### FDA APPROVED INDICATIONS AND DOSAGE

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indications and Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Doxycycline Products</strong></td>
<td></td>
</tr>
<tr>
<td>Acticlate™ (doxycycline hyclate tablet)</td>
<td>• For the treatment of infections due to susceptible strains of microorganisms (refer to labeling for additional details)</td>
</tr>
<tr>
<td>Adoxa®, Adoxa Pak (doxycycline monohydrate tablet, capsule)</td>
<td>• In acute intestinal amebiasis, doxycycline may be a useful adjunct to amebicides</td>
</tr>
<tr>
<td>Doryx®, Doryx MPC® (doxycycline hyclate delayed-release tablet)</td>
<td>• For the prophylaxis of malaria due to Plasmodium falciparum in short-term travelers (&lt;4 months) to areas with chloroquine and/or pyrimethamine-sulfadoxine resistant strains</td>
</tr>
<tr>
<td>Doxycycline® (doxycycline hyclate delayed-release capsule; doxycycline hyclate tablet)</td>
<td>• In severe acne, doxycycline may be useful adjunctive therapy</td>
</tr>
<tr>
<td>Monodox® (doxycycline hyclate capsule)</td>
<td>• Labeling does not include dosing recommendations for treatment of acne. Typical dosing is 50-100 mg twice daily</td>
</tr>
<tr>
<td>Targadox™ (doxycycline hyclate tablet)</td>
<td>• For the treatment of only inflammatory lesions (papules and pustules) of rosacea in adult patients. No meaningful effect was demonstrated for generalized erythema (redness) of rosacea. Oracea has not been evaluated for the treatment of the erythematous, telangiectatic, or ocular components of rosacea</td>
</tr>
<tr>
<td>Vibramycin® (doxycycline hyclate capsule)</td>
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<tr>
<td></td>
<td></td>
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<tr>
<td></td>
<td>a – generic equivalents are available</td>
</tr>
<tr>
<td>Oracea® (doxycycline monohydrate delayed-release capsule)</td>
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<tr>
<td><strong>Minocycline Products</strong></td>
<td></td>
</tr>
<tr>
<td>Minocin® (minocycline capsule)</td>
<td>• For the treatment of infections due to susceptible strains of microorganisms (see labeling for details)</td>
</tr>
<tr>
<td>minocycline tablet</td>
<td>• In acute intestinal amebiasis, minocycline may be a useful adjunct to amebicides</td>
</tr>
<tr>
<td></td>
<td>• For the treatment of asymptomatic carriers of Neisseria meningitidis to eliminate meningococci from the nasopharynx</td>
</tr>
<tr>
<td></td>
<td>• In severe acne, minocycline may be useful adjunctive therapy</td>
</tr>
<tr>
<td></td>
<td>• Labeling does not include dosing recommendations for treatment of acne. Typical dosing is 50-100 mg twice daily.</td>
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<td><strong>Minocycline Products</strong></td>
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</tbody>
</table>
| **Solodyn®, Minocycline SR**  (minocycline extended-release tablet)a | • To treat only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older. Solodyn did not demonstrate any effect on non-inflammatory lesions  
• The recommended dosage of Solodyn is approximately 1 mg/kg once daily for 12 weeks. |

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**CLINICAL RATIONALE**

**Acne**

The 2007 guidelines from the American Academy of Dermatology on treatment of acne vulgaris\(^\text{14}\) include the following recommendations:

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 \(P.\) *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.
   - Intralesional corticosteroid injections are effective in the treatment of individual acne nodules.\(^\text{14}\)

Reviews of tetracycline products used in the treatment of acne\(^\text{15,16}\) have found tetracycline, minocycline, and doxycycline all to be effective in the treatment of acne, particularly during the inflammatory stage. One review of seven randomized trials which were set up to compare the efficacy of tetracyclines found no evidence of superiority of one tetracycline over another in reducing acne lesion counts.\(^\text{15}\) Evidence-based recommendations for treatment of pediatric acne from the American Academy of Pediatrics consider oral antibiotics appropriate for moderate to severe inflammatory acne. Tetracycline derivatives, including tetracycline, doxycycline and minocycline are not to be used in children younger than 8 years of age.\(^\text{24}\)

**Rosacea**

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.\textsuperscript{21}

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.\textsuperscript{22}

The Medical Letter Treatment Guidelines (2013), Drugs of Choice for Rosacea,\textsuperscript{23} states that topical antimicrobials such as 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{23}

**Safety**

The use of tetracycline products, including doxycycline and minocycline, may cause fetal harm when administered during pregnancy. Drugs in the tetracycline class should not be used during pregnancy or by either gender when attempting to conceive. Photosensitivity reactions have been associated with tetracyclines. The use of drugs in the tetracycline class during tooth development may cause permanent tooth discoloration which is more common with long term use. Additionally, drugs in the tetracycline class have been associated with a reversible decrease in fibula growth rate caused by complexation with calcium. In general, tetracyclines should not be used in children under 8 years of age and extended-release minocycline should not be used in children under 12 years of age.\textsuperscript{9,14}

**Minocycline**

The safety and efficacy of Solodyn in the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris was assessed in two 12-week, multi-center, randomized, double-blind, placebo-controlled, studies in subjects ≥12 years. The mean age of subjects was 20 years and subjects were from the following racial groups: white (73%), Hispanic (13%), black (11%), Asian/Pacific islander (2%), and other (2%). In the two efficacy and safety trials, a total of 924 subjects with non-nodular moderate to severe acne vulgaris received 1 mg/kg of Solodyn or placebo for a total of 12 weeks. The two primary efficacy endpoints were:

1. Mean percent change in inflammatory lesion counts from baseline to 12 weeks
2. Percentage of subjects with an Evaluator’s Global Severity Assessment (EGSA) of clear or almost clear at 12 weeks.

Patients on Solodyn had a greater mean percent improvement in inflammatory lesions (43.1% and 45.8% in studies one and two respectively) compared to placebo (31.7% and 30.8%) (p<0.05). Solodyn did not demonstrate any effect on non-inflammatory lesions.\textsuperscript{13}

There are no clinical studies comparing extended-release minocycline with older immediate-release formulations. A Medical Letter review of Solodyn concluded “Solodyn is an expensive new formulation of minocycline labeled for once-daily use. Whether Solodyn is as effective as immediate-release minocycline and less likely to cause vertigo remains to be established.”\textsuperscript{17}
**Doxycycline**

Oracea, indicated for the treatment of inflammatory lesions (papules and pustules) of rosacea in adult patients, is comprised of 30 mg immediate release and 10 mg delayed release doxycycline. While the mechanism of action is not fully understood, it is thought to be due to an anti-inflammatory effect.\(^6\)

The safety and efficacy of Oracea was evaluated in two double blind, randomized, placebo controlled trials involving 537 patients for the treatment of rosacea. Both phase III trials were 16 weeks in duration. Oracea therapy resulted in a mean decrease in lesion count from baseline of 11.8 and 9.5 in study one and two respectively compared to 5.9 and 4.3 for placebo respectively (p<0.05). Patients on Oracea did not demonstrate improvement in erythema compared to placebo.\(^6\)

The FDA noted that the magnitude of efficacy shown is clinically somewhat limited and modest for an oral medication. The manufacturer has stated that at the systemic concentration provided by Oracea, doxycycline is not effective as an antimicrobial agent and appears to exert its action independent of antibacterial activity. The sponsor has not submitted data supporting this mechanism of action. Furthermore, there are some possible indicators of antibacterial action in the form of an increase in diarrhea in the active treatment arms of the pivotal trials.\(^19\)

A double-blind randomized trial compared Oracea 40 mg once daily to doxycycline 100 mg once daily in the treatment of moderate to severe rosacea for 16 weeks. There was no statistical significant difference in the primary efficacy endpoint of the change in total lesion count. There was a higher incidence of GI adverse events related to doxycycline 100 mg versus Oracea (26% vs 5%); however, the discontinuation rate was 50% higher with Oracea versus doxycycline 100 mg.\(^20\)

In the treatment of periodontitis, it is thought that doxycycline works by inhibiting collagenase. Collagenase breaks down connective tissue which leads to the separation of the gum from the tooth. Products (e.g., Oraxyl) used for treatment of periodontitis contain lower amounts of doxycycline. Doxycycline concentrations produced by these products appear too low to exert a direct antibacterial effect. These lower dose doxycycline products should not be used as an antibiotic.\(^9\)

To receive an AB rating by the Food and Drug Administration (FDA) generic agents must be pharmaceutical equivalents to the innovator brand drug (contain the same active ingredients, are the same dosage form, the same route of administration, and are identical in strength or concentration) and the agent can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the innovator drug labeling.\(^18\) Generics may differ in shape, scoring, configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration time, and, within certain limits, labeling.\(^10\) AB-rated agents have had actual or potential bioequivalence problems resolved with adequate in vivo and/or in vitro evidence supporting bioequivalence.\(^18\) Doxycycline in oral capsules, oral tablets, and oral suspension and minocycline in oral capsules, oral tablets, and extended-release tablets are available as AB-rated generics.\(^18\)

For additional clinical information see Prime Therapeutics Formulary Chapter 1.4 Tetracyclines and Chapter 14.5 A-C Topical Acne Agents

**REFERENCES**

DOXYCYCLINE/MINOCYCLINE PRIOR AUTHORIZATION

OBJECTIVE
The intent of the prior authorization (PA) criteria for brand and nonpreferred doxycycline and minocycline products is to ensure appropriate selection of patients for treatment according to product labeling and/or clinical studies and/or guidelines, and to encourage use of two first-line preferred oral agents – both doxycycline and minocycline - before use of these products. Requests for nonpreferred doxycycline and minocycline products will be reviewed when patient-specific documentation has been provided.

TARGET DRUGS
(Preferred and Nonpreferred generics determined by client)

DOXYCYCLINE PRODUCTS:
- Acticlate™ (doxycycline hyclate tablet)
- Adoxa® (doxycycline monohydrate tablet, capsule)
- Doryx®, Doryx MPC® (doxycycline hyclate delayed-release tablet)
- Doxycycline (doxycycline hyclate delayed-release capsule, doxycycline hyclate tablet, doxycycline monohydrate delayed release capsule)
- Monodox® (doxycycline monohydrate capsule)
- Oracea® (doxycycline monohydrate delayed-release capsule)
- Targadox™ (doxycycline hyclate tablet)
- Vibramycin® (doxycycline hyclate capsule, monohydrate suspension, doxycycline calcium syrup)

MINOCYCLINE PRODUCTS:
- Minocin® (minocycline capsule)
- minocycline tablet
- Minocycline SR (minocycline extended-release tablet)
- Solodyn® (minocycline extended-release tablet)

a - available as a generic; designated target or prerequisite as determined by client

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Brand and Nonpreferred doxycycline or minocycline products will be approved when all of the following are met:

1. The patient has an FDA-labeled indication for the requested agent
   AND
2. ONE of the following:
   a. The requested agent is minocycline, the patient’s diagnosis is moderate to severe acne vulgaris and the patient is 12 years of age or older
   OR
   b. The requested agent is minocycline, the patient’s diagnosis is other than moderate to severe acne vulgaris and the patient is 8 years of age or older
   OR
   c. The requested agent is doxycycline and the patient is 8 years of age or older
   AND
3. IF the patient’s diagnosis is acne or rosacea, ONE of the following:
   a. The patient is not currently being treated with another oral antibiotic for the treatment of acne or rosacea
   OR
   b. The patient is currently being treated with another oral antibiotic for the treatment of acne or rosacea and the antibiotic will be discontinued before starting the requested agent
   AND
4. BOTH of the following:
   a. The patient’s medication history includes use of a preferred oral generic doxycycline product OR the patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to a preferred oral generic doxycycline product
      **AND**
   b. The patient’s medication history includes use of a preferred oral generic minocycline product OR the patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to a preferred oral generic minocycline product

**Length of Approval:** 12 months