### FDA APPROVED INDICATIONS AND DOSAGE

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibiotic Products</strong></td>
<td></td>
</tr>
<tr>
<td>Aczone® (dapsone)</td>
<td>Topical treatment of acne vulgaris</td>
</tr>
<tr>
<td>Akne-Mycin (erythromycin)(^a)</td>
<td>Topical control of acne vulgaris</td>
</tr>
<tr>
<td>Azelex® (azelaic acid)</td>
<td>Topical treatment of mild-to-moderate inflammatory acne vulgaris</td>
</tr>
<tr>
<td>Cleocin-T (clindamycin)(^a)</td>
<td>Topical treatment of acne vulgaris</td>
</tr>
<tr>
<td>Clindagel (clindamycin)(^a)</td>
<td>Topical treatment of acne vulgaris</td>
</tr>
<tr>
<td>Erygel (erythromycin)(^a)</td>
<td>Topical control of acne vulgaris</td>
</tr>
<tr>
<td>Evoclin (clindamycin)(^a)</td>
<td>Topical application in the treatment of acne vulgaris in patients 12 years and older</td>
</tr>
<tr>
<td>Metrocream (metronidazole)(^a)</td>
<td>Topical treatment of inflammatory lesions (papules and pustules) of rosacea</td>
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<tr>
<td>Metrogel (metronidazole)(^a)</td>
<td>Topical treatment of inflammatory lesions (papules and pustules) of rosacea</td>
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<tr>
<td>Metrolotion (metronidazole)(^a)</td>
<td>Topical treatment of inflammatory lesions (papules and pustules) of rosacea</td>
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<tr>
<td>Noritate (metronidazole)</td>
<td>Topical treatment of inflammatory lesions and erythema of rosacea</td>
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<tr>
<td><strong>Combination Products</strong></td>
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<tr>
<td>Acanya (clindamycin phosphate/benzoyl peroxide gel)</td>
<td>Topical treatment of acne vulgaris in patients 12 years or older</td>
</tr>
<tr>
<td>Benzaclin (clindamycin phosphate/benzoyl peroxide gel)(^a)</td>
<td>Topical treatment of acne vulgaris</td>
</tr>
<tr>
<td>Benzamycin (erythromycin/benzoyl peroxide)(^a)</td>
<td>Topical treatment of acne vulgaris</td>
</tr>
<tr>
<td>Duac (clindamycin phosphate/benzoyl peroxide gel)(^a)</td>
<td>Topical treatment of acne vulgaris</td>
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<tr>
<td>Epiduo® (adapalene/benzoyl peroxide gel)</td>
<td>Topical treatment of acne vulgaris in patients 9 years of age or older</td>
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<tr>
<td>Epiduo® Forte (adapalene/benzoyl peroxide gel)</td>
<td>Topical treatment of acne vulgaris</td>
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<tr>
<td>Neuac™ (clindamycin/benzoyl peroxide gel)</td>
<td>Topical treatment of inflammatory acne vulgaris</td>
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<tr>
<td>Onexton™ (clindamycin/benzoyl peroxide gel)</td>
<td>Topical treatment of acne vulgaris in patients 12 years of age and older</td>
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<tr>
<td>Veltin™ (clindamycin/tretinoin)</td>
<td>Topical treatment of acne vulgaris in patients 12 years or older</td>
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<tr>
<td>Ziana® (clindamycin/tretinoin)</td>
<td>Topical treatment of acne vulgaris in patients 12 years or older</td>
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<tr>
<td>Agent</td>
<td>Indication</td>
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<tr>
<td><strong>BRAND Benzoyl peroxide products/combinations,</strong> including but not limited to benzoyl peroxide, Benzac, and Panoxyl products&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Treatment of acne vulgaris</td>
</tr>
<tr>
<td><strong>BRAND Sulfacetamide products,</strong> including but not limited to Klaran</td>
<td>Topical treatment of acne vulgaris</td>
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</tbody>
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<sup>a</sup> – generic equivalents are available  
<sup>b</sup> – brand not available

**CLINICAL RATIONALE**

**Acne**

Guidelines from the American Academy of Pediatrics (2013) suggest topical antibiotics are effective in acne both by inhibiting bacterial protein synthesis and by decreasing inflammation via inhibition of bacterial pro-inflammatory mediator and decreasing neutrophil chemotaxis.

Topical antibiotics (e.g., clindamycin, erythromycin) are not recommended as monotherapy because of slow onset of action and predictable emergence of antibiotic-resistant bacterial organisms. If topical antibiotic treatment is to be prolonged for more than a few weeks, topical benzoyl peroxide should be added, or used in combination products.<sup>17</sup>

Medical Letter Treatment Guidelines (2013) suggest Topical antibiotics clindamycin and erythromycin are commonly used to treat mild to moderate acne. They have antibacterial and anti-inflammatory properties. Products containing sulfur and/or sulfacetamide are also used, but clinical data supporting their efficacy for acne are limited. Topical antibiotics are generally safe and well tolerated, but bacterial resistance has occurred, especially to erythromycin. Concomitant use of topical antibiotics and benzoyl peroxide may be effective against resistant P. acnes. Dapsone is approved in a 5% gel formulation for treatment of acne. Azelaic acid is an anti-keratinizing agent with anti-bacterial and anti-inflammatory activity, and it may be less irritating than benzoyl peroxide.<sup>15</sup>

European evidence based guidelines (2012) on treatment of acne made the following treatment recommendations.<sup>16</sup>

- **Comedonal acne:** Due to the mild/moderate severity of comedonal acne, a topical therapy is recommended. The best efficacy was found for azelaic acid, benzoyl peroxide and topical retinoids. Use of fixed-dose combinations of benzoyl peroxide + clindamycin does not lead to a clinically relevant increase in efficacy against non inflammatory lesions. Benzoyl peroxide + adapalene trended towards better efficacy against non-inflammatory lesions vs the components as monotherapy. However, there was a trend towards inferiority for tolerability profile. Tolerability of topical retinoids and benzoyl peroxide is comparable; there is a trend towards azelaic acid having a better tolerability profile. Limited data suggests a patient preference for adapalene vs. topical retinoids.

- **Papular pustular acne:** The best efficacy against inflammatory lesions was with fixed-dose combinations of benzoyl peroxide + adapalene and benzoyl peroxide + clindamycin, vs topical monotherapies. Monotherapy with azelaic acid, benzoyl peroxide or topical retinoids all had comparable efficacy vs each other. Systemic antibiotic monotherapy shows no superiority vs topical treatment; therefore combining systemic therapy with topical agents is preferred.

- **Nodular/conglobate acne:** Systemic isotretinoin shows superior or comparable efficacy in treatment of conglobate acne vs combination systemic antibiotics + topical therapy. Experts suggest the greatest effectiveness in the treatment of conglobate acne in clinical...
practice is seen with systemic isotretinoin; this can only be partly supported by published evidence, due to lack of clinical trials in conglobate acne.

The 2007 guidelines from the American Academy of Dermatology on treatment of acne vulgaris include the following recommendations:\textsuperscript{12}

1. Topical therapy is a standard of care in acne treatment.
   - Topical retinoids, benzoyl peroxide, and antibiotics are strongly recommended.
   - Topical antibiotics used alone can be associated with the development of bacterial resistance.
   - Azelaic acid is effective but some experts consider its efficacy limited.
   - Employing multiple topical agents that affect different aspects of acne pathogenesis can be useful.

2. Systemic antibiotics are a standard of care in moderate and severe acne and treatment-resistant forms of inflammatory acne.
   - Doxycycline and minocycline are more effective than tetracycline, and there is evidence that minocycline is superior to doxycycline in reducing \textit{P. acnes}.
   - Although erythromycin is effective, use should be limited to those who cannot use the tetracyclines.
   - Trimethoprim-sulfamethoxazole and trimethoprim alone are also effective in instances where other antibiotics cannot be used.

3. Other Therapies
   - Estrogen-containing oral contraceptives can be useful in treatment of acne in some women.
   - Spironolactone and cyproterone can be useful, but the strength of recommendation is less.
   - Oral isotretinoin is useful for severe recalcitrant nodular acne and also lesser degrees of acne that are treatment-resistant or for acne that is scarring.
   - Intraleisional corticosteroid injections are effective in the treatment of individual acne nodules.\textsuperscript{12}

\textbf{Rosacea}

The American Acne and Rosacea Society (2013) consensus states patients with papulopustular rosacea generally are good candidates for treatment with metronidazole, azelaic acid, or sulfacetamide/sulfur, either as monotherapy or as part of a combination regimen based on available studies and extensive clinical experience. Sulfacetamide/sulfur formulations are not used as extensively now as they were in the past, likely because of the malodor of sulfur and limited efficacy data, especially pertaining to cleanser formulations. In clinical studies with metronidazole, azelaic acid, and sulfacetamide/sulfur, all enrolled patients had papulopustular rosacea, usually moderate in severity. Following treatment with all 3 topical agents, reductions in inflammatory lesions were statistically superior to vehicle (p<0.05). \textsuperscript{18}

The Medical Letter Treatment Guidelines (2013) state that topical antimicrobials (e.g., metronidazole and azelaic acid) are generally tried first for treatment of rosacea, sometimes in combination with oral antimicrobials, which can produce a more rapid response. Metronidazole and azelaic acid are standard topical antimicrobials used to treat the papules and pustules of rosacea; they appear to be about equally effective. Topical retinoids may be used for patients who do not respond to topical antimicrobials. Topical brimonidine is effective to treat moderate to severe erythema of rosacea. Systemic antibiotic therapy tends to be effective for treatment of papules, pustules, erythema and ocular inflammation.\textsuperscript{15}

An evidence based review on treatment of rosacea (2011) suggested topical metronidazole and azelaic acid are equally effective for papulopustular lesions of rosacea, although metronidazole may be better tolerated. Evidence also supports benefits for topical sodium...
sulfacetamide with sulfur. Oral doxycycline, tetracycline, and metronidazole are also effective, but not enough evidence exists to determine whether one is more effective than another or more effective than topical therapy.13

Another review (2009) suggests that first-line therapy for mild cases includes topical metronidazole, azelaic acid, or sulfacetamide/sulfur. For moderate to severe rosacea, recommended treatments are oral antibiotics alone (e.g., tetracycline, doxycycline, minocycline) or combined with topical agents. Topical regimens are first-line therapies for mild papulopustular rosacea because there is less risk of adverse events, drug interactions, and antibiotic resistance. The severity of the patient’s presentation helps guide the decision to initiate topical therapy alone or in combination with systemic therapy. Systemic therapy should be withdrawn when adequate response occurs.14

For additional clinical information see Prime Therapeutics Formulary Chapters 14.5 A Topical Acne Agents: Benzoyl Peroxide and Miscellaneous and 14.5 B Topical Acne Agents: Topical Antibacterials and Combinations.

References
Topical Antibiotics and Combinations Step Therapy

OBJECTIVE
The intent of the Topical Antibiotics/Combinations Step Therapy (ST) program is to encourage the use of the cost-effective preferred and generic topical antibiotic products prior to the use of nonpreferred brand topical antibiotic products and to accommodate for use of brand nonpreferred topical antibiotic products when the preferred products cannot be used due to previous trial, documented intolerance, FDA labeled contraindication, or hypersensitivity. The program allows continuation of therapy when there is documentation that the patient is receiving the requested agent. Requests for nonpreferred topical antibiotic products will be reviewed when patient-specific documentation has been provided.

TARGET DRUGS
- Acanya (clindamycin/benzoyl peroxide)
- Aczone® (dapsone)
- Akne-Mycin (erythromycin)a
- Azelex® (azelaic acid)
- Benzaclin (clindamycin/benzoyl peroxide)a
- Benzamycin (erythromycin/benzoyl peroxide)a
- Cleocin-T (clindamycin)a
- Clindagel (clindamycin)a
- Clindamel (clindamycin)a
- Duac (clindamycin/benzoyl peroxide)a
- Epiduo® (adapalene/benzoyl peroxide)
- Epiduo® Forte (adapalene/benzoyl peroxide)
- Erygel® (erythromycin)a
- Evoclin (clindamycin)a
- Metrocream (metronidazole)a
- Metrogel (metronidazole)a
- Metrolotion (metronidazole)a
- Neuac (clindamycin-benzoyl peroxide gel)
- Noritate (metronidazole)
- Onexton™ (clindamycin/benzoyl peroxide)
- Veltin™ (clindamycin/tretinoin)
- Ziana® (clindamycin/tretinoin)
- BRAND Benzoyl peroxide products/combinations, including but not limited to benzoyl peroxide, Benzac, and Panoxyl products
- BRAND Sulfacetamide products/combinations, including but not limited to Klaron
- a – available as a generic; included as a prerequisite in the step therapy program
- b – brand not available

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Nonpreferred Brand Topical Antibiotic products will be approved when ANY ONE of the following is met:

1. The patient’s medication history includes use of two preferred topical antibiotic products
   OR
2. There is documentation that the patient is currently using the requested agent
   OR
3. The prescriber states the patient is currently using the requested agent AND is at risk if therapy is changed
   OR
4. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to at least two preferred topical antibiotic products

Length of Approval: 12 months