

MTF Formulary Management for Topical Acne and Rosacea Agents

Defense Health Agency Pharmacy Operations Division

Bottom Line

- Clindamycin/benzoyl peroxide 1.2% - 5% (Duac) and metronidazole 1% (MetroGel) were added to the BCF to provide more options for topical acne and rosacea management.
- Clindamycin phosphate 1% gel, cream, lotion, and solution (generic Cleocin T) and tretinoin 0.025% and 0.05% cream (generic Retin-A) remain on the BCF.
- Twelve topical acne agents and 5 topical rosacea agents were designated Nonformulary and non step-preferred based on cost effectiveness and the availability of therapeutic alternatives. See Uniform Formulary table below.
- Step therapy (automated prior authorization) applies to the class. In general, cost-effective generic topical formulations are designated as step-preferred, with branded products non step-preferred. PA criteria apply to all new and current users (“no grandfathering”). See Prior Authorization information below.

Uniform Formulary Decision: The Director, DHA, approved the recommendations from the August 2016 DoD P&T Committee meeting on November 8, 2016, with an implementation date of February 8, 2017.

Uniform Formulary (UF) Agents		Nonformulary (NF) Agents
Basic Fore Formulary (BCF) MTFs <u>must</u> have on formulary	Not on BCF MTFs <u>may</u> have on formulary	MTFs <u>must not</u> have on formulary
Topical Acne Agents		
<p>ADDED TO BCF Step-Preferred</p> <ul style="list-style-type: none"> ▪ clindamycin/ benzoyl peroxide 1.2% - 5% gel (Duac, generics) <p>REMAIN ON BCF Step-Preferred</p> <ul style="list-style-type: none"> ▪ clindamycin phosphate 1% gel, cream, lotion, and solution (Cleocin, generics) ▪ tretinoin 0.025% and 0.05% cream (Retin-A, generics) 	<p>Step-Preferred</p> <ul style="list-style-type: none"> ▪ adapalene 0.1% lotion, gel, cream and 0.3% gel (Differin, generics) ▪ clindamycin phosphate 1% foam (Evoclin, generics) ▪ clindamycin/ benzoyl peroxide 1% - 5% gel (Benzaclin, generics) ▪ clindamycin/ benzoyl peroxide 1% - 5% gel kit (Duac CS Kit) ▪ sulfacetamide sodium/sulfur 10% lotion (generic) ▪ tretinoin 0.01% and 0.025% gel (Retin-A, generics) ▪ tretinoin 0.025% gel, cream (Avita, generics) ▪ tretinoin 0.05% solution, 0.1% cream (Retin-A, generics) ▪ tretinoin 0.0375%, 0.075% cream (Tretin-X, generics) ▪ tretinoin 0.05% gel (Atralin, generics) <p>Non Step-Preferred</p> <ul style="list-style-type: none"> ▪ azelaic acid 20% cream (Azelex) ▪ clindamycin/benzoyl peroxide 1.2% - 2.5% gel (Acanya) 	<p>Non Step-Preferred</p> <ul style="list-style-type: none"> ▪ adapalene/benzoyl peroxide 0.1% - 2.5% gel (Epiduo) ▪ adapalene/benzoyl peroxide 0.3% - 2.5% gel (Epiduo Forte) ▪ clindamycin 1% kits (Clindacin ETZ Kit; Clindacin PAC Kit) ▪ clindamycin 1% gel (Clindagel) ▪ clindamycin/benzoyl peroxide 1.2% - 3.75% gel (Onexton) ▪ clindamycin/benzoyl peroxide 1.2% - 5% gel/cream kit (Neuac Kit) ▪ clindamycin/tretinoin 1.2% - 0.025% gel (Veltin*; Ziana, generics) ▪ dapsone 5% and 7.5% gel (Aczone) ▪ tretinoin microsphere 0.04%, 0.08%, and 0.1% gel (Retin-A Micro, generics; Retin-A Micro Pump, generics) ▪ tazarotene 0.1% foam (Fabior)
Topical Rosacea Agent		
<p>ADDED TO BCF Step-Preferred</p> <ul style="list-style-type: none"> ▪ metronidazole 1% gel (MetroGel, generics) 	<p>Step-Preferred</p> <ul style="list-style-type: none"> ▪ metronidazole 0.75% cream (MetroCream, generics) ▪ metronidazole 0.75% lotion (MetroLotion, generics) <p>Non Step-Preferred</p> <ul style="list-style-type: none"> ▪ azelaic acid 15% gel, foam, kit (Finacea) 	<p>Non Step-Preferred</p> <ul style="list-style-type: none"> ▪ brimonidine tartrate 0.33% gel (Mirvaso) ▪ ivermectin 1% cream (Soolantra) ▪ metronidazole 1% cream (Noritrate) ▪ metronidazole 0.75% cream/cleanser kit (Rosadan Cream Kit) ▪ metronidazole 0.75% gel/cleanser kit (Rosadan Gel Kit)
<p>Drugs that are in bold font currently do not have AB-rated generics available on the market.</p> <p>* Veltin is BX rated to Ziana due to timing of FDA approval for new drug application; both products are pharmaceutically equivalent</p>		

Background

- There are currently at least 26 topical acne and 9 topical rosacea products available in the United States with respective generics, multiple strengths and/or multiple formulations. The reviewed products were further categorized based on mechanism of action, and included the topical antibiotics and combinations with benzoyl peroxide, topical retinoids, azelaic acid, dapson, metronidazole, sodium sulfacetamide/sulfur products, ivermectin, and brimonidine.
- Most of the branded topical acne and rosacea agents have generic and/or therapeutic alternatives. Many marketed branded products do not have any clear clinical advantages over available generics or therapeutic alternatives.
- Acne: For the topical acne products, clinical practice guidelines and systematic reviews conclude the following for the treatment of mild to moderate acne:
 - High quality evidence exists for use of (1) topical antibiotics in combination with benzoyl peroxide for treatment, and (2) azelaic acid as an adjunctive treatment. Benzoyl peroxide used in combination with the clindamycin 1% gel or solution is a first-line choice for treatment of mild to moderate acne.
 - Moderate to high quality of evidence exists for use of all other topical acne agents (retinoids and combinations, antibiotics, dapson and benzoyl peroxide).
 - No evidence was found to support efficacy of sulfacetamide sodium, sulfur, resorcinol, zinc, nicotinamide, or aluminum chloride for treatment of acne.
- Combination therapy of benzoyl peroxide with an antibiotic is recommended versus antibiotic monotherapy to prevent induction of bacterial resistance.
- Rosacea: For the topical rosacea products, clinical practice guidelines and systematic reviews conclude the following.
 - High quality of evidence exists for use of (1) azelaic acid for reduction of inflammatory (papulopustular) lesions and erythema, (2) topical brimonidine for reduction of facial erythema, and (3) ivermectin for reduction of inflammatory lesions associated with rosacea.
 - Moderate quality evidence exists for use of metronidazole for topical treatment of inflammatory lesions and erythema of rosacea; topical metronidazole is widely used as a first-line treatment.

Step Therapy and Prior Authorization Criteria

- Step therapy applies to all new and current users (“no grandfathering”) of the topical acne and rosacea drugs. The goal of the step therapy is to promote use of the least expensive generic products or therapeutic alternatives over the branded products. The majority of the cost avoidance for this drug class is attributed to the step therapy.
- Separate step therapies will be required for acne and rosacea products.
 - Within the acne subclass, there are additional step therapies, based on mechanism of action (combination benzoyl peroxide with antibiotics; retinoids and combinations; dapson; azelaic acid). All branded formulations are non step-preferred. Step therapy for the acne products generally requires use of at least three step-preferred products first, prior to use of a non-preferred product.
 - For the rosacea products, one generic metronidazole step-preferred formulation is required prior to use of the non step-preferred products
- Manual Prior Authorization can be used for patients where use of the non step-preferred product is clinically required (e.g., for those patients with an adverse reaction, inadequate therapeutic response, or medical contraindication to the step-preferred products).
- Refer to the August 2016 DoD P&T Minutes, Appendix C Table of Prior Authorization (PA) Criteria for the specific step therapy and manual prior authorization criteria.
- Single-ingredient formulations of benzoyl peroxide were not reviewed for formulary placement. However, expensive legend benzoyl peroxide (4% to 10%) products now have manual prior authorization criteria, requiring use of an OTC benzoyl peroxide product first. These formulations are primarily dispensed in the Retail Pharmacy Network.

Newer Products

Azelaic Acid

- The two branded azelaic acid products are specifically indicated for the treatment of either acne (Azelex 20% cream) or rosacea (Finacea 15% gel or foam). These two products were designated as UF, but non step-preferred. Azelaic acid has a pregnancy category B rating, which is an allowed use in the manual PA criteria.

Dapsone (Aczone)

- Dapsone (Aczone) topical gel is available in two branded strengths (5% and 7.5%) and approved for treatment of acne for patients as young as 12 years of age. Neither strength has undergone head-to-head studies to indicate relative superiority against each other or against other topical acne agents.
- Professional acne treatment guidelines recommend topical dapsone for inflammatory acne, particularly in adult females.

Brimonidine (Mirvaso)

- Brimonidine (Mirvaso) 0.33% topical gel is an alpha adrenergic agonist that has a clinical niche for the treatment of persistent facial erythema of rosacea in adults. Clinical trials showed once-daily brimonidine demonstrated significantly greater efficacy relative to vehicle gel. However, use of topical brimonidine does not change the underlying course of disease.
- In July 2016, the FDA required the product labeling to include the potential for hypersensitivity reactions, local vasomotor reactions, and systemic adverse reactions including hypotension, bradycardia, and dizziness associated with use of alpha-2 adrenergic agonists.

Ivermectin (Soolantra)

- Ivermectin (Soolantra) 1% topical cream is an anti-parasitic agent with anti-inflammatory properties approved for treatment of inflammatory lesions of rosacea in adults. This product has a clinical niche for papulopustular rosacea associated with proliferation of *Demodex* mites.

Safety & Tolerability

- Adverse effects associated with the use of topical acne and rosacea agents are primarily dermatological in nature, with some unique differences consistent with pharmacological nature of the drug (e.g., photosensitivity, potential to induce bacterial resistance, potential for methemoglobinemia, systemic effects, hypersensitivity reactions).
- Most topical acne and rosacea agents are rated as pregnancy category B or C, with the exception of tazarotene (Fabior), which is pregnancy category X, based on animal studies.
- Some topical retinoid-based acne products are safe for use in pre-adolescent populations. Tretinoin 0.05% can be used in patients older than 10 years, while adapalene/benzoyl peroxide 1%-2.5% (Epiduo) can be used in patients older than 9 years.

Summary

- Overall, the clinical data for many topical acne and rosacea products is limited by the lack of active controls, use of subjective rating scales, and non-rigorous study designs. The majority of the clinical trials used to obtain FDA approval showed statistical significance of the product over vehicle, but did not necessarily show clinical significance.
- The newer products, including dapsone 7.5% gel (Aczone), brimonidine 0.33% gel (Mirvaso), and ivermectin 1% cream (Soolantra), do not offer clinically compelling advantages over other therapeutic alternatives.
- The topical acne and rosacea products on the UF offer multiple strengths and formulations, which allow for potential benefit to individual patients and meet the needs of majority of the DoD beneficiaries.

References

- DoD P&T Committee minutes: <http://www.health.mil/PandT>
- Current/future drug classes under review by the DoD P&T Committee: <http://www.health.mil/About-MHS/Other-MHS-Organizations/DoD-Pharmacy-and-Therapeutics-Committee>
- TRICARE Formulary Search Tool: <http://www.health.mil/formulary>
- Prior Authorization/Medical Necessity forms: See Formulary Search Tool above.
- Formulary Management Documents (including this one) available at: <http://www.health.mil/DoDPTResources>
- Point of contact for additional information: dha.jbsa.pharmacy.list.poduf@mail.mil

Topical Acne and Rosacea Agents Price Comparison at MTF	
Drug	MTF Cost/Month (Aug 2016)
Uniform Formulary	
<ul style="list-style-type: none"> ▪ Topical Acne Agents <ul style="list-style-type: none"> ○ adapalene 0.1% lotion, gel, cream and 0.3% gel (Differin, generics) ○ clindamycin phosphate 1% gel, cream, foam, lotion, solution, and med swab (Cleocin, generics) ○ clindamycin phosphate 1% foam (Evoclin, generics) ○ sulfacetamide sodium/sulfur 10% lotion (generics) ○ tretinoin 0.025% and 0.05% cream (Retin-A, generics) ○ tretinoin 0.01% and 0.025% gel (Retin-A, generics) ○ tretinoin 0.025% gel, cream (Avita, generics) ○ tretinoin 0.05% solution, 0.1% cream (Retin-A, generics) ○ tretinoin 0.0375%, 0.075% cream (Tretin-X, generics) ○ tretinoin 0.05% gel (Atralin, generics) 	\$ Most Cost-Effective
<ul style="list-style-type: none"> ○ clindamycin/ benzoyl peroxide 1.2% - 5% gel (Duac, generics) ○ clindamycin/ benzoyl peroxide 1% - 5% gel (Benzacilin, generics) ○ clindamycin/ benzoyl peroxide 1% - 5% gel kit (Duac CS Kit) 	\$\$ - \$\$\$ Less Cost-Effective
<ul style="list-style-type: none"> ○ azelaic acid 20% cream (Azelex) *Non Step-Preferred ○ clindamycin/benzoyl peroxide 1.2% - 2.5% gel (Acanya) *Non Step-Preferred 	\$\$\$\$ Least Cost-Effective
Topical Rosacea Agents	
<ul style="list-style-type: none"> ○ metronidazole 1% gel (MetroGel, generics) 	\$ Most Cost-Effective
<ul style="list-style-type: none"> ○ azelaic acid 15% gel, foam, kit (Finacea) *Non Step-Preferred 	\$\$ - \$\$\$ Less Cost-Effective
<i>(MTFs should purchase the most cost-effective, contracted, AB-rated bioequivalent products.)</i>	
Nonformulary	
<ul style="list-style-type: none"> ▪ Topical Acne Agents <ul style="list-style-type: none"> ○ adapalene/benzoyl peroxide 0.1% - 2.5% gel (Epiduo) ○ adapalene/benzoyl peroxide 0.3% - 2.5% gel (Epiduo Forte) ○ clindamycin 1% kits (Clindacin ETZ Kit; Clindacin PAC Kit) ○ clindamycin 1% gel (Clindagel) ○ clindamycin/benzoyl peroxide 1.2% - 3.75% gel (Onexton) ○ clindamycin/benzoyl peroxide 1.2% - 5% gel/cream kit (Neuac Kit) ○ clindamycin/tretinoin 1.2% - 0.025% gel (Veltin; Ziana, generics) ○ dapsone 5% and 7.5% gel (Aczone) ○ tretinoin microsphere 0.04%, 0.08%, and 0.1% gel (Retin-A Micro, generics; Retin-A Micro Pump, generics) ○ tazarotene 0.1% foam (Fabior) 	\$\$\$\$ Least Cost-Effective
<ul style="list-style-type: none"> ▪ Topical Rosacea Agents <ul style="list-style-type: none"> ○ brimonidine tartrate 0.33% gel (Mirvaso) ○ ivermectin 1% cream (Soolantra) ○ metronidazole 1% cream (Noritate) ○ metronidazole 0.75% cream/cleanser kit (Rosadan Cream Kit) ○ metronidazole 0.75% gel/cleanser kit (Rosadan Gel Kit) 	
<p>Legend:</p> <p>\$ = "Most Cost-Effective" represents Rx's with the <u>lowest cost</u> and best clinical efficacy</p> <p>\$\$ = "Less Cost-Effective" represents <u>higher cost</u> Rx's with similar clinical efficacy</p> <p>\$\$\$ = "Less Cost-Effective" represents <u>next higher cost</u> Rx's with similar clinical efficacy</p> <p>\$\$\$\$ = "Least Cost-Effective" represents Rx's with the <u>highest cost</u> with similar clinical efficacy</p>	