate)<br>Foam (Lexette) |
| Class 2:<br>highly<br>potent | Amcinonide 0.1%<br>Ointment (generic only)<br>Betamethasone dipropionate augmented 0.05%<br>Cream (generic only)<br>Betamethasone dipropionate 0.05%<br>Ointment (Diprosone)<br>Gel (generic only)<br>Clobetasol propionate 0.025%<br>Cream (Impoyz)<br>Diflorasone diacetate 0.05%<br>Ointment (generic only)<br>Emollient cream (ApexiCon-E)<br>Desoximetasone 0.25%<br>Cream, ointment (Topicort [cr, ung])<br>Spray (Topicort spray)<br>Fluocinonide 0.05%<br>Gel, ointment (Lidemol [ung, g], Lidex [ung, g])<br>Solution (generic only)<br>Halcinonide 0.1%<br>Cream, solution (Halog)<br>Halobetasol propionate 0.01%<br>Lotion (Bryhali)                           |

(continued)



| Potency rating                 | Topical corticosteroid                                                                 |
|--------------------------------|----------------------------------------------------------------------------------------|
| Class 3:<br>mid-high<br>potent | Amcinonide 0.1%<br>Cream, lotion (generic only)                                        |
|                                | Betamethasone dipropionate 0.05%<br>Cream (Diprosone, TARO-sone)                       |
|                                | Betamethasone valerate 0.1%<br>Ointment (Betaderm)                                     |
|                                | Patch (Betaflam) 2.25 mg                                                               |
|                                | Desoximetasone 0.05%<br>Gel, ointment (Topicort)                                       |
|                                | Diflorasone diacetate 0.05%<br>Cream (generic only)                                    |
|                                | Diflucortolone valerate 0.1%<br>Ointment, oily cream (Nerisone, Temetex)               |
|                                | Fluocinonide 0.05%<br>Cream (Lidemol, Lidex, Lyderm, Tiamol)                           |
|                                | Fluticasone propionate 0.005%<br>Ointment (Cutivate)                                   |
|                                | Mometasone furoate 0.1%<br>Ointment (Elocom)                                           |
|                                | Triamcinolone acetonide 0.5%<br>Ointment (generic only)                                |
| Class 4:<br>mid-potent         | Betamethasone dipropionate 0.05%<br>Spray (Sernivo)                                    |
|                                | Betamethasone valerate 0.12%<br>Foam (generic only)                                    |
|                                | Clocortolone pivalate 0.1%<br>Cream (Cloderm)                                          |
|                                | Desoximetasone 0.05%<br>Cream (Topicort)                                               |
|                                | Fluocinolone acetonide 0.025%<br>Ointment (Synalar)                                    |
|                                | Fluticasone propionate 0.05%<br>Cream, lotion (generic only)                           |
|                                | Hydrocortisone butyrate 0.1%<br>Ointment (generic only)                                |
|                                | Hydrocortisone valerate 0.2%<br>Ointment (Hydroval)                                    |
|                                | Mometasone furoate 0.1%<br>Cream, lotion (Elocom [cr, ltn])<br>Solution (generic only) |
|                                | Prednicarbate 0.1%<br>Ointment (Dermatop)                                              |
|                                | Triamcinolone acetonide 0.1%<br>Ointment (Aristocort R)                                |
|                                | Triamcinolone acetonide 0.5%<br>Cream (generic only)                                   |

(continued)

| Potency rating          | Topical corticosteroid                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|-------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Class 5: mid-low potent | <p>Alclometasone dipropionate 0.05%<br/>Ointment (generic only)</p> <p>Betamethasone dipropionate 0.05%<br/>Lotion (Diprosone)</p> <p>Betamethasone valerate 0.1%<br/>Cream, lotion (Betaderm [cr, ltn])</p> <p>Desonide 0.05%<br/>Ointment (generic only)<br/>Gel (generic only)</p> <p>Flurandrenolide 0.05%<br/>Cream, lotion (Cordran [cr, ltn])</p> <p>Fluocinolone acetonide 0.025%<br/>Cream (Synalar)</p> <p>Hydrocortisone butyrate 0.1%<br/>Cream (Locoid Lipocream))<br/>Lotion (Locoid)<br/>Solution (generic only)</p> <p>Hydrocortisone probutate 0.1%<br/>Cream (Pandel)</p> <p>Hydrocortisone valerate 0.2%<br/>Cream (Hydroval)</p> <p>Prednicarbate 0.1%<br/>Cream (Dermatop)</p> <p>Triamcinolone acetonide 0.05%<br/>Ointment (generic only)</p> <p>Triamcinolone acetonide 0.1%<br/>Cream (Aristocort R)<br/>Lotion (generic only)<br/>Oral paste (Oracort, Kourzeq, Oralone)</p> <p>Triamcinolone acetonide 0.147 mg/g<br/>Aerosol solution (Kenalog)</p> |
| Class 6: weakly potent  | <p>Alclometasone dipropionate 0.05%<br/>Cream (generic only)</p> <p>Desonide 0.05%<br/>Cream (DesOwen)<br/>Lotion (generic only)<br/>Foam (Verddeso)</p> <p>Fluocinolone acetonide 0.01%<br/>Cream (generic only)<br/>Solution (Synalar)<br/>Shampoo (Capex)<br/>Oil (Derma-Smoothe, FS Body, FS Scalp)</p> <p>Hydrocortisone acetate 1%<br/>Ointment (generic only)</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

(continued)

| Potency rating                | Topical corticosteroid                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|-------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Class 7:<br>lowest<br>potency | Hydrocortisone acetate<br>Cream (Vanicream HC) 1%<br>Lotion (NuCort) 2%<br>Foam (Cortifoam) 10%<br>Suppository (Anucort-HC, Anusol-HC, Hemmorex-HC (25 mg), Proctocort (30 mg))                                                                                                                                                                                                                                                                                                                             |
|                               | Hydrocortisone base<br>Cream (Instacort 0.5%, Ala-cort 1%, Preparation H 1%, Proctocort 1%, Barriere-HC 1%, Hyderm 1%, Anusol-HC 2.5%, Proctomed-HC 2.5%, Proctosol-HC 2.5%, Proctozone-HC 2.5%, generics 0.5%, 1%, and 2.5%)<br>Enema (Cortenema 100 mg/60 mL)<br>Gel (Hydroxym 2%)<br>Lotion (Aquanil HC 1%, Beta HC 1%, Sarnol-HC 1%, Sarna-HC 1%, Ala Scalp 2%, generics 1% and 2.5%)<br>Ointment (Hydrocortisone Max Strength 1%, Cortoderm 1%, generics 0.5%, 1%, and 2%)<br>Solution (Texacort 2.5%) |

References

Introduction

1. Law RM, Gulliver W. Chapter 118: psoriasis. In: Dipiro’s pharmacotherapy: a pathophysiologic approach. 12th ed. NY: McGraw-Hill Medical; 2023. p. 1639–60.

2. Skinner TC, Law RM, Maibach HI. Topical corticosteroid potencies: reimagining a new universal classification system. J Drugs Dermatol. 2025;24(5):458–64. <https://doi.org/10.36849/JDD.8426>

3. De Groot AC. Patch testing. 3rd ed. Volume 3 Chapter 3 & De Groot AC. Patch testing, 4th edition: Update 2018–2022. Wapserveen, The Netherlands: acdegroot publishing, 2022 (37 pages). ISBN/EAN 978-90-813233-7-6.

4. <http://online.lexi.com.qe2a-proxy.mun.ca/lco/action/doc/retrieve/docid/disandproc/6577603?cesid=aI9TMWNASqF&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3Dcorticosteroid%26t%3Dname%26acs%3Dtrue%26acq%3Dcorticosteo#monograph-tab-content>

5. <https://pubmed.ncbi.nlm.nih.gov/2533778/#:~:text=Corticosteroids%20modify%20the%20functions%20of,form%20a%20steroid%2Dreceptor%20complex>

6. <https://www.verywellhealth.com/how-topical-steroids-work-1068833>

7. [https://www.rxlist.com/how\\_do\\_topical\\_corticosteroids\\_work/drug-class.htm](https://www.rxlist.com/how_do_topical_corticosteroids_work/drug-class.htm)
8. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3508578/>

## High to Super High Potency: Betamethasone Dipropionate

9. LexiComp drug monograph (betamethasone dipropionate). Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2024 UptoDate, Inc.
10. FDA drug monograph available at: <https://pubmed.ncbi.nlm.nih.gov/29128828/#:~:text=The%20half%20life%20of%20betamethasone,was%20estimated%20up%20to%2048days>
11. De Groot AC. Patch testing. 3rd ed. Volume 3 Chapter 3.

## High to Super High Potency: Clobetasol Propionate

12. FDA drug monographs (Clobetasol propionate). Available from ([https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2020/213691s0001bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213691s0001bl.pdf) for the lotion and [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2012/021835s0061bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021835s0061bl.pdf) for the spray and <https://www.drugs.com/pro/clobetasol-cream.html> for the cream). Accessed 7 July 2024.
13. LexiComp drug monograph (clobetasol propionate). Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2024 UptoDate, Inc.
14. De Groot AC. Patch testing. 3rd ed. Volume 3 Chapter 3.

## High to Super High Potency: Desoximetasone

15. US FDA PMR Final Study Report for 0.25% desoximetasone spray <https://www.fda.gov/media/154879/download> (Accessed 17 July 2024).
16. LexiComp drug monograph (Desoximetasone). Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2024 UptoDate, Inc.
17. De Groot AC. Patch testing. 3rd ed. Volume 3 Chapter 3.

## High to Super High Potency: Diflucortolone Valerate

18. Health Canada HRES (diflucortolone valerate). Available from: [https://pdf.hres.ca/dpd\\_pm/00037898.PDF](https://pdf.hres.ca/dpd_pm/00037898.PDF) Accessed 7 July 2024.
19. LexiComp drug monograph (diflucortolone valerate). Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2024 UptoDate, Inc.
20. De Groot AC. Patch testing. 3rd ed. Volume 3 Chapter 3.

## High to Super High Potency: Fluocinonide

21. FDA Drug Monograph (fluocinonide cream—Vanos) Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2006/021758s001bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/021758s001bl.pdf)
22. LexiComp drug monograph (fluocinonide). Available from: LexiComp Online at online.Lexi.com. Copyright 2024 UptoDate, Inc.
23. De Groot AC. Patch testing. 3rd ed. Volume 3 Chapter 3.

## High to Super High Potency: Flurandrenolide: Tape, Cream, and Lotion

24. FDA Drug Monographs for flurandrenolide ointment, cream, lotion (Cordran cream & ointment available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/012806s0371bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/012806s0371bl.pdf) Cream available at [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/205342Orig1s0001bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/205342Orig1s0001bl.pdf)).
25. LexiComp drug monograph (flurandrenolide). Available from: LexiComp Online at online.Lexi.com. Copyright 2024 UptoDate, Inc.
26. De Groot AC. Patch testing. 3rd ed. Volume 3 Chapter 3.

## High to Super High Potency: Halobetasol Propionate

27. FDA Drug Monograph (Halobetasol propionate). Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2012/019968s0111bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/019968s0111bl.pdf) Accessed 9 July 2024.
28. LexiComp drug monograph (halobetasol propionate). Available from: LexiComp Online at online.Lexi.com. Copyright 2024 UptoDate, Inc.

## High to Super High Potency: Amcinonide

29. NIH monograph Amcinonide. Available at: <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=ac5c3e79-52f7-434e-92ae-24bd32b45edc&type=display> Accessed 8 July 2024.
30. LexiComp drug monograph (amcinonide). Available from: LexiComp Online at online.Lexi.com. Copyright 2024 UptoDate, Inc.
31. De Groot AC. Patch testing. 3rd ed. Volume 3 Chapter 3.

## High to Super High Potency: Diflorasone Diacetate

32. FDA drug monograph (diflorasone diacetate 0.05% ointment). Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/019260s009lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/019260s009lbl.pdf) Accessed 17 July 2024.
33. LexiComp drug monograph (diflorasone diacetate). Available from: LexiComp Online at [online.lexi.com](https://online.lexi.com). Copyright 2024 UptoDate, Inc.
34. De Groot AC. Patch testing. 3rd ed. Volume 3 Chapter 3.

## High to Super High Potency: Halcinonide

35. FDA drug monograph (halcinonide 0.1% cream). [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2009/017556s038lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/017556s038lbl.pdf) Accessed 18 July 2024.
36. [http://online.lexi.com/qc2a-proxy.mun.ca/lco/action/doc/retrieve/docid/complete\\_ashp/413472?cesid=0z1zhOU0oEu&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DHalcinonide%26t%3Dname%26acs%3Dfalse%26acq%3DHalcinonide](http://online.lexi.com/qc2a-proxy.mun.ca/lco/action/doc/retrieve/docid/complete_ashp/413472?cesid=0z1zhOU0oEu&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DHalcinonide%26t%3Dname%26acs%3Dfalse%26acq%3DHalcinonide)
37. LexiComp drug monograph (halcinonide). Available from: LexiComp Online at [online.lexi.com](https://online.lexi.com). Copyright 2024 UptoDate, Inc.
38. De Groot AC. Patch testing. 3rd ed. Volume 3 Chapter 3.

## Mid-High to Mid-Low Potency (Class 3 to 5): Betamethasone Valerate

39. Drugs.com. <https://www.drugs.com/betamethasone-topical.html#:~:text=Betamethasone%20dipropionate%20contains%20two%20esters,which%20only%20contains%20one%20ester>. Accessed 19 July 2024.
40. [http://online.lexi.com/lco/action/doc/retrieve/docid/patch\\_f/5004842?cesid=6xmrwv6Xokb&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DBetamethasone%2Bvalerate%26t%3Dname%26acs%3Dfalse%26acq%3DBetamethasone%2Bvalerate](http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/5004842?cesid=6xmrwv6Xokb&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DBetamethasone%2Bvalerate%26t%3Dname%26acs%3Dfalse%26acq%3DBetamethasone%2Bvalerate)
41. LexiComp drug monograph (Betamethasone valerate). Available from: LexiComp Online at [online.lexi.com](https://online.lexi.com). Copyright 2024 UptoDate, Inc.
42. De Groot AC. Patch testing. 3rd ed. Volume 3 Chapter 3.

## Mid-High to Mid-Low Potency (Class 3 to 5): Fluticasone Propionate

43. [http://online.lexi.com/lco/action/doc/retrieve/docid/patch\\_f/341?cesid=9U5dGrCLvPk&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DFluticasone%2Bpropionate%26t%3Dname%26acs%3Dfalse%26acq%3DFluticasone%2Bpropionate#adr](http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/341?cesid=9U5dGrCLvPk&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DFluticasone%2Bpropionate%26t%3Dname%26acs%3Dfalse%26acq%3DFluticasone%2Bpropionate#adr)

44. <http://online.lexi.com/lco/action/doc/retrieve/docid/3/3674>
45. LexiComp drug monograph (Fluticasone propionate). Available from: LexiComp Online at [online.lexi.com](http://online.lexi.com). Copyright 2024 UptoDate, Inc.
46. De Groot AC. Patch testing. 3rd ed. Volume 3 Chapter 3.

### **Mid-High to Mid-Low Potency (Class 3 to 5): Mometasone Furoate**

47. [http://online.lexi.com/lco/action/doc/retrieve/docid/patch\\_f/1799125?cesid=3B3LcXliZK6&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DMometasone%2Bfuroate%26t%3Dname%26acs%3Dtrue%26acq%3DMometasone%2Bfuroate#adr](http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/1799125?cesid=3B3LcXliZK6&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DMometasone%2Bfuroate%26t%3Dname%26acs%3Dtrue%26acq%3DMometasone%2Bfuroate#adr)
48. [http://online.lexi.com/lco/action/doc/retrieve/docid/pdh\\_f/2850861?cesid=3B3LcXliZK6&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DMometasone%2Bfuroate%26t%3Dname%26acs%3Dtrue%26acq%3DMometasone%2Bfuroate](http://online.lexi.com/lco/action/doc/retrieve/docid/pdh_f/2850861?cesid=3B3LcXliZK6&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DMometasone%2Bfuroate%26t%3Dname%26acs%3Dtrue%26acq%3DMometasone%2Bfuroate)
49. LexiComp drug monograph (Mometasone furoate). Available from: LexiComp Online at [online.lexi.com](http://online.lexi.com). Copyright 2024 UptoDate, Inc.
50. De Groot AC. Patch testing. 3rd ed. Volume 3 Chapter.

### **Mid-High to Mid-Low Potency (Class 3 to 5): Triamcinolone Acetonide**

51. [http://online.lexi.com/lco/action/doc/retrieve/docid/patch\\_f/1802822?cesid=9uAZSL1oLGH&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DTriamcinolone%2Bacetonide%26t%3Dname%26acs%3Dfalse%26acq%3DTriamcinolone%2Bacetonide#](http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/1802822?cesid=9uAZSL1oLGH&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DTriamcinolone%2Bacetonide%26t%3Dname%26acs%3Dfalse%26acq%3DTriamcinolone%2Bacetonide#)
52. [http://online.lexi.com/lco/action/doc/retrieve/docid/pdh\\_f/2860023?cesid=9uAZSL1oLGH&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DTriamcinolone%2Bacetonide%26t%3Dname%26acs%3Dfalse%26acq%3DTriamcinolone%2Bacetonide#coi](http://online.lexi.com/lco/action/doc/retrieve/docid/pdh_f/2860023?cesid=9uAZSL1oLGH&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DTriamcinolone%2Bacetonide%26t%3Dname%26acs%3Dfalse%26acq%3DTriamcinolone%2Bacetonide#coi)
53. [http://online.lexi.com/lco/action/doc/retrieve/docid/essential\\_ashp/410301?cesid=9uAZSL1oLGH&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DTriamcinolone%2Bacetonide%26t%3Dname%26acs%3Dfalse%26acq%3DTriamcinolone%2Bacetonide](http://online.lexi.com/lco/action/doc/retrieve/docid/essential_ashp/410301?cesid=9uAZSL1oLGH&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DTriamcinolone%2Bacetonide%26t%3Dname%26acs%3Dfalse%26acq%3DTriamcinolone%2Bacetonide)
54. [http://online.lexi.com/lco/action/doc/retrieve/docid/complete\\_ashp/413424?cesid=9uAZSL1oLGH&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DTriamcinolone%2Bacetonide%26t%3Dname%26acs%3Dfalse%26acq%3DTriamcinolone%2Bacetonide](http://online.lexi.com/lco/action/doc/retrieve/docid/complete_ashp/413424?cesid=9uAZSL1oLGH&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DTriamcinolone%2Bacetonide%26t%3Dname%26acs%3Dfalse%26acq%3DTriamcinolone%2Bacetonide)
55. Goldstein BG, Goldstein AO. Comparison of representative topical corticosteroid preparations (classified according to the United States system). Waltham, MA: UpToDate. Available at: <https://www.uptodate.com/contents/topical-corticosteroids-use-and-adverse-effects>
56. Tadicherla S, Ross K, Shenefelt PD, Fenske NA. Topical corticosteroids in dermatology. *J Drugs Dermatol*. 2009;8(12):1093–1105.

57. LexiComp drug monograph (Triamcinolone acetonide). Available from: LexiComp Online at [online.lexi.com](http://online.lexi.com). Copyright 2024 UptoDate, Inc.
58. De Groot AC. Patch testing. 3rd ed. Volume 3 Chapter.

### **Mid-High to Mid-Low Potency (Class 3 to 5): Clocortolone Pivalate**

59. LexiComp drug monograph (clocortolone pivalate). Available from: LexiComp Online at [online.lexi.com](http://online.lexi.com). Copyright 2024 UptoDate, Inc.
60. De Groot AC. Patch testing. 3rd ed. Volume 3 Chapter 3.

### **Mid-High to Mid-Low Potency (Class 3 to 5): Fluocinolone Acetonide**

61. [http://online.lexi.com/lco/action/doc/retrieve/docid/patch\\_f/1796619?cesid=73uymJBy3vC&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DFluocinolone%2Bacetonide%26t%3Dname%26acs%3Dfalse%26acq%3DFluocinolone%2Bacetonide#coi](http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/1796619?cesid=73uymJBy3vC&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DFluocinolone%2Bacetonide%26t%3Dname%26acs%3Dfalse%26acq%3DFluocinolone%2Bacetonide#coi)
62. [http://online.lexi.com/lco/action/doc/retrieve/docid/pdh\\_f/2850762?cesid=73uymJBy3vC&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DFluocinolone%2Bacetonide%26t%3Dname%26acs%3Dfalse%26acq%3DFluocinolone%2Bacetonide](http://online.lexi.com/lco/action/doc/retrieve/docid/pdh_f/2850762?cesid=73uymJBy3vC&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DFluocinolone%2Bacetonide%26t%3Dname%26acs%3Dfalse%26acq%3DFluocinolone%2Bacetonide)
63. [http://online.lexi.com/lco/action/doc/retrieve/docid/patch\\_f/6925?cesid=73uymJBy3vC&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DFluocinolone%2Bacetonide%26t%3Dname%26acs%3Dfalse%26acq%3DFluocinolone%2Bacetonide](http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/6925?cesid=73uymJBy3vC&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DFluocinolone%2Bacetonide%26t%3Dname%26acs%3Dfalse%26acq%3DFluocinolone%2Bacetonide)
64. [http://online.lexi.com/lco/action/doc/retrieve/docid/complete\\_ashp/413471?cesid=73uymJBy3vC&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DFluocinolone%2Bacetonide%26t%3Dname%26acs%3Dfalse%26acq%3DFluocinolone%2Bacetonide#cauts-nested-1](http://online.lexi.com/lco/action/doc/retrieve/docid/complete_ashp/413471?cesid=73uymJBy3vC&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DFluocinolone%2Bacetonide%26t%3Dname%26acs%3Dfalse%26acq%3DFluocinolone%2Bacetonide#cauts-nested-1)
65. LexiComp drug monograph (clocortolone pivalate). Available from: LexiComp Online at [online.lexi.com](http://online.lexi.com). Copyright 2024 UptoDate, Inc.
66. De Groot AC. Patch testing. 3rd ed. Volume 3 Chapter 3.

### **Mid-High to Mid-Low Potency (Class 3 to 5): Hydrocortisone Salts (Valerate, Butyrate, Acetate, Probutate, Etc.)**

67. De Groot AC. Patch testing. 3rd ed. Volume 3 Chapter 3.
68. <http://online.lexi.com/lco/action/search?q=Hydrocortisone&t=name&acs=false&acq=Hydrocortisone>
69. [http://online.lexi.com/lco/action/doc/retrieve/docid/pdh\\_f/2848040?cesid=7j2fFT9cLDV&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DHydrocortisone%2Bvalerate%26t%3Dname%26acs](http://online.lexi.com/lco/action/doc/retrieve/docid/pdh_f/2848040?cesid=7j2fFT9cLDV&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DHydrocortisone%2Bvalerate%26t%3Dname%26acs)



%3Dfalse%26acq%3DHydrocortisone%2Bvalerate#peds-pated-tab-content

70. [http://online.lexi.com/lco/action/doc/retrieve/docid/complete\\_ashp/413425?cesid=7j2fFT9cLDV&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DHydrocortisone%2Bvalerate%26t%3Dname%26acs%3Dfalse%26acq%3DHydrocortisone%2Bvalerate](http://online.lexi.com/lco/action/doc/retrieve/docid/complete_ashp/413425?cesid=7j2fFT9cLDV&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DHydrocortisone%2Bvalerate%26t%3Dname%26acs%3Dfalse%26acq%3DHydrocortisone%2Bvalerate)
71. [http://online.lexi.com/lco/action/doc/retrieve/docid/essential\\_ashp/410302?cesid=7j2fFT9cLDV&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DHydrocortisone%2Bvalerate%26t%3Dname%26acs%3Dfalse%26acq%3DHydrocortisone%2Bvalerate](http://online.lexi.com/lco/action/doc/retrieve/docid/essential_ashp/410302?cesid=7j2fFT9cLDV&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DHydrocortisone%2Bvalerate%26t%3Dname%26acs%3Dfalse%26acq%3DHydrocortisone%2Bvalerate)
72. [http://online.lexi.com/lco/action/doc/retrieve/docid/martindale\\_f/1353657?cesid=7j2fFT9cLDV&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DHydrocortisone%2Bvalerate%26t%3Dname%26acs%3Dfalse%26acq%3DHydrocortisone%2Bvalerate](http://online.lexi.com/lco/action/doc/retrieve/docid/martindale_f/1353657?cesid=7j2fFT9cLDV&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DHydrocortisone%2Bvalerate%26t%3Dname%26acs%3Dfalse%26acq%3DHydrocortisone%2Bvalerate)
73. [http://online.lexi.com/lco/action/doc/retrieve/docid/gdh\\_f/2151227?cesid=7j2fFT9cLDV&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DHydrocortisone%2Bvalerate%26t%3Dname%26acs%3Dfalse%26acq%3DHydrocortisone%2Bvalerate](http://online.lexi.com/lco/action/doc/retrieve/docid/gdh_f/2151227?cesid=7j2fFT9cLDV&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DHydrocortisone%2Bvalerate%26t%3Dname%26acs%3Dfalse%26acq%3DHydrocortisone%2Bvalerate)

### **Mid-High to Mid-Low Potency (Class 3 to 5): Alclometasone Dipropionate**

74. [http://online.lexi.com/lco/action/doc/retrieve/docid/complete\\_ashp/413970?cesid=7xU0f4TrK0M&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DAlclometasone%2Bdipropionate%26t%3Dname%26acs%3Dfalse%26acq%3DAlclometasone%2Bdipropionate#cauts-nested-1](http://online.lexi.com/lco/action/doc/retrieve/docid/complete_ashp/413970?cesid=7xU0f4TrK0M&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DAlclometasone%2Bdipropionate%26t%3Dname%26acs%3Dfalse%26acq%3DAlclometasone%2Bdipropionate#cauts-nested-1)
75. [http://online.lexi.com/lco/action/doc/retrieve/docid/patch\\_f/6293?cesid=7xU0f4TrK0M&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DAlclometasone%2Bdipropionate%26t%3Dname%26acs%3Dfalse%26acq%3DAlclometasone%2Bdipropionate#](http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/6293?cesid=7xU0f4TrK0M&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DAlclometasone%2Bdipropionate%26t%3Dname%26acs%3Dfalse%26acq%3DAlclometasone%2Bdipropionate#)
76. [http://online.lexi.com/lco/action/doc/retrieve/docid/essential\\_ashp/988197#uses-nested](http://online.lexi.com/lco/action/doc/retrieve/docid/essential_ashp/988197#uses-nested) (Alclometasone Dipropionate (AHFS Essentials (Adult and Pediatric))).
77. [http://online.lexi.com/lco/action/doc/retrieve/docid/martindale\\_f/1353588?cesid=7xU0f4TrK0M&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DAlclometasone%2Bdipropionate%26t%3Dname%26acs%3Dfalse%26acq%3DAlclometasone%2Bdipropionate](http://online.lexi.com/lco/action/doc/retrieve/docid/martindale_f/1353588?cesid=7xU0f4TrK0M&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DAlclometasone%2Bdipropionate%26t%3Dname%26acs%3Dfalse%26acq%3DAlclometasone%2Bdipropionate)
78. De Groot AC. Patch testing. 3rd ed. Volume 3 Chapter 3.

## Mid-High to Mid-Low Potency (Class 3 to 5): Desonide

79. ([http://online.lexi.com/lco/action/doc/retrieve/docid/complete\\_ashp/413426?cesid=8MJLM9VISHJ&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3Ddesowen%26t%3Dname%26acs%3Dfalse%26acq%3Ddesowen](http://online.lexi.com/lco/action/doc/retrieve/docid/complete_ashp/413426?cesid=8MJLM9VISHJ&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3Ddesowen%26t%3Dname%26acs%3Dfalse%26acq%3Ddesowen) - Desonide (Topical) (AHFS DI (Adult and Pediatric))
80. [http://online.lexi.com/lco/action/doc/retrieve/docid/pdh\\_f/128606?cesid=98lgc24liE9&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3Ddesonide%26t%3Dname%26acs%3Dfalse%26acq%3Ddesonide](http://online.lexi.com/lco/action/doc/retrieve/docid/pdh_f/128606?cesid=98lgc24liE9&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3Ddesonide%26t%3Dname%26acs%3Dfalse%26acq%3Ddesonide)
81. [http://online.lexi.com/lco/action/doc/retrieve/docid/complete\\_ashp/413426?cesid=98lgc24liE9&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3Ddesonide%26t%3Dname%26acs%3Dfalse%26acq%3Ddesonide](http://online.lexi.com/lco/action/doc/retrieve/docid/complete_ashp/413426?cesid=98lgc24liE9&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3Ddesonide%26t%3Dname%26acs%3Dfalse%26acq%3Ddesonide)
82. [http://online.lexi.com/lco/action/doc/retrieve/docid/patch\\_f/6708?cesid=98lgc24liE9&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3Ddesonide%26t%3Dname%26acs%3Dfalse%26acq%3Ddesonide#monograph-tab-content](http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/6708?cesid=98lgc24liE9&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3Ddesonide%26t%3Dname%26acs%3Dfalse%26acq%3Ddesonide#monograph-tab-content)
83. De Groot AC. Patch testing. 3rd ed. Volume 3 Chapter 3.

## Mid-High to Mid-Low Potency (Class 3 to 5): Prednicarbate

84. [http://online.lexi.com/lco/action/doc/retrieve/docid/patch\\_f/7545?cesid=6g1fi79RDiT&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3Dprednicarbate%26t%3Dname%26acs%3Dtrue%26acq%3DPrednicarbate#spg](http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/7545?cesid=6g1fi79RDiT&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3Dprednicarbate%26t%3Dname%26acs%3Dtrue%26acq%3DPrednicarbate#spg)
85. [http://online.lexi.com/lco/action/doc/retrieve/docid/pdh\\_f/129094?cesid=6g1fi79RDiT&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3Dprednicarbate%26t%3Dname%26acs%3Dtrue%26acq%3DPrednicarbate](http://online.lexi.com/lco/action/doc/retrieve/docid/pdh_f/129094?cesid=6g1fi79RDiT&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3Dprednicarbate%26t%3Dname%26acs%3Dtrue%26acq%3DPrednicarbate)
86. [http://online.lexi.com/lco/action/doc/retrieve/docid/complete\\_ashp/4-14086?cesid=6g1fi79RDiT&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3Dprednicarbate%26t%3Dname%26acs%3Dtrue%26acq%3DPrednicarbate](http://online.lexi.com/lco/action/doc/retrieve/docid/complete_ashp/4-14086?cesid=6g1fi79RDiT&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3Dprednicarbate%26t%3Dname%26acs%3Dtrue%26acq%3DPrednicarbate)
87. De Groot AC. Patch testing. 3rd ed. Volume 3 Chapter 3.

### Least Potent Class 7: Hydrocortisone (Base $\geq 2\%$ )

88. [http://online.lexi.com/lco/action/doc/retrieve/docid/patch\\_f/1797823?cesid=3ACyDCSI90w&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3Dscalacort%26t%3Dname%26acs%3Dfalse%26acq%3Dscalacort#](http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/1797823?cesid=3ACyDCSI90w&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3Dscalacort%26t%3Dname%26acs%3Dfalse%26acq%3Dscalacort#)
89. (Hydrocortisone (Topical) (Lexi-Drugs)).
90. [http://online.lexi.com/lco/action/doc/retrieve/docid/essential\\_ashp/410302?cesid=9NCqUUuKIvZ&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3Dhytone%26t%3Dname%26acs%3Dfalse%26acq%3Dhytone](http://online.lexi.com/lco/action/doc/retrieve/docid/essential_ashp/410302?cesid=9NCqUUuKIvZ&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3Dhytone%26t%3Dname%26acs%3Dfalse%26acq%3Dhytone)
91. Hydrocortisone, Hydrocortisone Acetate, Hydrocortisone Buteprate, Hydrocortisone Butyrate, Hydrocortisone Valerate (Topical) (AHFS Essentials (Adult and Pediatric)).
92. [http://online.lexi.com/lco/action/doc/retrieve/docid/pdh\\_f/2848040?cesid=6ThRPQaITq3&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3Dhydrocortisone%26t%3Dname%26acs%3Dfalse%26acq%3Dhydrocortisone](http://online.lexi.com/lco/action/doc/retrieve/docid/pdh_f/2848040?cesid=6ThRPQaITq3&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3Dhydrocortisone%26t%3Dname%26acs%3Dfalse%26acq%3Dhydrocortisone)
93. De Groot AC. Patch testing. 3rd ed. Volume 3 Chapter 3.

### Least Potent Class 7: Hydrocortisone (Base $<2\%$ )

94. [http://online.lexi.com/lco/action/doc/retrieve/docid/patch\\_f/1797823?cesid=3ACyDCSI90w&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3Dscalacort%26t%3Dname%26acs%3Dfalse%26acq%3Dscalacort#](http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/1797823?cesid=3ACyDCSI90w&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3Dscalacort%26t%3Dname%26acs%3Dfalse%26acq%3Dscalacort#)
95. (Hydrocortisone (Topical) (Lexi-Drugs)).
96. [http://online.lexi.com/lco/action/doc/retrieve/docid/essential\\_ashp/410302?cesid=9NCqUUuKIvZ&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3Dhytone%26t%3Dname%26acs%3Dfalse%26acq%3Dhytone](http://online.lexi.com/lco/action/doc/retrieve/docid/essential_ashp/410302?cesid=9NCqUUuKIvZ&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3Dhytone%26t%3Dname%26acs%3Dfalse%26acq%3Dhytone)
97. Hydrocortisone, Hydrocortisone Acetate, Hydrocortisone Buteprate, Hydrocortisone Butyrate, Hydrocortisone Valerate (Topical) (AHFS Essentials (Adult and Pediatric)).
98. [http://online.lexi.com/lco/action/doc/retrieve/docid/pdh\\_f/2848040?cesid=6ThRPQaITq3&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3Dhydrocortisone%26t%3Dname%26acs%3Dfalse%26acq%3Dhydrocortisone](http://online.lexi.com/lco/action/doc/retrieve/docid/pdh_f/2848040?cesid=6ThRPQaITq3&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3Dhydrocortisone%26t%3Dname%26acs%3Dfalse%26acq%3Dhydrocortisone)



Dirk B. Robertson

## Contents

|                 |     |
|-----------------|-----|
| Ivermectin..... | 527 |
| Lindane.....    | 530 |
| Permethrin..... | 533 |
| Spinosad.....   | 537 |
| References..... | 541 |

## Ivermectin

Note that ivermectin also has anti-inflammatory properties and is used for treatment of rosacea. Please refer to Chap. 9 for discussion of its use in rosacea.

## Classification and Mode of Action

- Antiparasitic agent, topical; pediculicide
- Ivermectin 0.5% lotion (Sklice) is a topical antiparasitic agent approved for the treatment of pediculosis capitis (head lice).

---

D. B. Robertson (✉)

Department of Dermatology, Emory University School of Medicine,  
Atlanta, GA, USA

e-mail: [robertsons@prodigy.net](mailto:robertsons@prodigy.net)

The FDA initially approved ivermectin lotion, 0.5% for the treatment of head lice infestation in patients 6 months of age and older as a prescription drug in February 2012. Recently the FDA approved its use as an over-the-counter (OTC) nonprescription drug.

- Mechanism of action.
  - Ivermectin is a semisynthetic anthelmintic agent.
  - It binds selectively and with strong affinity to glutamate-gated chloride ion channels which occur in invertebrate nerve and muscle cells. This leads to increased permeability of cell membranes to chloride ions, then hyperpolarization of the nerve or muscle cell, and death of the parasite.

## **Indications and Dermatologic Uses**

- Topical treatment of head lice in patients 6 months and older

## **Formulations**

- Topical 0.5% lotion brand name Sklice. It is available as a generic.

## **Dosages and Administration**

- Topical lotion.
- Apply sufficient amount (up to 1 tube) to dry scalp and hair closest to the scalp first, and then apply outward toward ends of the hair, completely covering the scalp and hair. Leave on for 10 minutes (start timing treatment after the scalp and hair have been completely covered). The hair should then be rinsed thoroughly with warm water. Avoid contact with the eyes.
- Nit combing is not required, although a fine-tooth comb may be used to remove treated lice and nits.

## Pharmacokinetics

- Ivermectin is greater than 99% protein bound. It is metabolized hepatically by CYP3A4. Half-life elimination is approximately 6–7 days.

## Use in Special Populations

- Breastfeeding considerations
  - Following oral administration, ivermectin is measurable in low concentrations in breast milk. Breastfeeding is not recommended by the manufacturer.
- Use in Pregnancy
  - Although risk with use in pregnancy is likely low risk, other agents are currently recommended for the treatment of pediculosis pubis or scabies in breastfeeding women.
- Pediatric considerations
  - In infants <6 months, systemic absorption may be increased due to higher skin surface area to body mass ratio and immature skin barrier; risk for ivermectin toxicity is potentially increased. Avoid use in these patients.
- Renal insufficiency: No alterations in dosing recommended in renal insufficiency
- Hepatic insufficiency: No alterations in dosing recommended in hepatic insufficiency

## Contraindications and Cautions

- There are no contraindications listed in the US manufacturer's labeling.

## Adverse Effects

- Localized burning sensation and skin irritation has been noted in less than 1% of patients.

## Patch Test Concentration

- Not available

## Essential Patient Information

- For external use only. Avoid contact with the eyes while using on the scalp.
- Not for use in the eye, mouth, or vagina.
- Lotion is for one-time use; discard any unused portion.

---

## Lindane

### Classification and Mode of Action

- Antiparasitic agent, topical; pediculicide
- Lindane is an ectoparasiticide and ovicide agent used for the topical treatment of scabies and pediculosis capitis and pubis. It is directly absorbed by parasites and ova and overstimulates the neural system resulting in the death of the parasite.

### Indications and Dermatologic Uses

- Lindane is clinically indicated for the topical treatment of scabies (*Sarcoptes scabiei*) and pediculosis capitis or pubis. It is not recommended as a first line of treatment and should be reserved for patients who cannot tolerate other approved therapies or have failed first line treatments.

### Formulations

- 1% shampoo, 1% lotion

## Dosages and Administration

- **Pediculosis:** Apply lindane shampoo to clean dry hair and massage into the hair for 4 minutes. Add small amounts of water to form a lather, and then rinse thoroughly. Comb with a fine-tooth comb to remove nits. An average patient will need 30 ml. Do not exceed 60 ml. Do not retreat.
- **Scabies:** Apply a thin layer of lindane lotion over all the skin from the neck down. One ounce is sufficient for an average adult. Do not prescribe more than 2 ounces for larger adults. Apply only once. Wash off in 8 to 12 hours. Do not retreat.

## Pharmacokinetics

- Approximately 10% is absorbed percutaneously. Elimination half-life is approximately 20 hours with secretion in urine and feces.

## Use in Special Populations

- **Pregnancy:** Lindane should be given to pregnant women only if clearly needed and alternatives cannot be used.
- **Lactation:** Lindane is lipophilic and is present in human breast milk, but exact quantities are not known. Nursing mothers who require treatment with lindane lotion should be advised of the potential risks and be counseled to avoid large areas of skin-to-skin contact with the infant following lindane application. They should also interrupt breastfeeding, with expression and discarding of milk, for at least 24 hours following use.
- **Pediatrics.**
  - Lindane is contraindicated for premature infants because their skin may be more permeable than that of full-term infants, and their liver enzymes may not be sufficiently developed to metabolize lindane.



- Lindane is on the KIDs (Key Potentially Inappropriate Drugs in Pediatrics) list for pediatric patients less than 10 years of age or weighing less than 50 Kg and should be avoided due to the risk of seizure or spasm.
- Renal insufficiency: No dosage adjustments provided in the manufacturer's labeling.
- Hepatic insufficiency: No dosage adjustments provided in the manufacturer's labeling.

## **Contraindications and Cautions**

- Lindane lotion is contraindicated for patients with crusted (Norwegian) scabies and other skin conditions (e.g., atopic dermatitis and psoriasis) that may increase systemic absorption of the drug.
- Lindane lotion is contraindicated for patients with known uncontrolled seizure disorders
- Lindane lotion is contraindicated for individuals with a known sensitivity to the product or any of its components.

## **US Boxed Warnings**

- **Lindane should only be used in patients who cannot tolerate or have failed first-line treatment with safer medications for the treatment of lice/scabies.**
- **Neurologic toxicity including seizures and deaths have been reported following lindane use with repeat or prolonged application but also in rare cases following a single application according to directions. Lindane should be used with caution in infants, children, the elderly, individuals with other skin conditions, and those who weigh < 110 lbs (50 kg) as they may be at risk of serious neurotoxicity.**
- **Lindane is contraindicated in premature infants and individuals with known uncontrolled seizure disorders.**

- **Instruct patients on the proper use of Lindane, the amount to apply, how long to leave it on, and avoiding re-treatment.**

### **Essential Patient Information**

- Inform patients that itching occurs after the successful killing of lice and is not necessarily an indication for retreatment with lindane.
- **A Lindane Medication Guide must be given to the patient each time lindane is dispensed, as required by law.**

### **Adverse Effects**

- Lindane has been reported to cause central nervous system stimulation ranging from dizziness to seizures. Although seizures were almost always associated with ingestion or misuse of the product, including repeat treatment, seizures and deaths have been reported when lindane lotion was used according to directions.
- Irritant dermatitis from contact with this product has been reported.

### **Patch Test Concentration**

- Not available

---

## **Permethrin**

### **Classification and Mode of Action**

- Antiparasitic agent, topical; pediculicide
- Permethrin (synthetic pyrethroid cyclopropanecarboxylate ester); an ectoparasiticide and ovicide agent

- Inhibits sodium ion influx through nerve cell membrane channels in parasites, resulting in delayed repolarization and thus paralysis and death

## Indications and Dermatologic Uses

- Labeled indications for permethrin include the topical treatment of scabies (*Sarcoptes scabiei*) and head lice (pediculosis capitis).
- Off-label use in adults include pubic lice (*Pediculosis pubis*) and crusted scabies (Norwegian scabies).

## Formulations

- 5% cream brand name Elimite (generic available)
- 1% cream rinse/lotion OTC brand name Nix. (generic available)

## Dosages and Administration

### Dosing: Adult

- Head lice: Topical cream rinse/lotion 1%: Prior to application, wash hair with conditioner-free shampoo; rinse with water and towel dry. Apply a sufficient amount of lotion, or cream rinse to saturate the hair and scalp (especially behind the ears and nape of neck). Leave on hair for 10 minutes (but no longer), and then rinse off with warm water. Remove remaining nits with nit comb. A single application is generally sufficient. However, may repeat 7 days after first treatment if lice or nits are still present.
- Pubic lice (off-label use): Topical cream rinse/lotion 1%: Apply to affected areas and wash off after 10 minutes.
- Scabies: Topical cream 5%: Thoroughly massage cream (30 g for average adult) from the head to the soles of the feet. Leave on for 8 to 14 hours before removing (shower or bath). For

elderly patients, also apply onto the hairline, neck, scalp, temple, and forehead. May repeat if living mites are observed 14 days after the first treatment. One application is generally curative.

- Scabies, crusted (Norwegian scabies) (off-label use): Topical cream 5%: Apply to the entire body; leave on for 8 to 14 hours before washing off with water. Repeat this regimen daily for 7 days, and then twice weekly until symptoms have resolved.

### **Dosing: Pediatric**

- Head lice: Note first-line treatment if community resistance is not an issue.
- Infants  $\geq 2$  months, children, and adolescents: Topical: cream rinse, lotion 1%: After hair has been washed with conditioner-free shampoo, rinse with water, and towel dry. Apply a sufficient volume of permethrin cream/rinse lotion to saturate the hair and scalp. Also apply behind the ears and at the base of the neck. Leave on hair for 10 minutes before rinsing off with water; remove remaining nits. May repeat in 7 to 10 days if live lice or nits observed.
- Scabies: Infants  $\geq 2$  months, children, and adolescents: Topical: cream 5%: Apply and massage in cream from the head to toe (average adult requires 30 g). Leave on for 8 to 14 hours before washing off with water. For infants, also apply on the hairline, neck, scalp, temple, and forehead. May reapply in 14 days if live mites appear.

### **Pharmacokinetics**

- Permethrin is rapidly metabolized by ester hydrolysis to inactive metabolites which are excreted primarily in the urine.
- Although the amount of permethrin absorbed after a single application of the 5% cream has not been determined precisely, data from studies with  $^{14}\text{C}$ -labeled permethrin and absorption studies of the cream applied to patients with moderate to severe scabies indicate it is 2% or less of the amount applied.

## Use in Special Populations

- Pregnancy Considerations
  - The amount of permethrin absorbed systemically following topical application is  $\leq 2\%$ . The CDC considers the use of permethrin or pyrethrins with piperonyl butoxide the drugs of choice for the treatment of pubic lice during pregnancy. Permethrin is the preferred treatment for scabies during pregnancy.
- Breastfeeding Considerations
  - It is not known if permethrin is present in breast milk following topical administration for the treatment of scabies or lice. Permethrin exhibits minimal systemic absorption following topical administration ( $\leq 2\%$  of applied amount), and any absorbed drug is rapidly metabolized to inactive metabolites. Therefore, breastfeeding is not expected to result in significant exposure to a breastfed child.
- Pediatrics
  - When used for self-medication, do not use on infants  $< 2$  months of age.

## Carcinogenicity

- No data on the carcinogenicity of permethrin in humans.
- Evidence of permethrin's possible carcinogenicity in humans is derived from bioassays in rodents. Based on the weight of evidence from animal studies, EPA has classified permethrin as "likely to be carcinogenic to humans" by ingestion. This rating is based on benign lung and liver tumors found in mice and similar, though inconclusive, evidence in rats, as well as corroborative Structure-Activity Relationships (SAR) information.

## Contraindications and Cautions

- Contraindications: Hypersensitivity to permethrin, pyrethroid, pyrethrin, or any component of the formulation.
- OTC labeling (cream rinse/lotion): When used for self-medication, do not use on infants <2 months of age.
- Do not use near the eyes or inside the nose, ear, mouth, or vagina. Consult health care provider for use on eyebrows or eyelashes.

## Adverse Effects

- Central nervous system: Local discomfort (scalp), localized burning, localized numbness, and tingling of the skin
- Dermatologic: Pruritus, erythema, skin rash (scalp), and stinging of the skin

## Patch Test Concentration

- Not available

---

## Spinosad

### Classification and Mode of Action

- Antiparasitic agent, topical; pediculicide
- Spinosad (a mixture of two glycosylated macrolactones spinosyn A and spinosyn D) is pediculicidal and ovicidal used for the topical treatment of scabies and pediculosis capitis and pubis. Insect paralysis and death is caused by central nervous system excitation and involuntary muscle contractions.

## Comparative Efficacy

- Spinosad, which does not require nit combing, is significantly more effective than permethrin in the comparative efficacy studies reflecting actual-use conditions. Most spinosad-treated participants required only one application. Spinosad is a more convenient and effective treatment for pediculosis capitis than permethrin.

## Indications and Dermatologic Uses

- Clinically indicated for the topical treatment of scabies (*Sarcoptes scabiei*) in adults and pediatric patients greater than 4 years of age and pediculosis capitis in adults and pediatric patients greater than 6 months of age

## Formulations

- Natroba 0.9% topical suspension (brand name), generic formulations are available.

## Dosages and Administration

### Dosing: Adult

- Head lice, topical: Apply sufficient amount to cover dry scalp and completely cover dry hair. One hundred twenty mL may be necessary depending on hair length. If live lice are seen 7 days after the first treatment, repeat with second application.
- Scabies, topical: Apply sufficient amount to completely cover body from the neck to the toes (including soles of the feet). Apply to the forehead, hairline, scalp, and temples in patients who are balding. Leave on the skin for  $\geq 6$  hours prior to bathing or showering.

**Dosing: Pediatric**

- Head lice: Infants  $\geq 6$  months, children, and adolescents: Topical suspension: Apply sufficient amount to cover dry scalp and completely cover dry hair (maximum single application dose: 120 mL). Leave on for 10 minutes and then rinse out with warm water. If live lice are seen 7 days after the first treatment, repeat with second application.
- Scabies: Children  $\geq 4$  years and adolescents: Topical suspension: Apply sufficient amount to cover the body from the neck to the toes (including the soles of feet). If patient is bald, apply to the forehead, hairline, scalp, and temples. Allow to absorb into the skin for 10 minutes before putting on clothes. Leave on the skin for  $\geq 6$  hours prior to bathing or showering.

**Pharmacokinetics**

Absorption: Spinosad is not absorbed topically ( $<3$  ng/mL in a pediatric patient plasma sampling study). Absorption of the benzyl alcohol was not analyzed in this study.

**Use in Special Populations**

- Pregnancy considerations
  - The amount of spinosad absorbed systemically following topical administration is below the limit of quantification ( $<3$  ng/mL). Human studies did not assess the absorption of benzyl alcohol, an ingredient in the product. However, maternal use is not likely to result in fetal exposure.
- Breastfeeding considerations
  - It is not known if spinosad is present in breast milk following topical application.



- The amount of spinosad absorbed systemically following topical administration is below the limit of quantification ( $<3$  ng/mL). Maternal use is not likely to result in infant exposure to spinosad or benzyl alcohol via breast milk. According to the manufacturer, the decision to breastfeed during therapy should take into consideration the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother.
- Spinosad should be removed from the breast area with soap and water prior to breastfeeding to minimize direct infant exposure.
- Pediatric considerations
  - Some dosage forms may contain benzyl alcohol. Large amounts of benzyl alcohol ( $\geq 99$  mg/kg/day) have been associated with a potentially fatal toxicity (“gasping syndrome”) in neonates. The “gasping syndrome” consists of metabolic acidosis, respiratory distress, gasping respirations, CNS dysfunction (including convulsions, intracranial hemorrhage), hypotension, and cardiovascular collapse.
  - Avoid or use dosage forms containing benzyl alcohol with caution in neonates. See manufacturer’s labeling.

## **Carcinogenicity**

- In multiple studies, animals were fed low to moderate amounts of spinosad in their diet for 1.5 to 2 years. No increased incidence of cancer was observed. Moreover, spinosad has not been found to be mutagenic. As a result of these experiments, the EPA has classified spinosad as not likely to cause cancer.

## **Contraindications and Cautions**

- There are no contraindications listed in the US manufacturer’s labeling.

- Appropriate use: For topical use only; not for oral, ophthalmic, or intravaginal use. Avoid contact with eyes. Wash hands after application.
- See cautions discussed under Use in Special Populations above.

## Monitoring Parameters

Patients should be monitored for persistence of scabies or lice.

## Adverse Effects

- Dermatologic: Erythema of eyelid (2%), xeroderma (2%)
- Local: Application site burning ( $\leq 3\%$ ), application site erythema (3%), application site irritation ( $\leq 3\%$ ), and application site pain ( $\leq 3\%$ )

---

## References

### Ivermectin

1. FDA drug monograph (Ivermectin) FDA drug monograph SKLICE lotion. Available from [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/202736s003lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/202736s003lbl.pdf).
2. LexiComp drug monograph (name of monograph). Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2024 UptoDate, Inc.
3. Frankowski BL, Bocchini JA Jr. Head lice. Pediatrics. 2010;126(2):392–403. [PubMed 20660553].

### Lindane

4. FDA drug monograph (Lindane).
5. LexiComp drug monograph (Lindane).
6. Feldmann RJ, Maibach HI. Toxicol Appl Pharmacol. 1974;28:126.
7. Leone PA. Scabies and pediculosis pubis. An update of treatment regimens and general review. Clin Infect Dis. 2007;44(Suppl 3):S153.

## Permethrin

8. FDA drug monograph (Permethrin).
9. LexiComp drug monograph (Permethrin).
10. Devore CD, Schutze GE, Council on School Health and Committee on Infectious Diseases, American Academy of Pediatrics. Head lice. *Pediatrics*. 2015;135(5):e1355–65. [PubMed 25917986].

## Spinosad

11. FDA drug monograph (Spinosad).
12. LexiComp drug monograph (Spinosad).
13. Stough D, Shellabarger S, Quiring J, Gabrielsen AA Jr. Efficacy and safety of spinosad and permethrin creme rinses for pediculosis capitis (head lice). *Pediatrics*. 2009;124(3):e389–95. [PubMed 19706558].
14. Centers for Disease Control (CDC). Neonatal deaths associated with use of benzyl alcohol—United States. *MMWR Morb Mortal Wkly Rep*. 1982;31(22):290–1. <http://www.cdc.gov/mmwr/preview/mmwrhtml/00001109.htm> [PubMed 6810084].
15. Shehab N, Lewis CL, Streetman DD, Donn SM. Exposure to the pharmaceutical excipients benzyl alcohol and propylene glycol among critically ill neonates. *Pediatr Crit Care Med*. 2009;10(2):256–9. [PubMed 19188870].



# Depigmenting and Pigmenting Agents

# 20

Anuk Burli and Chavy Chiang

## Contents

|                                               |     |
|-----------------------------------------------|-----|
| Hydroquinone/Triluma.....                     | 544 |
| Monobenzone.....                              | 547 |
| Mequinol (Solage = Mequinol + Tretinoin)..... | 549 |
| Methoxsalen.....                              | 552 |
| References.....                               | 555 |

Hyper-/hypopigmentation in dermatology patients remains a challenge for many physicians. Treatment options for hyperpigmentation in conditions such as melasma include hydroquinone/triluma. Mequinol is used primarily for the treatment of hyperpigmented solar lentigines. With regard to hypo-/depigmentation, monobenzone has been used for extensive vitiligo (greater than

---

A. Burli (✉)

Department of Dermatology, Stanford University School of Medicine,  
Redwood City, CA, USA

e-mail: [anukb@stanford.edu](mailto:anukb@stanford.edu)

C. Chiang

Department of Dermatology, University of Rochester Medical Center,  
Rochester, NY, USA

e-mail: [chavyz@gmail.com](mailto:chavyz@gmail.com)

© The Author(s), under exclusive license to Springer Nature  
Switzerland AG 2025

543

R. M. Law, H. I. Maibach (eds.), *Handbook of Topical Drug  
Treatment in Dermatology*,

[https://doi.org/10.1007/978-3-031-93616-6\\_20](https://doi.org/10.1007/978-3-031-93616-6_20)

50% body surface area) to depigment normal skin. Methoxsalen has been used off-label for the treatment of depigmentation in vitiligo—to increase pigmentation in vitiligious skin. Methoxsalen is also used together with UVA for the treatment of psoriasis. There is also an oral formulation for methoxsalen.

---

## Hydroquinone/Triluma

### Classification and Mode of Action

- Hydroquinone: Depigmenting agent: Reversibly depigments the skin by inhibiting tyrosine hydroxylase which oxidizes tyrosine to DOPA (3,4-dihydroxyphenylalanine). Sun exposure however can reverse this, leading to repigmentation.
- Triluma: Depigmenting agent combined with topical corticosteroid and topical retinoid.

### Indications and Dermatological Uses

- *Clinical indications (not FDA approved)*: Skin bleaching. This product has been banned for over the counter use as part of the Coronavirus Aid, Relief, and Economic Security (CARES) Act.
- *Comparative trials*
  - A double-blind randomized clinical trial showed that hydroquinone had a near 10% improvement of hyperpigmentation compared to skin whitening agents, but with 25% more side effects.

### Formulations/Presentation

- US hydroquinone: 1.5% cream, 2% cream, 4% cream, 2% gel, 3% external solution
- Canada hydroquinone: 4% cream, 4% gel
- US Triluma: 0.01% cream, 4% cream, 0.05% cream

## **Dosages and Suggested Regimens**

- Topical: Apply a thin layer to hyperpigmented areas and rub the cream in twice daily, both in the morning and at night before sleep.
- Patient can discontinue use if there is no depigmentation seen after 2 to 3 months of treatment.

## **Baseline Investigations and Considerations**

- None

## **Pharmacokinetics**

- Onset and duration of the depigmentation effect varies among individuals depending on genetic profile.

## **Use in Special Populations**

- Approved for use in children. Adult dosing can be used for patients 12 years old and above.
- Listed as FDA pregnancy classification C (former classification system).
- Unknown whether hydroquinone is present in breast milk.
- Renal insufficiency: dose adjustment is not expected to be needed.
- Hepatic insufficiency: dose adjustment is not expected to be needed.

## **Monitoring**

- Skin irritation

## **Contraindications and Cautions**

- Certain individuals have hypersensitivity to hydroquinone or any component of the formulation in triluma.

## **Important Drug Interactions**

- No known significant interactions

## **Adverse Effects and Their Management**

- Patients can have allergic skin reaction or dermatitis in response to component of formulation.
- Erythema and inflammation as a result of excessive application.
- Mild stinging of the skin when initially applying.
- Xeroderma.
- Exogenous ochronosis: discontinue treatment if this occurs.

## **Patch Test Concentration**

- 1% pet. (Chemotechnique, SmartPracticeEurope; SmartPracticeCanada); this test concentration may cause irritant reactions.

## **Essential Patient Information**

- Sunscreen use is necessary to use during hydroquinone therapy, as sunlight can sustain melanocytic activity. To avoid repigmentation, during treatment and maintenance therapy, sun exposure on affected areas should be avoided by applying a broad spectrum sunscreen (SPF 15 or greater) or by using sun-protective clothing.
- Avoid contact with eyes and mucous membranes when applying.

- Keep hydroquinone out of reach of children. In the case of accidental ingestion, call a physician or a poison control center immediately.
- 

## **Monobenzone**

### **Classification and Mode of Action**

- Depigmenting agent. Monobenzone is the monobenzyl ether of hydroquinone.
- The proposed mechanism of action is increasing the excretion of melanin from melanocytes where the melanin is then lost with normal loss and sloughing of stratum corneum.

### **Indications and Dermatological Uses**

- Clinical indications (FDA): Help to permanently depigment normal skin surrounding vitiligious lesions, used only in patients with extensive disseminated vitiligo (greater than 50% body surface area)

### **Formulations/Presentation**

- USA: Monobenzone cream 20%
- Canada: Monobenzone cream 20%

### **Dosages and Suggested Regimens**

A thin layer of monobenzone cream 20% can be applied two or three times daily. Depigmentation can be seen after 1 to 4 months of topical treatment. If satisfactory results are not obtained after 4 months of treatment, the drug should be discontinued.



## Pharmacokinetics

- Onset of the depigmentation effect varies among individuals

## Use in Special Populations

- Pregnancy: Category C (former classification system).
- Lactation: It is not known whether this drug is excreted in human milk.
- Pediatric population: The safety and effectiveness of monobenzone cream 20% in pediatric patients below the age of 12 years have not been established.
- Renal insufficiency: No FDA guidance.
- Hepatic Insufficiency: No FDA guidance.

## Monitoring

- Discontinue use if patient has severe irritation, burning sensation, or dermatitis.

## Contraindications and Cautions

- Monobenzone cream 20% is contraindicated for any other conditions other than disseminated vitiligo (>50% body surface area).
- Monobenzone cream 20% can produce irreversible depigmentation and should not be a substitute for hydroquinone.
- Monobenzone cream 20% is contraindicated in individuals with a history of sensitivity or allergic reactions to monobenzone product, or any of the ingredients.

## Important Drug Interactions

- Limited information

## Adverse Effects and Their Management

- Mild, transient skin irritation and sensitization, such as erythematous and eczematous skin reactions.
- Discontinue use if patient has irritation, a burning sensation, or dermatitis.

## Patch Test Concentration

- 1% pet. (Chemotechnique, SmartPractice Europe, SmartPractice Canada)

## Essential Patient Information

- Monobenzone cream should only be used when having disseminated vitiligo (greater than 50%). Stop the use if no improvement after 4 months and pet. Stop severe irritation, burning, or dermatitis occur.

---

## Mequinol (Solage = Mequinol + Tretinoin)

For the tretinoin monograph, please see Chap. 23.

## Classification and Mode of Action

- Substrate for the enzyme tyrosinase acts as a competitive inhibitor of the formation of melanin precursors.

## Indications and Dermatological Uses

- *Clinical indications (FDA)*: Treatment of solar lentigines

## Formulations/Presentation

- USA: Solage: mequinol 2%, tretinoin 0.01% topical solution
- Canada: Solage: mequinol 2%, tretinoin 0.01% topical solution

## Dosages and Suggested Regimens

- Apply Solage to solar lentigines using the applicator tip given with the topical solution while avoiding application to the surrounding non-affected skin. Use twice daily, morning and evening at least 8 hours apart, or as stated by the physician.
- Patients should not shower or wash with water the treatment areas for at least 6 hours after application of Solage.
- Special caution is needed when applying Solage to avoid the eyes, mouth, and mucous membranes throughout the body.

## Pharmacokinetics

- The percutaneous absorption of tretinoin and mequinol in Solage was assessed in healthy subjects ( $n = 8$ ) following 2 weeks of twice daily topical treatment of Solage for solar lentigines. Approximately 0.8 mL of Solage was applied to a 400 cm<sup>2</sup> area of the back, corresponding to a dose of 37.3 mg/cm<sup>2</sup> for mequinol and 0.23 mg/cm<sup>2</sup> for tretinoin.
- The percutaneous absorption of tretinoin was 4.4%, and systemic concentrations did not increase over baseline endogenous levels.
- The mean C<sub>max</sub> for mequinol was 9.92 ng/mL with a range 4.22 to 23.62 ng/mL, and the T<sub>max</sub> was 2 hours with a range 1 to 2 hours.

## Use in Special Populations

- **Pregnancy:** Pregnancy category X (former classification). Teratogenic. Contraindicated in pregnancy.
- **Lactation:** It is not known to what extent mequinol and/or tretinoin is excreted in human milk.
- **Children:** The safety of this product have not been established in pediatric patients. Solage should not be used in the pediatric population.
- **Renal insufficiency:** Unknown.
- **Hepatic insufficiency:** Unknown.

## Monitoring

If a drug sensitivity, chemical irritation, or a systemic adverse reaction occurs, patient should discontinue use of Solage

## Contraindications and Cautions

- Absolutely contraindicated in pregnancy
- History of hypersensitivity to any of the ingredients.

## Important Drug Interactions

- Topical products with a strong drying effect, high concentrations of alcohol, astringents, spices /lime, medicated soaps or shampoos, permanent wave solutions, electrolysis, hair depilatories or waxes, or various other products that might dry or irritate the skin should be used with caution in patients using Solage as they can increase irritation.

## **Adverse Effects and Their Management**

- Erythema occurred in 49% of patients in a clinical trial; burning, stinging or tingling occurred in 26%; desquamation occurred in 14%; pruritus occurred in 12% of patients; and skin irritation occurred in 5%.
- Some patients experienced temporary hypopigmentation of treated lesions (5%) or of the unaffected skin surrounding the lesion. This hypopigmentation generally resolved after discontinuation of the product within 120 days.

## **Patch Test Concentration**

- No data available (mequinol)
- 0.005 alcohol (tretinoin); if higher is used (0.01% or 0.02%), perform adequate controls.

## **Essential Patient Information**

Solage should only be used as an adjunct treatment along with sun protection and sun avoidance for solar lentigos.

---

## **Methoxsalen**

### **Classification and Mode of Action**

- Psoralen: Methoxsalen covalently bonds to DNA, specifically the pyrimidine bases. This inhibits DNA synthesis and suppresses cell division. A sunburn reaction excites methoxsalen with UVA radiation, transferring energy to methoxsalen, allowing it to reach an excited state or a “triplet state.” The molecule, in this “triplet state,” then reacts with skin DNA. An erythematous reaction then is repaired with increased melanization of the epidermis and stratum corneum thickening.

## Indications and Dermatological Uses

- *Clinical indications (FDA)*: Palliative treatment of cutaneous T-cell lymphoma
- *Off-label common uses*: Repigmentation of idiopathic vitiligo

## Formulations/Presentation

- USA: Sterile solution 20 mcg/mL (this was difficult for me to find how it is actually dosed). 1% cream
- Canada
- Europe

## Dosages and Suggested Regimens

Topical: Prior to UVA light exposure, methoxsalen location is applied. These sessions are done no more than once weekly, but the ultimate frequency is decided by the level of erythema.

## Baseline Investigations and Considerations

### Pharmacokinetics

Half-life of 2 hours and rapidly excreted in both humans and rats

### Use in Special Populations

- Pregnancy Risk Factor C. (Former FDA pregnancy risk classification system)
- Lactation: Unknown if excreted in breast milk.
- Children: Dosing can be same as adults in children greater than 12 years old. Contraindicated less than 12 years old.
- Renal insufficiency: No specific guidelines regarding changes in dosing.
- Hepatic insufficiency: No specific guidelines regarding changes in dosing.

## **Monitoring**

- Patients require sunlight precautions while using this drug.

## **Contraindications and Cautions**

- Hypersensitivity to methoxsalen or any component of the drug formulation
- Photosensitivity and associated diseases such as porphyria, albinism, lupus erythematosus, or xeroderma pigmentosum
- Any kind of invasive skin cancer
- Active melanoma or a personal history of melanoma
- Contraindicated in children <12 years of age
- Use with caution in patients with basal cell carcinoma or history of basal cell carcinoma

## **Important Drug Interactions**

- No known significant drug interactions. However, ensure sun protection if on concomitant medication with photosensitizing potential.

## **Adverse Effects and Their Management**

- Burns: Wear protective clothing and sunscreen to prevent.
- Cataracts: Eyes should be shielded for 24 hours to prevent.
- Photosensitivity: Avoid sun exposure for 8 hours after methoxsalen, and sun protective clothing, eye wear, and sunscreen should be used for several days after treatment.
- Skin cancer: Use with caution in patients with sun damage, history of arsenic exposure, or history of radiation exposure

## Patch Test Concentration

- 0.15% alcohol; for photopatch testing, a dilution series (0.15%, 0.015%, 0.0015%) may be necessary to differentiate photoallergy from phototoxicity.

## Essential Patient Information

- Sun protection is essential when undergoing treatment with this medication.

---

## References

### Hydroquinone/Triluma

1. FDA Drug Monograph Hydroquinone/Triluma. Available from <http://assets.openstudy.com/updates/attachments/4f0d5cb6e4b084a815fccd72-chmvijay-1326448458607-dipolemoment.pdf>. Accessed 11/04/2021.
2. LexiComp drug monograph Hydroquinone/Triluma. Available from: LexiComp Online at [online.lexi.com](https://online.lexi.com) Copyright 2021 UpToDate, Inc.
3. Schwartz C, Jan A, Zito PM. Hydroquinone. [Updated 2021 May 10]. In: StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2021. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK539693/>.
4. Kim GH, Cheong KA, Lee AY. Increased skin irritation by hydroquinone and retinoic acid used in combination. *Ann Dermatol*. 2017;29(6):715–21. <https://doi.org/10.5021/ad.2017.29.6.715>. Epub 2017 Oct 30. PMID: 29200759; PMCID: PMC5705352.
5. Haddad AL, Matos LF, Brunstein F, Ferreira LM, Silva A, Costa D Jr. A clinical, prospective, randomized, double-blind trial comparing skin whitening complex with hydroquinone vs. placebo in the treatment of melasma. *Int J Dermatol*. 2003;42(2):153–6. <https://doi.org/10.1046/j.1365-4362.2003.01621.x>. PMID: 12709008.



## Monobenzone

6. FDA Drug Monograph Monobenzone. Accessed from: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2003/08173slr015\\_benoquin\\_lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2003/08173slr015_benoquin_lbl.pdf). Accessed 11/04/2021.
7. van den Boorn JG, Melief CJ, Luiten RM. Monobenzone-induced depigmentation: from enzymatic blockade to autoimmunity. *Pigment Cell Melanoma Res.* 2011;24(4):673–9. <https://doi.org/10.1111/j.1755-148X.2011.00878.x>. Epub 2011 Jul 6. PMID: 21689385.
8. Catona A, Lanzer D. Monobenzone, Superfade, vitiligo and confetti-like depigmentation. *Med J Aust.* 1987;146(6):320–1. <https://doi.org/10.5694/j.1326-5377.1987.tb120272.x>. PMID: 3821640.

## Mequinol (Solage = Mequinol + Tretinoin)

9. FDA Drug Monograph Mequinol. Accessed from: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2007/020922s0031bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/020922s0031bl.pdf). Accessed 11/04/2021.
10. Jarratt M. Mequinol 2%/tretinoin 0.01% solution: an effective and safe alternative to hydroquinone 3% in the treatment of solar lentigines. *Cutis.* 2004;74(5):319–22. PMID: 15605971.
11. Fleischer AB Jr, Schwartzel EH, Colby SI, Altman DJ. The combination of 2% 4-hydroxyanisole (Mequinol) and 0.01% tretinoin is effective in improving the appearance of solar lentigines and related hyperpigmented lesions in two double-blind multicenter clinical studies. *J Am Acad Dermatol.* 2000;42(3):459–67. [https://doi.org/10.1016/s0190-9622\(00\)90219-6](https://doi.org/10.1016/s0190-9622(00)90219-6). PMID: 10688717.

## Methoxsalen

12. FDA Drug Monograph Methoxsalen. Accessed from: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2007/020922s0031bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/020922s0031bl.pdf). Accessed 11/04/2021.
13. LexiComp drug monograph Methoxsalen. Available from: LexiComp Online at [online.lexi.com](https://online.lexi.com) Copyright 2021 UpToDate, Inc.
14. von Weymarn LB, Zhang QY, Ding X, Hollenberg PF. Effects of 8-methoxypsoralen on cytochrome P450 2A13. *Carcinogenesis.* 2005;26(3):621–9. <https://doi.org/10.1093/carcin/bgh348>. Epub 2004 Dec 3.

15. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs, NIH Publication No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402.
16. AMA Council Report. Guidelines for Handling of Parenteral Antineoplastics. *JAMA*. 1985;253 (11):1590-2.
17. National Study Commission on Cytotoxic Exposure- Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
18. Clinical Oncological Society of Australia. Guidelines and recommendations for safe handling of reference ID: 4204794 antineoplastic agents. *Med J Australia*. 1983;1:426-8.
19. Jones RB, et al. Safe handling of chemotherapeutic agents: a report from the Mount Sinai Medical Center. *CA Cancer J Clin*. 1983;33:258-63.
20. American Society of Hospital Pharmacists Technical Assistance Bulletin of Handling Cytotoxic and Hazardous Drugs. *Am J Hosp Pharm*. 1990;47:1033-49.
21. Controlling Occupational Exposure to Hazardous Drugs. (OSHA Work-Practice Guidelines). *Am J Health Syst Pharm*. 1996;53:1669-85.



Rebecca M. Law , Erin Bartholomew,  
Mimi Chung, Sarah J. Currie,  
Marwa Hakimi, Samuel Yeroushalmi,  
and Wilson Liao

## Contents

|                      |     |
|----------------------|-----|
| Introduction.....    | 560 |
| Drug Monographs..... | 561 |
| References.....      | 588 |

---

R. M. Law (✉)

School of Pharmacy and Faculty of Medicine (Discipline of Family  
Medicine), Memorial University of Newfoundland,  
St. John's, NL, Canada  
e-mail: [rlaw@mun.ca](mailto:rlaw@mun.ca); [rlawUCSF@gmail.com](mailto:rlawUCSF@gmail.com)

E. Bartholomew

Department of Dermatology, Eastern Virginia Medical School,  
Norfolk, VA, USA  
e-mail: [erin.bartholomew@ucsf.edu](mailto:erin.bartholomew@ucsf.edu)

M. Chung

University of Alabama at Birmingham, Birmingham, AL, USA  
e-mail: [mimi.chung@ucsf.edu](mailto:mimi.chung@ucsf.edu)

S. J. Currie

Faculty of Medicine, Memorial University of Newfoundland,  
St. John's, NL, Canada  
e-mail: [sarahjcurrie@gmail.com](mailto:sarahjcurrie@gmail.com)

M. Hakimi

Department of Dermatology, University of California  
San Francisco (UCSF), San Francisco, CA, USA  
e-mail: [marwa.hakimi@ucsf.edu](mailto:marwa.hakimi@ucsf.edu)

© The Author(s), under exclusive license to Springer Nature  
Switzerland AG 2025

559

R. M. Law, H. I. Maibach (eds.), *Handbook of Topical Drug  
Treatment in Dermatology*,  
[https://doi.org/10.1007/978-3-031-93616-6\\_21](https://doi.org/10.1007/978-3-031-93616-6_21)

## Introduction

Rebecca M. Law and Wilson Liao

Psoriasis is a progressive T-lymphocyte-mediated systemic inflammatory disease that results from a complex interplay between multiple genetic factors and environmental influences. Management involves nonpharmacologic and pharmacologic therapies, with attention to also manage any comorbid conditions (such as metabolic syndrome, depression), and other specific patient considerations such as hepatic or renal dysfunction [1].

Treatment of psoriasis is based on managing the underlying pathophysiology. Agents that modulate the abnormal immune response, such as topical corticosteroids (TCS) and biologic agents, are important treatment strategies for psoriasis. Topical therapies that affect cell turnover, such as retinoids, are also effective for psoriasis. In addition, nonpharmacologic therapies are effective adjuncts and should be considered for all patients with psoriasis. A treatment regimen should always be individualized, taking into consideration severity of disease, patient responses, and tolerability to various interventions. Furthermore, if comorbidities exist, they must be taken into treatment considerations and managed early. Optimal psoriasis care needs to maintain a focus on the patient's overall health-related quality of life [1].

Nonpharmacologic alternatives such as stress reduction and the liberal use of moisturizers may be beneficial and should always be considered and initiated when appropriate [1]. These will not be discussed in this chapter.

Pharmacologic alternatives for psoriasis include topical agents, phototherapy, and systemic agents (traditional, biologics, and newer nonbiologics, e.g., apremilast and deucravacitinib). There are also

---

S. Yeroushalmi

Department of Dermatology, University of California San Francisco,  
San Francisco, USA

e-mail: [samuel.yeroushalmi@ucsf.edu](mailto:samuel.yeroushalmi@ucsf.edu)

W. Liao (✉)

Department of Dermatology, University of California (UCSF),  
San Francisco, CA, USA

e-mail: [wilson.liao@ucsf.edu](mailto:wilson.liao@ucsf.edu)

many more biologics on the horizon. Pharmacologic therapy is generally guided by the severity of disease and its impact on the patient's quality of life [1]. For limited or mild-to-moderate disease, topical treatments are the mainstay of care [1–3]. Phototherapy and photochemotherapy are used in moderate-to-severe cases [1, 4, 5]. For patients presenting with extensive or moderate-to-severe disease, systemic therapies (non-biologic and biologic) with or without the use of topical treatments are the usual standard of care.<sup>1, 6, 7</sup> Newer systemic treatments such as biologic agents or targeted oral agents may be the treatments of choice, especially for patients with comorbidities such as PsA or if traditional systemic treatments (such as methotrexate or cyclosporine) are contraindicated [1, 7–9]. This chapter will only include drug monographs for topical agents.

Approximately 80% of patients with psoriasis have mild-to-moderate disease, and the majority of these patients can be treated with topical therapies alone [3]. Individualized approaches are essential because of the wide variation in patients' presentations, their psychosocial health, and their personal opinions as to what would be acceptable treatment [10, 11]. Traditional topical therapies include corticosteroids, vitamin D<sub>3</sub> analogs, retinoids, anthralin, and coal tar [1, 3]. In addition, topical calcineurin inhibitors may be useful for difficult-to-treat sites such as the intertriginous areas or the face. More biologic agents and targeted nonbiologic agents are on the horizon [1]. Topical agents are also used as adjunctive therapy for patients with more extensive disease, who are being treated concurrently with phototherapy or systemic agents [1].

---

## Drug Monographs

### Anthralin [12]

Rebecca M. Law

#### Classification and Mode of Action

- Anthralin has a direct antiproliferative effect on epidermal keratinocytes [12–14], normalizing keratinocyte differentiation [15].

- It has a direct effect on mitochondria [15, 16] and reduces the mitotic activity of epidermal cells [14]. It inhibits synthesis of nucleic protein from inhibition of DNA synthesis [17].
- It also prevents T-lymphocyte activation [15].
- Small placebo-controlled studies demonstrated efficacy for anthralin used continuously or as short contact (1 minute of treatment) [15].

### **Indications and Dermatologic Uses**

- Clinical indication (FDA): Plague psoriasis. (Anthralin is not as commonly used as other topical therapies currently available for psoriasis; however, there are situations where its use is appropriate and efficacious.)

### **Formulations**

- Anthralin 1% cream, anthralin 1% shampoo
  - USA: Drithocrema, Dithro-Scalp, Psoriatec, and Zithranol
  - Can: Anthraforte 2, Anthraforte 3, and Anthrascalp
- Extemporaneously compounded anthralin used in short-contact anthralin therapy (SCAT) (various formulations—see under dosages)

### **Dosages and Suggested Regimens**

- Short-contact anthralin therapy (SCAT) is usually the preferred regimen, where the anthralin ointment is applied only to the thick plaque lesions for 2 hours or less and then wiped off [15, 18]. To minimize irritation, it can be applied for 5 to 10 minutes daily initially and then titrating up the application time to 20 to 30 minutes or more as tolerated [14]. Because lesions are generally well demarcated, zinc oxide ointment or a nonmedicated stiff paste should be applied to the surrounding normal skin to protect it from irritation and burning [15].
- Concentrations for SCAT range from 1% to 4% or as tolerated
- Concentrations for continuous anthralin therapy vary from 0.05% to 0.4%

### Contraindications and Cautions

- Anthralin should be used with caution, if at all, on the face and intertriginous areas because of the risk of severe skin irritation [15].
- Anthralin powder causes skin irritation. People who handle the dry anthralin powder should avoid skin contact (e.g., by wearing gloves while compounding) [18].

### Use in Special Populations

- Elderly skin is more fragile and friable. Be cautious if using anthralin in elderly patients, if used at all. Use other alternative treatments.
- Anthralin should not be applied to broken skin.

### Adverse Effects and Their Management

- Aside from significant and often severe skin irritation, other adverse effects include folliculitis and allergic contact dermatitis, but these are uncommon.

## Calcipotriene (Calcipotriol) Drug Monograph [20, 21]

Samuel Yeroushalmi, Rebecca M. Law, and Wilson Liao

### Classification and Mode of Action

- Vitamin D3 analog. Calcipotriene (calcipotriol) is a synthetic derivative of vitamin D3 (cholecalciferol) that binds to vitamin D receptors on keratinocytes in order to enhance both keratinocyte proliferation and differentiation.
- For patients with mild to moderate psoriasis, calcipotriene has been shown to be superior to fluocinonide 500ug/g twice daily and betamethasone valerate 1–1.2 mg/g twice daily [22] (Kragballe, 1991).
- Calcipotriene has been shown to be effective and safe in combination with other topical, systemic, or phototherapy treatments for psoriasis, and its use can reduce the dosage of these treatments [23].

## Indications and Dermatologic Uses

- *Clinical indications (FDA)*: Plaque psoriasis
- *Off label common uses*: Vitiligo, acantholytic disorders, ichthyoses, morphea/linear scleroderma, lichen planus, prurigo nodularis, and pityriasis alba

## Formulations/Presentation

- USA: 0.005% cream, 0.005% foam, 0.005% ointment, 0.005% solution
- Canada: 0.005% ointment

## Dosages and Suggested Regimens

- Apply to skin once to twice daily.
- No suggested dosing adjustments for renal or hepatic impairment as per manufacturer.

## Baseline Investigations and Considerations

### Pharmacokinetics

- Absorption when applied to psoriasis plaques: ointment: 6%; solution: <1%; cream and foam undetermined. Serum half-life in rats shown to be 4 minutes. Converted to inactive metabolites and excreted in bile.
- Onset of effect: About 2 weeks, with marked improvement after 8 weeks.

*Carcinogenicity*: No indications of increased carcinogenic risk

### Use in Special Populations

- Approved for use in children, though higher risk of systemic adverse events.
- Severity of skin-related adverse events may be increased in the elderly.
- FDA pregnancy category C.
- No dosage adjustment for hepatic or renal impairment.

### Breast Milk

- Unknown if excreted in human breast milk



**Monitoring**

- Hypercalcemia has been observed with excessive topical use.
- Rash, skin irritation.
- Pruritus.
- Signs of allergic reaction such as hives, swollen lips or mouth, wheezing, trouble breathing, etc.

**Contraindications and Cautions**

- Hypersensitivity to calcipotriene or any formulation component
- Vitamin D toxicity
- Hypercalcemia
- Cream and ointment contraindicated for face use
- Scalp solution contraindicated for acute eruptions

**Important Drug Interactions**

- Acidic topical agents may inactivate calcipotriene (e.g., topical hydrocortisone valerate, lactic acid, and salicylic acid). If used together, consider separating the administration time by 10–12 hours to minimize the interaction. *Do not* compound these agents with calcipotriene into a combination product.
- Aluminum hydroxide: Calcipotriene may increase serum concentration of aluminum hydroxide by increasing aluminum absorption, resulting in increased serum aluminum concentrations. Avoid chronic use of aluminum-containing agents. If used together, monitor serum aluminum and aluminum-related toxicities.
- Thiazide and thiazide-like diuretics: Greater risk of hypercalcemia when used with calcipotriene.
- Calcium salts; may enhance toxicity of calcipotriene.
- Cardiac glycosides; calcipotriene may increase arrhythmogenic effects.
- Multivitamins/fluoride with ADE, or multivitamins/minerals with ADEK, iron, and folate may enhance toxicity of calcipotriene. Avoid combination.
- Sucralfate; calcipotriene may increase serum concentration of sucralfate, resulting in an increase in serum aluminum concentration. (Sucralfate is an aluminum-containing agent). Manage as per aluminum hydroxide discussion above.

- Calcipotriene may potentiate the effects of other vitamin D analogs

### **Adverse Effects and Their Management**

- Tingling, burning, itching, and skin irritation are most commonly reported with use.
- May cause erythema, dry skin, and peeling were less commonly reported.
- May cause worsening of psoriasis, including development of facial or scalp psoriasis.
- May cause skin atrophy, hyperpigmentation, or folliculitis.
- May cause allergic contact dermatitis or contact dermatitis.
- Hypercalcemia may occur with excessive use. Calcipotriene should be discontinued until serum calcium returns to normal.

### **Patch Test Concentration [24]**

- 2mcg/ml in citrate-buffered isopropyl alcohol is recommended. Positive test should be repeated in >3 months to ensure consistency over time; a repeated open application test may be needed.

### **Essential Patient Information**

- For external use only.
- Wash hands after each use.
- Avoid application to mucous membranes or eyes.
- If excessive irritation or sensitivity reaction occurs on uninvolved areas, discontinue use.
- Avoid exposure to natural or artificial sunlight in areas where drug is applied.
- Foam may be flammable, keep away from open flame.

## Calcitriol

Mimi Chung, Rebecca M. Law, and Wilson Liao

### Classification and Mode of Action

- Vitamin D analog. Calcitriol is a synthetic version of vitamin D3. The mechanism behind its effectiveness in psoriasis is unclear, but it has been suggested that calcitriol may inhibit inflammatory mediators and decrease keratinocytes proliferation [32].
- High potency and super-high potency topical corticosteroids are slightly more efficacious than calcitriol [33]; however, topical calcitriol has been reported in one study to have a greater proportion of psoriasis patients to remain in remission post-treatment compared to betamethasone [34].
- Topical calcitriol and calcipotriene appear equally effective for psoriasis [33]. One study showed mild skin irritation and perilesional irritation on sensitive areas such as the intertriginous areas occurred less often with calcitriol than calcipotriene [35].
- Combination treatment of topical corticosteroids with vitamin D analogs has been shown to be more effective than topical corticosteroids or vitamin D analogs alone [33].

### Indications and Dermatological Uses

- Clinical indications (FDA): Mild-to-moderate plaque psoriasis
- Off label common uses: Vitiligo (in combination with corticosteroids and phototherapy), some acantholytic disorders, morphea, pityriasis alba, prurigo nodularis, and polymorphous light eruption [36]

### Formulations/Presentation

- USA: 3 mcg/g ointment
- Canada: 3 mcg/g ointment

## Dosages and Suggested Regimens

- Apply topically twice daily to affected areas. Two hundred grams weekly maximum for adults and children 7 years and older.
- No recommendations regarding suggested dosage adjustment for renal or hepatic impairment.

## Baseline Investigations and Considerations

- Topical corticosteroids are the preferred initial topical treatment for psoriasis compared to vitamin D analogs alone like calcitriol and calcipotriene based on data showing better efficacy and lower price point [37].

## Pharmacokinetics

- Minimal topical absorption. Topical absorption when applied twice daily for 21 days caused an increase of 36% geometric mean plasma concentration values and an increase of 44% in geometric mean value of  $AUC_{(0-12\text{ hr})}$ . Calcitriol is a minor substrate of CYP3A4. Terminal half-life was not determined, as plasma levels of calcitriol were relatively flat during pharmacokinetic studies. Excretion in urine and bile, via enterohepatic system [37].
- Onset of effect: Approximately 2 weeks [38].

## Use in Special Populations

- Approved for use in children 2 years or older. Maximum use for children ages 2–7 years old should not exceed 100 g per week.
- Listed as FDA pregnancy classification C. Other topical agents other than calcitriol recommended for treatment in pregnant women, though the limited available data has not shown any drug-associated risk for major birth defects or adverse maternal outcomes.
- Unknown whether calcitriol is present in breast milk. Recommend against using topical calcitriol on the nipple and areola and avoidance of infant exposure if breastfeeding.
- Renal insufficiency: Not evaluated; monitoring of calcium and phosphorus levels is recommended in patients with renal failure with concurrent appropriate nutritional counseling.

- Hepatic insufficiency: Not evaluated.
- *Canadian labeling*: Contraindications for topical calcitriol use include severe renal impairment or end-stage renal disease. Hepatic impairment is also a contraindication for use.

### Monitoring

- Consider monitoring for hypercalcemia and hypercalciuria per the drug interactions listed below
- Skin discomfort and irritation
- Pruritus
- Acute blistering dermatitis (reported postmarketing)

### Contraindications and Cautions

- Calcitriol should not be used in combination with other vitamin D analogs.
- Use caution in patients with known calcium disorders, including patients taking calcium supplementation, high doses of vitamin D, or other medications known to cause hypercalcemia.
- Calcitriol may enhance the photosensitizing effect of both systemic and topical aminolevulinic acid. Avoid combination therapy.
- Calcitriol may exacerbate the side effects of burosumab. Avoid combination therapy.
- *Canadian labeling*: Contraindications to treatment include the following: hypersensitivity to calcitriol or any of its components; disorders of calcium metabolism, history of hypercalcemia, or active treatment of calcium abnormalities; and hepatic impairment or significant renal impairment/end-stage renal disease (ESRD). Ophthalmic and internal use is contraindicated.

### Important Drug Interactions

- *Other vitamin D analogs*: Adverse effects may be exacerbated by calcitriol. Avoid concomitant use.
- *Burosumab*: Adverse effects of burosumab may be exacerbated by vitamin D analogs like calcitriol. Avoid concomitant use.
- *Multivitamins with folate, iron, fluoride, and vitamin A, D, E, or K* may enhance adverse events related to calcitriol. Avoid combination therapy.

- *Aminolevulinic acid*: Calcitriol should not be used with systemic aminolevulinic acid due to enhanced photosensitivity. Use with topical aminolevulinic acid should be monitored.
- *Aluminum hydroxide and sucralfate*: Calcitriol may increase serum aluminum levels when used in combination with aluminum hydroxide and sucralfate. Alternative therapies should be considered; if used concurrently, monitoring of aluminum levels and signs of aluminum-related toxicities is recommended.
- *Thiazides and thiazide diuretics*: Effects on calcium homeostasis may be influenced by calcitriol. Monitoring therapy and response recommended.
- *Cardiac glycosides*: Antiarrhythmic effects may be enhanced with calcitriol. Monitoring treatment recommended.
- *Photosensitizing agents*: Calcitriol will potentially exacerbate photosensitizing effect of medications that cause photosensitivity (e.g., systemic methoxsalen, porfimer, and verteporfin). Therapy should be monitored.

### **Adverse Effects and Their Management**

- *Hypercalcemia*: Alterations in calcium metabolism causing hypercalcemia were seen, though symptomatic elevations are extremely rare. Cases in postmarketing reporting were generally in older adults who used topical calcitriol on larger areas of the body. If lab abnormalities are noted, discontinue treatment until values normalize.
- *Hypercalciuria*: Urine lab abnormalities, specifically hypercalciuria, were reported to occur. Discontinue treatment until values normalize.
- *Skin discomfort and irritation*: Skin discomfort, erythema, acute blistering dermatitis, and skin burning sensation were reported to occur. Discontinue treatment with topical calcitriol.
- *Kidney stones*: Kidney stones were reported in a small number of patients during open label trial.

**Patch Test Concentration**

- Not available

**Essential Patient Information**

- Apply medication only to lesional skin. Do not apply to healthy skin.
- Do not ingest. For external use only. Avoid contact with face, eyes, lips, or other mucous membranes (e.g., inside nose).
- Avoid using photosensitizing medications. Calcitriol ointment may make skin more photosensitive.
- Do not use at the same time as multivitamins containing folate, iron, and fluoride. Do not take with multivitamins with vitamin A, vitamin D, vitamin E, and/or vitamin K.
- Do not use at the same time as vitamin D or other vitamin D analogs.

**Corticosteroids**

Kiha Kim, Taylor Skinner, and Rebecca M. Law

See Chap. 18 for a discussion of topical corticosteroids (TCS), the drug monographs of TCS, and a Corticosteroid Potency Table.

**Crisaborole**

Rebecca M. Law

See Chap. 17 for the crisaborole drug monograph.

## Coal Tar & Tar Distillates

Sarah J. Currie and Rebecca M. Law

### Classification and Mode of Action

Coal tar and tar distillates loosen and soften scales and crusts through their antiseptic, antibacterial, and antiseborrheic properties. Coal tar has been shown to be very effective for full-body psoriasis, although there is a lack of data regarding its efficacy in the scalp. One study demonstrated that use of a coal tar gel for 5 days was effective in improving scalp psoriasis. Another study showed the effectiveness of a topical coal tar foam combined with topical steroids for treatment-resistant scalp psoriasis. One prospective randomized study compared the application of a coal tar ointment overnight (on one side of the lesion) with calcipotriol ointment (on the other side of the lesion). The calcipotriol ointment showed superior cosmetic acceptability and faster initial response; however, coal tar ointment had comparable efficacy after a long period of treatment, i.e., a comparable reduction in the ESI (erythema, scaling, and induration) score after 12 weeks. There was no statistically significant difference in the relapse rates between the two treatments in this study.

### Indications and Dermatological Uses

- *Clinical indications (FDA)*
  - *Scalp conditions (dandruff, psoriasis, seborrheic dermatitis):* Shampoo. See under Chap. 23 monograph.
  - *Skin conditions (psoriasis, seborrheic dermatitis):* Cream, foam, lotion, ointment, bath, and foot/hand soak. To relieve symptoms (itching, scaling, flaking, redness, and irritation).
- *Off-label common uses*
  - *Atopic dermatitis in children and adolescents:* Two percent to 5% coal tar cream applied once daily or once every other day, to reduce inflammation. Limited data available.



## Formulations/Presentation

- USA:
  - Emulsion, external: Cutar: 1.5% (177 mL) (contains methylparaben, polysorbate 80, propylparaben)
  - Foam, external: Scytera: 2% (100 g) (contains disodium edta)
  - Ointment, external: Psoriasin: 2% (113 g (DSC)) (contains alcohol, usp, polysorbate 80)

## Dosages and Suggested Regimens

- *Scalp conditions (dandruff, psoriasis, seborrheic dermatitis):* Topical shampoo. Rub shampoo onto wet hair and scalp, leave on for 5 minutes, and then rinse thoroughly. Repeat. Apply at least twice weekly or more often if needed. (See under Chap. [23](#) monograph).
- *Skin conditions (psoriasis, seborrheic dermatitis)*
  - *Cream, foam, lotion, ointment:* Apply to the affected area one to four times/day.
  - *Bath (Cutar):* Add 60 to 120 mL to bath water and mix well. Soak for 10 to 20 minutes or as directed, and then pat dry.
  - *Foot/hand soak (Cutar):* Add 30 to 60 mL of lotion to a sink or basin filled with water, and then mix well. Soak for 5 to 10 minutes or as directed.

## Baseline Investigations and Considerations

- None documented

## Use in Special Populations:

- *Pregnancy:* Limit application of coal tar during pregnancy in treating psoriasis to maximize safety in pregnant women.
- *Lactation:* Avoid direct contact by the infant if coal tar is used in a nursing mother, as one case report described the absorption of the components of coal tar containing ointment by a nursing infant. The components were not detected in breast milk, however were assumed to be absorbed by the infant following skin-to-skin contact with the mother while nursing.

- *Children:* For external use only; avoid contact with eyes. Do not apply in or near anogenital areas unless directed by a physician. Wash hands before and after application
- *Renal insufficiency:* There are no dosage adjustments provided in the manufacturer's labeling for renal impairment.
- *Hepatic insufficiency:* There are no dosage adjustments provided in the manufacturer's labeling for liver impairment.

## **Contraindications and Cautions**

- *Concerns related to adverse effects*
  - Hair color changes: shampoo may cause discoloration of gray, blonde, tinted, or bleached hair.
  - Photosensitivity: May increase photosensitivity; avoid exposure to direct sunlight for 24 hours following application.
  - Staining: May stain light colored fabrics; do not use in plastic or fiberglass tubs, sinks, or basins.
- *Other warnings/precautions*
  - Polysorbate 80: Some dosage forms may contain polysorbate 80 (Tweens). Hypersensitivity reactions, usually delayed, have been reported following exposure to pharmaceutical products containing polysorbate 80 in certain individuals.
  - Self-medication (OTC use): for external use only; avoid the eyes. If the condition covers a large area of the body or is around the genital, groin, or rectal area, talk to your health-care provider before application. Do not use this product with other forms of psoriasis therapy such as ultraviolet radiation or prescription drugs unless directed by healthcare provider. Overuse may make the condition worse; do not use more often or longer than recommended by your health-care provider. Discontinue use and contact healthcare provider if condition worsens, does not improve after regular use as directed, or excessive irritation occurs.
- *Additional pediatric considerations*
  - Some dosage forms may contain propylene glycol; in neonates, large amounts of propylene glycol delivered orally, intravenously, or topically have been associated with poten-

tially fatal toxicities which can include metabolic acidosis, seizures, renal failure, and CNS depression.

### **Important drug interactions**

There are no known significant interactions.

### **Adverse Effects and Their Management**

- *Dermatologic*: dermatitis, folliculitis, skin irritation, skin photosensitivity.
- *Hair color changes*: shampoo may cause discoloration of gray, blonde, tinted, or bleached hair.
- *Photosensitivity*: may increase photosensitivity, avoid exposure to direct sunlight for 24 hours following application.
- *Staining*: may stain light colored fabrics. Do not use in plastic or fiberglass tubs, sinks, or basins.
- *Polysorbate 80*: some dosage forms contain polysorbate 30 (Tweens). In certain individuals, hypersensitivity reactions, usually a delayed reaction, have been reported following exposure to pharmaceutical products containing polysorbate 80.

### **Carcinogenicity**

There have been cancer warnings on some coal tar products in California. This warning was added due to animal studies where the animals were exposed to a significantly higher amount of coal tar than is used to treat psoriasis. Studies, however, fail to demonstrate an increased risk of cancer in people using coal tar to treat psoriasis or atopic dermatitis. People who work with industrial coal tar have an increased risk of developing cancer of the lungs, scrotum, and skin, however.

### **Patch Test Concentration**

- 5.0% pet. (Chemotechnique, SmartPracticeEurope, SmartPracticeCanada)

### **Essential Patient Information**

- Prior to use, tell your doctor if you are allergic to this drug, any part of this drug, or any other drugs, foods, or substances. Tell your doctor if you have lupus, if your skin is sensitive to light, and if large areas need to be treated.

- Inform all your healthcare providers that you take this drug, including doctors, nurses, pharmacists, and dentists.
- May stain the fingernails, hair, and skin. Protect clothing and fabrics from staining.
- Avoid sun, sunlamps, and tanning beds. Use sunscreen and wear clothing and eyewear that protects you from the sun, as you may get sunburned more easily.
- Tell your doctor if you are pregnant, plan on getting pregnant, or are breastfeeding. You will need to discuss the benefits and risks to you and the baby.
- Tell your doctor or get medical help immediately if you have any of the following signs and symptoms of an allergic reaction that may be related to a bad side effect: rash, hives, itching, red, swollen, blistered, or peeling skin with or without fever, wheezing, chest or throat tightness, trouble breathing, swallowing, or talking, unusual hoarseness, or swelling of the mouth, face, lips, tongue, or throat.
- Topical use only: Use only on the skin. Do not take this drug by mouth. Keep out of your mouth, nose, and eyes (may burn). If this drug gets in the eyes, rinse with cool water.
- Wash your hands before and after use. If your hand is the affected area requiring treatment, do not wash your hand after use.
- Put a thin layer on the skin and rub in gently.
- This drug may catch on fire. Do not use near an open flame or while smoking.
- Store all products at room temperature in a dry place. Do not store in bathroom. Keep all drugs in a safe place and out of reach of children and pets.

## Ruxolitinib

Marwa Hakimi and Wilson Liao

*Note that at time of publication, ruxolitinib has FDA-labeled indications for atopic dermatitis and vitiligo. It is used off label for psoriasis.*

## Classification and Mode of Action

- Janus kinase (JAK) inhibitor. Ruxolitinib is a selective inhibitor of Janus kinase 1 (JAK1) and Janus kinase 2 (JAK2), key components of the JAK-STAT signaling pathway, which is involved in the pathogenesis of various inflammatory and autoimmune diseases. By inhibiting these kinases, ruxolitinib reduces the production and signaling of pro-inflammatory cytokines, thereby reducing inflammation and abnormal cell proliferation associated with skin disorders.
- Ruxolitinib has been shown to decrease the expression of inflammatory mediators and the hyperactivation of immune pathways implicated in conditions like atopic dermatitis and vitiligo. The cream is generally well-tolerated and has demonstrated efficacy in reducing the severity of these conditions.
  - TRuE-AD1 and TRuE-AD2 Trials: These two randomized, double-blind, vehicle-controlled phase 3 trials evaluated the efficacy and safety of ruxolitinib cream in patients with mild to moderate atopic dermatitis. The trials demonstrated that ruxolitinib cream was significantly more effective than the vehicle in reducing the severity of atopic dermatitis, as measured by the Investigator's Global Assessment (IGA) score and Eczema Area and Severity Index (EASI-75). The trials reported that approximately 50% of patients achieved an IGA score of 0 or 1 by week 8, compared to around 15% in the vehicle group.
  - TRuE-V1 and TRuE-V2 Trials: These phase 3, randomized, double-blind, vehicle-controlled studies assessed the efficacy and safety of ruxolitinib cream in patients with vitiligo. The studies found that ruxolitinib cream led to significant repigmentation of facial vitiligo, with about 30% of patients achieving at least 75% improvement in the facial Vitiligo Area Scoring Index (F-VASI75) at week 24 compared to about 10% with the vehicle. The trials also noted a favorable safety profile.

## Indications and Dermatological Uses

- *Clinical indications (FDA)*
  - Atopic dermatitis (mild to moderate)
  - Nonsegmental vitiligo
- *Off-label common uses*
  - Alopecia areata
  - Lichen planus
  - Psoriasis

## Formulations/Presentation

- USA: 1.5% cream in 5-g and 60-g tubes
- Canada: No data available
- Europe: 1.5% cream in 30-g and 60-g tubes

## Dosages and Suggested Regimens

- Atopic dermatitis: Apply a thin layer to the affected areas twice daily. Application should be limited to less than 20% of body surface area (BSA). Discontinue use once signs and symptoms have resolved. If symptoms persist beyond 8 weeks, reassess the treatment plan.
- Vitiligo: Apply twice daily to affected areas until repigmentation occurs or as directed by a healthcare provider. Application should be limited to less than 20% of body surface area (BSA). Reevaluate the necessity of ongoing treatment if meaningful improvement with repigmentation has not occurred by 24 weeks.
- Maximum dosage: Do not exceed 60 g per week or 100 g per 2 weeks to minimize systemic absorption.

## Baseline Investigations and Considerations

- Patient has a diagnosis of mild to moderate atopic dermatitis and meets one of the following:
  - Trial and failure (of at least a 30-day supply), contraindication, or intolerance to one prescription strength topical corticosteroid, unless the affected area is sensitive (i.e., face, axillae, and groin)

- Trial and failure (of a minimum 30-day supply) or intolerance to one generic topical calcineurin inhibitor, unless the patient is not a suitable candidate for therapy
- Patient has a diagnosis of nonsegmental vitiligo and trial and failure of a minimum 30-day supply, contraindication, or intolerance to ONE of the following:
  - Medium or higher potency topical corticosteroid
  - Pimecrolimus cream
  - Tacrolimus ointment
- Consideration of baseline complete blood count (CBC) with differential as clinically indicated to monitor for potential cytopenias during treatment, especially in long-term use.

### Pharmacokinetics

- *Absorption*: Minimal systemic absorption observed with topical application. In clinical trials, plasma concentrations were low and not expected to lead to systemic immunosuppression.
- *Distribution*: Primarily stays localized to the site of application with minimal distribution to systemic circulation.
- *Metabolism*: Metabolized by hepatic CYP3A4 enzymes.
- *Excretion*: Predominantly excreted in the urine as metabolites.

### Use in Special Populations:

- *Pediatrics*: Approved for use in children aged 12 years and older for atopic dermatitis and nonsegmental vitiligo. Safety and efficacy in younger children have not been established.
- *Pregnancy*: There is no adequate data on ruxolitinib use in pregnant women. Use only if the potential benefit justifies the potential risk to the fetus.
- *Lactation*: It is unknown whether ruxolitinib is present in human breast milk following topical application. The manufacturer advises against breastfeeding during therapy and for approximately 4 weeks following the last dose of ruxolitinib
- *Renal insufficiency*: No dose adjustment is necessary for patients with renal impairment.
- *Hepatic insufficiency*: No specific dose adjustments recommended; however, systemic exposure could be higher in these patients, and monitoring is recommended. Use is not advised in patients with active hepatitis B or C.

## Monitoring

- Atopic dermatitis/segmental vitiligo: Monitor for signs of local skin reactions, including irritation or hypersensitivity.
- Periodic CBCs may be considered in patients on long-term therapy to monitor for potential cytopenias.
- Infection risk: Monitor for signs of infections, as ruxolitinib may increase the risk of bacterial, fungal, or viral infections, including herpes zoster.
- Malignancy risk: Periodic skin examinations for basal cell and squamous cell carcinoma.

## Contraindications and Cautions

- *Contraindications:* Hypersensitivity to ruxolitinib or any of the components in the formulation.
- *Cautions:* Use with caution in patients with a history of skin malignancies or with active, untreated infections. Avoid use in immunocompromised patients unless the benefit outweighs the risks.
- *Serious infections:* Monitor for and promptly manage serious bacterial, mycobacterial, fungal, and viral infections.
- *Non-melanoma skin cancers:* Periodically examine the skin for basal cell and squamous cell carcinomas.
- *Thrombosis:* Be aware of the risk of thromboembolic events.
- *Hematologic issues:* Monitor for thrombocytopenia, anemia, and neutropenia with CBC tests as needed.

## Important Drug Interactions

- CYP3A4 inhibitors: Concurrent use of strong CYP3A4 inhibitors (e.g., ketoconazole) may increase plasma concentrations of ruxolitinib, increasing the risk of systemic side effects.
- Immunosuppressants: Co-administration with other immunosuppressants (e.g., methotrexate and cyclosporine) may increase the risk of infections or exacerbate immunosuppression.
- Avoid using topical ruxolitinib concurrently with therapeutic biologics, other Janus kinase inhibitors, or potent immunosuppressants (e.g., azathioprine and cyclosporine).



## Adverse Effects and Their Management

- *Local skin reactions:* Redness, itching, and irritation at the site of application. Usually mild and transient. Discontinue use if severe skin reactions occur.
- *Infections:* Increased risk of upper respiratory tract infections and herpes zoster. Discontinue treatment in the presence of a serious infection.
- *Hematological effects:* Rare cases of anemia and thrombocytopenia reported. Regular monitoring with CBC is recommended during prolonged therapy

## Patch Test Concentration

- Not available

## Essential Patient Information

- Apply only to affected areas and avoid healthy skin.
- Wash hands thoroughly after application unless the hands are the treatment area.
- Do not cover the treated area with occlusive dressings unless directed by a healthcare provider.
- Report any signs of infection or severe irritation to your healthcare provider.
- Do not use this medication if pregnant or planning to become pregnant without consulting a healthcare provider.

## Salicylic Acid

Erin Bartholomew, Rebecca M. Law, and Wilson Liao

## Classification and Mechanism of Action

Salicylic acid is an active ingredient in topical acne products. It is a keratolytic agent. It produces desquamation of hyperkeratotic epithelium by dissolution of the intercellular cement causing the cornified tissue to swell, soften, macerate, and desquamate.

## Indications and Dermatological Use

- *Acne*: Topical management: often used in combination products. See Chap. 8 for a discussion of acne and other topical treatments for acne and the drug monographs.
- *Hyperkeratotic skin disorders*: Removal of excess keratin in various hyperkeratotic skin disorders and psoriasis (including affected areas of the scalp, skin, and feet; treatment and removal of common and plantar warts).

## Off-Label Common Uses

- Seborrheic dermatitis. See Chap. 24 for a discussion of topical treatments and the drug monographs.

## Formulations/Presentations

### USA

#### Cream, External

Atrix medicated formula: 2% (59 mL) (contains disodium EDTA)

- Salimez: 6% (227 g)
- Salimez Forte: 10% (227 g)

#### Foam, External

- SalAc: 2% (100 g) (contains alcohol, usp)
- Salvax: 6% (70 g, 200 g) (contains ethylparaben, methylparaben, polysorbate 80, propylene glycol, propylparaben, trolamine (triethanolamine))
- Generic: 6% (70 g, 200 g)

#### Gel, External

- AcNesic: 0.5% (48 g) (contains benzalkonium chloride, butylparaben, eggshells, ethylparaben, isobutylparaben, methylparaben, propylene glycol, propylparaben, trolamine (triethanolamine))
- Keralyt: 3% (28.4 g) (contains alcohol, usp)
- Keralyt: 6% (40 g, 60 g, 100 g) (contains hydroxypropyl cellulose, propylene glycol, sd alcohol 40)

**Kit, External**

- Atrix system 1: 2% (contains disodium EDTA, menthol)
- Keralyt Scalp: 6% (contains edetate (EDTA) sodium (tetrasodium), propylene glycol, sd alcohol 40)
- Generic: 6%

**Liquid, External**

- DermacinRx Atrix Antibac Wash: 2% (118 mL) (contains disodium EDTA, menthol)
- DermacinRx Atrix Clarify Toner: 2% (118 mL) (contains benzalkonium chloride, benzyl alcohol, menthol)
- Neutrogena Oil-Free Acne Wash: 2% (124 mL) (contains benzalkonium chloride, disodium EDTA, FD&C red #40, propylene glycol)
- Psoriasin: 3% (177 mL) (dye free, fragrance free)
- Salicylic acid wart remover: 27.5% (10 mL) (contains isopropyl alcohol)
- Virasal: 27.5% (10 mL) (contains isopropyl alcohol, isopropylm-cresol)

**Ointment, External**

- Bensal HP: 3% (30 g)

**Pad, External**

- Clear Away 1-Step Wart Remover: 40% (14 ea)
- Corn Remover One Step: 40% (6 ea)

**Shampoo, External**

- Betasal: 3% (480 mL)
- Ionil: 2% (120 mL)
- Keralyt: 6% (160 mL) (contains cocamidopropyl betaine, edetate (EDTA) sodium (tetrasodium), propylene glycol)
- P & S: 2% (236 mL) (contains edetate (EDTA) sodium (tetrasodium), methylparaben, propylparaben, trolamine (triethanolamine))
- Salex: 6% (177 mL) (contains methylparaben, propylparaben, trolamine (triethanolamine))
- Generic: 6% (177 mL)

### Solution, External

- Gordofilm: 16.7% (15 mL)
- UltraSal-ER: 28.5% (10 mL) (contains isopropyl alcohol, phenol, polysorbate 80)
- Xalix: 28% (10 g) (contains isopropyl alcohol)
- Generic: 26% (10 mL); 28.5% (10 mL)

## Dosages and Suggested Regimens: Adult

### Acne

#### Topical

- Salicylic acid 0.5% to 2%: OTC labeling: Apply thin layer to affected area one to time times daily. Products that are labeled for multiple daily doses should be initiated with 1 dose daily and increased gradually, because excessive drying may occur. Reduce to once daily or every other day if dryness or peeling occurs.
- Cream, gel, liquid, lotion, and pads: Salicylic acid  $\leq 2\%$ : Apply thin layer to affected area one to three times daily; reduce to once daily or every other day if dryness or peeling occurs.
- Cleansers: Salicylic acid  $\leq 2\%$ : Use to cleanse skin one to two times daily; reduce to once daily or every other day if dryness or peeling occurs.

### Dandruff, Psoriasis, or Seborrheic Dermatitis

- Topical: *Note:* Product-specific indications may vary; refer to manufacturer's labeling.
- Cream, gel: Salicylic acid 2% or 3%: OTC labeling: Apply to affected area one to four times daily.
- Shampoo: Salicylic acid 3%: OTC labeling: Apply to wet hair and gently massage into scalp; work up lather; rinse thoroughly. Use at least twice weekly.

### Pharmacokinetics

- *Onset of action:* Treatment of warts: 1 to 2 weeks; full resolution may take  $>4$  to 6 weeks. Treatment of psoriasis: topical salicylic acid use for 8 to 16 weeks is recommended for the treatment of mild to moderate plaque psoriasis.

- *Absorption:* Salicylic acid gel 6%: >60% under occlusion. Percutaneous; systemic toxicity unlikely with normal use.
- *Protein binding:* 50% to 80% to albumin.
- *Time to peak, serum:* Salicylic acid gel 6%: Within 5 hours of application with occlusion.
- *Excretion:* Urine (salicyluric acid (52%), salicylate glucuronides (42%), and salicylic acid (6%)).

## **Use in special populations:**

### **Pregnancy Considerations**

- Salicylic acid crosses the placenta. Systemic absorption of topical salicylic acid occurs and varies depending on duration and vehicle (~9% to 25%) and is increased with occlusion.
- Current guidelines do not recommend salicylic acid for the treatment of psoriasis in pregnant women due to limited safety data and the potential for systemic absorption.
- For the topical treatment of acne or warts, salicylic acid can be used in pregnant women if the area of exposure and duration of therapy is limited, although other agents may be preferred due to limited safety data and the potential for systemic absorption.
- Consider maternal/fetal adverse events associated with aspirin if significant systemic exposure occurs.

### **Breastfeeding Considerations**

- Salicylates are excreted in breast milk after oral administration.
- Systemic absorption of topical salicylic acid occurs and varies depending on duration and vehicle (~9% to 25%) and is increased with occlusion.
- Consider adverse events associated with aspirin in nursing infants if significant systemic exposure occurs.
- For the topical treatment of warts, salicylic acid can be used in breastfeeding women (systemic absorption is usually minimal).
- Breastfeeding women should avoid use around the chest area to prevent exposure to the nursing infant.

- Due to the potential for serious adverse reactions in the nursing infant, the manufacturer recommends making a decision whether to discontinue nursing or discontinue the drug, taking into account the importance of treatment to the mother.

**Altered Kidney Function, Adult**

There are no dosage adjustments provided in the manufacturer's labeling.

**Hepatic Impairment: Adult**

There are no dosage adjustments provided in the manufacturer's labeling.

**Monitoring**

Signs of salicylate toxicity

**Contraindications and Cautions**

- Hypersensitivity to salicylic acid or any component of the formulation
- Additional contraindications
  - Bensal HP: hypersensitivity to topical polyethylene glycols
  - Keralyt, Salex: children <2 years
  - UltraSal-ER, Virasal: impaired circulation or diabetes; moles and birthmarks; and warts with hair growth or on the face

**OTC Labeling**

- Corns/warts: When used for self-medication, do not use if you have diabetes or have poor blood circulation; do not use on irritated skin, on any area that is infected or reddened, on moles, birthmarks, warts with hair growing from them, genital warts, or warts on the face or mucous membranes.
- Documentation of allergenic cross-reactivity for salicylates is limited. However, because of similarities in chemical structure and/or pharmacologic actions, the possibility of cross-sensitivity cannot be ruled out with certainty.

### Important Drug Interactions

- Calcipotriene: Salicylic acid may diminish the therapeutic effect of calcipotriene.
- Management: Monitor for reduced calcipotriene efficacy if combined with salicylic acid.
- Consider separating the administration of these agents by 10 to 12 hours to minimize the risk of this potential interaction.
- *Risk C: Monitor therapy.*

### Adverse Effects and Their Management

The following adverse drug reactions and incidences are cited from product labeling. Frequency is not defined.

- Central nervous system: headache, dizziness, and localized burning at site of exposure on normal tissue
- Dermatologic: desquamation and exfoliation of the skin
- Local: irritation and burning at site of application on normal tissue
- Otic: tinnitus
- Respiratory: hyperventilation

### Patch Test Concentration

- 5% pet. (SmartPracticeCanada)

### Common Brand Names

AcNesic; Atrix medicated formula; Bensal HP; Betasal (OTC); Clear Away 1-Step Wart Remover (OTC); Corn Remover One Step (OTC); DermacinRx Atrix Antibac Wash (OTC); DermacinRx Atrix Clarify Toner (OTC); Exuviance Blemish Treatment (OTC) (DSC); Gordofilm; Ionil (OTC); Keralyt; Keralyt Scalp; Keralyt (OTC); Neutrogena Oil-Free Acne Wash (OTC); P & S (OTC); Psoriasin (OTC); SalAc (OTC); Salex; Salicylic Acid Wart Remover; Salimez; Salimez Forte; UltraSal-ER; Virasal; Xalix

## References

### Introduction

1. Law RM, Gulliver W. Chapter 118: Psoriasis. In: Dipiro's pharmacotherapy: a pathophysiologic approach. 12th ed. McGraw-Hill Medical; 2023. p. 1639–60.
2. Jeon C, Sekhon S, Bhutani T, Koo J. Topical treatments. In: Bhutani T, Liao W, Nakamura M, eds. Evidence-Based Psoriasis, Diagnosis and Treatment. (A textbook in the series Updates in Clinical Dermatology, with series editors Berth-Jones J, Gob CL, and Maibach HI, at <http://www.springer.com/series/13203>). Cham, Switzerland: Springer International Publishing AG; 2018, pp. 17–29.
3. Elmetts CA, Korman NJ, Prater EF, et al. Joint AAD–NPF guidelines of care for the management and treatment of psoriasis with topical therapy and alternative medicine modalities for psoriasis severity measures. *J Am Acad Dermatol*. 2021;84:432–70.
4. Griffith JL, Zarbo AJ, Lim HW. Phototherapy and photochemotherapy. In: Bhutani T, Liao W, Nakamura M, eds. Evidence-Based Psoriasis, Diagnosis and Treatment. (A textbook in the series Updates in Clinical Dermatology, with series editors Berth-Jones J, Gob CL, and Maibach HI, at <http://www.springer.com/series/13203>). Cham: Springer International Publishing AG; 2018, pp. 31–53.
5. Elmetts CA, Lim HW, Stoff B, et al. Joint American Academy of Dermatology–National Psoriasis Foundation guidelines of care for the management and treatment of psoriasis with phototherapy. *J Am Acad Dermatol*. 2019;81:775–804.
6. Menter A, Gelfand JM, Connor C, et al. Joint American Academy of Dermatology–National Psoriasis Foundation guidelines of care for the management of psoriasis with systemic nonbiologic therapies. *J Am Acad Dermatol*. 2020;82:1445–86.
7. Menter A, Strober BE, Kaplan DH, et al. Joint AAD–NPF guidelines of care for the management and treatment of psoriasis with biologics. *J Am Acad Dermatol*. 2019;80(4):1029–72.
8. Smith CH, Yiu ZZN, Bale T, et al. British Association of Dermatologists guidelines for biologic therapy for psoriasis 2020: a rapid update. *Br J Dermatol*. 2020;183(3):628–37. <https://doi.org/10.1111/bjd.19039>.
9. Elmetts CA, Leonardi CL, Davis DMR, et al. Joint AAD–NPF guidelines of care for the management and treatment of psoriasis with awareness and attention to comorbidities. *J Am Acad Dermatol*. 2019;80(4):1073–113.
10. Basavaraj KH, Ashok NM, Rashmi R, Praveen TK. The role of drugs in the induction and/or exacerbation of psoriasis. *Int J Dermatol*. 2010;49:1351–61.



11. Papp KA, Gulliver W, Lynde CW, Poulin Y. Canadian Guidelines for the Management of Plaque Psoriasis. 1st Edition, June 2009. Available at: (Steering Committee). Also see: Canadian Psoriasis Guidelines Addendum Committee. Addendum to the Canadian Guidelines for the Management of Plaque Psoriasis, May 2016. *J Cutan Med Surg.* 2016;20(5):375–431. Available at: <https://dermatology.ca/dermatologists/guidelines/psoriasis>. Also see: Canadian Psoriasis Guidelines Addendum Committee. Addendum to the Canadian Guidelines for the Management of Plaque Psoriasis, May 2016. *J Cutan Med Surg.* 2016;20(5):375–431. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5014087/>. Accessed 28 Feb 2022.

## Drug Monographs

12. Law RM, Gulliver W. Chapter 118: Psoriasis. In: Dipiro's pharmacotherapy: a pathophysiologic approach. 12th ed. McGraw-Hill Medical; 2023. p. 1639–60.
13. Papp KA, Gulliver W, Lynde CW, Poulin Y. Canadian Guidelines for the Management of Plaque Psoriasis. 1st Edition, June 2009. Available at: (Steering Committee). Also see: Canadian Psoriasis Guidelines Addendum Committee. Addendum to the Canadian Guidelines for the Management of Plaque Psoriasis, May 2016. *J Cutan Med Surg.* 2016;20(5):375–431. Available at: <https://dermatology.ca/dermatologists/guidelines/psoriasis>. Also see: Canadian Psoriasis Guidelines Addendum Committee. Addendum to the Canadian Guidelines for the Management of Plaque Psoriasis, May 2016. *J Cutan Med Surg.* 2016;20(5):375–431. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5014087/>. Accessed 29 Aug 2024.
14. Jeon C, Sekhon S, Bhutani T, Koo J. Topical treatments. In: Bhutani T, Liao W, Nakamura M, eds. Evidence-based psoriasis, diagnosis and treatment. (A textbook in the series Updates in Clinical Dermatology, with series editors Berth-Jones J, Gob CL, and Maibach HI, at <http://www.springer.com/series/13203>). Cham: Springer International Publishing AG; 2018, pp. 17–29.
15. Menter A, Korman NJ, Elmetts CA, et al. 2009 Guidelines of care for the management of psoriasis and psoriatic arthritis—section 3. Guidelines of care for the management and treatment of psoriasis with topical therapies. *J Am Acad Dermatol.* 2009;60:643–59.
16. McGill A, Frank A, Emmett N, et al. The anti-psoriatic drug anthralin accumulates in keratinocyte mitochondria, dissipates mitochondrial membrane potential, and induces apoptosis through a pathway dependent on respiratory competent mitochondria. *FASEB J.* 2005;19:1012–4.

17. LexiComp drug monograph (anthralin). Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2024 UptoDate, Inc.
18. Law RM. Chapter 64: Psoriasis. In: Chisholm-Burns M, editor. *Pharmacotherapy principles and practice*. 3rd ed. New York: McGraw-Hill; 2013. p. 1127–41.
19. Mayo Clinic Drugs and Supplements: Anthralin (Topical Route). Last updated Feb. 1, 2024. Available at: <https://www.mayoclinic.org/drugs-supplements/anthralin-topical-route/description/drg-20061896>. Accessed 29 Aug 2024.

## Calcipotriene (Calcipotriol) Drug Monograph

20. FDA drug monograph (calcipotriene). Available from ([https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2015/020273s013\\_020554s012lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020273s013_020554s012lbl.pdf)). Accessed 6 Jan 2022.
21. LexiComp drug monograph (calcipotriene). Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2021 UptoDate, Inc.
22. Kragballe K, Gjertsen BT, de Hoop D, van de Kerkhof PCM, Karlsmark T, Larko O, Nieboer C, Roed-Petersen J, Strand A, Tikjob G. Double-blind, right/left comparison of calcipotriol and betamethasone valerate in treatment of psoriasis vulgaris. *Lancet*. 1991;337(8735):193–6. [https://doi.org/10.1016/0140-6736\(91\)92157-W](https://doi.org/10.1016/0140-6736(91)92157-W).
23. Ashcroft DM, Li Wan Po A, Williams HC, Griffiths CEM. Combination regimens of topical calcipotriene in chronic plaque psoriasis: systematic review of efficacy and tolerability. *Arch Dermatol*. 2000;136(12):1536–43. <https://doi.org/10.1001/archderm.136.12.1536>.
24. De Groot AC. Monographs in contact allergy, volume 3 topical drugs. CRC Press; 2021.
25. Frosch PJ, Rustemeyer T. Contact allergy to calcipotriol does exist. Report of an unequivocal case and review of the literature. *Contact Derm*. 1999;40(2):66–71. <https://doi.org/10.1111/j.1600-0536.1999.tb05993.x>.
26. Kissmeyer AM, Binderup L. Calcipotriol (MC 903): pharmacokinetics in rats and biological activities of metabolites. A comparative study with 1, 25(OH)2D3. *Biochem Pharmacol*. 1991;41(11):1601–6. [https://doi.org/10.1016/0006-2952\(91\)90160-7](https://doi.org/10.1016/0006-2952(91)90160-7).
27. Pearce DJ, Camacho F, Balkrishnan R, Fleischer AB Jr, Feldman SR. Trends in on and off-label calcipotriene use. *J Dermatolog Treat*. 2006;17(5):308–13. <https://doi.org/10.1080/09546630600813659>.
28. Scott LJ, Dunn CJ, Goa KL. Calcipotriol ointment. A review of its use in the management of psoriasis. *Am J Clin Dermatol*. 2001;2(2):95–120. <https://doi.org/10.2165/00128071-200102020-00008>.
29. Elmets CA, Korman NJ, Prater EF, et al. Joint AAD-NPF Guidelines of care for the management and treatment of psoriasis with topical therapy

- and alternative medicine modalities for psoriasis severity measures. *J Am Acad Dermatol.* 2021;84(2):432–70. <https://doi.org/10.1016/j.jaad.2020.07.087>.
30. Oranje AP, Marcoux D, Svensson A, et al. Topical calcipotriol in childhood psoriasis. *J Am Acad Dermatol.* 1997;36(2):203–8.
31. Zeichner JA, Lebwohl MG, Menter A, et al. Optimizing topical therapies for treating psoriasis: a consensus conference. *Cutis.* 2010;86(3 Suppl):5–31.

## Calcitriol

32. Raychaudhuri S, Mitra A, Datta-Mitra A. Immunomodulatory mechanisms of action of calcitriol in psoriasis. *Indian J Dermatol.* 2014;59(2):116–22. <https://doi.org/10.4103/0019-5154.127668>.
33. Mason AR, Mason J, Cork M, Dooley G, Hancock H. Topical treatments for chronic plaque psoriasis. *Cochrane Datab Syst Rev* 2013;3:CD005028. <https://doi.org/10.1002/14651858.CD005028.pub3>.
34. Camarasa JM, Ortonne JP, Dubertret L. Calcitriol shows greater persistence of treatment effect than betamethasone dipropionate in topical psoriasis therapy. *J Dermatolog Treat.* 2003;14(1):8–13. <https://doi.org/10.1080/09546630305545>.
35. Ortonne JP, Humbert P, Nicolas JF, et al. Intra-individual comparison of the cutaneous safety and efficacy of calcitriol 3 microg g(–1) ointment and calcipotriol 50 microg g(–1) ointment on chronic plaque psoriasis localized in facial, hairline, retroauricular or flexural areas. *Br J Dermatol.* 2003;148(2):326–33. <https://doi.org/10.1046/j.1365-2133.2003.05228.x>.
36. Wat H, Dytoc M. Off-label uses of topical vitamin D in dermatology: a systematic review. *J Cutan Med Surg.* 2014;18(2):91–108. <https://doi.org/10.2310/7750.2013.13109>.
37. Food and Drug Administration Center for Drug Evaluation and Research. Application Number 22-087: Pharmacology Review. 30 Jun 2008. [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2009/022087s000\\_PharmR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022087s000_PharmR.pdf)
38. Lebwohl M, Menter A, Weiss J, et al. Calcitriol 3 microg/g ointment in the management of mild to moderate plaque type psoriasis: results from 2 placebo-controlled, multicenter, randomized double-blind, clinical studies. *J Drugs Dermatol.* 2007;6(4):428–35.
39. Elmetts CA, Korman NJ, Prater EF, et al. Joint AAD-NPF Guidelines of care for the management and treatment of psoriasis and alternative medicine modalities for psoriasis severity measures. *J Am Acad Dermatol.* 2021;84(2):432–70. <https://doi.org/10.1016/j.jaad.2020.07.087>.
40. Maul JT, Anzengruber F, Conrad C, Cozzio A, Häusermann P, Jalili A, Kolios AGA, Laffitte EH, Lapointe AK, Mainetti C, Schlapbach C, Trüeb

- R, Yawalkar N, Dippel M, Navarini AA. Topical treatment of psoriasis vulgaris: the Swiss treatment pathway. *Dermatology*. 2021;237:166–78. <https://doi.org/10.1159/000512930>.
41. Maul JT, Anzengruber F, Conrad C, et al. Topical treatment of psoriasis vulgaris: the Swiss treatment pathway. *Dermatology*. 2021;237(2):166–78. <https://doi.org/10.1159/000512930>.
  42. Silkis (calcitriol) [product monograph]. Thornhill: Galderma Canada Inc.; October 2017.
  43. Simionescu AA, Danciu BM, Stanescu AMA. State-of-the-art review of pregnancy-related psoriasis. *Medicina (Kaunas)*. 2021;57(8):804. <https://doi.org/10.3390/medicina57080804>.
  44. Vectical (calcitriol) [prescribing information]. Fort Worth: Galderma Laboratories LP; September 2021.

## Coal Tar and Tar Distillates

45. FDA drug monograph (Drug Products for the Control of Dandruff, Seborrheic Dermatitis, and Psoriasis for Over-the-Counter Human Use). Available from FDA weblink at [https://www.accessdata.fda.gov/drug-satfda\\_docs/omuf/OTC%20Monograph\\_M032-Drug%20Products%20for%20the%20Control%20of%20Dandruff%20Seborrheic%20Dermatitis%20and%20Psoriasis%2012.16.2021.pdf](https://www.accessdata.fda.gov/drug-satfda_docs/omuf/OTC%20Monograph_M032-Drug%20Products%20for%20the%20Control%20of%20Dandruff%20Seborrheic%20Dermatitis%20and%20Psoriasis%2012.16.2021.pdf). Accessed 19 Aug 2024.
46. LexiComp drug monograph (coal tar). Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2024 UptoDate, Inc. Available from: [https://ssouptodate.com/contents/coal-tar-drug-information?search=coal%20tar&source=search\\_result&selectedTitle=1%7E18&usage\\_type=panel&kp\\_tab=drug\\_general&display\\_rank=1](https://ssouptodate.com/contents/coal-tar-drug-information?search=coal%20tar&source=search_result&selectedTitle=1%7E18&usage_type=panel&kp_tab=drug_general&display_rank=1). Accessed 10 Aug 2024.
47. De Groot AC. Patch testing. 3rd edition. Vol. 3, Chapter 3.
48. De Groot AC. Patch testing, 4th Edition: Update 2018–2022. Wapserveen: Acdegroot Publishing, 2022 (37 pages). ISBN/EAN 978-90-813233-7-6.
49. Mosca M, Hong J, Haderl E, Brownstone N, Bhutani T, Liao W. Scalp psoriasis: a literature review of effective therapies and updated recommendations for practical management. *Dermatol Ther (Heidelb)* [Internet]. 2021;11(3):769–97. <https://doi.org/10.1007/s13555-021-00521-z>.
50. Fargnoli MC, De Simone C, Gisondi P, Pellacani G, Calzavara-Pinton P. Topical treatment for the management of mild-to-moderate psoriasis: a critical appraisal of the current literature. *Dermatol Ther (Heidelb)* [Internet]. 2023;13(11):2527–47. <https://doi.org/10.1007/s13555-023-01024-9>.



64. Bensal HP (salicylic acid) [prescribing information]. Easley: 7 Oaks Pharmaceuticals; 2010.
65. Butler DC, Heller MM, Murase JE. Safety of dermatologic medications in pregnancy and lactation: part II. Lactation. *J Am Acad Dermatol*. 2014;70(3):417.e1–e10; quiz 427.
66. FDA Drug Safety Communication. FDA warns of rare but serious hypersensitivity reactions with certain over-the-counter topical acne products, June 25, 2014. <http://www.fda.gov/Drugs/DrugSafety/ucm400923.htm>.
67. Menter A, Korman NJ, Elmets CA, et al. American Academy of Dermatology. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 3. Guidelines of care for the management and treatment of psoriasis with topical therapies. *J Am Acad Dermatol*. 2009;60(4):643–59.
68. Elmets CA, Korman NJ, Prater EF, Wong EB, Rupani RN, Kivelevitch D, Armstrong AW, Connor C, Cordoro KM, Davis DMR, Elewski BE, Gelfand JM, Gordon KB, Gottlieb AB, Kaplan DH, Kavanaugh A, Kiselica M, Kroshinsky D, Lebwohl M, Leonardi CL, Lichten J, Lim HW, Mehta NN, Paller AS, Parra SL, Pathy AL, Siegel M, Stoff B, Strober B, Wu JJ, Hariharan V, Menter A. Joint AAD-NPF Guidelines of care for the management and treatment of psoriasis with topical therapy and alternative medicine modalities for psoriasis severity measures. *J Am Acad Dermatol*. 2021;84(2):432–70. <https://doi.org/10.1016/j.jaad.2020.07.087>. Epub 2020 Jul 30. PMID: 32738429.



Enzo Berardesca

## Contents

|                                  |     |
|----------------------------------|-----|
| Introduction.....                | 595 |
| Anti-inflammatory Retinoids..... | 596 |
| Antineoplastic Retinoids.....    | 606 |
| References.....                  | 612 |

## Introduction

Retinoids may be classified into two different categories based on their pharmacologic actions and uses [1, 2, 3]. Retinoids with anti-inflammatory activities are used to modulate the inflammatory conditions acne, rosacea, and psoriasis. Retinoids with anti-neoplastic activities are used in the treatment of various neoplastic conditions.

Topical retinoids for inflammatory conditions include adapalene, tretinoin, and tazarotene,

Please refer to Chaps. 8, 9, 14, and 21 for discussions of other topical antineoplastic agents.

---

E. Berardesca (✉)

Dr. Phillip Frost Department of Dermatology and Cutaneous Surgery,  
Miller School of Medicine, University of Miami, Miami, FL, USA  
e-mail: [Berardesca@berardesca.it](mailto:Berardesca@berardesca.it)

---

© The Author(s), under exclusive license to Springer Nature  
Switzerland AG 2025

595

R. M. Law, H. I. Maibach (eds.), *Handbook of Topical Drug  
Treatment in Dermatology*,  
[https://doi.org/10.1007/978-3-031-93616-6\\_22](https://doi.org/10.1007/978-3-031-93616-6_22)

## Anti-inflammatory Retinoids

### Adapalene

#### Classification and Mode of Action

- Retinoic acid derivative. Adapalene is a retinoid-like substance that modulates cellular differentiation, keratinization, and inflammation. Adapalene is better than tretinoin or tazarotene in reducing inflammatory acne lesions and total lesion count and causes less irritation.

#### Indications and Dermatological Uses

- *Clinical indications (FDA):* acne vulgaris
- *Off-label common uses:* Rosacea (level of evidence: C)

#### Formulations/Presentation

- USA: 0.1% gel, 0.1% cream, 0.1% lotion, 0.1% pad, and 0.1% solution
- Canada: 0.1% cream and 0.1% gel
- Europe: 0.1% cream and 0.1% gel

#### Dosages and Suggested Regimens

- Apply once daily before bedtime.
- No suggested dosage adjustment for renal or hepatic impairment due to low systemic absorption.

#### Baseline Investigations and Considerations

##### Pharmacodynamics/Kinetics

- Minimal topical absorption, even after chronic use (trace amounts measured in serum). Elimination half-life between 7 and 51 hours (gel). Excreted in bile.
- Onset of effect: Between 8 and 12 weeks.

##### Use in Special Populations

- Approved for use in children. May cause mild hyperglycemia which is more common in children. Avoid internal use.



- Listed as FDA pregnancy classification C (former classification system).
- Unknown whether adapalene is present in breast milk.
- Renal insufficiency: Not evaluated; dose adjustment is not expected to be needed.
- Hepatic insufficiency: Not evaluated; dose adjustment is not expected to be needed.

### **Monitoring**

- Skin irritation/dryness
- Initial acne flare
- Severe skin reactions (exfoliation, desquamation)
- Allergy (angioedema, lip swelling, facial edema—reported postmarketing with gel)

### **Contraindications and Cautions**

- Accidental ingestion especially of large amounts of products containing propylene glycol may result in toxicity (metabolic acidosis/lactic acidosis, hyperosmolality, respiratory depression, seizures). Fatalities have been reported in neonates given large amounts of propylene glycol internally (po or IV).

### **Important Drug Interactions**

- Other topical medications which may cause skin irritation will potentially exacerbate the skin irritation (e.g., benzoyl peroxide, medicated soaps, and cleansers).
- Other topical medications (or cosmetics) containing alcohol, acetone, or astringents may exacerbate adapalene's drying effect.
- Adapalene may increase the levels/effects of aminolevulinic acid (topical or systemic). Avoid concomitant use.
- Levels/effects of adapalene may be increased by concomitant use of multivitamins with minerals (i.e., ADEK, folate, or iron).

### **Adverse Effects and Their Management**

- Skin irritation can occur. Less skin irritation than other retinoids, i.e., tretinoin. Erythema, stinging/burning, dryness, or

pruritus may occur especially during the initial 2–4 weeks of use. These may lessen with continued use.

- May cause initial exacerbation of acne.
- May cause increased sensitivity to UV rays. Use sunscreen and avoid sunlamp use.
- Hypersensitivity reactions including facial and eyelid edema and swelling have been reported. Use must be discontinued immediately as anaphylactoid/anaphylactic reactions may occur.

### **Patch Test Concentration**

- 0.1% and 0.01% pet.

### **Essential Patient Information**

- Avoid contact with broken, sunburned, eczematous, or abraded skin.
- Avoid contact with eyes, lips, or other mucous membranes (e.g., inside nose).
- Avoid using products including cosmetics which contain alpha hydroxyl or glycolic acid, as they may further irritate the skin.
- Do not ingest. For external use only.
- Use sun protection. Apply sunscreen with SPF 30 daily. If there is a sunburn, discontinue use until sunburn has healed.

## **Tretinoin**

### **Classification and Mode of Action**

- Retinoic acid derivative. Tretinoin is a retinoid-like substance that modulates cellular differentiation, keratinization, and inflammation. Improves stratum corneum turnover and dermal fibroblast differentiation. Tretinoin is more irritating than adapalene even though more effective in reducing the count of inflammatory lesions in acne. It is also used to improve keratinocyte turnover in the treatment of early signs of photoaging, thus improving skin texture and wrinkles.

## Indications and Dermatological Uses

- *Clinical indications (FDA)*: acne vulgaris, photoaging, wrinkles, and hyperpigmentation

## Formulations/Presentation

- USA: 0.01%–0.1% gel, 0.025%–0.05% cream, and 0.01% lotion
- Canada: 0.01%–0.1% cream and 0.01%–0.1% gel
- Europe: 0.05% cream, 0.025% gel, and 0.05% solution

## Dosages and Suggested Regimens

- Apply once daily before bedtime.
- No suggested dosage adjustment for renal or hepatic impairment due to low systemic absorption.

## Baseline Investigations and Considerations

### Pharmacodynamics/Kinetics

Onset of action: Acne:  $\geq 2$  weeks, may take  $\geq 7$  weeks. Facial wrinkles: Up to 6 months

Absorption: Minimal

Bioavailability: Avita cream and gel:  $<0.3\%$ ; Retin A Micro 0.1% gel:  $\sim 1\%$

Metabolism: Hepatic; forms metabolites

Excretion: Urine and feces

### Use in Special Populations

- Approved for use in children. Some dosage forms may contain propylene glycol; in neonates large amounts of propylene glycol delivered topically have been associated with potentially fatal toxicities which can include metabolic acidosis, seizures, renal failure, and CNS depression; toxicities have also been reported in children and adults including hyperosmolality, lactic acidosis, seizures, and respiratory depression; use caution (AAP 1997; Shehab 2009).
- Adverse events were observed in some animal reproduction studies following topical application of tretinoin. Teratogenic

effects were also observed in pregnant women following topical use; however, a causal association has not been established. When treatment for acne is needed during pregnancy, other agents are preferred (Chien 2016; Kong 2013; Leachman 2006). These products should not be used in women who are pregnant.

- Unknown whether tretinoin is present in breast milk.
- Renal insufficiency: Not evaluated; dose adjustment is not expected to be needed.
- Hepatic insufficiency: Not evaluated; dose adjustment is not expected to be needed.

### **Monitoring**

- Skin irritation/dryness
- Photosensitivity
- Severe skin reactions (exfoliation, desquamation)
- Allergy (angioedema, lip swelling, facial edema, reported postmarketing with gel)

### **Contraindications and Cautions**

- Accidental ingestion especially of large amounts of products containing propylene glycol may result in toxicity (metabolic acidosis/lactic acidosis, hyperosmolality, respiratory depression, seizures). Fatalities have been reported in neonates given large amounts of propylene glycol internally (po or IV).

### **Important Drug Interactions**

- Other topical medications which may cause skin irritation will potentially exacerbate the skin irritation (e.g., benzoyl peroxide, medicated soaps, and cleansers).
- Other topical medications (or cosmetics) containing alcohol, acetone, or astringents may exacerbate tretinoin's drying effect.
- Tretinoin may interact with aminolevulinic acid (topical or systemic). Avoid concomitant use.
- Levels/effects of tretinoin may be increased by concomitant use of multivitamins with minerals (i.e., ADEK, folate, or iron).

**Adverse Effects and Their Management**

- Skin irritation can occur.
- Erythema, stinging/burning, dryness, or pruritus may occur especially during the initial 2–4 weeks of use. These may lessen with continued use.
- May cause initial exacerbation of acne.
- May cause increased sensitivity to UV rays. Use sunscreen and avoid sunlamp use.
- Hypersensitivity reactions including facial and eyelid edema and swelling have been reported. Use must be discontinued immediately as anaphylactoid/anaphylactic reactions may occur.

**Patch Test Concentration**

- 0.005% alcohol; if higher (0.01% or 0.02%), perform adequate controls; petrolatum is not suitable for patch testing tretinoin.

**Essential Patient Information**

- Avoid contact with broken, sunburned, eczematous, or abraded skin.
- Avoid contact with eyes, lips, or other mucous membranes (e.g., inside the nose).
- Avoid using products including cosmetics which contain alpha hydroxyl or glycolic acid, as they may further irritate the skin
- Do not ingest. For external use only.
- Use sun protection. Apply sunscreen with SPF 30 daily. If there is a sunburn, discontinue use until sunburn has healed.

**Tazarotene****Classification and Mode of Action**

- Retinoic acid derivative. Tazarotene is a retinoid-like substance that modulates cellular differentiation, keratinization, and inflammation. Improves stratum corneum turnover and dermal fibroblast differentiation. Tazarotene is slightly irritating. It is used to improve keratinocyte turnover in the treatment of pso-

riasis and other disorders of keratinization. Like other retinoids can be used to treat early signs of photoaging and to improve white and black comedones.

### **Indications and Dermatological Uses**

- *Clinical indications (FDA)*: psoriasis, acne vulgaris, photoaging, wrinkles, and hyperpigmentation

### **Formulations/Presentation**

- USA: 0.05%–0.1% cream/gel
- Canada: 0.05%–0.1% cream/gel
- Europe: 0.05% gel and 0.1% gel

### **Dosages and Suggested Regimens**

- Apply once daily before bedtime.
- No suggested dosage adjustment for renal or hepatic impairment due to low systemic absorption.
- In patients experiencing excessive pruritus, burning, skin redness, or peeling, discontinue until integrity of the skin is restored, or reduce dosing to an interval the patient is able to tolerate.

### **Baseline Investigations and Considerations**

#### **Pharmacodynamics/Kinetics**

Onset of action: psoriasis: 1 week

Duration: therapeutic: psoriasis: Effects have been observed for up to 3 months after a 3-month course of topical treatment.

Absorption: Minimal following cutaneous application ( $\leq 6\%$  of dose).

Distribution: Retained in the skin for prolonged periods after topical application.

Protein binding:  $>99\%$  (tazarotenic acid).

Metabolism: Prodrug, rapidly metabolized via esterase hydrolysis to an active metabolite (tazarotenic acid) following topical application and systemic absorption; tazarotenic acid undergoes further hepatic metabolism.

Excretion: Urine and feces.

**Use in Special Populations**

- Approved for use in children. Some dosage forms may contain propylene glycol; in neonates large amounts of propylene glycol delivered topically have been associated with potentially fatal toxicities which can include metabolic acidosis, seizures, renal failure, and CNS depression; toxicities have also been reported in children and adults including hyperosmolality, lactic acidosis, seizures, and respiratory depression; use with caution (AAP 1997; Shehab 2009).
- Tazarotene products should not be used in women who are pregnant.
- Unknown whether tretinoin is present in breast milk.
- Renal insufficiency: Not evaluated; dose adjustment is not expected to be needed.
- Hepatic insufficiency: Not evaluated; dose adjustment is not expected to be needed.

**Monitoring**

- Skin irritation/dryness
- Photosensitivity
- Severe skin reactions (exfoliation, desquamation)
- Allergy (angioedema, lip swelling, facial edema)

**Contraindications and Cautions**

- Accidental ingestion especially of large amounts of products containing propylene glycol may result in toxicity (metabolic acidosis/lactic acidosis, hyperosmolality, respiratory depression, seizures). Fatalities have been reported in neonates given large amounts of propylene glycol internally (po or IV).

**Important Drug Interactions**

- Other topical medications which may cause skin irritation will potentially exacerbate the skin irritation (e.g., benzoyl peroxide, medicated soaps, and cleansers).
- Other topical medications (or cosmetics) containing alcohol, acetone, or astringents may exacerbate tretinoin's drying effect.

### **Adverse Effects and Their Management**

- Skin irritation can occur.
- Erythema, stinging/burning, dryness, or pruritus may occur especially during the initial 2–4 weeks of use. These may lessen with continued use.
- May cause initial exacerbation of acne.
- May cause increased sensitivity to UV rays. Use sunscreen and avoid sunlamp use.
- Hypersensitivity reactions including facial and eyelid edema and swelling have been reported. Use must be discontinued immediately as anaphylactoid/anaphylactic reactions may occur.

### **Essential Patient Information**

- Avoid contact with broken, sunburned, eczematous, or abraded skin.
- Avoid contact with eyes, lips, or other mucous membranes (e.g., inside nose).
- Avoid using products including cosmetics which contain alpha hydroxyl or glycolic acid, as they may further irritate the skin.
- Do not ingest. For external use only.
- Use sun protection. Apply sunscreen with SPF 30 daily. If there is a sunburn, discontinue use until sunburn has healed.

## **Trifarotene**

### **Classification and Mode of Action**

- Trifarotene is a new fourth-generation topical retinoid. Trifarotene is a strong and selective agonist of RAR- $\gamma$ , with lower activity on RAR- $\beta$  and RAR- $\alpha$  (16- and 65-fold, respectively), and has no activity on RXRs. Trifarotene exerts anti-inflammatory, comedolytic, and depigmenting actions.

### **Indications and Dermatological Uses**

- *Clinical indications (FDA):* acne of the face and the trunk



**Formulations/Presentation**

- USA: cream, 0.005%
- Canada: cream, 0.005%
- Europe: cream, 0.005%

**Dosages and Suggested Regimens**

- Apply once daily before bedtime.
- No suggested dosage adjustment for renal or hepatic impairment due to low systemic absorption.

**Pharmacodynamics/Kinetics**

- Protein binding: ~99.9%
- Metabolism: Primarily metabolized by CYP2C9, CYP3A4, and CYP2C8
- Half-life elimination: Terminal: 2 to 9 hours
- Excretion: Feces

**Use in Special Populations**

- Patients exposed to photosensitizing agents may have an increased risk of a phototoxic skin reaction. Despite these local adverse effects and photosensitization, trifarotene is safer than other retinoids due to its hepatic instability and degradation.
- Due to its RAR- $\gamma$  selectivity, it could be hypothesized that trifarotene is safer than other retinoids in pregnancy as the placenta presents a lower expression of RAR- $\gamma$  ( $4.739 \pm 0.399$ ), with consequent minor absorption of the drug compared to other topical retinoids
- Trifarotene may share the characteristic of teratogenicity with other retinoids, other agents may be preferred. Avoid applying large amounts over prolonged periods of time to decrease the potential for systemic absorption.
- It is not known if trifarotene is present in breast milk following topical application.
- According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother.

**Important Drug Interactions**

- Other topical medications which may cause skin irritation will potentially exacerbate the skin irritation (e.g., benzoyl peroxide, medicated soaps, and cleansers).
- Other topical medications (or cosmetics) containing alcohol, acetone, or astringents may exacerbate trifarotene's drying effect.

**Monitoring**

- Skin irritation/dryness
- Skin reactions (exfoliation, desquamation)

**Essential Patient Information**

- Patients using trifarotene cream may experience erythema, scaling, dryness, and stinging/burning. Use a moisturizer from the initiation of treatment, and, if appropriate, depending upon the severity of these adverse reactions, reduce the frequency of application of trifarotene cream, suspend, or discontinue use. Avoid application of trifarotene cream to cuts, abrasions, or eczematous or sunburned skin. Use of "waxing" as a depilatory method should be avoided on skin treated with trifarotene cream. Minimize exposure to sunlight and sunlamps. Use sunscreen and protective clothing over treated areas when exposure cannot be avoided.

---

**Antineoplastic Retinoids****Alitretinoin****Classification and Mode of Action**

- Retinoic acid derivative. It is used as antineoplastic (topical) and anti-inflammatory (oral) agent. Alitretinoin is a naturally occurring endogenous retinoid that binds to and activates intracellular retinoid receptors (RAR and RXR subtypes); this results in altered expression of the genes controlling cellular differentiation and proliferation in normal and neoplastic cells, inhibiting the growth of Kaposi sarcoma.

**Indications and Dermatological Uses**

- *Clinical indications:* Topical: Kaposi sarcoma, pyogenic granuloma. Oral: chronic hand dermatitis

**Formulations/Presentation**

- USA: 0.1% cream/gel (topical)
- Canada:
- Europe: Tablets 10 mg and 30 mg (Oral)

**Dosages and Suggested Regimens**

- Topical: Apply several times a day on the skin affected.
- Oral: 10 mg to 30 mg once a day
- No suggested dosage adjustment for renal or hepatic impairment due to low systemic absorption.

**Baseline Investigations and Considerations****Pharmacodynamics/Kinetics**

Onset of action: Oral: 2 weeks

Duration: Therapeutic: Hand dermatitis 12 to 24 weeks

Absorption: Minimal following cutaneous application

Distribution: Retained in skin for prolonged periods after topical application

Excretion: Urine and feces

**Use in Special Populations: Pregnancy (FDA Guidance), Lactation, Children, Renal Insufficiency, and Hepatic Insufficiency**

- Alitretinoin should not be used in women who are pregnant.
- Unknown whether alitretinoin is present in breast milk.
- Renal insufficiency: Not evaluated; dose adjustment is not expected to be needed.
- Hepatic insufficiency: Not evaluated; dose adjustment is not expected to be needed.

**Monitoring**

- Skin irritation
- Dermal irritation

- Photosensitivity
- Severe skin reactions (exfoliation, desquamation)
- Allergy (angioedema, lip swelling, facial edema)

### **Contraindications and Cautions**

Products containing DEET: Do not use concurrently with topical products containing DEET (e.g., insect repellent); an increase in DEET toxicity has been observed.

### **Important Drug Interactions**

Aminolevulinic acid (systemic): Photosensitizing agents may enhance the photosensitizing effect of aminolevulinic acid (systemic). Risk X: Avoid combination.

Aminolevulinic acid (topical): Photosensitizing agents may enhance the photosensitizing effect of aminolevulinic acid (topical). Risk C: Monitor therapy.

Multivitamins/fluoride (with ADE): May enhance the adverse/toxic effect of retinoic acid derivatives. Risk X: Avoid combination.

Multivitamins/minerals (with ADEK, folate, iron): May enhance the adverse/toxic effect of retinoic acid derivatives. Risk X: Avoid combination.

Multivitamins/minerals (with AE, no iron): May enhance the adverse/toxic effect of retinoic acid derivatives. Risk X: Avoid combination.

Porfimer: Photosensitizing agents may enhance the photosensitizing effect of Porfimer. Risk C: Monitor therapy.

Verteoporphin: Photosensitizing agents may enhance the photosensitizing effect of verteoporphin. Risk C: Monitor therapy.

### **Adverse Effects and Their Management**

- Skin irritation can occur.
- Erythema, stinging/burning, dryness, or pruritus may occur especially during the initial 2–4 weeks of use. These may lessen with continued use.
- May cause initial exacerbation of acne.
- May cause increased sensitivity to UV rays. Use sunscreen and avoid sunlamp use.

- Hypersensitivity reactions including facial and eyelid edema and swelling have been reported. Use must be discontinued immediately as anaphylactoid/anaphylactic reactions may occur.

### **Essential Patient Information**

- Avoid contact with broken, sunburned, eczematous, or abraded skin.
- Avoid contact with eyes, lips, or other mucous membranes (e.g., inside nose).
- Avoid using products including cosmetics which contain alpha hydroxyl or glycolic acid, as they may further irritate the skin.
- Use sun protection. Apply sunscreen with SPF 30 daily. If there is a sunburn, discontinue use until sunburn has healed.

## **Bexarotene**

### **Classification and Mode of Action**

Bexarotene binds to and activates retinoid X receptor subtypes. Once activated, these receptors function as transcription factors that regulate the expression of genes which control cellular differentiation and proliferation, resulting in decreased cell proliferation, apoptosis of some cancer cell types, and tumor regression.

- *Clinical indications:* Topical or oral: cutaneous T-cell lymphoma

### **Formulations/Presentation**

- USA: 1% cream/gel (topical)
- Canada
- Europe: tablets 75 mg (oral)

### **Dosages and Suggested Regimens**

- Topical: Apply to lesions once every other day for the first week, and then increase on a weekly basis to once daily, two times daily, three times daily, and finally four times daily, according to individual lesion tolerance.

- Oral: 300 mg/sq meter/day.
- No suggested dosage adjustment for renal or hepatic impairment due to low systemic absorption.

## **Baseline Investigations and Considerations**

### **Pharmacodynamics/Kinetics**

Onset: Response may be seen at 4 weeks, although longer application may be required for response (range: up to 56 weeks).

Absorption: Systemically absorbed following topical application (1% gel: generally less than 5 ng/mL and did not exceed 55 ng/mL).

Protein binding: >99% to plasma proteins.

Metabolism: Oral bexarotene metabolism is primarily hepatic via CYP450 3A4 to form oxidative metabolites, which may then be glucuronidated.

### **Use in Special Populations: Pregnancy (FDA Guidance), Lactation, Children, Renal Insufficiency, and Hepatic Insufficiency**

- Bexarotene is contraindicated in women who are pregnant.
- Unknown whether bexarotene is present in breast milk.
- Due to the potential for serious adverse reactions in a breast-feeding infant, a decision should be made to discontinue bexarotene gel or to discontinue breastfeeding during therapy, considering the importance of treatment to the mother.
- Renal insufficiency: Not evaluated; dose adjustment is not expected to be needed.
- Hepatic insufficiency: Not evaluated; dose adjustment is not expected to be needed.

### **Monitoring**

- In females of reproductive potential, obtain a pregnancy test 1 week before initiation and then monthly while on bexarotene; monitor for signs/symptoms of hypersensitivity.
- Skin irritation.
- Dermal irritation.
- Photosensitivity.

- Severe skin reactions (exfoliation, desquamation).
- Allergy (angioedema, lip swelling, facial edema).

### **Contraindications and Cautions**

Products containing DEET: Do not use concurrently with topical products containing DEET (e.g., insect repellent); an increase in DEET toxicity has been observed.

### **Important Drug Interactions**

Aminolevulinic acid (systemic): Photosensitizing agents may enhance the photosensitizing effect of aminolevulinic acid (systemic). Risk X: Avoid combination.

Aminolevulinic acid (topical): Photosensitizing agents may enhance the photosensitizing effect of aminolevulinic acid (topical). Risk C: Monitor therapy.

Multivitamins/fluoride (with ADE): May enhance the adverse/toxic effect of retinoic acid derivatives. Risk X: Avoid combination.

Multivitamins/minerals (with ADEK, folate, iron): May enhance the adverse/toxic effect of retinoic acid derivatives. Risk X: Avoid combination.

Multivitamins/minerals (with AE, no iron): May enhance the adverse/toxic effect of retinoic acid derivatives. Risk X: Avoid combination.

Porfimer: Photosensitizing agents may enhance the photosensitizing effect of Porfimer. Risk C: Monitor therapy.

Verteporfin: Photosensitizing agents may enhance the photosensitizing effect of verteporfin. Risk C: Monitor therapy.

### **Adverse Effects and Their Management**

- Skin irritation can occur.
- Erythema, stinging/burning, dryness, or pruritus may occur especially during the initial 2–4 weeks of use. These may lessen with continued use.
- May cause initial exacerbation of acne.
- May cause increased sensitivity to UV rays. Use sunscreen and avoid sunlamp use.

- Hypersensitivity reactions including facial and eyelid edema and swelling have been reported. Use must be discontinued immediately as anaphylactoid/anaphylactic reactions may occur.

### **Essential Patient Information**

- Burning
- Itching
- Redness
- Peeling
- Loss of strength and energy
- Sweating a lot
- Headache
- Infection
- Burning or numbness feeling
- Swelling
- Swollen glands
- Severe skin irritation

---

### **References**

1. FDA drug monographs for each of the drugs. Available from Accessdata.fda.gov
2. Lexicomp drug monographs for each of the drugs. Available from: LexiComp/lexidrug Online at [online.Lexi.com](https://online.lexi.com). Copyright 2024 UptoDate, Inc.
3. De Groot AC. Patch testing. 3rd edition. Volume 3 Chapter 3

### **Anti-inflammatory Retinoids**

4. Brogden R, Goa K. Adapalene: a review of its pharmacological properties and clinical potential in the management of mild to moderate acne. *Drugs*. 1997;53(3):511–9.
5. Altinyazar HC, Koca R, Tekin NS, et al. Adapalene vs metronidazole gel for the treatment of rosacea. *Int J Dermatol*. 2005;44(3):252–5.



6. Autret E, Berjot M, Jonville-Bera AP, et al. Anophthalmia and agenesis of optic chiasma associated with adapalene gel in early pregnancy. *Lancet*. 1997;350(9074):339.
7. Shehab N, Lewis CL, Streetman DD, et al. Exposure to the pharmaceutical excipients benzoyl alcohol and propylene glycol among critically ill neonates. *Pediatr Crit Care Med*. 2009;10(2):256–9.
8. Kong YL, Tey HL. Treatment of acne vulgaris during pregnancy and lactation. *Drugs*. 2013;73(8):779–87.
9. Eichenfield LF, Krakowski AC, Piggott C et al. Evidence-based recommendations for the diagnosis and treatment of pediatric acne. *Pediatrics* 2013 (131 Suppl 3):S163–86.
10. Asai Y, Baibergenova A, Dutil M, et al. Management of acne: Canadian clinical practice guideline. *CMAJ*. 2016.
11. Maguiness S. Acne. 5-minute video available from the Society for Pediatric Dermatology Website at <https://tinyurl.com/saa9t4s>

## Tretinoin

12. Shehab N, Lewis CL, Streetman DD, Donn SM. Exposure to the pharmaceutical excipients benzyl alcohol and propylene glycol among critically ill neonates. *Pediatr Crit Care Med*. 2009;10(2):256–9.
13. Chien AL, Qi J, Rainer B, Sachs DL, Helfrich YR. Treatment of acne in pregnancy. *J Am Board Fam Med*. 2016;29(2):254–62.
14. Kong YL, Tey HL. Treatment of acne vulgaris during pregnancy and lactation. *Drugs*. 2013;73(8):779–87. <https://doi.org/10.1007/s40265-013-0060-0>.
15. Leachman SA, Reed BR. The use of dermatologic drugs in pregnancy and lactation. *Dermatol Clin*. 2006;24(2):167–97.
16. Vitamin A Acid (tretinoin) [product monograph]. Laval, Quebec, Canada: Bausch Health, Canada Inc; September 2020.

## Tazarotene

17. Arazlo (tazarotene) [prescribing information]. Bridgewater: Bausch Health US. LLC; December 2019.
18. Avage (tazarotene) [prescribing information]. Irvine: Allergan, Inc; July 2017.
19. Bae YS, Van Voorhees AS, Hsu S, et al; National Psoriasis Foundation. Review of treatment options for psoriasis in pregnant or lactating women:

- from the Medical Board of the National Psoriasis Foundation. *J Am Acad Dermatol.* 2012;67(3):459–77. <https://doi.org/10.1016/j.jaad.2011.07.039>.
20. Butler DC, Heller MM, Murase JE. Safety of dermatologic medications in pregnancy and lactation: Part II. Lactation. *J Am Acad Dermatol.* 2014;70(3):417.e1–10; quiz 427. <https://doi.org/10.1016/j.jaad.2013.09.009>.
21. Centers for Disease Control (CDC). Neonatal deaths associated with use of benzyl alcohol—United States. *MMWR Morb Mortal Wkly Rep.* 1982;31(22):290–1. <http://www.cdc.gov/mmwr/preview/mmwrhtml/00001109.htm>.
22. Chien AL, Qi J, Rainer B, Sachs DL, Helfrich YR. Treatment of acne in pregnancy. *J Am Board Fam Med.* 2016;29(2):254–62. <https://doi.org/10.3122/jabfm.2016.02.150165>.

## Trifarotene

23. Akliel (trifarotene) [prescribing information]. Fort Worth: Galderma Laboratories LP; January 2022.
24. Akliel (trifarotene) [product monograph]. Fort Worth: Galderma Laboratories LP; November 2019.
25. American Academy of Pediatrics Committee on Drugs. “Inactive” ingredients in pharmaceutical products: update (subject review). *Pediatrics.* 1997;99(2):268–78.
26. Kong YL, Tey HL. Treatment of acne vulgaris during pregnancy and lactation. *Drugs.* 2013;73(8):779–87. <https://doi.org/10.1007/s40265-013-0060-0>.
27. Naik PP. Trifarotene: a novel therapeutic option for acne. *Dermatol Res Pract* 2022; 2022:1504303. <https://doi.org/10.1155/2022/1504303>.
28. Shehab N, Lewis CL, Streetman DD, Donn SM. Exposure to the pharmaceutical excipients benzyl alcohol and propylene glycol among critically ill neonates. *Pediatr Crit Care Med.* 2009;10(2):256–9.
29. Tan J, Thiboutot D, Popp G, et al. Randomized phase 3 evaluation of trifarotene 50 µg/g cream treatment of moderate facial and truncal acne. *J Am Acad Dermatol.* 2019;80(6):1691–9. <https://doi.org/10.1016/j.jaad.2019.02.044>.

## Antineoplastic Retinoids

30. Panretin (alitretinoin) [prescribing information]. Concordia Pharmaceuticals; May 2020.

31. Walmsley S, Northfelt DW, Melosky B, Conant M, Friedman-Kien AE, Wagner B. Treatment of AIDS-related cutaneous Kaposi's sarcoma with topical alitretinoin (9-cis-retinoic acid) gel. Panretin Gel North American Study Group. *J Acquir Immune Defic Syndr*. 1999;22(3):235–46.

## Bexarotene

32. Breneman D, Duvic M, Kuzel T, Yocum R, Truglia J, Stevens VJ. Phase 1 and 2 trial of bexarotene gel for skin-directed treatment of patients with cutaneous T-cell lymphoma [published correction appears in *Arch Dermatol*. 2002;138(10):1386]. *Arch Dermatol*. 2002;138(3):325–32. <https://doi.org/10.1001/archderm.138.3.325>
33. Heald P, Mehlmauer M, Martin AG, Crowley CA, Yocum RC, Reich SD; Worldwide Bexarotene Study Group. Topical bexarotene therapy for patients with refractory or persistent early-stage cutaneous T-cell lymphoma: results of the phase III clinical trial. *J Am Acad Dermatol*. 2003;49(5):801–15. [https://doi.org/10.1016/s0190-9622\(03\)01475-0](https://doi.org/10.1016/s0190-9622(03)01475-0)
34. Targretin (bexarotene) [prescribing information]. Bridgewater, NJ: Valeant; October 2016.



Aileen Feschuk and Nadia Kashetsky

## Contents

|                                                      |     |
|------------------------------------------------------|-----|
| Introduction.....                                    | 618 |
| Betamethasone Valerate Foam.....                     | 619 |
| Coal Tar Shampoo.....                                | 619 |
| Fluocinolone Acetonide.....                          | 624 |
| Ketoconazole Gel, Cream, Kit, Foam, and Shampoo..... | 624 |
| Selenium Sulfide Shampoo.....                        | 630 |
| Zinc Pyrithione Shampoo.....                         | 633 |
| References.....                                      | 636 |

---

A. Feschuk (✉)

Faculty of Medicine, Memorial University of Newfoundland,  
St. John's, NL, Canada  
e-mail: [afeschuk@mun.ca](mailto:afeschuk@mun.ca)

N. Kashetsky

Department of Dermatology and Skin Science, Faculty of Medicine,  
University of British Columbia, Vancouver, BC, Canada  
e-mail: [nkashetsky@mun.ca](mailto:nkashetsky@mun.ca)

## Introduction

Seborrheic dermatitis, a common condition, affects the seborrheic areas of the body and causes, scaling, flaking, inflammation, pruritus, and erythema [1, 2]. Sebaceous glands are present all over the body sparing only the palms and soles [1] and are particularly dense on the scalp, face, and body folds [2]. The central third of the face, central forehead, eyebrows, postauricular area, and the external ear canal are particularly vulnerable to this condition [2].

Dandruff, a form of seborrheic dermatitis, involves itchy, flaky skin, but unlike seborrheic dermatitis, it is restricted to the scalp [1]. Both seborrheic dermatitis and dandruff are characterized by an inflammatory genomic signature [3].

Seborrheic dermatitis affects about 5% of the population worldwide; however, almost 50% of the population are affected by dandruff [2]. Furthermore, seborrheic dermatitis has a bimodal age distribution, most commonly affecting infants and adults [2]. Infants commonly present with seborrheic dermatitis around the scalp, or “cradle cap” [1]. This usually occurs during the first three months of life, is mild, and self-limiting [2]. Unfortunately, in adults, seborrheic dermatitis is chronic, relapsing and remitting [2].

The main hypothesis regarding the pathophysiology of seborrheic dermatitis includes the interplay of individual susceptibility, the yeast *Malassezia* spp., and inflammatory processes [1, 2]. Therefore, the most common treatments for seborrheic dermatitis include anti-fungals and/or anti-inflammatories [1]. It is important these patients receive treatment, as seborrheic dermatitis can have emotional symptoms (e.g., embarrassment) as well as a negative effect on overall quality of life (e.g., pruritis) [4].

## Betamethasone Valerate Foam

Betamethasone valerate foams contains betamethasone valerate—a synthetic topical corticosteroid, which has anti-inflammatory, antipruritic and vasoconstrictive actions.

It is indicated as treatment for inflammatory and pruritic manifestations of dermatoses of the scalp (including seborrheic dermatitis) that are corticosteroid responsive. For further details, see Chap. 18.

---

## Coal Tar Shampoo

### Classification and Mode of Action

- Coal tar shampoos are classified as dandruff, seborrheic dermatitis, and psoriasis controlling agents. Coal tar's mode of action is related to its keratoplastic and mild local irritant properties. Although the exact mechanism is currently unknown, it is thought that coal tar abstracts oxygen from the skin which in turn inhibits mitosis causing a decrease in the number of stratum germinativum and stratum corneum cells.
- In addition, coal tar is thought to possibly remove the scales produced by the abovementioned skin disorders.
- Coal tar possibly reacts with epidermal sulfhydryl groups, affecting the skin in a similar way to when it is exposed to sunlight, which theoretically decreases epidermal mitosis and dermal infiltration.
- Coal tar is thought to have weak antiseptic and antipruritic effects. Additionally, coal tar is thought to be a vasoconstrictor and astringent. Specific coal tar shampoos have not been evaluated by the FDA. However, the active ingredient, coal tar, has been approved by the FDA for over-the-counter use in the treatment of seborrheic dermatitis.

## Indications and Dermatological Uses

- *Clinical indications:* Coal tar shampoos have not been approved by the FDA but are informally indicated for the temporary relief of symptoms associated with dandruff, psoriasis, and seborrheic dermatitis including itching, flaking, scaling, redness, and irritation of the scalp.
- *Off-label common uses:* Common off-label uses of coal tar and its preparations include for the treatment of eczema, atopic dermatitis, chronic exudative, or lichenoid dermatitis and used in conjunction with ultraviolet therapy (UVA) for psoriasis (Goeckerman therapy).

## Formulations/Presentation (Table 23.1)

According to the CPS, coal tar is also available in Canada as an emulsion, gel, liquid, ointment, and shampoo. Specifically, the shampoo is available in various concentrations between 0.05 and 10%.

**Table 23.1** Coal tar shampoos available in the United States according to Lexicomp

| Strengths (equivalent to coal tar)                                                                                       | Brand names                             | Manufacturer         |
|--------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|----------------------|
| <i>Coal tar (crude coal tar; pix carbonis)</i>                                                                           |                                         |                      |
| Equivalent to coal tar 0.5%                                                                                              | DHS <sup>®</sup> Tar                    | Person an Covey      |
| equivalent to coal tar 2%                                                                                                | Ionil T <sup>®</sup> Plus               | Healthpoint          |
| <i>Coal tar combinations</i>                                                                                             |                                         |                      |
| Equivalent to coal tar 0.5% (4.5% Polytar <sup>®</sup> consisting of a solution of crude coal tar and coal tar solution) | Polytar <sup>®</sup> Shampoo            | Stiefel              |
| 0.5% with salicylic acid 2% and sublimed sulfur 2%                                                                       | Sebutone <sup>®</sup> (cream or lotion) | Bristol-Myers Squibb |
| <i>Coal tar distillate</i>                                                                                               |                                         |                      |
| 3% (equivalent to coal tar 1.2%)                                                                                         | Doak <sup>®</sup> Tar                   | Doak                 |

(continued)

**Table 23.1** (continued)

| Strengths (equivalent to coal tar)                                                  | Brand names                                                                     | Manufacturer |
|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|--------------|
| <i>Coal tar extract</i>                                                             |                                                                                 |              |
| 2% (equivalent to coal tar 0.5%)                                                    | Neutrogena® T/Gel® (with Neutar®, a solubilized coal tar extract)               | Neutrogena   |
| 4% (equivalent to coal tar 1%)                                                      | Neutrogena® T/Gel Extra Strength (with Neutar®, a solubilized coal tar extract) | Neutrogena   |
| <i>Coal tar topical solution (liquid carbonis detergens, liquor picis carbonis)</i> |                                                                                 |              |
| 5% (equivalent to coal tar 1%)                                                      | Ionil T® (with SD alcohol 40 12% and isopropyl alcohol 4%)                      | Healthpoint  |
| 10% (equivalent to coal tar 2%)                                                     | X-Seb® T Plus                                                                   | Teva         |
| 15% (equivalent to coal tar 3%)                                                     | MG 217® Medicated Tar Extra Strength with Conditioners                          | Triton       |
| <i>Coal tar solution combinations</i>                                               |                                                                                 |              |
| 10% (equivalent to coal tar 2%) with salicylic acid 2%                              | Tarsum®                                                                         | Summers      |

## Dosages and Suggested Regimens

- The exact dosages and suggested regimens for using a coal tar shampoo vary depending on the specific preparation and strength used. However, it is generally suggested that the coal tar shampoo is applied thoroughly to wet hair and massaged into the scalp. The shampoo should be left on the hair and scalp to lather for several minutes before rinsing.
- For best results, car tar shampoos should be used at least twice weekly.

## Pharmacokinetics

- No data available.



## Use in Special Populations

- No data available.

*Monitoring:* No data available

## Contraindications and Cautions

- Coal tar shampoos are for external use only and are contraindicated in those with a history of hypersensitivity to it, and should not be applied to acutely damaged, inflamed, or infected skin.
- The use of a coal tar shampoo should be discontinued if the condition worsens or does not improve after using this product as directed.
- Coal tar shampoos should be kept out of reach of children, and if swallowed, one should seek medical attention or contact a poison control center immediately.
- This product should also be kept away from the eyes, and if the eyes are affected, they should be rinsed thoroughly with water.

## Important Drug Interactions

- Coal tar has no known drug interactions. However, it is recommended that coal tar is not used with other phototoxic/photoactive agents.

## Adverse Effects and Their Management

- Coal tar may produce dermatitis which may be allergic or irritant in nature. In hypersensitive patients, coal tar may cause a pustular eruption/keratocystic response.
- Additionally, prolonged use of coal tar may result in chronic folliculitis, also called tar acne. This is generally painless and clears following discontinuance or reduction in application frequency.

- Coal tar preparations may also stain hair and clothing.
- Coal tar preparation use results in photosensitivity and therefore exposure to sunlight should be avoided.

NOTE: Coal tar contains chemicals (PAH dibenzo[a,h]anthracene and benzo[a]pyrene (B[a]P) recognized by the State of California to cause cancer (California Proposition 65 Warning), and is classified as a Group 1 carcinogen by the International Agency for Research on Cancer. Animal and occupational studies have shown a clear increased risk of cancer following exposure to coal tar. There are case reports attributing skin cancer to the use of coal tar, most of which occurred in the anogenital region. Therefore, it is recommended to avoid using coal tar in the genital, groin, or rectal area. However, studies on patients treated with coal tar for dermatological conditions such as dandruff have not shown an increased risk of skin cancer. Shampoos have very limited contact time with the skin before they are rinsed off and are therefore generally considered safe. However, other preparations of coal tar that are to be left on the skin for prolonged periods should be used with caution. The combined risk of the carcinogenicity of coal tar in addition to the increased risk of UV damage due to its photoactivating potential has yet to be determined.

### **Patch Test Concentration**

- 5% pet. (Chemotechnique, SmartPracticeeurope, SmartPracticeCanada)

### **Essential Patient Information**

- Contact with the eyes should be avoided. If contact with the eyes does occur, they should be rinsed thoroughly with water.
- Use caution when in the sun, as coal tar shampoos may cause an increased vulnerability to sunburns for up to 24 hours following use.

- Do not use this product with other psoriasis therapies, including ultraviolet radiation or prescription medications unless directed by a physician. Do not use this product for prolonged periods of time unless directed by a physician.
- Although rare, temporary discoloration of bleached, tinted, blonde, or grey hair may occur.

---

## Fluocinolone Acetonide

### Classification and Mode of Action

- Fluocinolone acetonide (6 $\alpha$ ,9-Difluoro-11 $\beta$ ,16 $\alpha$ , 17,21- tetrahydroxypregna-1,4-diene-3, 20-dione cyclic 16,17-acetal with acetone) comes as both a scalp oil and a shampoo, sold under the name Capex. It is indicated for seborrheic dermatitis but has not been proven effective in other corticosteroid-responsive dermatoses.
- For further details see Chap. 18.

## Ketoconazole Gel, Cream, Kit, Foam, and Shampoo

Note: Ketoconazole is also discussed in Chap. 13. Please see the discussion in that chapter for additional information about ketoconazole.

### Classification and Mode of Action

- Ketoconazole (( $\pm$ )-cis-1-acetyl-4-[p-[[2-(2,4-dichlorophenyl)-2-(1Himidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine) is commonly used as a topical antifungal agent. The proposed mode of action of ketoconazole is the reduction of a yeast—*Malassezia furfur* (also known as *Pityrosporum ovale*)—by inhibiting the synthesis of ergosterol (a key sterol

in the membrane of *M. furfur*/*P. ovale*) resulting in the death of the yeast. Note that this mode of action has yet to be proven.

- In vehicle-controlled studies, 25.3% of those using Xolegel gel (ketoconazole USP at 2% in a topical anhydrous gel vehicle) were considered to have been effectively treated, whereas only 13.9% of those using vehicle gel were considered to have been effectively treated. Effective treatment in this case was defined based on Investigator's Global Assessment Score of  $\leq 1$  (completely or almost completely clear), and an Erythema and Scaling score of 0 (none) or 1 (mild) if baseline scores were 2 or 3, respectively.

## Indications and Dermatological Uses

- *Clinical indications (FDA)*: Ketoconazole creams are indicated for the treatment of tinea corporis, tinea cruris, tinea pedis, tinea versicolor, cutaneous candidiasis, and seborrheic dermatitis. Foams and gels are indicated for the treatment of seborrheic dermatitis in immunocompetent individuals over 12. According to US labelling, ketoconazole shampoos are indicated for the treatment of tinea versicolor caused by *P. orbiculare* (*M. furfur* or *Malassezia orbiculare*). According to Canadian labelling, ketoconazole shampoos are indicated for prophylaxis and treatment of dandruff and seborrheic dermatitis.
- *Off-label common uses*: There is a level of evidence C for the use of ketoconazole in tinea manuum.

## Formulations/Presentation (Table 23.2)

**Table 23.2** Ketoconazole gel, foam, and shampoo available in the United States and Canada according to Lexicomp

| Strength                                                                                                                | Brand       |
|-------------------------------------------------------------------------------------------------------------------------|-------------|
| <i>Dosage forms: United States</i>                                                                                      |             |
| <i>Cream, external</i>                                                                                                  |             |
| 2% (15 g, 30 g, 60 g)                                                                                                   | Generic     |
| <i>Foam, external</i>                                                                                                   |             |
| 2% (50 g (DSC), 100 g (DSC)) (contains alcohol, usp, cetyl alcohol, propylene glycol)                                   | Extina      |
| 2% (50 g, 100 g) (cfc free; contains alcohol, usp, cetyl alcohol, propylene glycol)                                     | Extina      |
| 2% (100 g) (contains alcohol, usp, cetyl alcohol, propylene glycol)                                                     | Ketodan     |
| 2% (50 g, 100 g)                                                                                                        | Generic     |
| <i>Gel, external</i>                                                                                                    |             |
| 2% (45 g) *contains alcohol, usp, fd&c yellow #10 (quinoline yellow), fd&c yellow #6 (sunset yellow), propylene glycol) | Xolegel     |
| <i>Kit, external</i>                                                                                                    |             |
| 2% (contains cetyl alcohol, edetate (edta) disodium, propylene glycol)                                                  | Ketodan     |
| <i>Shampoo, external</i>                                                                                                |             |
| 2% (120 mL (DSC)) [contains fd&c red #40]                                                                               | Nizoral     |
| 1% (125 mL, 200 mL (DSC))                                                                                               | Nizoral A-D |
| 1% (125 mL (DSC), 200 mL (DSC)) (contains brilliant blue fcf (fd&c blue #1), edetate (edta) sodium (tetrasodium))       | Nizoral A-D |
| 2% (120 mL)                                                                                                             | Generic     |
| <i>Dosage forms: Canada</i>                                                                                             |             |
| <i>Cream, external</i>                                                                                                  |             |
| 2% (30 g) (contains cetyl alcohol, polysorbate 80, propylene glycol)                                                    | Ketoderm    |

## Dosages and Suggested Regimens

- For seborrheic dermatitis, creams and foams should be applied to the affected area twice a day for 4 weeks. Gels should be applied once daily for 2 weeks. Two percent shampoos (products only in Canada) should be used twice daily for 2–4 weeks by lathering 5–10 mL into wet hair, leaving for 3–5 minutes and rinsing.
- For dandruff, 1% shampoo can be applied to wet hair, lathered and rinsed every 3–4 days for up to 8 weeks. Two percent shampoo can be used prophylactically once every 1–2 weeks, or as a treatment twice a week for 2–4 weeks.

## Pharmacokinetics

- In a pharmacokinetic absorption study of Xolegel gel (ketoconazole USP at 2% in a topical anhydrous gel vehicle), 18 individuals (both male and female) with between 1 and 14% of body surface area affected by seborrheic dermatitis used Xolegel gel once daily for 14 days. Daily doses ranged from 0.05 to 3.47 g, giving a median total amount of 4.6 g of gel applied over the 2 weeks. The mean  $\pm$  standard deviation of peak plasma levels was  $1.35 \pm 3.18$  ng/mL on day 7 and was  $0.80 \pm 1.22$  ng/mL on day 14. The median time taken to reach maximum concentration ( $T_{max}$ ) was 8 hrs on day 7 and 7 hrs on day 14. The mean  $\pm$  standard deviation area under the plasma concentration time curve over the last 24-hour dosing interval ( $AUC_{0-24}$ ) were  $20.8 \pm 44.7$  (ng)(hr)/mL on day 7 and  $15.6 \pm 26.4$  (ng)(hr)/mL on day 14.

## Use in Special Populations

- Chronic use of ketoconazole shampoo does not result in detectable plasma levels, and Vestergaard (2019) showed that topical ketoconazole is safe for the treatment of atopic dermatitis in pregnant individuals.

- When used orally, ketoconazole has been detected in the breast-milk. However, when ketoconazole is used as a gel, it has a plasma concentration less than 250 times that of when it is given orally. Therefore, it is suggested that breastfeeding individuals weigh the risk to the fetus and the benefit of treatment. The nipple, area surrounding the nipple, and direct contact with the child should all be avoided in breastfeeding individuals.
- Of 933 subjects who have participated in safety and efficacy studies of Xolegel gel (ketoconazole USP at 2% in a topical anhydrous gel vehicle), 20.7% were 65 and older, and 6.5% were 75 and older. Differences in safety of effectiveness of Xolegel in those patient populations were not found.

*Monitoring:* No data available

## **Contraindications and Cautions**

- Hypersensitivity reactions have been reported (contact sensitization, photoallergenicity, and rarely, anaphylaxis). Discontinue use if hypersensitivity or irritation occurs.
- Refer to Chap. 13 for additional contraindications and cautions.

## **Important Drug Interactions**

- There are no known significant drug interactions.

## **Adverse Effects and Their Management**

- Adverse effects that affect 1–10% include dermatological reactions such as application site pruritus, skin stinging, and xeroderma and local reactions such as application site reactions, local irritation, and application site burning.
- The following adverse reactions have been reported in less than 1% of users and are listed alphabetically directly from the

Lexicomp drug monograph: “abnormal texture of hair, acne vulgaris, alopecia, anaphylaxis, angioedema, application site dermatitis, application site discharge, application site erythema, application site pain, cheilitis, contact dermatitis, dizziness, dry eye syndrome, eye irritation, facial swelling, hair discoloration, headache, hypersensitivity reaction, impetigo, localized warm feeling, nail discoloration, paresthesia, pustules, pyogenic granuloma, skin irritation, skin rash, swelling of eye, and urticaria.”

- Although the adverse reaction rates observed in clinical trials may not reflect rates observed in clinical practice, they do provide a basis for identifying adverse effects that appear to be related to the use of a treatment. In safety and efficacy studies of Xolegel gel (ketoconazole USP at 2% in a topical anhydrous gel vehicle) to date, 65/933, or 7%, of users experienced at least one treatment-related adverse effect, the most common being application site burning. Other treatment-related adverse reactions occurring at the application site included dermatitis, dryness, irritation, discharge, erythema, pustules, pain, and pruritus. Treatment-related adverse effects which did not occur at the application site included eye irritation and swelling, keratoconjunctivitis, impetigo, granuloma, sicca, pyogenic, headache, dizziness, paresthesia, acne, facial swelling, and nail discoloration.
- Although long-term studies assessing carcinogenicity of Xolegel gel (ketoconazole USP at 2% in a topical anhydrous gel vehicle) have not been conducted, a long-term feeding study in Swiss albino mice and Wistar rats was conducted. There was no evidence of carcinogenicity from this study. Additionally, 5 mg/kg/dose of ketoconazole gel was topically applied to hairless mice 5 days a week for 40 weeks, and no evidence of photocarcinogenicity was found. When ketoconazole was given as a single oral dose up to 80 mg/kg to mice, no evidence of mutagenicity in the dominant lethal mutation test was found. An Ames assay (an assay which is used with bacteria to determine if a compound can cause DNA mutations) was conducted and ketoconazole was not found to cause mutation in *Salmonella typhimurium*, both in the presence and absence of metabolic activation.



## **Patch Test Concentration**

- 1% alcohol

## **Essential Patient Information**

- Xolegel gel (ketoconazole USP at 2% in a topical anhydrous gel vehicle)
  - Should be used as directed by a healthcare provider.
  - Is for external use only.
  - May irritate mucous membranes, and therefore, contact with the nostrils, mouth, and eyes should be avoided.
  - Should not be used for anything other than that for which it was prescribed.
  - Warrants handwashing after use.
  - Adverse health effects to a healthcare provider.

## **Selenium Sulfide Shampoo**

### **Classification and Mode of Action**

- Selenium sulfide shampoo is classified as an antiseborrheic and antifungal, although the exact mode of action is unknown. However, selenium sulfide shampoo appears to have a cytostatic effect on epidermal and follicular epithelial cells, resulting in a reduction of corneocyte production. The active ingredient, selenium sulfide, has been approved by the FDA for over-the-counter treatment of seborrheic dermatitis, although specific selenium sulfide shampoos have not been approved.
- Danby et al. (1993) investigated the use of ketoconazole 2% shampoo versus selenium sulfide 2.5% shampoo for the treatment of dandruff. They found that both were effective treatments, with the mean total adherent dandruff scores declining throughout the treatment period. Ketoconazole was statistically superior to selenium sulfide on day 8 only.

## Indications and Dermatological Uses

- *Clinical indications (FDA)*: Selenium sulfide is approved for over-the-counter use by the FDA, and selenium sulfide shampoos are indicated for use in those with seborrheic dermatitis of the scalp, dandruff, and tinea versicolor.
- *Off-label common uses*: No data available.

## Formulations/Presentation (Table 23.3)

### Dosages and Suggested Regimens

- The exact dosages and suggested regimens for using this product may vary depending on the specific brand used. Generally, after wetting the hair and skin, gently massage into the skin working into a full lather, and then rinse thoroughly and pat dry. This should be repeated twice per week for 2 weeks. The shampoo should not be used more frequently than what is necessary for managing the condition.

### Pharmacokinetics

- No information available

**Table 23.3** Selenium sulfide shampoos available in the United States according to Lexicomp

| Strengths                                                                                   | Brand names   |
|---------------------------------------------------------------------------------------------|---------------|
| 1% (207 mL) (contains brilliant blue fcf (fd&c blue #1), menthol)                           | Anti-Dandruff |
| 2.3% (180 mL (DSC)) (contains fd&c red #40, methylparaben, propylene glycol, propylparaben) | SelRx         |
| 2.25% (180 mL); 2.3% (180 mL)                                                               | Generic       |

## Use in Special Populations

- Whether this product is safe to use during pregnancy or while nursing is unknown. No animal reproductive studies with this product have been conducted, and its effect on fertility is unknown. Safety and effectiveness in children under the age of 12 is also unknown.

*Monitoring:* No information available

## Contraindications and Cautions

- Selenium sulfide shampoos are contraindicated in those with known or suspected hypersensitivity to any ingredients in the shampoo. The product should be kept out of reach of children and is for external use only. Selenium sulfide shampoos are not for ophthalmic use. The product should only be used as directed by a physician and should not be used to treat anything other than that for which it was prescribed. In the event of redness or irritation, discontinue use and consult a physician.

*Important drug interactions:* No known interactions

## Adverse Effects and Their Management

- The following adverse effects, in decreasing order of sensitivity, may occur: skin irritation, occasional increased hair loss, and discoloration of the hair (although this can be minimized through thorough rinsing of hair after use).
- Systemic toxicity has been reported. Selenium sulfide lotion was used topically on an open scalp lesion, resulting in tremors, hyperhidrosis, garlicky breath, lower abdominal pain, weakness, lethargy, anorexia, and occasional emesis. Symptoms resolved within 10 days of discontinuation. Therefore, it is important to ensure selenium sulfide is not used on damaged skin.

- When 25–50% solutions of 2.5% selenium sulfide were dermally applied to mice over an 88-week period, no carcinogenic effects were observed.

### **Patch Test Concentration**

- 2% pet. Perform controls.

### **Essential Patient Information**

- This product should be discontinued if a rash develops in the treated area or elsewhere, or if the condition worsens. Contact with the eyes, lips, and mucous membranes should be avoided. If contact with any of these areas occurs, they should be rinsed thoroughly with water. The product should not be used on broken or inflamed skin.

---

## **Zinc Pyrithione Shampoo**

### **Classification and Mode of Action**

- Zinc pyrithione shampoo is classified as an anti-dandruff shampoo. The active ingredient, zinc pyrithione, has been approved for over the counter treatment of seborrheic dermatitis; however, specific zinc pyrithione shampoos have not been approved by the FDA.
- In a comparative study by Shin et al. (2009), patients with dandruff were randomly assigned to a treatment of topical betamethasone, topic tacrolimus, or zinc pyrithione. After 4 weeks, all treatment groups displayed significant improvements on clinical assessment. Interestingly though, the cohort of patients receiving zinc pyrithione continued to improve, even after treatment cessation.

Indications and Dermatological Uses

- *Clinical indications (FDA):* Zinc pyrithione shampoos have not been approved by the FDA but are informally indicated for the relief of symptoms such as scalp itch, irritation, redness, and flaking associated with seborrheic dermatitis, dandruff, and other hyperkeratotic skin conditions.
- *Off-label common uses:* None found.

Formulations/Presentation (Table 23.4)

Dosages and Suggested Regimens

- Zinc pyrithione should be applied to wet hair and scalp. The product should be massaged to a lather, and then let sit for 2–3 minutes before rinsing thoroughly. This should be done at least twice a week or as directed by a physician.

*Pharmacokinetics (percutaneous absorption, distribution, metabolism, excretion) as relevant:* No data available

*Use in special populations: Pregnancy (FDA guidance), lactation, children, renal insufficiency, hepatic insufficiency:* No data available

*Monitoring:* No data available

**Table 23.4** Zinc pyrithione shampoos available in the United States according to Lexicomp

| Strengths                                                     | Brand names |
|---------------------------------------------------------------|-------------|
| 2% (480 mL)                                                   | Beta Med    |
| 2% (240 mL, 480 mL) (contains fd&c yellow #6 (sunset yellow)) | DHS Zinc    |
| 2% (240 mL)                                                   | Theraplex Z |

## Contraindications and Cautions

- Zinc pyrithione shampoo is for external use only, and contact with the eyes should be avoided. If contact with the eyes does occur, they should be rinsed thoroughly with water. This product should not be used on wounded areas and should be kept out of reach of children. If any redness, swelling, itching, or other symptom occurs following the use of a zinc pyrithione shampoo, consult a physician.

*Important drug interactions:* No significant interactions known

*Adverse effects and their management:* Zinc pyrithione has been classified as a category 1B carcinogen, meaning that based on animal studies, the substance presumably has carcinogenic effects in humans. In March of 2020, The European Commission's Scientific Committee on Consumer Safety (SCCS) determined that zinc pyrithione was safe for use as a rinse-off anti-dandruff ingredient at a concentration of 1%. However, because there are suitable anti-dandruff alternatives, the SCCS concluded that zinc pyrithione will be removed from Annex III (where it was listed as permitted for use in leave-on hair products up to a concentration of 0.1%) and Annex V (where it was listed as permitted in concentrations up to 1% and 0.5% in rinse off hair products and other products, respectively). In addition, zinc pyrithione will be added to the SCCS's list of prohibited cosmetic products in Annex II in March of 2022.

## Patch Test Concentration

- No data available

*Essential Patient Information:* No data available

## References

### Introduction

1. Borda LJ, Wikramanayake TC. Seborrheic dermatitis and dandruff: a comprehensive review. *J Clin Invest Dermatol*. 2015; <https://doi.org/10.13188/2373-1044.1000019>.
2. Tucker D, Masood S. Seborrheic dermatitis. Treasure Island: StatPearls Publishing; 2021.
3. Mills KJ, Hu J, Henry M, Tamura M, Tiesman JP, Xu J. Dandruff/ seborrheic dermatitis is characterized by an inflammatory genomic signature and possible immune dysfunction: transcriptional analysis of the condition and treatment effects of zinc pyrithione. *Br J Dermatol*. 2012; <https://doi.org/10.1111/j.1365-2133.2012.10863.x>.
4. Xuan M, Lu C, He Z. Clinical characteristics and quality of life in seborrheic dermatitis patients: a cross-sectional in China. *Health Qual Life Outcomes*. 2020; <https://doi.org/10.1186/s12955-020-01558-y>.

### Betamethasone Valerate Foam

5. <https://fda.report/DailyMed/801BAC90-2ED7-4F68-9FA4-BE1705B1F98C.pdf>. Revised: July 2020. Accessed 22 Oct 2021.

### Coal Tar Shampoo

6. <https://fda.report/DailyMed/7CAFB511-0AB7-F3B4-E053-2991AA0A2E0B.pdf>. Revised: October 2018. Accessed 22 Oct 2021.
7. <https://fda.report/DailyMed/DB9941FD-8861-4E8C-B564-CC01CF3ABB82.pdf>. Revised: May 2020. Accessed 22 Oct 2021.
8. <https://fda.report/DailyMed/35F3C56D-CC4C-4A0C-866B-8D4133D8FCE6.pdf>. Revised: May 2021. Accessed 22 Oct 2021.
9. <https://www.fda.gov/media/75758/download>. Revised: April 2010. Accessed 28 Oct 2021.
10. Van Schooten F-J, Godschalk R. Coal tar therapy. *Drug Saf*. 1996;15(6):374–7. <https://doi.org/10.2165/00002018-199615060-00002>.
11. Roelofzen JHJ, Aben JKH, Oldenhof UTH, Coenraads P-J, Alkemade HA, van de Kerkhof PCM, van der Valk PGM, Kiemenee LALM. No increased risk of cancer after coal tar treatments in patients with psoriasis or eczema. *J Invest Dermatol*. 2010;130(4):953–61. <https://doi.org/10.1038/jid.2009.389>.

12. <https://www.drugs.com/mtm/coal-tar-topical.html>. Revised: March 2021. Accessed: 01 Jan 2022.
13. Lexicomp Monograph: Coal Tar Preparations (Topical). [http://online.lexi.com.qe2a-proxy.mun.ca/lco/action/doc/retrieve/docid/complete\\_ashp/413896?cesid=0qF7a5Ssy0V&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DCoal%252520Tar%252520Shampoo%26t%3Dname%26va%3DCoal%252520Tar%252520Shampoo#preps-nested](http://online.lexi.com.qe2a-proxy.mun.ca/lco/action/doc/retrieve/docid/complete_ashp/413896?cesid=0qF7a5Ssy0V&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DCoal%252520Tar%252520Shampoo%26t%3Dname%26va%3DCoal%252520Tar%252520Shampoo#preps-nested). Revised: June 2021. Accessed 10 Jan 2022.
14. CPS Monograph: Coal Tar. <https://www-myrxtx-ca.qe2a-proxy.mun.ca/search>. Revised: June 2018. Accessed 15 Jan 2022.

## Fluocinolone Acetonide

15. <https://fda.report/DailyMed/A52763D0-7024-48A8-9CCA-3127333DFB01.pdf>. Revised: June 2018. Accessed 22 Oct 2021

## Ketoconazole Gel, Cream, Kit, Foam, and Shampoo

16. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2008/021946s002lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021946s002lbl.pdf). Revised: August 2008. Accessed 22 Oct 2021.
17. <https://fda.report/DailyMed/EFBC6388-90CE-11DE-B92C-8B7156D89593.pdf>. Revised April 2020. Accessed 22 Oct 2021.
18. <https://fda.report/DailyMed/63840ff7-d447-4f4e-a05b-1fbed2da8a25>. Accessed 22 Oct 2021.
19. Lexicomp Monographs: Ketoconazole (Topical). [http://online.lexi.com.qe2a-proxy.mun.ca/lco/action/doc/retrieve/docid/patch\\_f/1797827?cesid=6sltmghPUfn&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DKetoconazole%252520topical%26t%3Dname%26va%3DKetoconazole%252520topical#foc](http://online.lexi.com.qe2a-proxy.mun.ca/lco/action/doc/retrieve/docid/patch_f/1797827?cesid=6sltmghPUfn&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DKetoconazole%252520topical%26t%3Dname%26va%3DKetoconazole%252520topical#foc). Revised: January 2022. Accessed 10 Jan 2022.
20. Vestergaard C, Wollenberg A, Barbarot S, Christen-Zaech S, Deleuran M, Spuls P, Flohr C, Trzeciak M, von Kobyletzki L, Seneschal J, Paul C, Bieber T, Werfel T, Folster-Holst R, Darsow U, Gieler U, Svensson A, Corl M, Stalder J-F, De Raeve L, Kunz B, Simon D, Chernyshov P, Hijnen D, Gelmetti C, Ring J, Taieb A, de Bruin-Weller M, Thyssen JP. European task force on atopic dermatitis position paper: treatment of parental atopic dermatitis during preconception, pregnancy and lactation period. *J Eur Acad Dermatol Venereol*. 2019;33(9):1644–59. <https://doi.org/10.1111/jdv.15709>.



## Selenium Sulfide Shampoo

21. <https://fda.report/DailyMed/CA97B19F-2195-4F9C-A6C1-14161B026231.pdf>. Revised: February 2020. Accessed 22 Oct 2021.
22. <https://www.fda.gov/media/75758/download>. Revised: April 2010. Accessed 28 Oct 2021.
23. Danby FW, Maddin WS, Margesson LJ, Rosenthal D. A randomized, double-blind, placebo-controlled trial of ketoconazole 2% shampoo versus selenium sulfide 2.5% shampoo in the treatment of moderate to severe dandruff. *J Am Acad Dermatol*. 1993;129(6):1008–12. [https://doi.org/10.1016/0190-9622\(93\)70282-x](https://doi.org/10.1016/0190-9622(93)70282-x).
24. Lexicomp Monographs: Selenium Sulfide (Topical). [http://online.lexi.com.qe2a-proxy.mun.ca/lco/action/doc/retrieve/docid/complete\\_ashp/413464?cesid=9EXjTQDPbpk&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3Dselenium%252520sulfide%26t%3Dname%26va%3Dselenium%252520sulfide#uses-nested](http://online.lexi.com.qe2a-proxy.mun.ca/lco/action/doc/retrieve/docid/complete_ashp/413464?cesid=9EXjTQDPbpk&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3Dselenium%252520sulfide%26t%3Dname%26va%3Dselenium%252520sulfide#uses-nested). Revised February 2021. Accessed 10 January 2022.
25. Lexicomp Monographs: Selenium Sulfide. [http://online.lexi.com.qe2a-proxy.mun.ca/lco/action/doc/retrieve/docid/patch\\_f/7657?cesid=9EXjTQDPbpk&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3Dselenium%252520sulfide%26t%3Dname%26va%3Dselenium%252520sulfide#](http://online.lexi.com.qe2a-proxy.mun.ca/lco/action/doc/retrieve/docid/patch_f/7657?cesid=9EXjTQDPbpk&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3Dselenium%252520sulfide%26t%3Dname%26va%3Dselenium%252520sulfide#). Revised: December 2021. Accessed 10 Jan 2022.

## Zinc Pyrithione Shampoo

26. <https://fda.report/DailyMed/373692F9-A056-4333-BCF9-EA9B1553D17C.pdf>. Revised: March 2021. Accessed 22 Oct 2021.
27. <https://fda.report/DailyMed/984780FD-4969-150B-E053-2995A90AED77.pdf> Revised: November 2020. Accessed 22 Oct 2021.
28. <https://www.fda.gov/media/75758/download>. Revised: April 2010. Accessed 28 Oct 2021.
29. Shin H, Kwon OS, Won CH, Kim BJ, Lee YW, Choe YB, Ahn KJ, Eun HC. Clinical efficacies of topical agents for the treatment of seborrheic dermatitis of the scalp: a comparative study. *J Dermatol*. 2009;36:131–7. <https://doi.org/10.1111/j.1346-8138.2009.00607.x>.
30. <https://chemicalwatch.com/208245/european-commission-to-ban-more-cmrs-in-cosmetics> January 2021. Accessed 01 Jan 2022.
31. Lexicomp Drug Monographs: Pyrithione Zinc. [http://online.lexi.com.qe2a-proxy.mun.ca/lco/action/doc/retrieve/docid/patch\\_f/7596?cesid=9eND8QPieHX&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DZinc%252520Pyrithione%26t%3Dname%26va%3DZinc%252520Pyrithione#](http://online.lexi.com.qe2a-proxy.mun.ca/lco/action/doc/retrieve/docid/patch_f/7596?cesid=9eND8QPieHX&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3DZinc%252520Pyrithione%26t%3Dname%26va%3DZinc%252520Pyrithione#). Revised: January 2021. Accessed 10 Jan 2022.



Victoria Nguyen, Linda B. Ou,  
and Rebecca M. Law 

## Contents

|                                           |     |
|-------------------------------------------|-----|
| Classification and Mode of Action.....    | 640 |
| Indications and Dermatological Uses.....  | 640 |
| Formulations/Presentation.....            | 640 |
| Dosages and Suggested Regimens.....       | 641 |
| Pharmacokinetics.....                     | 641 |
| Use in Special Populations.....           | 641 |
| Monitoring.....                           | 641 |
| Contraindications and Cautions.....       | 642 |
| Important Drug Interactions.....          | 642 |
| Adverse Effects and Their Management..... | 642 |

---

V. Nguyen (✉)

School of Pharmacy, University of Waterloo, Kitchener, ON, Canada

e-mail: [vtpnguye@uwaterloo.ca](mailto:vtpnguye@uwaterloo.ca)

L. B. Ou

Sunnybrook Health Sciences Centre, Toronto, ON, Canada

e-mail: [lindaou25@gmail.com](mailto:lindaou25@gmail.com)

R. M. Law

School of Pharmacy and Faculty of Medicine (Discipline of Family  
Medicine), Memorial University of Newfoundland, St. John's, NL, Canada

e-mail: [rlaw@mun.ca](mailto:rlaw@mun.ca); [rlawUCSF@gmail.com](mailto:rlawUCSF@gmail.com)

© The Author(s), under exclusive license to Springer Nature  
Switzerland AG 2025

639

R. M. Law, H. I. Maibach (eds.), *Handbook of Topical Drug  
Treatment in Dermatology*,

[https://doi.org/10.1007/978-3-031-93616-6\\_24](https://doi.org/10.1007/978-3-031-93616-6_24)

|                                                                    |     |
|--------------------------------------------------------------------|-----|
| Carcinogenicity (If Known (Including Mouse Painting Studies))..... | 642 |
| Patch Test Concentration.....                                      | 643 |
| Essential Patient Information.....                                 | 643 |
| References.....                                                    | 643 |

---

## Classification and Mode of Action

- Sinecatechins 10% and 15% (Veregen®) is a botanical drug product indicated in the treatment of genital and perianal warts.
- Sinecatechins, the active ingredient in Veregen® ointment, is a water extract of green tea leaves from *Camellia sinensis*.
- The mechanism of action of Veregen® is not fully elucidated. In vitro studies have shown that sinecatechins inhibit the activation of keratinocytes. Sinecatechins also exhibit anti-oxidative and anti-inflammatory activity which block kinases involved in tumor cell signaling and induce apoptosis.
- Comparative efficacy:
  - In a pooled analysis of two randomized, double-blind, multicenter studies, Veregen®-treated patients had a higher clearance rate than placebo-treated patients at 60.7% and 44.2%, respectively.

---

## Indications and Dermatological Uses

- *Clinical indications (FDA):* external genital and perianal warts
- *Off-label common uses:* No data available

---

## Formulations/Presentation

- USA: Veregen® ointment (15%)
- Canada: Veregen® ointment (10%)
- Europe: Veregen® ointment (10%, 15%)

---

## Dosages and Suggested Regimens

- External genital and perianal warts: Apply a thin film, around a 0.5 cm strand of ointment, three times daily to each wart until they have been cleared or for a maximum of 16 weeks.

---

## Pharmacokinetics

- Has not been characterized. Data suggests that systemic exposure after repeated topical application of Veregen® is minimal and likely to be less than after a single oral intake of 400 mL of green tea.

---

## Use in Special Populations

- Pregnancy: No data on use of Veregen® in pregnant women. Veregen® should not be used in pregnancy unless benefits outweigh potential risks to the fetus.
- Lactation: Unknown whether Veregen® is secreted into breast milk but manufacturer recommends use with caution in breast-feeding patients.
- Children: Safety and efficacy of Veregen® not established in children under 18 years of age.
- Renal insufficiency: No dose adjustments on manufacturer's labelling.
- Hepatic insufficiency: No dose adjustments on manufacturer's labelling.

---

## Monitoring

- Intense application site reactions, including severe discomfort, desquamation, or association with lymph nodes may occur. Dosing interruption may be warranted. Treatment can be resumed after resolution of skin reaction. In the event of a vesicular local reaction, genital herpes infections should be ruled out before resuming treatment.
- Signs and symptoms of hypersensitivity.

---

## **Contraindications and Cautions**

- Known sensitivity to extract from green tea leaves or to any ingredients in formulation.

## **Important Drug Interactions**

- No drug interactions on manufacturer's labelling.
- Concomitant use of alternative local treatments for warts should be avoided.

---

## **Adverse Effects and Their Management**

- Application site reactions like erythema, pruritus, vesicular eruption, bleeding, discharge, localized burning, and discomfort. Acute cases can be managed by temporary dosing interruption and use of cold compresses. The frequency of reactions should decrease with continued use.
- Application of ointment on genital warts in vulvar region are associated more often with severe local reactions. Accidental application into vagina should be immediately rinsed with warm water and mild soap. If patient uses tampons, advise inserting tampon prior to application of ointment.
- Phimosis is a risk when uncircumcised patients treat warts under the foreskin. The foreskin should be retracted, and the affected area should be cleaned daily for prevention.
- Type IV hypersensitivity reaction observed in 2% of patients.

---

## **Carcinogenicity (If Known (Including Mouse Painting Studies))**

- Treatment with oral sin catechins administered daily for 26 weeks to p53 transgenic mice was not associated with increased carcinogenicity. Dermal carcinogenicity studies have not been conducted.

---

## Patch Test Concentration

- No data available

---

## Essential Patient Information

- Do not apply to open wounds, broken, or inflamed skin.
- For topical use only. Do not administer orally, intravaginally, or intra-anally.
- Avoid contact with the eyes, nostrils, lips, and mouth. Rinse immediately if contact occurs.
- Avoid use of occlusive dressings over treatment area.
- Avoid exposure of treated areas to sun/UV light.
- Tampons should be inserted prior to application of Veregen® to prevent accidental application into vagina.
- Uncircumcised patients treating warts beneath the foreskin should retract foreskin, and clean the affected area daily.
- Veregen® is not a cure. New warts may develop during or after treatment.
- Sexual contact should be avoided while ointment is on the skin.
- Veregen® may weaken condom and vaginal diaphragms. Alternative methods of contraception are recommended.
- Veregen® may stain clothes and bedding.

---

## References

1. FDA drug monograph Veregen® (sinecatechins) ointment, for topical use. Available from [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/021902s033lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021902s033lbl.pdf). Accessed 30 Apr 2023.
2. LexiComp drug monograph Sinecatechins. Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2023 UptoDate, Inc.
3. Deeb M, Levy R, Pope E, Lara-Corrales I. Sinecatechins ointment for the treatment of warts in children. *Pediatr Dermatol*. 2019;36(1):121–4.

4. Gross G, Meyer KG, Pres H, Thielert C, Tawfik H, Mescheder A. A randomized, double-blind, four-arm parallel-group, placebo-controlled Phase II/III study to investigate the clinical efficacy of two galenic formulations of Polyphenon E in the treatment of external genital warts. *J Eur Acad Dermatol Venereol*. 2007;21(10):1404–12.
5. Health Canada drug monograph Veregen® (sin catechins) ointment 10% w/w. Available from [https://www.paladin-labs.com/our\\_products/Veregen-PM-En.pdf?ver=3.0](https://www.paladin-labs.com/our_products/Veregen-PM-En.pdf?ver=3.0). Accessed 30 Apr 2023.
6. Singh BN, Shankar S, Srivastava RK. Green tea catechin, epigallocatechin-3-gallate (EGCG): mechanisms, perspectives and clinical applications. *Biochem Pharmacol*. 2011;82(12):1807–21.
7. Stockfleth E, Beti H, Orasan R, Grigorian F, Mescheder A, Tawfik H, Thielert C. Topical Polyphenon E in the treatment of external genital and perianal warts: a randomized controlled trial. *Br J Dermatol*. 2008;158(6):1329–38.
8. Stockfleth E, Meyer T. Sin catechins (Polyphenon E) ointment for treatment of external genital warts and possible future indications. *Expert Opin Biol Ther*. 2014;14(7):1033–43.
9. Tatti S, Swinehart JM, Thielert C, Tawfik H, Mescheder A, Beutner KR. Sin catechins, a defined green tea extract, in the treatment of external anogenital warts: a randomized controlled trial. *Obstet Gynecol*. 2008;111(6):1371–9.
10. Tying SK. Sin catechins: effects on HPV-induced enzymes involved in inflammatory mediator generation. *J Clin Aesthet Dermatol*. 2012;5(1):19.
11. Tying SK. Effect of sin catechins on HPV-activated cell growth and induction of apoptosis. *J Clin Aesthet Dermatol*. 2012;5(2):34.



# Sirolimus for Facial Angiofibroma Associated with Tuberous Sclerosis Complex

# 25

Arian Farahani, Michael Pham,  
Sreedevi Boggarapu, and Eric Beresford

## Contents

|                         |     |
|-------------------------|-----|
| Introduction.....       | 645 |
| Sirolimus 0.2% Gel..... | 647 |
| References.....         | 651 |

## Introduction

Facial angiofibroma are small swellings consisting of fibrous dermal tissue and blood vessels typically appearing on the malar, nasal dorsum, nasolabial fold, forehead, and chin areas that progressively enlarge and multiply over time [1–3]. They are one of the predominant cutaneous manifestations of tuberous sclerosis

---

A. Farahani · M. Pham · S. Boggarapu (✉) · E. Beresford  
Nobelpharma America, LLC, Bethesda, MD, USA  
e-mail: [arian.farahani@nobelpharma-us.com](mailto:arian.farahani@nobelpharma-us.com);  
[michael.pham@nobelpharma-us.com](mailto:michael.pham@nobelpharma-us.com);  
[Sreedevi.boggarapu@nobelpharma-us.com](mailto:Sreedevi.boggarapu@nobelpharma-us.com);  
[Eric.beresford@nobelpharma-us.com](mailto:Eric.beresford@nobelpharma-us.com)



complex (TSC), an autosomal dominant genetic rare disorder caused by mutations in tumor-suppressor genes, *TSC1* or *TSC2*, leading to dysfunction of hamartin or tuberin, respectively [4]. Hamartin and tuberin are critical negative regulators of mechanistic target of rapamycin (mTOR), which has a central role in the regulation of cell growth and tumorigenesis [2, 4, 5]. Dysfunction in hamartin and tuberin leads to chronic activation of mTOR pathway, resulting in tumor growth in multiple organs, including the skin, brain, eyes, heart, and kidneys.[2, 5].

TSC affects 1 in 6000 to 10,000 live births [3]. Over one million people worldwide may have TSC with ~50,000 in the USA. No difference in the prevalence has been observed by gender, race, or ethnicity [3].

TSC is a complex and highly variable disease, with differing intra- and inter-individual topical and systemic clinical presentations that may change over time [3, 6]. This necessitates a multidisciplinary approach involving dermatologists, neurologists, pulmonologists, urologists, cardiovascular specialists, pediatricians, and geneticists [3, 5]. TSC typically first appears in infancy or early childhood; >60% of patients are diagnosed under 2 years of age [7]. Skin manifestations (including facial angiofibromas, hypomelanotic macules, shagreen patches, and cephalic plaques) are common and appear in >90% of TSC [1, 2].

Germline mutations cause TSC in about 30% of cases, while sporadic (or somatic) mutations, frequently in *TSC2*, cause the majority of cases [2]. TSC can be diagnosed via molecular identification, or by using TSC clinical diagnostic criteria [4], which yields a positive result in ~75–90% of TSC cases [2, 4]. There is an International TSC Consensus Group clinical diagnostic criteria [4].

There are currently no US-specific guidelines for the management of TSC-related skin manifestations, including facial angiofibroma. Updated International TSC Consensus Group recommendations suggest that more evidence is necessary to guide the choice of treatment for TSC-related skin lesions but recognize existing evidence supporting several approaches [4]. Pharmacological (topical or oral mTOR inhibitors) and non-pharmacological (surgical or excision) treatment options are currently in clinical practice [4]. Physical removal using methods

such as laser therapy, dermabrasion, radiofrequency ablation, cryotherapy, and electrocoagulation potentially yield good results, however, may be associated with the risk of adverse effects such as pain, scarring, pigmentation disorders, skin texture changes, postoperative infections, and high recurrence rates, often making follow-up treatment necessary.[4, 8] The International TSC Consensus Group does not recommend systemic therapy for the exclusive treatment of facial angiofibroma due to the risk of systemic side effects [4].

Topical mTOR inhibitors was suggested as a safe and effective approach for treating facial angiofibroma.

Topical sirolimus 0.2% gel was approved in Japan in 2018 for the treatment of skin lesions and in the USA in 2022 for the treatment of facial angiofibroma associated with TSC. A placebo-controlled phase III randomized clinical trial showed the efficacy and safety of topical sirolimus 0.2% gel for the management of facial angiofibroma over 12 weeks [9], which was maintained over 52 weeks [10].

In a postmarketing surveillance [11], topical sirolimus 0.2% gel showed improvement in overall cutaneous manifestations (facial angiofibroma, hypomelanotic macules, shagreen patches, fibrous plaque, and periungual fibroma) in 74.8% of patients over 52 weeks, and the responder rate was the highest for facial angiofibroma (86.2%). Topical sirolimus 0.2% gel was generally well tolerated with major drug-related AEs were application site irritation, dry skin, acne, eye irritation, pruritus, erythema, dermatitis acneiform, and contact dermatitis [10].

---

## Sirolimus 0.2% Gel

### Drug Monograph [12, 13]

#### Classification and Mode of Action

- Sirolimus, a macrocyclic lactone produced by *Streptomyces hygroscopicus* [14] is a mechanistic target of rapamycin (mTOR) inhibitor immunosuppressant.[13]

- The mechanism of action of sirolimus in the treatment of tuberous sclerosis complex (TSC)-related facial angiofibroma is unknown. TSC is associated with genetic defects in *TSC1* and *TSC2* which leads to chronic activation of mTOR. Sirolimus inhibits mTOR activation.
- In a multicenter, placebo-controlled, stratified, randomized, double-blind phase 3 trial [9] treatment with topical sirolimus 0.2% gel resulted in improvement in the size and color of facial angiofibroma, which was further confirmed in the long-term extension study [10].
- Postmarketing surveillance (conducted in Japan) further confirmed the findings from clinical studies [11].

### Indications and Dermatologic Uses

- *Clinical indications (FDA)*: Indicated for the treatment of facial angiofibroma associated with TSC in adults and pediatric patients 6 years of age and older in the USA [12].
- *Clinical indications (Japan)*: Skin lesions associated with TSC [15].
- *Off-label common uses*: Vascular anomalies, cutaneous lymphatic malformations, pachyonychia congenita, lingual microcystic lymphatic malformations, epidermolysis bullosa simplex, epidermolysis bullosa simplex Kobner, and Weber-Cockayne syndrome.

### Formulations/Presentation

- USA and Japan: Hyftor (topical sirolimus 0.2% gel).

### Dosages and Suggested Regimens

- Apply to the skin of the face affected with angiofibroma twice daily.
  - The maximum daily dosage is as follows:
    - 600 mg (2 cm) for patients 6 to 11 years of age
    - 800 mg (2.5 cm) for patients 12 years of age and older.

## Baseline Investigations and Considerations

### Pharmacokinetics

- Blood concentrations ranged from undetectable to 0.50 ng/mL after multiple doses.
- Maximum sirolimus concentration measured at any time was 3.27 ng/mL in adults and 1.80 ng/mL in pediatric subjects.
- No evidence on the systemic accumulation of sirolimus upon topical application in patients with tuberous sclerosis for periods of up to 1 year.

### Carcinogenicity

#### Oral Carcinogenicity Studies

##### Mice Studies

- Once daily oral administration for 86 weeks was associated with a statistically significant increase in malignant lymphoma.
- Sirolimus-related hepatocellular adenoma and carcinoma were induced.

##### Rat Study

- There were no significant findings.

### Use in Special Populations

- Approved for use in children >6 years old.
- No sufficient numbers of subjects aged 65 years old.
- *Pregnancy*: Based on animal studies, oral sirolimus may cause fetal harm when administered to pregnant women. The available data from case reports on HYFTOR use in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.
- Oral sirolimus may compromise the male and female fertility based on animal studies.
- *Breastfeeding*: Breastfeeding not recommended.
- *Renal insufficiency*: No dosage adjustment needed.
- *Hepatic insufficiency*: No dosage adjustment needed.

**Monitoring**

- Oral sirolimus has been associated with increased serum cholesterol and triglycerides.
- Concomitant use of topical sirolimus gel with CYP3A4 inhibitors require monitoring for potential adverse reactions.

**Contraindications and Cautions**

- History of hypersensitivity to sirolimus or any other component.
- Oral sirolimus has been associated with hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, angioedema, exfoliative dermatitis, and hypersensitivity vasculitis.
- Serious infection: Serious infections, including opportunistic infections and latent viral infections, such as progressive multifocal leukoencephalopathy, have been reported with oral sirolimus.
- Oral sirolimus has been associated with malignancy, including lymphoma and skin cancer.

**Important Drug Interactions**

- Concomitant use of topical sirolimus gel with CYP3A4 inhibitors require monitoring for potential drug interactions.

**Adverse Effects and Their Management**

- Most common adverse reactions ( $\geq 1\%$ ) are dry skin, application site irritation, pruritus, acne, acneiform dermatitis, ocular hyperemia, skin hemorrhage, and skin irritation.

**Patch Test Concentration**

- 0.1% oral solution; also patch test with excipients; test controls.

**Essential Patient Information**

- Apply to affected skin of the face in the morning and at bedtime.
- Do not use with occlusive dressings. Do not cover treated skin with bandages, dressings, or wraps.

- Wash hands before and after application.
- For topical use only; not for oral, ophthalmic, or intravaginal use.
- For pediatric patients limit exposure to natural or artificial sunlight; protective clothing should be worn.

---

## References

1. Cardis MA, DeKlotz CMC. Cutaneous manifestations of tuberous sclerosis complex and the paediatrician's role. *Arch Dis Child*. 2017;102(9):858–63. <https://doi.org/10.1136/archdischild-2016-312001>.
2. Portocarrero LKL, Quental KN, Samorano LP, Oliveira ZNP, Rivitti-Machado MCDM. Tuberous sclerosis complex: review based on new diagnostic criteria. *An Bras Dermatol*. 2018;93(3):323–31. <https://doi.org/10.1590/abd1806-4841.20186972>.
3. Northrup H, Krueger DA, Group ITSCC. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. *Pediatr Neurol*. 2013;49(4):243–54. <https://doi.org/10.1016/j.pediatrneurol.2013.08.001>.
4. Northrup H, Aronow ME, Bebin EM, et al. Updated international tuberous sclerosis complex diagnostic criteria and surveillance and management recommendations. *Pediatr Neurol*. 2021;123:50–66. <https://doi.org/10.1016/j.pediatrneurol.2021.07.011>.
5. Schwartz RA, Fernández G, Kotulska K, Jóźwiak S. Tuberous sclerosis complex: advances in diagnosis, genetics, and management. *J Am Acad Dermatol*. 2007;57(2):189–202. <https://doi.org/10.1016/j.jaad.2007.05.004>.
6. Zöllner JP, Franz DN, Hertzberg C, et al. A systematic review on the burden of illness in individuals with tuberous sclerosis complex (TSC). *Orphanet J Rare Dis*. 2020;15(1):23. <https://doi.org/10.1186/s13023-019-1258-3>.
7. Boggarapu S, Roberds SL, Nakagawa J, Beresford E. Characterization and management of facial angiofibroma related to tuberous sclerosis complex in the United States: retrospective analysis of the natural history database. *Orphanet J Rare Dis*. 2022;17(1):355. <https://doi.org/10.1186/s13023-022-02496-2>.
8. Salido-Vallejo R, Garnacho-Saucedo G, Moreno-Giménez JC. Current options for the treatment of facial angiofibromas. *Actas Dermosifiliogr*. 2014;105(6):558–68. <https://doi.org/10.1016/j.ad.2012.11.020>.

9. Wataya-Kaneda M, Ohno Y, Fujita Y, et al. Sirolimus gel treatment vs placebo for facial angiofibromas in patients with tuberous sclerosis complex: a randomized clinical trial. *JAMA Dermatol*. 2018;154(7):781–8. <https://doi.org/10.1001/jamadermatol.2018.1408>.
10. Wataya-Kaneda M, Nagai H, Ohno Y, et al. Safety and efficacy of the Sirolimus gel for TSC patients with facial skin lesions in a long-term, open-label, extension, uncontrolled clinical trial. *Dermatol Ther (Heidelb)*. 2020;10(4):635–50. <https://doi.org/10.1007/s13555-020-00387-7>.
11. Egami A, Takahashi S, Kokubo T, Boggarapu S, Beresford E. Topical sirolimus 0.2% gel for the management of tuberous Sclerosis complex-related cutaneous manifestations: an interim analysis of postmarketing surveillance in Japan. *Dermatol Ther (Heidelb)*. 2023.
12. FDA drug monograph (Hyftor). Available from [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2022/213478s0001bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/213478s0001bl.pdf). Accessed 27 Mar 2023.
13. Sirolimus (Topical) (Lexi-drugs). LexiComp drug monograph Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2023 UptoDate, Inc.
14. Kahan BD, Chang JY, Sehgal SN. Preclinical evaluation of a new potent immunosuppressive agent, rapamycin. *Transplantation*. 1991;52(2):185–91. <https://doi.org/10.1097/00007890-199108000-00001>.
15. Rapalimus Gel 0.2%. Information for people using this medication. <https://www.rad-ar.or.jp/siori/english/search/result?n=44731>. Accessed 27 Mar 2023.



# Trichogenic and Antitrichogenic Agents

# 26

Sheeva Shahinfar, Rebecca M. Law ,  
and Howard I. Maibach

## Contents

|                          |     |
|--------------------------|-----|
| Bimatoprost.....         | 654 |
| Minoxidil (Topical)..... | 657 |
| Eflornithine.....        | 661 |
| References.....          | 664 |

---

S. Shahinfar (✉)  
Texas A&M University College of Medicine, Bryan, TX, USA  
e-mail: [Sheeva.Shahinfar@tamu.edu](mailto:Sheeva.Shahinfar@tamu.edu)

R. M. Law  
School of Pharmacy and Faculty of Medicine (Discipline of Family  
Medicine) Memorial University of Newfoundland,  
St. John's, NL, Canada  
e-mail: [rlaw@mun.ca](mailto:rlaw@mun.ca); [rlawUCSF@gmail.com](mailto:rlawUCSF@gmail.com)

H. I. Maibach  
Department of Dermatology, University of California San Francisco  
(UCSF), San Francisco, CA, USA  
e-mail: [howard.maibach@ucsf.edu](mailto:howard.maibach@ucsf.edu)

© The Author(s), under exclusive license to Springer Nature  
Switzerland AG 2025  
R. M. Law, H. I. Maibach (eds.), *Handbook of Topical Drug  
Treatment in Dermatology*,  
[https://doi.org/10.1007/978-3-031-93616-6\\_26](https://doi.org/10.1007/978-3-031-93616-6_26)

653



## Bimatoprost

It contains benzalkonium chloride.

### Classification and Mode of Action

- Bimatoprost is a prostaglandin analog that increases the thickness, darkness, and length of eyelashes.
- Mechanism of action is unknown, although it is thought to be due to an increased number of hairs in the anagen phase along with melanogenesis stimulation.

### Indications and Dermatological Uses

- *Clinical indications (FDA):* Hypotrichosis of eyelashes, elevated intraocular pressure
- *Off-label common uses:* Hair thinning on the scalp and eyebrows

### Formulations/Presentation

- USA: 0.03% ophthalmic solution
- Canada: 0.03% ophthalmic solution
- Europe: 0.03% ophthalmic solution

### Dosages and Suggested Regimens

- Remove make-up and contact lenses before application. Ensure a clean face. Place one drop of solution on provided applicator, and apply evenly on the skin of the upper eyelid at the base of eyelashes once daily at night. Perform on both eyes, using a separate clean applicator for each eye. Do not use other applicators or brushes; do not reuse applicators. May re-insert contacts 15 mins post application.

- No suggested dosage adjustment for renal or hepatic impairment due to low systemic absorption.

## **Baseline Investigations and Considerations**

### **Pharmacokinetics (Percutaneous Absorption, Distribution, Metabolism, Excretion) as Relevant**

- Minimal topical absorption. Oxidation, N-demethylation, and glucuronidation occur after entering systemic circulation with subsequent metabolite formation.
- Excreted primarily in urine; also excreted in feces.
- Onset of effect: 4–6 months.

### **Use in Special Populations: Pregnancy (FDA Guidance), Lactation, Children, Renal Insufficiency, and Hepatic Insufficiency**

- Approved for use in children  $\geq 5$  years old. The same dosage and regimen as adults.
- There are no studies in pregnant women. In animal studies, at doses more than 41 times the maximum intended human use, fetal abortion was noted. Bimatoprost should be administered in pregnancy only when benefits outweigh the potential risks.
- Unknown if bimatoprost is present in breast milk, although animal studies show its excretion in breast milk. Due to short half-lives, bimatoprost may be considered safe in breastfeeding; application after breastfeeding may help decrease possible exposure to infant during lactation.
- Contact lens users: Topical solution contains benzalkonium chloride, which can potentially result in change in coloration of soft contact lenses. Remove prior to application, and reinsert contact lenses 15 minutes postapplication.

### **Monitoring**

- Intraocular pressure
- Ocular pigmentation changes

## **Contraindications and Cautions**

- Consult physician prior to using if simultaneously using medications to reduce intraocular pressure.

## **Important Drug Interactions**

- Latanoprost: Simultaneous use may cause increased intraocular pressure.
- Latanoprostene bunod: Simultaneous use may cause increased intraocular pressure
- Nonsteroidal anti-inflammatory agents (oral and ophthalmic): May decrease or increase the proposed effects of prostaglandins (e.g., bimatoprost).

## **Adverse Effects and Their Management**

- Eye irritation. Notify physician if bothersome or does not go away.
- Dark eyelids. Notify physician if bothersome or does not go away.
- Serious side effects warrant seeking medical help and immediately discontinuing drug: change in eyesight, eye pain, very bad eye irritation, photophobia, eye discharge, and eye color changes.
- Allergic reactions include rash, hives, itching, redness, swelling, blistered/peeling skin, wheezing, chest/throat tightness, difficulty breathing, difficulty swallowing, difficulty talking, unusual hoarseness, and swollen mouth/face/lips/tongue/throat. Discontinue medication and seek immediate help if experiencing an allergic reaction.
- May cause bacterial keratitis and change in pigmentation of iris/eyelid skin/periorbital skin/eyelashes. May increase thickness, length, or number of eyelashes. Long-term effects of increased pigmentation are possible, but unknown.
- May cause eyelid erythema, periorbital erythema, hypertrichosis, local skin hyperpigmentation of the skin/eyelashes/eyelid/iris, blurred vision, conjunctival edema, conjunctival hemorrhage, decreased visual acuity, dry eye syndrome, eye irritation, eye pain, eye pruritus, eyelid pruritus, punctate keratitis, foreign body sensation in the eye, hypotony of the eye, allergic dermatitis, erythematous rash, periocular dryness of the skin, macular eruption, trichorrhexis, eyelid xeroderma, madarosis,

blepharoptosis, deepening of the eyelid sulcus, eye discharge, eyelid edema, eyelid entropion, hordeolum, intraocular inflammation, increased lacrimation, macular edema, misdirected growth of eyelashes, ocular allergy, ocular edema, periorbital swelling, photophobia, and scaling of the eyelid.

- May cause hypertension, dizziness, headache, dyspnea, or pulmonary complications.

### **Carcinogenicity**

- Mice studies of bimatoprost used as an antiglaucoma agent have not shown carcinogenic potential. Studies have not been performed for the carcinogenicity of bimatoprost used for hypotrichosis.

### **Patch Test Concentration**

- N/A

### **Essential Patient Information**

- Eyelash growth will return to baseline if therapy is discontinued.
- May cause unwanted hair growth if applied to unintended areas repeatedly. When using, only apply to upper eyelid and remove excess.

*Relative efficacy to innovator drug:* None

---

## **Minoxidil (Topical)**

### **Classification and Mode of Action**

- Minoxidil is a mitogenic agent that was first used as an antihypertensive medication. Side effects of hypertrichosis helped in the development of a topical version that now is known to promote hair growth.
- Mechanism of action is not entirely understood, but it is thought to be due to a combination of factors including vasodilation, increased blood flow to the skin, and hair follicle stimulation.

- Minoxidil is also recognized as an agonist for potassium channels, causing cell membrane hyperpolarization.
- It is believed that the synergistic effect of vasodilation and hyperpolarization allows more blood, nutrients, and oxygen into the hair follicle.
- Some clinical trials suggest that the 5% formulation has a higher efficacy and earlier treatment response than 2% for both men and women.
- Continuous therapy of at least 4 months may be needed for visible results.

## Indications and Dermatological Uses

- *Clinical indications (FDA):* Androgenetic alopecia.
- *Off-label common uses:* Used for other hair loss conditions including telogen effluvium, scarring alopecia, alopecia areata, chemotherapy-induced alopecia, monilethrix, and eyebrow hypotrichosis.
- Oral minoxidil is not FDA approved for hair loss, but clinical trials show efficacy.

## Formulations/Presentation

- USA: 2% solution, 5% solution, 5% aerosol foam
- Canada: 2% solution, 5% solution, 5% aerosol foam
- Europe: 2% solution, 5% solution, 5% aerosol foam

## Dosages and Suggested Regimens

- Apply directed amount topically to hair-thinning areas of the scalp, and massage in with fingers. Wash hands after use.
- No suggested dosage adjustment for renal or hepatic impairment due to low systemic absorption.

## **Pharmacokinetics (Percutaneous Absorption, Distribution, Metabolism, Excretion) as Relevant**

- Metabolism/transport effects are unknown.

## **Use in Special Populations: Pregnancy (FDA Guidance), Lactation, Children, Renal Insufficiency, and Hepatic Insufficiency**

- Adverse effects have been seen in pregnancy.
- Present in breast milk after oral administration.
- Not approved for use in children <18 years old.
- For renal insufficiency or hepatic insufficiency, no dosage adjustments have been provided by the manufacturer.

## **Monitoring**

- Allergic dermatitis
- Change in hair texture
- Hair discoloration

## **Contraindications and Cautions**

- Caution for those with heart disease: Due to the possibility of systemic absorption followed by fluid/electrolyte changes, risk-vs-benefit analysis should be done in patients with heart disease.

## **Adverse Effects and Their Management**

- Change in hair texture. Notify physician if bothersome or does not go away.
- Hair discoloration. Notify physician if bothersome or does not go away.

- Allergic reactions include rash, hives, itching, red/swollen/blistered/peeling skin, wheezing, chest/throat tightness, difficulty breathing/swallowing/talking, unusual hoarseness, and swollen mouth/face/lips/tongue/throat. Discontinue medication, and seek immediate medical help if experiencing an allergic reaction.
- Local erythema or pruritus may occur.
- Allergic reaction may occur to propylene glycol, which is a nonactive ingredient present in some formulations.

## **Carcinogenicity**

- Minoxidil is a mitogenic agent, which are a class of drugs that induce cell division and thus have the increased risk for inducing DNA damage. Mice studies have shown that topical administration of high minoxidil doses can induce DNA damage without producing cytotoxicity.

## **Patch Test Concentration**

- 5% alcohol

## **Essential Patient Information**

- OTC Labeling: Do not use if amount of hair loss differs from that displayed on product label, if you do not have a family history of hair loss, if you have sudden/patchy hair loss, if your hair loss is triggered by childbirth, if you are unaware of the reason for your hair loss, if you are <18 years old, if your scalp is red/inflamed/painful/irritated/infected, or if you use other topical scalp medications.
- Do not use products on women intended for men.
- Avoid contact with the eyes, lips, or other mucous membranes. In the event of contact with eyes, wash eyes with a large amount of cool, filtered water.

- Not formulated for receding hairline or frontal baldness.
- Continued use is needed in order to maintain hair growth.
- Discontinue use if you experience chest pain, rapid heartbeat, faintness, dizziness, unexplained weight gain, swollen hands/feet, scalp irritation/redness, unwanted facial hair growth, or no hair growth results seen after 4–6 months.
- Flammable product. Avoid fire, flame, or smoking immediately after application.

---

## Eflornithine

### Classification and Mode of Action

- Eflornithine irreversibly inhibits ornithine decarboxylase. This process is thought to inhibit cell division and synthetic functions, which, in turn, affects the rate of hair growth.

### Indications and Dermatological Uses

- *Clinical indications (FDA):* Facial hair reduction
- *Off-label common uses:* West African trypanosomiasis with CNS involvement (level of evidence: B)

### Formulations/Presentation

- USA: 13.9% cream
- Canada: 13.9% cream
- Europe: 11.5% cream

### Dosages and Suggested Regimens

- Apply a thin layer of cream to affected areas of face and chin two times a day, at least 8 hours apart. Massage in with fingers.



- Wait at least 5 minutes after hair removal to apply cream. Hair removal techniques can still be used concomitant with eflornithine.
- Do not wash affected area at least 4 hours after application.

## **Baseline Investigations and Considerations**

### **Pharmacokinetics (Percutaneous Absorption, Distribution, Metabolism, Excretion) as Relevant**

- Onset of effect: 4–8 weeks.
- Continued results until about 8 weeks after discontinuing treatment.
- Elimination half-life is 8 hours.
- Excreted primarily in urine as unchanged drug.

### **Use in Special Populations: Pregnancy (FDA Guidance), Lactation, Children, Renal Insufficiency, and Hepatic Insufficiency**

- Unknown if eflornithine is present in breast milk. Caution should be exercised if using eflornithine while breastfeeding.
- Pregnancy category C (former). Eflornithine should be administered in pregnancy only when benefits outweigh the potential risks; although, it is recommended to not be used or discontinued due to unknown effects.
- Approved in children  $\geq 12$  years old.
- Renal insufficiency: Not evaluated; dose adjustment is not expected to be needed.
- Hepatic insufficiency: Not evaluated; dose adjustment is not expected to be needed.

## **Monitoring**

- Hypersensitivity reaction

**Contraindications and Cautions**

- Hypersensitivity to eflornithine or any part of formula
- For topical facial use for females only

**Important Drug Interactions**

- None known

**Adverse Effects and Their Management**

- May cause pimples, burning or stinging sensation, redness, skin tingling, or hair bumps. Notify physician if bothersome or does not go away.
- Immediately discontinue and seek medical help if experiencing very bad skin irritation.
- Allergic reactions include rash, hives, itching, redness, swelling, blistered/peeling skin, wheezing, chest/throat tightness, difficulty breathing, difficulty swallowing, difficulty talking, unusual hoarseness, and swollen mouth/face/lips/tongue/throat. Discontinue medication and seek immediate help if experiencing an allergic reaction.
- May cause acne vulgaris, pseudofolliculitis barbae, headache, skin tingling, dizziness, stinging of skin, burning skin sensation, pruritus, rash, xeroderma, erythema, alopecia, skin irritation, folliculitis, ingrown hair, dyspepsia, anorexia, acne rosaces, cheilitis, contact dermatitis, dermal hemorrhage, facial edema, herpes simplex infection, nausea, numbness, swollen lips, vertigo, and weakness.

**Carcinogenicity**

- Animal studies do not show carcinogenicity comparable to the maximum recommended dosage in humans. Eflornithine inhibits ornithine decarboxylase, which is an enzyme active in the cell cycle and thought to play a role in carcinogenesis. It can be postulated that eflornithine may even have anticarcinogenetic properties, although this has not been tested in clinical trials.

## Patch Test Concentration

- N/A

## Essential Patient Information

- Do not wash area for at least 4 hours after application.
- Makeup and sunscreen can be applied on treated areas after topical cream has dried.

*Relative efficacy to innovator drug:* None

---

## References

### Bimatoprost

1. FDA drug monograph Latisse® (bimatoprost ophthalmic solution). Available from [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2012/022369s0051bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022369s0051bl.pdf). Accessed 05/01/2022.
2. LexiComp drug monograph Bimatoprost. Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2021 UptoDate, Inc.
3. Vergilis-Kalner JJ. Application of bimatoprost ophthalmic solution 0.03%; for the treatment of eyebrow hypotrichosis: series of Ten cases. *Dermatol Online J*. 2014;20
4. Elias MJ, Weiss J, Weiss E. Bimatoprost Ophthalmic Solution 0.03% for eyebrow growth. *Dermatologic Surg*. 2011;37:1057–9.
5. Harii K, Arase S, Tsuboi R, Weng E, Daniels S, VanDenburgh A. Bimatoprost for eyelash growth in Japanese subjects: two multicenter controlled studies. *Aesth Plast Surg*. 2014;38:451–60.
6. Smith S, Fagien S, Whitcup SM, Ledon F, Somogyi C, Weng E, Beddingfield FC. Eyelash growth in subjects treated with Bimatoprost: a multicenter, randomized, double-masked, vehicle-controlled, parallel-group study. *J Am Acad Dermatol*. 2012;66:801–6.
7. Glaser DA, Hossain P, Perkins W, Griffiths T, Ahluwalia G, Weng E, Beddingfield FC. Long-term safety and efficacy of bimatoprost solution 0.03% application to the eyelid margin for the treatment of idiopathic and chemotherapy-induced eyelash hypotrichosis: a randomized controlled trial. *Br J Dermatol*. 2015;172:1384–94.
8. Centofanti M, Oddone F, Chimenti S, Tanga L, Citarella L, Manni G. Prevention of dermatologic side effects of bimatoprost 0.03% topical therapy. *Am J Ophthalmol*. 2006;142:1059–60.

9. Woodward DF, Phelps RL, Krauss AH-P, Weber A, Short B, Chen J, Liang Y, Wheeler LA. Bimatoprost: a novel antiglaucoma agent. *Cardiovasc Drug Rev*. 2006;22:103–20.
10. Patil AJ, Vajaranant TS, Edward DP. Bimatoprost—a review. *Expert Opin Pharmacother*. 2009;10:2759–68.

## Minoxidil (Topical)

11. FDA drug monograph Minoxidil. Available from [https://www.accessdata.fda.gov/drugsatfda\\_docs/anda/2001/75-839\\_Minoxidil.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/anda/2001/75-839_Minoxidil.pdf). Accessed 05/01/2022.
12. LexiComp drug monograph Minoxidil. Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2021 UptoDate, Inc.
13. Naranjo-Vázquez E, Sánchez-Parada MG, Gómez-Meda BC, Zamora-Perez AL, Gallegos-Arreola MP, González-Santiago AE, Zúñiga-González GM. Effect of high-dose topical minoxidil on erythrocyte quality in SKH1 hairless mice. *Animals*. 2020;10:731.
14. Suchonwanit P, Thammarucha S, Leerunyakul K. Minoxidil and its use in hair disorders: a review. *Drug Des Dev Ther*. 2019;13:2777–86.
15. Randolph M, Tosti A. Oral Minoxidil treatment for hair loss: a review of efficacy and safety. *J Am Acad Dermatol*. 2021;84:737–46.
16. Stoehr JR, Choi JN, Colavincenzo M, Vanderweil S. Off-label use of Topical Minoxidil in alopecia: a review. *Am J Clin Dermatol*. 2019;20:237–50.
17. Rossi A, Cantisani C, Melis L, Iorio A, Scali E, Calvieri S. Minoxidil use in dermatology, side effects and recent patents. *Recent Patents Inflamm Allergy Drug Discov*. 2012;6:130–6.
18. Gupta AK, Talukder M, Venkataraman M, Bamimore MA. Minoxidil: a comprehensive review. *J Dermatol Treat*. 2021;1–11.
19. Olsen EA, Dunlap FE, Funicella T, Koperski JA, Swinehart JM, Tschen EH, Trancik RJ. A randomized clinical trial of 5% topical minoxidil versus 2% topical minoxidil and placebo in the treatment of androgenetic alopecia in men. *J Am Acad Dermatol*. 2002;47:377–85.
20. Lucky AW, Piacquadio DJ, Ditre CM, Dunlap F, Kantor I, Pandya AG, Savin RC, Tharp MD. A randomized, placebo-controlled trial of 5% and 2% topical minoxidil solutions in the treatment of female pattern hair loss. *J Am Acad Dermatol*. 2004;50:541–53.
21. Ramos PM, Sinclair RD, Kasprzak M, Miot HA. Minoxidil 1 mg oral versus minoxidil 5% topical solution for the treatment of female-pattern hair loss: a randomized clinical trial. *J Am Acad Dermatol*. 2020;82:252–3.

## Eflornithine

22. FDA drug monograph Vaniqa™ (eflornithine hydrochloride) cream 13.9%. Available from [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2000/211451bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2000/211451bl.pdf). Accessed 05/01/2022.
23. LexiComp drug monograph (name of monograph). Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2021 UptoDate, Inc.
24. Wolf JE, Shander D, Huber F, Jackson J, Lin C-S, Mathes BM, Schrode K. Randomized, double-blind clinical evaluation of the efficacy and safety of topical eflornithine hcl 13.9% cream in the treatment of women with facial hair. *Int J Dermatol*. 2006;46:94–8.
25. Jackson J, Caro JJ, Caro G, Garfield F, Huber F, Zhou W, Lin C-S, Shander D, Schrode K. The effect of eflornithine 13.9% cream on the bother and discomfort due to hirsutism. *Int J Dermatol*. 2007;46:976–81.
26. Hamzavi I, Tan E, Shapiro J, Lui H. A randomized bilateral vehicle-controlled study of eflornithine cream combined with laser treatment versus laser treatment alone for facial hirsutism in women. *J Am Acad Dermatol*. 2007;7:54–9.
27. Vissing AC, Taudorf EH, Haak CS, Philipsen PA, Haedersdal M. Adjuvant eflornithine to maintain IPL-induced hair reduction in women with facial hirsutism: a randomized controlled trial. *J Eur Acad Dermatol Venereol*. 2015;30:314–9.
28. Barman Balfour JA, McClellan K. Topical eflornithine. *Am J Clin Dermatol*. 2001;2:197–201.
29. Ramot Y, Pietilä M, Giuliani G, Rinaldi F, Alhonen L, Paus R. Polyamines and hair: a couple in search of perfection. *Exp Dermatol*. 2010;19:784–90.



Rebecca M. Law , Victoria Nguyen,  
Linda B. Ou, Sheeva Shahinfar,  
and Howard I. Maibach

## Contents

|                                                |     |
|------------------------------------------------|-----|
| Becaplermin.....                               | 668 |
| Hydrogen Peroxide.....                         | 671 |
| Sodium Hypochlorite and Hypochlorous Acid..... | 675 |
| Imiquimod.....                                 | 678 |
| Podofilox (Podophyllotoxin).....               | 683 |
| Podophyllum Resin.....                         | 686 |

---

R. M. Law (✉)

School of Pharmacy and Faculty of Medicine (Discipline of Family  
Medicine), Memorial University of Newfoundland,  
St. John's, NL, Canada  
e-mail: [rlaw@mun.ca](mailto:rlaw@mun.ca); [rlawUCSF@gmail.com](mailto:rlawUCSF@gmail.com)

V. Nguyen

School of Pharmacy, University of Waterloo, Kitchener, ON, Canada  
e-mail: [vtpnguye@uwaterloo.ca](mailto:vtpnguye@uwaterloo.ca)

L. B. Ou

Sunnybrook Health Sciences Centre, Toronto, ON, Canada  
e-mail: [lindaou25@gmail.com](mailto:lindaou25@gmail.com)

S. Shahinfar

Texas A&M University, College of Medicine, Bryan, TX, USA  
e-mail: [Sheeva.Shahinfar@tamu.edu](mailto:Sheeva.Shahinfar@tamu.edu)

© The Author(s), under exclusive license to Springer Nature  
Switzerland AG 2025

667

R. M. Law, H. I. Maibach (eds.), *Handbook of Topical Drug  
Treatment in Dermatology*,  
[https://doi.org/10.1007/978-3-031-93616-6\\_27](https://doi.org/10.1007/978-3-031-93616-6_27)

|                       |     |
|-----------------------|-----|
| Propylene Glycol..... | 690 |
| Urea.....             | 694 |
| References.....       | 697 |

---

## **Becaplermin**

Rebecca M. Law

### **Classification and Mode of Action**

- Becaplermin is a recombinant B-isoform homodimer of human platelet-derived Growth Factor (rPDGF-BB). It helps in the formation of new granulation tissue, induces fibroblast proliferation and differentiation, thus promoting wound healing. It also promotes angiogenesis.

### **Indication & Dermatological Use**

- Diabetic ulcers (lower extremity) in adults and adolescents 16 years of age and older. It is indicated as an adjunctive treatment of lower extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond and there is an adequate blood supply.
- Efficacy has not been established for other other ulcers (ie. Pressure and venous stasis ulcers) and has not been evaluated in diabetic neuropathic ulcers that do not extend into subcutaneous tissue or in diabetic ischemic ulcers.

---

H. I. Maibach

Department of Dermatology, University of California San Francisco (UCSF), San Francisco, CA, USA

e-mail: [howard.maibach@ucsf.edu](mailto:howard.maibach@ucsf.edu)

- Not for use in wounds that close by primary intention. Effects on exposed joints, tendons, ligaments and bone have not been established.
- No overall differences in efficacy or safety were seen between patients <60 vs >65 years of age.

## **Formulation/Presentation**

- 0.01% gel

## **Dosages & Suggested Regimens**

- Apply once daily as a coating over the ulcer. Squeeze appropriate amount of gel onto a clean measuring surface and spread onto the entire ulcer area in a thin, continuous layer about 1/16 inch thick. Cover with saline moistened dressing and leave dressing in place for about 12 hours. After 12 hrs, remove dressing and rinse with saline or water and cover with saline moistened dressing without becaplermin gel for the remainder of the day. Continue use once daily until the ulcer is healed.
- The amount to be applied will vary depending on the size of the ulcer area. To estimate the gel requirement: measure the greatest length of the ulcer by the greatest width of the ulcer; and recalculate the amount needed every 1-2 weeks, as the ulcer heals. If the ulcer does not reduce in size by about 30% after 10 weeks of treatment, or if complete healing has not occurred by 20 weeks, continued treatment with becaplermin gel should be reassessed.

## **Pharmacokinetics**

- Low systemic absorption



## **Use in Special Populations**

- No dosage adjustment provided for altered kidney function or altered hepatic function in the manufacturer's labelling. Dosement adjustment is unlikely due to low systemic absorption.
- No overall differences in safety or effectiveness were observed between patients <65 and >65 years of age.
- Safety in pregnancy has not been established.
- Unknown whether becaplermin is present in breast milk.

## **Monitoring**

- Monitor for adverse effects as described below under Warnings/Precautions and Adverse Reactions.
- Monitor for effectiveness: ulcer volume, wound area, evidence of closure, drainage.

## **Warnings/Precautions**

- Monitor for application site reactions: Sensitization or irritation of skin may occur. This may be due to preservatives parabens or m-cresol. If seen, interruption or discontinuation of treatment should be considered, and further evaluation (e.g. via patch testing) may be necessary.
- Malignancies of varying types have been reported. These were all remote from the becaplermin treatment site. Use with caution in patients with known malignancy. Becaplermin should only be used with benefits can be expected to outweigh the risks.

## **Adverse Reactions**

- Erythematous rash
- Application site burning, application-site erythema

## Drug Interactions

- None known

## Carcinogenicity

- See under Warnings/Precautions for discussion.
- Use with caution in patients with known malignancy.

## Patch Test Concentration

- Not available

---

## Hydrogen Peroxide

Rebecca M. Law

## Classification and Mode of Action

- Hydrogen peroxide is an oxidizing agent with antiseptic properties. It is an antiseptic oxidant that slowly releases oxygen and water upon contact with tissue catalase or serum (i.e., catalase decomposes hydrogen peroxide to protect cells and tissues.) The mechanism of action for the treatment of seborrheic keratosis is unknown.

## Indications and Dermatological Uses

- *Clinical indications (FDA):* Antiseptic for minor dermal abrasions; oral rinse for mouth, gum or dental irritation; topical solution for removal of oral secretions; a potent topical solution (40%) for treatment of raised seborrheic keratoses

## Formulations/Presentation

- USA: Topical solution (3%), topical solution (40%), topical spray (3%), oral rinse (1.5%), oral gel (1.7%).

## Dosages and Suggested Regimens

- As antiseptic: Clean the affected area and apply the 3% solution/spray. May cover the area with a sterile bandage after the solution has dried. Solutions >3% are irritants and must be diluted prior to application.
- As treatment of raised seborrheic keratoses: Use the 40% solution—not for oral, ophthalmic, or intravaginal use. Apply to lesion four times during a single in-office treatment session. If the treated lesions have not completely cleared after 3 weeks, may repeat. However, do not start a second treatment course until the skin has recovered from any reaction caused by the previous treatment.
- As oral rinse: Use 1.5% solution to swish over the affected for one or more minutes and then spit out. Do not swallow.
- As oral gel: Use 1.7% spray on affected area, leave on for at least 1 min, and then spit out. Do not swallow.

## Pharmacokinetics

- Duration of action: only while bubbling action occurs
- Absorption: none

## Use in Special Populations

- Some dosage forms may include propylene glycol. In neonates, large amounts of propylene glycol (IV, orally, or topically) have been associated with fatal toxicities including seizures, metabolic acidosis, renal failure, and CNS depression. Toxicities

- have also been reported in children and adults including hyperosmolality, lactic acidosis, seizures, and respiratory depression.
- Renal insufficiency: No dose adjustments on manufacturer's labelling.
  - Hepatic impairment: No dose adjustments on manufacturer's labelling.

## Monitoring

- For adverse effects as discussed below. Repeated/frequent uses may increase the risk of irritation and other adverse effects.

## Contraindications and Cautions

- Not to be used in the eyes or over large areas of the body.
- Not to be used for longer than a week.
- Bandages should not be applied too quickly after using hydrogen peroxide.
- Ten percent and 30% solutions must be diluted prior to use.
- Topical solution 40%: Do not apply to eyes or mucous membranes. Avoid treating seborrheic keratoses within the orbital rim.

## Important Drug Interactions

- Avoid using with taurolidine: Concomitant use of taurolidine and hydrogen peroxide may increase the risk of metabolic acidosis. Risk X: Avoid combination.

## Adverse Effects and Their Management

- Irritation may occur at the site of application (for all uses of hydrogen peroxide).
- Other adverse effect for use in seborrheic keratoses: Stinging, red and blistered or swollen skin, crusting, scaling, and change in skin color may occur.

- Avoid the eyes. Direct contact with the eye can cause corneal injury (erosion, scarring, ulceration, perforation), chemical conjunctivitis, eyelid edema, and severe eye pain. And there may be permanent eye injury including blindness. For accidental exposure, immediately flush with water for 15–30 min, and further evaluate as appropriate.
- Repeat use as a mouthwash or gargle may cause irritation of the buccal mucous membrane or “hairy tongue.”

## **Carcinogenicity**

- Unknown

## **Patch Test Concentration**

- Not available

## **Essential Patient Information**

- Hydrogen peroxide may cause skin irritation, redness, itching, stinging, blistering or swelling, and change in skin color. Avoid using in or near the eye. If drug accidentally gets in the eye, immediately flush with water for 15–30 min, and contact a health care professional.
- Do not use the 10% or 30% solution undiluted.
- If using as a mouth rinse or gargle, must spit out. Do not swallow.
- Repeated/frequent uses of hydrogen peroxide may cause increased irritation.

## Sodium Hypochlorite and Hypochlorous Acid

Rebecca M. Law

### Classification and Mode of Action

- Topical antiseptic with activity against bacterial, viral, and fungal microorganisms.

### Indications and Dermatological Uses

- *Clinical indications (FDA)*: Antiseptic for prevention and treatment of skin and tissue infections and treatment of cuts, abrasions, and skin ulcers (e.g., stage I to IV pressure ulcers, diabetic foot and leg ulcers, postsurgical wounds).

### Formulations/Presentation

- USA
  - Gel: Anasept antimicrobial 0.057% (latex free); H-Chlor Wound 0.062%
  - Liquid: Anasept 0.057% (two formulations with one being latex free)
  - Solution: Avenova 0.01% (as hypochlorous acid). Various formulations available from 0.012% to 0.5% from various manufacturers including generic products
  - Spray solution: Avenova 0.01%

## **Dosages and Suggested Regimens**

- Gel can be applied as a thin layer for ostomy or skin care and as a thick layer (1/4–1/2 inch) to entire wound bed for wound care, with a thin layer to periwound skin areas.
- Liquid/solution/spray can be poured on or sprayed onto entire wound bed, including margins (avoid pooling), or saturate sterile gauze, and apply to wound site. Cover with sterile gauze/wound dressing, and ensure that the wound bed remains moist between dressing changes.

## **Pharmacokinetics**

- Not available

## **Use in Special Populations**

- Renal insufficiency: no dose adjustments on manufacturer's labelling.
- Hepatic impairment: no dose adjustments on manufacturer's labelling.
- Use in older adults, children and pregnancy are similar to use in adults.

## **Monitoring**

- For signs of redness, swelling, or irritation

## **Contraindications and Cautions**

- Contraindication: Hypersensitivity to sodium hypochlorite, chlorine compounds, or any component of the formulations

## **Important Drug Interactions**

- Avoid using with taurolidine: Concomitant use of taurolidine and hydrogen peroxide may increase the risk of metabolic acidosis. Risk X: Avoid combination.

## **Adverse Effects and Their management**

- No adverse reactions listed in the manufacturer's labeling.
- Irritation, swelling, and redness would be signs of a hypersensitivity reaction.

## **Carcinogenicity**

- Unknown

## **Patch Test Concentration**

- Not available

## **Essential Patient Information**

- When used for self-medication (OTC use): Patients should be instructed to discontinue use and consult a health care professional if irritation, swelling, redness, or pain persists or increases.
- The products may bleach clothing.



## Imiquimod

Victoria Nguyen, Linda Ou, and Rebecca M. Law

### Classification and Mode of Action

- Imiquimod is an immune response modulator from the imidazoquinolinamines drug class.
- It is a Toll-like receptor 7 (TLR-7) agonist that stimulates the innate immune system. Consequently, this leads to the production of cytokines, like IFN- $\alpha$ , IL-6, and TNF- $\alpha$ , which modulate immune responses.
- Topically applied imiquimod has been found to activate Langerhans cells, which then migrate to local lymph nodes to stimulate the adaptive immune system.
- A randomized, double-blind, Phase III trial found that 3.5% imiquimod cream was superior to placebo in the clearance of genital warts at 24.9% and 9%, respectively.

### Indications and Dermatological Uses

- *Clinical indications (FDA)*—actinic keratosis, superficial basal cell carcinoma, external genital, and perianal warts
- *Off-label common uses*—cutaneous flat wart, acyclovir resistant genital herpes simplex virus infection, nongenital warts, epidermodysplasia verruciformis, keratoacanthoma, keratoacanthoma, oral leukoplakia, verrucous carcinoma, mycosis fungoides, pyogenic granuloma, and keloid, follicular mucinosis
  - Level of evidence for cutaneous flat wart: C
  - Level of evidence for acyclovir resistant genital herpes simplex virus infection: C, G

## Formulations/Presentation

- USA: Zyclara® cream (2.5%, 3.75%)
- Canada: Cream (2.5%, 3.75%, 5%)
- Europe: Cream (3.75%, 5%)

## Dosages and Suggested Regimens

- Actinic keratosis
  - 2.5% and 3.5% cream: Apply a thin film to affected areas once daily for 2 weeks. Leave on for 8 h and then remove with mild soap and water.
  - 5% cream: Apply to affected areas two times per week for 16 weeks. Leave on for 8 h and then remove with mild soap and water.
- Superficial basal cell carcinoma
  - 5% cream: Apply to tumor and 1 cm of skin surrounding tumor once daily 5 times per week for 6 weeks. Leave on for 8 h and then remove with mild soap and water. Tumor treatment area, including 1 cm of surrounding skin, should not be greater than 3 cm.
- External genital and perianal warts
  - 3.75% cream: Apply a thin film once daily. Leave on for 8 h and then remove with mild soap and water. Continue treatment until clearance of warts or for a maximum of 8 weeks.
  - 5% cream: Apply a thin film three times per week. Leave on for 6–10 h and then remove with mild soap and water. Continue treatment until clearance of warts or for a maximum of 16 weeks.
- Cutaneous flat warts (off-label use)
  - 5% cream: Apply once daily until clearance of warts or for a maximum of 12 weeks.
- Acyclovir resistant genital herpes simplex virus (off-label)
  - 5% cream: Apply to affected areas three times per week. Leave on skin for 8 h. Continue treatment until resolution.

## Pharmacokinetics

- Minimal systemic absorption across affected skin. Systemic absorption is more dependent on the body surface area of application than dose. Peak plasma concentrations range from 0.1 to 3.5 ng/mL. Half-life is approximately 30 h. Peak effect occurs at 9–12 h. Excreted in urine.

## Use in Special Populations

- Pregnancy: Listed as pregnancy category C. Appears to be low risk when used topically for anogenital warts but manufacturer's caution against use during pregnancy unless potential benefits outweigh risks.
- Lactation: Unknown whether imiquimod is secreted into breast milk, but the manufacturer recommends use with caution in breastfeeding patients.
- Children: Safety and efficacy not established in patients less than 18 years of age.
  - Actinic keratosis and superficial basal cell carcinoma: These conditions are not often seen in children. Safety and efficacy not established in children less than 18 years of age.
  - External genital/perianal warts: Safety and efficacy not established in patients less than 12 years of age.
- Renal insufficiency: No dose adjustments on manufacturer's labelling.
- Hepatic impairment: No dose adjustments on manufacturer's labelling.

## Monitoring

- Intense local inflammatory reactions may occur. Dosing interruption may be warranted.
- Severe local inflammatory reaction can lead to vulvar swelling and, consequently, urinary retention. Dose should be interrupted or discontinued.

- Flu-like symptoms including malaise, fever, and myalgias may occur. Dosing interruption may be warranted.
- Increased serum glucose.
- Signs and symptoms of hypersensitivity.

## **Contraindications and Cautions**

- Hypersensitivity to imiquimod or any ingredient in formulation

## **Important Drug Interactions**

- No drug interactions on manufacturer's labelling.
- Not recommended for concomitant use with immunosuppressive drugs like tacrolimus, cyclosporine, or methotrexate.
- Concomitant use with corticosteroids may limit efficacy.

## **Adverse Effects and Their Management**

- Local skin reaction (50–96%) like crusting, edema, flaking, itching, scaling, and ulceration. Acute cases can be managed by temporary dosing interruption and the use of cold compresses. Imiquimod increases the risk of sun-induced skin damage. Minimizing exposure to UV light and use of sunscreens is advised.
- Gastrointestinal symptoms like nausea, diarrhea, vomiting, and dyspepsia may occur
- May increase incidence of infections like herpes simplex, lymphadenopathy, urinary tract infection, upper respiratory tract infections, and fungal infections.
- May cause respiratory symptoms like cough, pharyngitis, and rhinitis.

## **Carcinogenicity**

- Not teratogenic in animal studies

## **Patch Test Concentration**

- Not available

## **Essential Patient Information**

- Medication should not be administered orally, intravaginally, or intra-anally.
- Avoid getting medication in the eyes, lips, and nostrils. If contact occurs, immediately rinse with water.
- Apply cream at bedtime and leave on skin for 8 h. Do not bathe or get treated area wet until the next morning.
- Avoid using occlusive dressings. If desired, cotton gauze dressings can be used.
- Imiquimod increases risk of sunburns. Use sun protection including sunscreen and sunglasses.
- Imiquimod may decrease efficacy of condoms and diaphragms. Use other forms of contraception while on therapy.
- Seek immediate medical attention if you experience signs of an allergic reaction like rash, hives, peeling skin with or without fever, and difficulty breathing.

## Podofilox (Podophyllotoxin)

Rebecca M. Law and Howard I. Maibach

### Classification and Mode of Action

- Podofilox (podophyllotoxin) is a keratolytic agent. It binds to a protein subunit of spindle microtubules (tubulin) to arrest mitosis in the epithelial cell, thus causing wart necrosis.
- Podofilox is *not* podophyllum resin—also a keratolytic agent with a similar mechanism of action. Although both are available commercially in the USA, podophyllum resin is not recommended in the CDC sexually transmitted diseases guidelines due to reports of significant systemic toxicity when applied incorrectly. (Podophyllin resin, if used, must be administered by a physician—see podophyllin as a separate drug monograph below.)

### Indications and Dermatological Uses

- *Clinical indications (FDA):* External genital warts (solution or gel); perianal warts (gel only)
- *Off-label common uses:* Molluscum contagiosum

### Formulations/Presentation

- USA: 0.5% solution or gel
- Canada: 0.5% solution

### Dosages and Suggested Regimens

- Apply to warts using either the supplied applicator or with finger (gel only) while minimizing contact with surrounding normal tissue. Do not apply to mucous membrane warts.

## Pharmacokinetics

- In systemic absorption studies in 52 patients
  - topical application of 0.05 mL of 0.5% podofilox solution to external genitalia did not result in detectable serum levels.
  - Applications of 0.1–1.5 mL resulted in peak serum levels of 1–17 ng/mL 1–2 h after application.
  - The elimination half-life ranged from 1.0 to 4.5 h.
  - The drug was not found to accumulate after multiple treatments.

## Use in Special Populations

- Should not be used during pregnancy.
- Unknown if podofilox is present in breast milk.
- Renal insufficiency: no dose adjustments on manufacturer's labelling.
- Hepatic impairment: no dose adjustments on manufacturer's labelling.
- Use in older adults is similar to use in adults.

## Monitoring

- Efficacy and adverse effects: Monitor treated areas for adequate healing and for tolerability of treatment.

## Contraindications and cautions

- Not for use in pregnancy or breastfeeding.
- Do not use concurrently with other podophyllin-containing products.
- Do not use if open wounds or inflamed or bleeding lesions exist.

- Do not use in children <12 years old.
- Severe skin reactions can occur, most frequently within the first 2 weeks of treatment.

## **Important Drug Interactions**

- Any other podophyllin-containing product should not be used concurrently.

## **Adverse Effects and Their Management**

- >10%: Localized burning and pain, skin erosion, local hemorrhage, inflammation, and pruritus.
- Others: dermal ulcer, desquamation, skin blister/tenderness, skin discoloration, and xeroderma.
- Although most skin reactions are mild to moderate, severe skin reactions can occur—most frequently within the first 2 weeks of treatment.

## **Carcinogenicity**

- Published animal studies, in general, have not shown the drug substance, podofilox, to be carcinogenic.
- There are published reports that, in mouse studies, crude podophyllin resin (containing podofilox) applied topically to the cervix produced changes resembling carcinoma in situ [15]. These changes were reversible at 5 weeks after cessation of treatment. In one reported experiment, epidermal carcinoma of the vagina and cervix was found in 1 out of 18 mice after 120 applications of podophyllin [16] (the drug was applied twice weekly over a 15-month period).



## Patch Test Concentration

- Not available

## Essential Patient Information

- Avoid contact with eyes. If drug accidentally gets in eyes, flush eyes with water and get medical help.
- The gel and solution are flammable. Keep away from fire or flame.
- Wash hands before and after application.
- Do not apply to mucous membrane warts.
- Storage: Avoid excessive heat. Do not freeze.

---

## Podophyllum Resin

Rebecca M. Law and Howard I. Maibach

## Classification and Mode of Action

- Podophyllum is a keratolytic agent. It directly affects epithelial cell metabolism by binding to tubulin (a protein subunit of spindle microtubules). It arrests mitosis in metaphase (i.e., cytotoxic). This is *not* podofilox.
- Podophyllum resin is not recommended in the CDC sexually transmitted diseases guidelines due to reports of significant systemic toxicity when applied incorrectly.

## Indications and Dermatological Uses

- *Clinical indications (FDA)*: For removal of genital warts. However, it is no longer recommended in the CDC sexually transmitted diseases guidelines due to significant systemic toxicity reported. It is to be used by physician only; it is *not* to be dispensed to the patient.

## Formulations/Presentation

- USA: Podophyllin 25% solution (Podocon-25 external). The podophyllin resin used in this product is exclusively the American podophyllin (rather than the Indian resin). American podophyllin typically has a reduced level of podophyllotoxin (see drug monograph above).
- Canada: Podofilm.

## Dosages and Suggested Regimens

- Use a toothpick or a cotton-tipped or glass applicator to apply the podophyllin solution. Apply 1 drop at a time, allowing time for drying between drops, until the affected area is covered. Allow solution to remain on wart as directed, and then remove by washing with soap and water.
- Do not touch adjacent normal skin.
- Avoid contact with eyes and other mucous membranes, e.g., the inside of the nose, mouth, or vagina.
- If contact with eyes occur, immediately flush the eyes with water for 15 min.
- If contact with normal skin occurs, thoroughly wash the skin with soap and water.

## Pharmacokinetics

- Oral absorption: Podophyllum is very well and rapidly absorbed after accidental ingestion. *Avoid* route.
- Dermal absorption: Systemic poisoning was reported after topical application in some cases. Symptoms were delayed between 2 and 24 h.

## **Use in Special Populations**

- Use in breastfeeding is contraindicated by the manufacturer. Unknown whether it is present in breast milk.
- Contraindicated in pregnancy. Fetal abnormalities, fetal death, and stillbirth have been reported following the use of podophyllin resin in pregnant patients.

## **Monitoring**

- Efficacy and adverse effects: Monitor treated areas for adequate healing and for tolerability of treatment.

## **Contraindications and Cautions**

- Not for use on bleeding warts, birthmarks, moles, or warts with hair growth
- Not for use in patients with diabetes or poor circulation
- Not to be used in patients on concurrent steroids
- Contraindicated in pregnancy or if breastfeeding

## **Important Drug Interactions**

- Any other podophyllin-containing product should not be used concurrently.

## **Adverse Effects and Their Management**

- May cause severe skin irritation.
- The use of topical podophyllin has been known to result in paresthesia, polyneuritis, paralytic ileus, pyrexia, leukopenia, thrombocytopenia, coma, and death.

## Carcinogenicity

- There are published reports that, in mouse studies, crude podophyllin resin (containing podofilox) applied topically to the cervix produced changes resembling carcinoma in situ [21]. These changes were reversible at five weeks after cessation of treatment. In one reported experiment, epidermal carcinoma of the vagina and cervix was found in 1 out of 18 mice after 120 applications of podophyllin [22] (the drug was applied twice weekly over a 15-month period).

## Patch Test Concentration

- Not available

## Essential Patient Information

- This product is to be used *only* by a physician.
- Podophyllum is a poison. It is harmful if swallowed.
- Avoid contact with eyes and other mucous membranes, e.g., the inside of the nose, mouth, or vagina.
- May cause severe irritation.
- If contact with eyes occur, immediately flush the eyes with water for 15 min.
- If contact with normal skin occurs, thoroughly wash the skin with soap and water.

## Propylene Glycol

Sheeva Shahinfar, Rebecca M. Law, and Howard I. Maibach

### Classification and Mode of Action

- Propylene glycol is a product that has humectant properties. Its mechanism of action is simple in that, when applied topically, it attracts and retains water in the skin layers to increase the moisture and improve hydration in the skin. It can also be used as a vehicle or solvent, in combination with lipophilic drugs that are not stable in water.

### Indications and Dermatological Uses

- *Clinical indications (FDA):* dry skin
- *Off-label common uses*

### Formulations/Presentation

- USA: Not sold individually for dermatologic use. Combined with pharmaceutical and cosmetic products for increased moisture
- Canada: Not sold individually for dermatologic use. Combined with pharmaceutical and cosmetic products for increased moisture
- Europe: Not sold individually for dermatologic use. Combined with pharmaceutical and cosmetic products for increased moisture

## Dosages and Suggested Regimens

- N/A—not applied individually as dermatological therapy. Follow dosage and regimen guidelines for labeled drugs that propylene glycol is combined with.

## Pharmacokinetics

- Absorption of propylene glycol may be quick, although much research has not been performed on it.
- Of note, a case was reported of an infant with burns who was instructed to apply cream with propylene glycol as one of the ingredients. The patient skipped 2 days of application. Subsequent use resulted in cardiopulmonary arrest within 1 h of re-exposure to the cream [33].
- Half-life was described as 16.9 h in an infant [33].
- Propylene glycol is metabolized into pyruvic acid, lactic acid, acetic acid, and propionaldehyde via liver oxidation.
- Elimination of the drug depends on the dosage used. Most undergoes urinary excretion as the glucuronide conjugate, but up to 45% of the drug may be excreted unchanged.

## Use in Special Populations

- No studies have been done on the use of topical propylene glycol in pregnancy
- No studies have been done on the use of topical propylene glycol in lactation
- No recommendations have been given on the use of topical propylene glycol in children.
- No dose adjustments for renal insufficiency noted in research, although adverse effect of renal impairment noted in animal studies.
- No dose adjustments for hepatic insufficiency noted in research, although adverse effect of hepatic impairment noted in animal studies

## Monitoring

- Product should not be ingested. Ingestion may result in drowsiness, stupor, unconsciousness, or coma. Serum hyperosmolality, hypoglycemia, and lactic acidosis may also be noted.
- Skin absorption into systemic system is minimal.
- Monitor for local irritations or hypersensitivity.
- System effects unlikely, although may be increased with repeated use.
- Monitor for eye irritation if product comes into contact with eye.

## Contraindications and Cautions

- Do not use on open wounds, irritated skin, or burns.

## Important Drug Interactions

- No data available

## Adverse Effects and Their Management

- Skin irritation and hypersensitivity reactions may occur. Discontinue drug and treat irritation in the event of an allergic reaction.
- Application into the ear may result in cochlear toxicity in patients with tympanic membrane damage.
- System adverse effects are highly unlikely due to the low systemic absorption of the drug. Immediately discontinue drug if patient experiences shortness of breath, chest pain, fever, allergic reaction, or anaphylaxis after product use.
- If dosage is high resulting in high systemic concentration, the primary adverse effect is CNS depression, particularly in children.

- Other adverse effects include hyperosmolarity, hepatic impairment, renal impairment, arrhythmias, cardiorespiratory arrest, seizures, and intravascular hemolysis, and lactic acidosis.
- Toxicity should be managed symptomatically. If patients do not respond to supportive management, alcohol or fomepizole may be used to inhibit the metabolism of propylene glycol. Hemodialysis may also be considered as an alternative treatment.
- Chronic use of propylene glycol may have increased skin irritation if impermeable pads are used to cover the application site.

## **Carcinogenicity**

- No data available

## **Patch Test Concentration**

- Not available

## **Essential Patient Information**

- Discontinue use and contact your health provider if skin irritation occurs.
- Do not apply to open wounds, irritated skin, or burns. Do not apply to eye or inner ear.
- Immediately discontinue medication and seek medical attention if you experience shortness of breath, chest pain, fever, allergic reaction, or anaphylaxis after product use.
- It is recommended to not cover the application site with an impermeable pad, as this may increase the chance of skin irritation.



## Urea

Victoria Nguyen, Linda Ou, and Rebecca M. Law

### Classification and Mode of Action

- Urea is a hygroscopic substance naturally occurring in the epidermis. It improves skin barrier function and maintains hydration.
- Urea-containing formulations are commonly used in dermatology as moisturizers and keratolytic agents.
- Urea induces the expression of genes involved in keratinocyte differentiation, like filaggrin, loricrin, and transglutaminase 1, which are important for skin barrier function. Also, urea exhibits keratolytic action on hyperkeratotic areas by dissolving the intercellular matrix of cells in the stratum corneum.
- Urea has been shown to increase skin and nail penetration which can improve the therapeutic action of topical drugs.
- While urea has historically been used to improve skin hydration and treat hyperkeratotic conditions, the FDA has not given approval for this indication. Generally, at low concentrations, urea is used as moisturizers and keratolytics. At higher concentrations ( $\geq 30\%$ ), urea is used for conditions like psoriasis, xerosis, eczema, and for the debridement of necrotic tissue.

### Indications and Dermatological Uses

- *Clinical indications (FDA)*—no labelling has been approved by the FDA.
- *Off-label common uses*—hyperkeratotic conditions.

## Formulations/Presentation

- USA: Cream (10–40%), foam (30–35%), gel (45%), lotion (10–40%), ointment (10–20%), solution (25%), suspension (40–50%)
- Canada: Cream (10–40%)
- Europe: Cream (10–40%)

## Dosages and Suggested Regimens

- Hyperkeratotic conditions (off-label): Apply topically to affected area one to three times daily.

## Pharmacokinetics

- No published studies on pharmacokinetics

## Use in Special Populations

- Pregnancy: Studies have not been conducted with all products. Animal studies have not demonstrated adverse effects on the fetus.
- Lactation: Unknown whether urea is secreted into breast milk. Caution is warranted when used by nursing women.
- Children: Not assessed; use not recommended in children under 2 years of age
- Renal insufficiency: Not assessed; dosage adjustments likely unnecessary.
- Hepatic insufficiency: Not assessed; dosage adjustments likely unnecessary.

## Monitoring

- Intense application site reactions may occur. Dosing interruption may be warranted.
- Signs and symptoms of hypersensitivity like rash, urticaria, dyspnea, and angioedema

## Contraindications and Cautions

- Known hypersensitivity to urea or any ingredients of formulation.
- Contraindicated to use on open wounds and irritated and infected skin.

## Important Drug Interactions

- No documented significant interactions

## Adverse effects and Their Management

- Local skin reactions including transient itching, burning, and/or stinging sensation. Symptoms generally resolve upon discontinuing therapy.
- Some formulations contain tartrazine (FD&C yellow #5 or E102), an aniline dye. Allergic reactions to tartrazine-containing products include anaphylactic reactions, like urticaria and angioedema, and asthmatic reactions. Patients with a known hypersensitivity should avoid the product. There is no conclusive evidence about whether tartrazine can cause asthma exacerbations. Patients with aspirin-sensitive or insensitive asthmatics are not contraindicated to tartrazine-containing drugs unless they have had a proven sensitivity.
- Some formulations contain ammonium lactate or lactic acid which can increase sensitivity to UV light and increase the risk of sunburns. The use of sunscreen and protective clothing while outdoors is advised.

## Carcinogenicity

- No published studies on carcinogenicity

## Patch Test Concentration

- Not Available

## Essential Patient Information

- For topical use only.
- Avoid contact with the mouth, nose, and eyes. Contact may cause burning sensation.
- Do not apply to open wounds, irritated, or infected skin.
- Seek immediate medical attention if you experience signs of an allergic reaction like rash, hives, peeling skin with or without fever, and difficulty breathing.
- If using foam or lotion, shake well before use.
- Some products may stain clothing.

---

## References

### Becaplermin

1. Lexidrug/LexiComp drug monograph (Becaplermin). Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2025 UptoDate, Inc.

### Hydrogen Peroxide

2. FDA drug monograph (name of monograph). Available from (FDA web-link). Accessed (date).
3. Lexidrug/LexiComp drug monograph (hydrogen peroxide). Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2024 UptoDate, Inc.

## Sodium Hypochlorite and Hypochlorous Acid

4. FDA drug monograph (name of monograph). Available from (FDA web-link). Accessed (date).
5. LexiComp drug monograph (name of monograph). Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2024 UptoDate, Inc.

## Imiquimod

6. FDA drug monograph Zyclara® (imiquimod) Cream, 3.75%. Available from [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2011/201153s000,022483s0011b1.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/201153s000,022483s0011b1.pdf). Accessed 30 Apr 2023.
7. LexiComp drug monograph (imiquimod). Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2023 UptoDate, Inc.
8. Hadley G, Derry S, Moore RA. Imiquimod for actinic keratosis: systematic review and meta-analysis. *Journal of Investig Dermatol.* 2006;126(6):1251–5.
9. Hanna E, Abadi R, Abbas O. Imiquimod in dermatology: an overview. *Int J Dermatol.* 2016;55(8):831–44.
10. Korman N, Moy R, Ling M, Matheson R, Smith S, McKane S, Lee JH. Dosing with 5% imiquimod cream 3 times per week for the treatment of actinic keratosis: results of two phase 3, randomized, double-blind, parallel-group, vehicle-controlled trials. *Arch Dermatol.* 2005;141(4):467–73.
11. National Library of Medicine (U.S). (2008–2011) Phase 3 Study of Imiquimod Creams in the Treatment of External Genital Warts. Identifier NCT00735462. <https://clinicaltrials.gov/ct2/show/results/NCT00735462>
12. Miller RL, Gerster JF, Owens ML, Slade HB, Tomai MA. Review article imiquimod applied topically: a novel immune response modifier and new class of drug. *Int J Immunopharmacol.* 1999;21(1):1–14.
13. Moore RA, Edwards JE, Hopwood J, Hicks D. Imiquimod for the treatment of genital warts: a quantitative systematic review. *BMC Infect Dis.* 2001;1(1):1–9.
14. Navi D, Huntley A. Imiquimod 5 percent cream and the treatment of cutaneous malignancy. *Dermatol Online J.* 2004;10(1)
15. Stockfleth E, Meyer T, Benninghoff B, Salasche S, Papadopoulos L, Ulrich C, Christophers E. A randomized, double-blind, vehicle-controlled study to assess 5% imiquimod cream for the treatment of multiple actinic keratoses. *Arch Dermatol.* 2002;138(11):1498–502.

## Podofilox (Podophyllotoxin)

16. FDA drug monograph (podofilox topical solution 0.5%). Available from <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=6af07697-5203-43e0-ba35-83683af851c3>. Assessed 15 Nov 2024.
17. FDA drug guidance (podofilox topical gel 0.5%). Oct 2022. Available from [https://www.accessdata.fda.gov/drugsatfda\\_docs/psg/PSG\\_020529.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_020529.pdf). Accessed 15 Nov 2024.
18. LexiComp drug monograph (podofilox). Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2024 UptoDate, Inc.
19. Podofilox (Condylox) product monograph. Health Canada. Available at: [https://pdf.hres.ca/dpd\\_pm/00062150.PDF](https://pdf.hres.ca/dpd_pm/00062150.PDF). Accessed 13 Nov 2024.
20. Kaminetzky HA, McGrew EA, Phillips RL. Experimental cervical epithelial dysplasia. J Obst Gyn. 1959;14:1–10.
21. Kaminetzky HA, McGrew EA. Podophyllin and mouse cervix: effect of long term application. Arch Path. 1962;73:481–5.

## Podophyllum Resin

22. Podocon-25 drug monograph (podophyllin). Available from [Drugs.com](https://www.drugs.com/pro/podocon-25.html) at: <https://www.drugs.com/pro/podocon-25.html>. Accessed 17 Nov 2024.
23. FDA drug monograph (podofilox topical solution 0.5%). Available from <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=6af07697-5203-43e0-ba35-83683af851c3>. Assessed 15 Nov 2024.
24. LexiComp drug monograph (podophyllin resin). Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2024 UptoDate, Inc.
25. Podophyllum resin (topical route). Mayo Clinic Drugs & Supplements. Available at: <https://www.mayoclinic.org/drugs-supplements/podophyllum-resin-topical-route/description/drg-20065566>. Accessed 17 Nov 2024.
26. Podophyllum resin. PubChem. Available at: <https://pubchem.ncbi.nlm.nih.gov/compound/Podophyllum-Resin#section=ATC-Code>. Accessed 17 Nov 2024.
27. Kaminetzky HA, McGrew EA, Phillips RL. Experimental cervical epithelial dysplasia. J Obst Gyn. 1959;14:1–10.
28. Kaminetzky HA, McGrew EA. Podophyllin and mouse cervix: effect of long term application. Arch Path. 1962;73:481–5.

## Propylene Glycol

29. FDA drug monograph CFR – Code of Federal Regulations Title 21. Sec. 184.1666 Propylene glycol. Available from <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=184.1666>. Accessed 20 Nov 2024.
30. Propylene glycol. In: Propylene glycol (PIM 443). <https://inchem.org/documents/pims/chemical/pim443.htm#SectionTitle:7.6%20%20Interactions>. Accessed 20 Nov 2024.
31. Adams RM, Maibach HI, Adams RM, et al. A five-year study of cosmetic reactions. *J Am Acad Dermatol*. 1985;13:1062–9.
32. Bekeris L, Baker C, Fenton J, Kimball D, Bermes E. Propylene glycol as a cause of an elevated serum osmolality. *Am J Clin Pathol*. 1979;72:633–6.
33. Bizjak M, Adamič K, Bajrovič N, Eržen R, Jošt M, Kopač P, Košnik M, Lalek N, Zidarn M, Dinevski D. Patch testing with the European Baseline Series and 10 added allergens: Single-centre study of 748 patients. *Contact Dermat*. 2022;87:439–46.
34. Fligner CL. Hyperosmolality induced by propylene glycol. *JAMA*. 1985;253:1606.
35. Goldsmith LA. Propylene glycol. *Int J Dermatol*. 1978;17:703–5.
36. Hannuksela M, Förström L. Reactions to peroral propylene glycol. *Contact Dermat*. 1978;4:41–5.
37. Kaur G, Woodruff CM, Botto N. Life after patch testing: allergic contact dermatitis caused by propylene glycol in Vivelle transdermal estradiol patch. *JAAD Case Rep*. 2021;9:34–5.
38. Kulik MI, Lewis NS, Bansal V, Warpeha R. Hyperosmolality in the burn patient. *J Trauma Injury Infect Crit Care*. 1980;20:223–8.
39. Lalla SC, Nguyen H, Chaudhry H, Killian JM, Drage LA, Davis MDP, Yiannias JA, Hall MR. Patch testing to propylene glycol: the Mayo Clinic experience. *Dermatitis*. 2018;29:200–5.
40. Martin G, Finberg L. Propylene glycol: a potentially toxic vehicle in liquid dosage form. *J Pediatr*. 1970;77:877–8.
41. Miller ON, Bazzano G. Propanediol metabolism and its relation to lactic acid metabolism\*. *Annals NY Acad Sci*. 2006;119:957–73.
42. Ruddick JA. Toxicology, metabolism, and biochemistry of 1,2-propanediol. *Toxicol Appl Pharm*. 1972;21:102–11.
43. Soni H. Martindale: The Complete Drug Reference Brayfield alison (ED) martindale: The Complete Drug Reference £459 4,688pp pharmaceutical press 9780857111395 0857111396. *Emerg Nurse*. 2014; 22:12
44. Silverberg JI, Chaubal M, Warshaw EM, et al. Prevalence and trend of allergen sensitization in patients with cheilitis referred for patch testing, North American contact dermatitis group data, 2001–2018. *Contact Dermat*. 2022; <https://doi.org/10.1111/cod.14265>.

45. Trancik RJ, Maibach HI. Propylene glycol: irritation or sensitization? *Contact Dermat.* 1982;8:185–9.
46. Yu DK, Elmquist WF, Sawchuk RJ. Pharmacokinetics of propylene glycol in humans during multiple dosing regimens. *J Pharm Sci.* 1985;74:876–9.
47. Zhu YY, Liang J, Xiao W. Enhancing effects of chemical permeation enhancer propylene glycol and ultrasonic technology on transdermal permeation of Baimai Ointment. *Zhongguo Zhong Yao Za Zhi.* 2022;24:6607–14.

## Urea

48. LexiComp drug monograph Urea (Topical). Available from: LexiComp Online at [online.Lexi.com](https://online.lexi.com). Copyright 2024 UptoDate, Inc.
49. Bissonnette R, Maari C, Provost N, Bolduc C, Nigen S, Rougier A, Seite S. A double-blind study of tolerance and efficacy of a new urea-containing moisturizer in patients with atopic dermatitis. *J Cosmet Dermatol.* 2010;9(1):16–21.
50. Emtestam L, Kaaman T, Rensfeldt K. Treatment of distal subungual onychomycosis with a topical preparation of urea, propylene glycol and lactic acid: results of a 24-week, double-blind, placebo-controlled study. *Mycoses.* 2012;55(6):532–40.
51. Hagemann I, Proksch E. Topical treatment by urea reduces epidermal hyperproliferation and induces differentiation in psoriasis. *Acta Dermato-Venereologica.* 1996;76(5):353–6.
52. Lodén M. Urea-containing moisturizers influence barrier properties of normal skin. *Arch Dermatol Res.* 1996;288:103–7.
53. Pan M, Heinecke G, Bernardo S, Tsui C, Levitt J. Urea: a comprehensive review of the clinical literature. *Dermatol Online J.* 2013;19(11)
54. Piquero-Casals J, Morgado-Carrasco D, Granger C, Trullàs C, Jesús-Silva A, Krutmann J. Urea in dermatology: a review of its emollient, moisturizing, keratolytic, skin barrier enhancing and antimicrobial properties. *Dermatol Ther.* 2021;11(6):1905–15.



---

# Index

## A

- Abametapir lotion, 105
- Abametapir PK parameters, 106
- Acetasol HC, 243–247
- Acetic acid, 242–247, 494–498
- Acne, 584
- Acne combination products, 169–174
- Acne vulgaris, 102, 117, 129
- Actinic keratosis, 118, 233, 679
- Active pharmaceutical ingredients (APIs), 33, 50–61
- Acyclovir, 415–418
- Adapalene, 132–135, 596–598
- Age-related hepatic dysfunction, 113
- Age-related renal impairment, 112
- Alclometasone dipropionate, 499–501
- Alcohol, 399
- Alcohol-based or acetone-based vehicles, 6
- Aldesleukin, 246, 465
- Alitretinoin, 363, 606–609
- Allergic dermatitis, 119
- Allergic reactions, 656
- Allylamines
  - naftifine, 299–302
  - terbinafine, 302–306
- Aluminum hydroxide, 565, 570
- Amcinonide, 477–478
- Aminolevulinic acid, 212–215, 570
- Androgen hormones, 130
- Anthralin, 561–563
- Anti-inflammatory retinoids
  - adapalene, 596–598
  - tazarotene, 601–604
  - tretinoin, 598–601
  - trifarotene, 604–606
- Antineoplastic retinoids
  - alitretinoin, 606–609
  - bexarotene, 609–612
- Anti-pruritic agents
  - doxepin, 384–403
  - pramoxine, 403–410
  - topical anesthetics, 411
- Antiviral agents, 414
  - acyclovir, 415–418
  - berdazimer, 418–421
  - famciclovir, 422–426
  - penciclovir, 426–429
  - valacyclovir, 430, 431, 433–436
- Anusol Plus, 406
- Apremilast, 440

- ARAZLO (tazarotene) lotion, 104  
Atopic dermatitis (AD), 12, 102,  
119, 439, 498, 578  
    crisaborole, 449, 450  
    janus kinase (JAK) inhibitors,  
    441  
    phosphodiesterase (PDE)-4  
    inhibitors, 440  
    pimecrolimus, 445–449  
    tacrolimus, 441–445  
    topical calcineurin inhibitors,  
    440  
    topical corticosteroids, 440  
AVAGE (tazarotene) cream, 104  
Azelaic acid, 202–206  
Azoles  
    ciclopirox olamine, 344–346  
    clotrimazole, 306–311  
    econazole, 311–315  
    ketoconazole, 316, 317, 319–321  
    luliconazole, 321–324  
    miconazole nitrate, 324–329  
    nystatin, 346–350  
    oxiconazole nitrate, 329–334  
    sertaconazole nitrate, 334–337  
    sulconazole, 338–343  
    tavaborole, 350–352  
    tolnaftate, 352–354
- B**  
Bacitracin, 247–250  
Bacterial keratitis, 656  
Basal cell carcinomas, 118  
Benzocaine, 411  
Benzoyl peroxide, 131, 135–139  
Berdazimer, 418–421  
Best Pharmaceuticals for Children  
    Act (BPCA) 2002, 85  
Betamethasone dipropionate,  
    463–465, 481, 482  
Betamethasone valerate foam, 619  
Bexarotene, 363, 609–612  
Bimatoprost, 654–657  
Binding, 14  
    Biological products, 91  
    Biomarker screening, 76  
    Brimonidine, 185–194  
    Burning, 184  
    Burosumab, 569  
    Butenafine HCl, 341–343  
    Butyrate, 494–498
- C**  
Calcipotriene (calcipotriol), 246,  
    563–566  
Calcitriol, 567–571  
Carcinogenicity, 134, 689  
    atopic dermatitis, 444–445  
    berdazimer, 421  
    clobetasol propionate, 468  
    crisaborole, 450  
    desoximetasone, 470  
    diflucortolone valerate, 472  
    eflornithine, 663–664  
    famciclovir, 425–426  
    fluocinonide, 474  
    flurandrenolide, 476  
    penciclovir, 429  
    permethrin, 536  
    pimecrolimus, 448  
    podofilox, 685  
    sinecatechins, 642  
    spinosad, 540  
    valacyclovir, 436  
Cardiac glycosides, 570  
Chickenpox, 433  
Ciclopirox olamine, 344–346  
Cimetidine, 399  
Clascoterone, 139–143  
Clindamycin, 143–147  
Clindamycin gel, 131  
Clinical pharmacogenomics  
    implementation  
    (CPIC), 70  
Clobetasol propionate, 466–468  
Clobex (clobetasol) lotion, 104  
Clocortolone pivalate, 489  
Clotrimazole, 306, 308–311

- Coal tar and tar distillates, 572–576
- Coal tar shampoo, 619–624
- Communication, 62, 63
- Compounding bases, 39–45
- Contact dermatitis, 301, 498
- Contact sensitization, 389
- Corticosteroid(s), 102–106
- Corticosteroid hypersensitivity, 245
- Crisaborole, 440, 449, 450
- Cross-hypersensitivity, 253
- Cumulative toxicity, 254
- Cushing's syndrome, 15
- Cutaneous candidiasis*, 307, 312, 316
- CYP3A4 inhibitors, 465
- D**
- Dandruff, 317, 584, 618
- Dapsone, 147–151
- Depigmenting and pigmenting agents
  - hydroquinone/triluma, 544–547
  - mequinol, 549, 551, 552
  - methoxsalen, 552–555
  - monobenzone, 547–549
- Dermal absorption, 687
- Dermatologic diseases, 84
- Dermatologic drugs, 72
- Dermatologic manifestations, 84
- Desonide, 501–503
- Desoximetasone, 469, 470
- Diaper dermatitis*, 325
- Diclofenac
  - adverse effects, 236
  - carcinogenicity, 236
  - classification, 231–232
  - contraindications, 234
  - dosages, 232
  - drug interactions, 234–235
  - indications & dermatological uses, 232
  - monitoring, 234
  - patch test, 236
  - patient information, 237–238
  - pharmacokinetics, 232–233
- Diflorasone diacetate, 478–480
- Diflucortolone valerate, 471, 472
- Diprolene AF (betamethasone) cream, 103
- Dosing, 98
- Doxepin, 384–400
  - adverse reactions, 400
  - overdosage and management, 401, 402
  - patch test concentration, 402
  - patient information, 403
- Doxepin hydrochloride, 384
- Doxepine, 389
- Drowsiness, 388
- Drug interactions
  - betamethasone dipropionate, 465
  - hydrogen peroxide, 673
  - oxepin, 389
  - pimecrolimus, 447
  - pramoxine, 409–410
- Drug transfer, 18
- E**
- Econazole, 311–315
- Ectoparasiticides
  - ivermectin, 527–530
  - lindane, 530–533
  - permethrin, 533–537
  - spinosad, 537, 539–541
- Edema, 184
- Educating caregiver, 106
- Eflornithine, 661–664
- eMERGE-PGx project, 71
- Erythromycin, 151–154
- Ethnicity, 9
- Excretion kinetics, 22
- Exfoliation, 16
- Exfoliative dermatitis, 290
- Exposure-response (E-R) analysis, 90
- External genital, 679

**F**

Facial angiofibroma, 645–647  
Famciclovir, 422–426  
Fluocinolone acetonide, 490–494, 624  
Fluocinonide, 472–474, 492  
Fluorouracil (5-FU), 118, 218–221, 364  
Flurandrenolide, 475, 476  
Fluticasone propionate, 482, 483  
Food and Drug Administration  
  Modernization Act  
  (FDAMA) 1997, 85  
Food Drug and Cosmetic Act  
  1938, 84  
Frailty, 113  
Fungi, 298

**G**

Genetic Information  
  Nondiscrimination Act  
  (GINA), 71  
Genital herpes  
  adult, 431  
  pediatric, 432  
Genital pruritis, 498, 512  
Gentamicin sulfate, 250–255  
Geriatrics, 267, 387  
Germline mutations, 646  
Glycolic acid, 117  
Gramicidin, 255–258

**H**

Hair follicle drug screening test, 18  
Halcinonide, 480, 481  
Halobetasol propionate, 476, 477  
Hamartin, 646  
Hand eczema, 98  
Head lice, 535  
Hemodialysis, 693  
Hemoperfusion, 402  
Hemorrhoids, 512  
Hepatic dysfunction, 121

Hepatic insufficiency, 233, 387  
Hepatotoxicity, 310  
Herpes zoster, 433  
Hydration, 11  
Hydrocortisone, 243–247, 496, 505–507, 509–511, 513  
Hydrocortisone butyrate, 497  
Hydrocortisone hemisuccinate, 497  
Hydrocortisone probutate, 497  
Hydrocortisone salts, 494–498  
Hydrocortisone valerate, 497  
Hydrogen peroxide, 671–674  
Hydroquinone/triluma, 118, 544–547  
Hyper/hypopigmentation, 543  
Hypercalcemia, 570  
Hypercalciuria, 570  
Hyperglycemia, 377  
Hyperpigmentation, 120  
Hypersensitivity, 692  
Hypertension, 15  
Hypoalbuminemia, 123  
Hypochlorous acid, 675, 676, 698  
Hypothalamic pituitary adrenal  
  (HPA) axis suppression, 102

**I**

Imiquimod, 678–682  
Inadvertent systemic toxicity, 15  
Intravenous (IV) line insertion, 14  
Irritation, 570, 673  
Ivermectin, 199–202, 527–530

**J**

Janus kinase (JAK) inhibitor, 441, 577

**K**

Kaposi sarcoma, 472  
Ketoconazole, 316–321, 624–630  
Kidney stones, 570

**L**

Lactation, 233, 268, 386, 416  
Lateral spread, 23  
Lexicomp, 389  
Lichen planus, 119  
Lidocaine, 411  
Lindane, 530–533  
Lipid bilayers, 6  
Lipophilicity, 5  
Luliconazole, 100, 101, 321–324

**M**

*Malassezia* spp., 618  
MAO inhibitors, doxepin, 399  
Mechlorethamine gel, 364–368  
Melasma, 118, 120  
Mequinol, 543, 549, 551, 552  
Metabolic transformation, 20, 21  
Metabolism and excretion, 22, 120  
Methoxsalen, 544, 552–555  
Metronidazole, 194–199  
Miconazole nitrate, 324–329  
Minocycline, 154–158  
Minoxidil, 657–661  
Miscellaneous agents  
    hydrogen peroxide, 671–674  
    imiquimod, 678–682  
    podofilox, 683–686  
    podophyllum resin, 686–689  
    propylene glycol, 690–693  
    sodium hypochlorite and  
        hypochlorous acid,  
        675–677  
    urea, 694–697  
Missed dose, 243  
Modeling and simulation  
(M&S), 91  
Mometasone furoate, 484, 485  
Monobenzene, 547–549  
Mupirocin, 258–262  
MUsT assessment, 102

**N**

Naftifine, 299–302  
Neomycin sulfate, 263–273

Nitrogen mustard, 364  
Numerous bases, 39  
Nystatin, 346–350

**O**

Occlusive dressings, 389, 509  
Occlusive vehicles, 6  
Off-label drug use, 84, 85  
Oil-based vehicles, 6  
Ointment bases, 42–43  
Online resources, 70  
Ontogeny, 96  
Onychomycosis, 99  
Orolabial HSV, 432  
Orphan Drug Act, 88  
Otomycosis, 307  
Overdosage, 244  
Oxiconazole nitrate, 329–334  
Oxymetazoline, 184,  
    190–194  
Ozenoxacin, 273–276

**P**

P450 2D6, 389–399  
Partition coefficient, 5  
Patch test  
    acyclovir, 418  
    atopic dermatitis, 445  
    betamethasone dipropionate,  
        465  
    crisaborole, 450  
    desoximetasone, 470  
    diflucortolone valerate, 472  
    famciclovir, 426  
    fluocinonide, 474  
    flurandrenolide, 475  
    penciclovir, 429  
    pimecrolimus, 448  
    podofilox, 686  
    sinecatechins, 643  
    valacyclovir, 436  
Pediatric dermatology, 84, 91  
Pediatric dosing  
    and ontogeny, 96  
    of topical products, 97–99

- Pediatric drug development studies
  - E-R analysis, 90, 91
  - modeling and simulation, 91
  - multiple indicators, 86
  - off-label drug use, 84, 85
  - patient population, 89, 90
  - pediatric and adult efficacy trials, 87
  - placebo-controlled trials, 88
  - successful trials, 87
- Pediatric maximal use trial, 99–102
- Pediatric MUSt study, 100
- Pediatric Research Equity Act (PREA) 2003, 85
- Pediatric skin, 10
- Penciclovir, 426–429
- Percutaneous absorption
  - binding sites and chemical affinities, 14
  - conditions of drug exposure, 7–8
  - exfoliation, 16
  - hydration, 11
  - inadvertent systemic toxicity, 15
  - lateral spread, 23
  - metabolic transformation, 20, 21
  - occlusive vehicles, 6
  - oil-based vehicles, 6
  - particle size/molecular weight, 5
  - partition coefficient, 5
  - pH, 5
  - pH of the vehicle, 7
  - photochemical transformation, 21, 22
  - pKa, 5
  - population variability, 9–11
  - rub enhancement, 17
  - rub resistance, 17
  - skin appendages, 8
  - skin health and skin integrity, 12–13
  - skin pH, 11
  - skin sites of application, 8–9
  - skin temperature, 11
  - systemic distribution, 14
  - systemic toxicity, 15
  - volatility, 19, 20
  - wash effects, 16
- Permethrin, 533–537
- pH, 5
- Pharmaceutical compounding
  - active pharmaceutical ingredients, 50–61
  - appropriate/inappropriate, 35
  - communication, 62, 63
  - compounding bases, 39–45
  - creams, 44
  - excipients, 45
  - gels, 44
  - legal requirements, 63
  - lotions, 44
  - master formula creation, 36
  - ointment bases, 42–43
  - preparations, 46–49
  - quality assurance, 34
  - solutions, 44
  - techniques and equipment, 36–39
- Pharmacogenomic biomarkers, 72
- Pharmacogenomic tests, 77, 78
- Pharmacogenomics
  - biomarker screening, 76
  - clinicians and patients' knowledge, 77–78
  - databases, 69–71
  - definition, 68, 69
  - dermatologic drugs, 72
  - germline/somatic gene variants, 69
  - history, 68–69
  - insurance coverage, 76–77
  - online resources, 70
  - regulations, 72
  - test result presentation, 78
- Pharmacogenomics iPSC library & services (PiLS), 70
- Pharmacogenomics knowledge base (PharmGKB), 70
- Pharmacokinetics
  - betamethasone dipropionate, 464
  - clobetasol propionate, 466–467
  - doxepin, 385–386
  - fluocinonide, 473

- hydrogen peroxide, 672
- penciclovir, 427
- pimecrolimus, 446
- Phosphodiesterase (PDE)-4 inhibitors, 440
- Photochemical transformation, 21, 22
- Photosensitivity, 21
- Photosensitizing agents, 570
- Physician's global assessment (PGA), 89
- Pimecrolimus, 445–449
- pKa, 5
- Placebo-controlled trials, 88
- Podofilox, 683–686
- Podophyllin, 687
- Podophyllum resin, 686–689
- Polymyxin-B sulfate, 277–280
- Polysorbate, 574
- Pramoxine, 403–410
- Prednicarbate, 504, 505
- Pregnancy, 233
  - acyclovir, 416
  - anti-pruritic agents, 386
  - clobetasol propionate, 467
  - dermatologic conditions, 119–120
  - desoximetasone, 469
  - permethrin, 536
  - physiologic changes, 116
  - systemic absorption, 117–119
- Probutate, 494–498
- Proctodan-HC, 406
- Progesterone, 310
- Propylene glycol, 690–693
- Pruritus, 113
- Psoriasis, 99, 102, 119, 513, 560, 561, 584
  - drug monographs
    - anthralin, 561–563
    - calcipotriene (calcipotriol), 563–566
    - calcitriol, 567–571
    - coal tar and tar distillates, 572–576
    - ruxolitinib, 577–581
    - salicylic acid, 581–587
  - Pulmonary embolism, 377
  - Pyoderma gangrenosum, 119
- Q**
  - Quality assurance program, 34
- R**
  - Regional variability, 8
  - Renal dysfunction, 120–121
  - Renal insufficiency, 233, 267, 387
  - Resorcinol, 158–160
  - Retapamulin (Altabax), 281–288
  - Retinoids, 363, 595
    - anti-inflammatory retinoids
      - adapalene, 596–598
      - tazarotene, 601–604
      - tretinoin, 598–601
      - trifarotene, 604–606
    - antineoplastic retinoids
      - alitretinoin, 606–609
      - bexarotene, 609–612
  - Romidepsin, 368–373
  - Rosacea
    - diagnostic features for, 184
    - inflammatory lesions, 185
    - non-transient erythema, 185
  - Rub enhancement, 17
  - Rub resistance, 17
  - Rub resistance factor (RRF), 17
  - Ruxolitinib, 105, 577–581
- S**
  - Salicylic acid, 117, 581–587
  - Scabies, 535
  - Seborrheic dermatitis, 317, 494, 498, 513, 582, 584, 618
    - betamethasone valerate foam, 619
    - coal tar shampoo, 619–624
    - fluocinolone acetonide, 624
    - ketoconazole, 624–630

- Selective serotonin reuptake inhibitors (SSRIs), 399
- Sensitivity reactions, 253
- Sertaconazole nitrate, 334–337
- Short-contact anthralin therapy (SCAT), 562
- Silver sulfadiazine, 288–292
- Sinecatechins, 640–643
- Sirolimus, 647–651
- Skin absorption, 13
- Skin aging, 9
- Skin appendages, 8
- Skin changes, 111, 112
- Skin damage/trauma, 12
- Skin discomfort, 570
- Skin diseases, 12
- Skin hydration, 10
- Skin irritation, 692
- Skin membrane proteins, 5
- Skin pH, 11
- Skin surface topography, 12, 23
- Skin temperature, 11
- Sodium hypochlorite, 675–677
- Spinosad, 537, 539–541
- Squamous cell carcinomas, 118
- Stasis dermatitis, 486, 498
- Stevens-Johnson syndrome (SJS), 290
- Stinging, 184
- Striae, 120
- Substantivity, 13
- Sucralfate, 570
- Sulconazole, 338–341
- Sulfacetamide, 160–166
- Sulfur, 160–166
- Sun protection, 555
- Sunscreens, 102, 546
- Superficial basal cell carcinoma, 679
- Superficial fungal infections, 298
- Superinfection, 253
- Systemic absorption, 106
- Systemic distribution, 14
- Systemic salicylate toxicity, 15
- Systemic toxicity, 15, 123–124
- T**
- Tacrolimus, 119, 441–445
- Tavaborole, 350–352
- Tazarotene, 601–604
- TAZORAC (tazarotene) gel, 104
- Tea tree oil, 166–168
- Telangiectasia, 184
- Terbinafine, 302, 304–306
- Theophylline gel, 10
- Thiazide diuretics, 570
- Thiazides, 570
- Tinea corporis*, 303, 307, 317, 342
- Tinea cruris*, 303, 307, 317, 342
- Tinea infection*, 312
- Tinea pedis*, 308, 317, 342
- Tinea manuum*, 303, 342
- Tinea versicolor*, 303, 308, 312, 317, 341
- Tirbanibulin, 215–217
- Tolazamide, 400
- Tolnaftate, 352–355
- Topical absorption, 10
- Topical analgesics
- adverse effects, 230
  - carcinogenicity, 231
  - children, 228
  - classification, 226
  - contraindications, 229
  - dosages, 227
  - formulations/presentation, 227
  - indications and dermatological uses, 226
  - lactation, 228
  - monitoring, 229
  - patient information, 231
  - pharmacokinetics, 227
  - pregnancy, 228
- Topical antibiotics
- acetic acid, 242–247
  - bacitracin, 247–250
  - gentamicin sulfate, 250–255
  - gramicidin, 255–258
  - hydrocortisone, 243–247
  - mupirocin, 258–262
  - neomycin sulfate, 263–273



- ozenoxacin, 273–276
- polymyxin-B sulfate, 277–280
- retapamulin (Altabax), 281–288
- silver sulfadiazine, 288–292
- Topical antifungals, 297–299
  - allylamines
    - naftifine, 299–302
    - terbinafine, 302–306
  - azoles
    - ciclopirox olamine, 344–346
    - clotrimazole, 306–311
    - econazole, 311–315
    - ketoconazole, 316, 317, 319–321
    - luliconazole, 321–324
    - miconazole nitrate, 324–329
    - nystatin, 346–350
    - oxiconazole nitrate, 329–334
    - sertaconazole nitrate, 334–337
    - sulconazole, 338–343
    - tavaborole, 350–352
    - tolnaftate, 352–354
- Topical antineoplastics
  - fluorouracil, 364
  - mechlorethamine gel, 364–368
  - retinoids, 363
  - romidepsin, 368–373
  - vorinostat, 373–374, 376, 378
- Topical brimonidine, 184
- Topical calcineurin inhibitors (TCI), 440
- Topical corticosteroids (TCS), 103, 104, 118, 440, 514–517
  - adverse effects, 457–459
  - alclometasone dipropionate, 499–501
  - amcinonide, 477–478
  - antiinflammatory potency
    - classifications, 456
  - betamethasone dipropionate, 463–465, 481, 482
  - clobetasol propionate, 466–468
  - clocortolone pivalate, 489
  - contraindications, 459
  - desonide, 501–503
  - desoximetasone, 469, 470
  - diflorasone diacetate, 478–480
  - diflucortolone valerate, 471, 472
  - drug interactions, 461, 462
  - fluocinolone acetonide, 490–494
  - fluocinonide, 472–474
  - flurandrenolide, 475, 476
  - fluticasone propionate, 482, 483
  - formulations, 454, 455
  - halcinonide, 480, 481
  - halobetasol propionate, 476, 477
  - hydrocortisone, 505–507, 509–511, 513
  - hydrocortisone salts, 494–498
  - indications for use, 454
  - mechanisms of action, 454
  - mometasone furoate, 484, 485
  - monitoring considerations, 460
  - patch test concentration, 461
  - patient information, 462
  - pharmacokinetic considerations, 456
  - potency, sites and methods of application, 457
  - prednicarbate, 504, 505
  - regimens and usage guidance, 455
  - skin reactions, 460
  - systemic effects, 460
  - triamcinolone acetonide, 485–489
- Topical drug absorption
  - age-related hepatic dysfunction, 113
  - age-related renal impairment, 112
  - skin changes, 111, 112
- Topical econazole and warfarin, 122
- Topical medications, 131
- Topical miconazole and warfarin, 122
- Topical non-steroidal antiinflammatory drugs (NSAIDs), 119

- Topical salicylates, 15  
Topical sirolimus, 647  
Topical-only therapy, 130  
Topicort (desoximetasone) spray, 104  
Toxic epidermal necrolysis (TEN), 290  
Tretinoin, 131, 598–601  
Triamcinolone acetonide, 485–489  
Trichogenic and antitrichogenic agents  
    bimatoprost, 654–657  
    eflornithine, 661–664  
    minoxidil, 657–661  
Trifarotene, 604–606  
Tuberin, 646  
Tuberous sclerosis complex (TSC), 648
- U**  
United States Pharmacopeia (USP), 32  
Urea, 694–697  
US Environmental Protection Agency (EPA), 16  
UV radiation, 21
- V**  
Vaginitis, 513  
Valacyclovir, 430, 431, 433–436  
Valerate, 494–498  
Varicella-zoster virus (VZV)  
    in hematopoietic cell transplant (HCT), 433  
    in solid organ transplant recipients, 434  
Veregen®, 640  
Vitamin D3 analog, 563  
Vitamin K antagonists, 314  
Vitiligo, 119, 442, 578  
Volatility, 19, 20  
Vorinostat, 373–374, 376, 378  
Vulvovaginal burning, 310  
*Vulvovaginal candidiasis*, 307
- W**  
Wash effects, 16  
Weakened immune system, 114
- X**  
Xerosis, 113
- Z**  
Zonalon, 384