This program applies to FlexRx Open, FlexRx Closed, GenRx Open, GenRx Closed, Health Insurance Marketplace and KeyRx formularies.

FlexRx Standard and GenRx Standard prior authorization program.

The BCBS MN Step Therapy Supplement also applies to this program for all Commercial/HIM lines of business.

**FDA APPROVED INDICATIONS AND DOSAGE**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indications and Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Doxycycline Agents</strong></td>
<td></td>
</tr>
<tr>
<td>Acticlate™</td>
<td>- For the treatment of infections due to susceptible strains of microorganisms (refer to labeling for additional details)</td>
</tr>
<tr>
<td>(doxycycline hyclate tablet)⁠</td>
<td></td>
</tr>
<tr>
<td>Doxycycline monohydrate (tablet, capsule)⁠</td>
<td></td>
</tr>
<tr>
<td>Doryx®</td>
<td>- In <em>acute intestinal amebiasis</em>, doxycycline may be a useful adjunct to amebicides</td>
</tr>
<tr>
<td>(doxycycline hyclate delayed-release tablet)⁠</td>
<td></td>
</tr>
<tr>
<td>Doryx MPC®</td>
<td>- For the prophylaxis of malaria due to <em>Plasmodium falciparum</em> in short-term travelers (&lt;4 months) to areas with chloroquine and/or pyrimethamine-sulfadoxine resistant strains</td>
</tr>
<tr>
<td>(doxycycline hyclate delayed-release tablet)</td>
<td></td>
</tr>
<tr>
<td>doxycycline hyclate⁠ (doxycycline hyclate delayed-release capsule; doxycycline hyclate delayed-release tablet; doxycycline hyclate tablet)</td>
<td></td>
</tr>
<tr>
<td>Monodox®</td>
<td>- In <em>severe acne</em>, doxycycline may be useful adjunctive therapy</td>
</tr>
<tr>
<td>(doxycycline monohydrate capsule)⁠</td>
<td></td>
</tr>
<tr>
<td>Targadox™</td>
<td>- Labeling does not include dosing recommendations for treatment of acne. Typical dosing is 50-100 mg twice daily</td>
</tr>
<tr>
<td>(doxycycline hyclate tablet)</td>
<td></td>
</tr>
<tr>
<td>Vibramycin®</td>
<td></td>
</tr>
<tr>
<td>(doxycycline hyclate capsule)⁠</td>
<td></td>
</tr>
<tr>
<td>(doxycycline monohydrate suspension)⁠</td>
<td></td>
</tr>
<tr>
<td>(doxycycline calcium syrup)</td>
<td></td>
</tr>
<tr>
<td>Oracea®</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.</td>
</tr>
<tr>
<td>(doxycycline monohydrate delayed-release capsule)</td>
<td></td>
</tr>
</tbody>
</table>

⁠a - generic equivalents are available
### Minocycline Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indications and Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Minocin®</strong>&lt;br&gt;(minocycline capsule <em>a</em>)&lt;br&gt;<strong>minocycline tablet</strong></td>
<td>- For the treatment of infections due to susceptible strains of microorganisms (see labeling for details)&lt;br&gt;- In <em>acute intestinal amebiasis</em>, minocycline may be a useful adjunct to amebicides&lt;br&gt;- For the treatment of asymptomatic carriers of <em>Neisseria meningitidis</em> to eliminate meningococci from the nasopharynx&lt;br&gt;- In <em>severe acne</em>, minocycline may be useful adjunctive therapy&lt;br&gt;- Labeling does not include dosing recommendations for treatment of acne. Typical dosing is 50-100 mg twice daily.</td>
</tr>
<tr>
<td><strong>Solodyn®, Minocycline ER tablet</strong>&lt;br&gt;(minocycline extended-release tablet) <em>a</em></td>
<td>- 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-inflamatory lesions&lt;br&gt;- The recommended dosage of Solodyn is approximately 1 mg/kg once daily for 12 weeks</td>
</tr>
<tr>
<td><strong>Minolira™</strong>&lt;br&gt;(minocycline extended-release tablet)</td>
<td>- To treat only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older. Minolira has not been evaluated in the treatment of infections&lt;br&gt;- The recommended dosage is approximately 1 mg/kg once daily for 12 weeks</td>
</tr>
<tr>
<td><strong>Ximino™, Minocycline ER capsule</strong>&lt;br&gt;(minocycline extended-release capsule)</td>
<td>- To treat only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older&lt;br&gt;- Ximino did not demonstrate any effect on non-inflammatory acne lesions. Safety of Ximino has not been established beyond 12 weeks of use&lt;br&gt;- The recommended dosage of Ximino is approximately 1 mg/kg once daily for 12 weeks</td>
</tr>
</tbody>
</table>

*a* - generic equivalents are available

### Tetracycline Agents
**Seysara™**
(sarecycline tablets)

- To treat inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age or older
- Limitations of Use: Efficacy of Seysara beyond 12 weeks and safety beyond 12 months have not been established. Seysara has not been evaluated in the treatment of infections. To reduce the development of drug-resistant bacteria as well as to maintain the effectiveness of other antibacterial drugs, Seysara should be used only as indicated.
- Dosage: The recommended dosage is once daily with or without food.
  - 60 mg for patients who weigh 33-54 kg
  - 100 mg for patients who weigh 55-84 kg
  - 150 mg for patients who weigh 85-136 kg

**CLINICAL RATIONALE**

**Acne Vulgaris**
The American Academy of Dermatology suggests several options for treatment of acne vulgaris. Recommendations for topical acne therapies include benzoyl peroxide or combination of topical antibiotics (e.g. erythromycin or clindamycin) as monotherapy for mild acne, or in conjunction with topical retinoid, or systemic antibiotic therapy for moderate to severe acne. Topical antibiotics are not recommended in monotherapy due to risk of bacterial resistance. Topical adapalene, tretinoin, and benzoyl peroxide can be safely used in the management of preadolescent acne in children. Azelaic acid is useful as an adjunctive acne treatment and is recommended in the treatment of postinflammatory dyspigmentation. Topical dapsone 5% gel is recommended for inflammatory acne, particularly in adult females with acne. There is limited data to support sulfur, nicotinamide, resorcinol, sodium sulfacetamide, aluminum chloride, and zinc in the treatment of acne.14

Systemic antibiotics have been a mainstay for acne treatment for years.14 They are indicated for use in moderate to severe inflammatory acne and should be used in combination with a topical retinoid and benzoyl peroxide. Tetracyclines are considered first-line therapy in moderate to severe acne, except when contraindicated. Doxycycline and minocycline are more effective than tetracycline but neither is superior to each other. Oral erythromycin and azithromycin should be reserved for those who cannot use tetracyclines. The use of other systemic antibiotics is discouraged due to limited data for use in acne. Trimethoprim-sulfamethoxazole and trimethoprim use should be restricted to patients who are unable to tolerate tetracycline or in treatment-resistant patients.14 Concomitant topical therapy with benzoyl peroxide or a retinoid should be used with systemic antibiotics and for maintenance after completion of systemic antibiotic therapy.14

Reviews of tetracycline agents used in the treatment of acne15,16 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.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.23
There are several other treatment options for acne. Hormonal therapy or oral contraceptives and isotretinoin are suggested; however, caution is needed for both therapies for adverse events and monitoring. There is limited evidence for the use and benefit of physical modalities for the routine treatment of acne, including pulsed dye laser, glycolic acid peels, and salicylic acid peels. Intralosomal corticosteroid injections are effective in the treatment of individual acne nodules. Furthermore, no current data supports any specific dietary changes to manage acne. However, data suggests that high glycemic index diets maybe associated with acne and limited evidence suggests that some dairy products, particularly skim milk, may influence acne.\textsuperscript{14}

**Rosacea**

Although there is no cure for rosacea, its features may be reduced or controlled with a range of topical and oral therapies as well as appropriate skin care and lifestyle management. Combination therapy to target the specific features of each patient with rosacea is often necessary for effective treatment. Patients and features of the disease may respond well or less well to various agents, and when treatments are effective, the mechanism(s) of action may be unclear. First-line therapies include topical agents, such as azelaic acid and metronidazole. When first-line treatments for inflammation are inadequate or when rosacea is more severe, oral antibiotics or retinoids are sometimes used, although data is sparse. Oral antibiotics often used include tetracycline, doxycycline, and minocycline.\textsuperscript{9}

**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 \( \geq \)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.\textsuperscript{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.¹⁸

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 statistically 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.¹⁹

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

REFERENCES

7. Doxycycline hyclate prescribing information (20 mg). Lannett. 07/2020


Oral Tetracycline Derivatives Prior Authorization

TARGET AGENTS

Doxycycline Agents:
  Acticlate™ (doxycycline hyclate tablet)
  doxycycline monohydrate (doxycycline monohydrate tablet, capsule)
  Doryx® (doxycycline hyclate delayed-release tablet)
  Doryx MPC® (doxycycline hyclate delayed-release tablet)
  doxycycline (doxycycline hyclate delayed-release capsule, doxycycline hyclate delayed release tablet, 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 Agents:
  Minocin® (minocycline capsule)
  minocycline tablet
  Minocycline ER capsule
  Minocycline ER tablet (minocycline extended-release tablet)
  Minolira™ (minocycline extended-release tablet)
  Solodyn® (minocycline extended-release tablet)
  Ximino™ (minocycline extended-release capsule)

Tetracycline Agents:
  Seysara™ (sarecycline tablets)

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Targeted agents 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 patient’s age is within FDA label for the requested indication for the requested agent OR
   b. The prescriber has provided information in support of using the requested agent for the patient’s age AND
3. If the patient’s diagnosis is acne, ONE of the following:
   a. The requested agent will be used in combination with a benzoyl peroxide agent OR a retinoid agent OR
   b. The patient has an intolerance or hypersensitivity to a benzoyl peroxide agent OR a retinoid agent OR
   c. The patient has an FDA labeled contraindication to ALL benzoyl peroxide agents AND ALL retinoid agents OR
   d. The patient’s medication history includes use of a benzoyl peroxide agent OR a retinoid agent in the past 999 days
OR

e. BOTH of the following:
   i. The prescriber has stated that the patient has tried a benzoyl peroxide agent OR a retinoid agent
   AND
   ii. The benzoyl peroxide agent or retinoid agent was discontinued due to lack of effectiveness or an adverse event

OR

f. The patient is currently being treated with the requested agent as indicated by ALL of the following:
   A. A statement by the prescriber that the patient is currently taking the requested agent
   AND
   B. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent
   AND
   C. The prescriber states that a change in therapy is expected to be ineffective or cause harm

OR

g. The prescriber has provided documentation that ALL benzoyl peroxide agents AND ALL retinoid agents cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm

AND

4. If the patient’s diagnosis is acne or rosacea, the patient will NOT be using the requested agent in combination with another tetracycline derivative for the treatment of acne or rosacea

AND

5. ONE of the following:
   a. The patient’s medication history includes use of a preferred oral generic doxycycline agent in the past 999 days
   OR
   b. The patient has an intolerance or hypersensitivity to a preferred oral generic doxycycline agent
   OR
   c. The patient has an FDA labeled contraindication to ALL preferred oral generic doxycycline agents
   OR
   d. The patient is currently being treated with the requested agent as indicated by ALL of the following:
      A. A statement by the prescriber that the patient is currently taking the requested agent
      AND
      B. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent
      AND
      C. The prescriber states that a change in therapy is expected to be ineffective or cause harm
   OR
   e. BOTH of the following:
      A. The prescriber has stated that the patient has tried preferred oral generic doxycycline agent
AND

B. The preferred oral generic doxycycline agent was discontinued due to lack of effectiveness or an adverse event

OR

f. The prescriber has provided documentation that ALL preferred oral generic doxycycline agents cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm

AND

6. ONE of the following:
   a. The patient’s medication history includes use of a preferred oral generic minocycline agent within the past 999 days
   OR
   b. The patient has an intolerance or hypersensitivity to a preferred oral generic minocycline agent
   OR
   c. The patient has an FDA labeled contraindication to ALL preferred oral generic minocycline agents
   OR
   d. The patient is currently being treated with the requested agent as indicated by ALL of the following:
      A. A statement by the prescriber that the patient is currently taking the requested agent
      AND
      B. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent
      AND
      C. The prescriber states that a change in therapy is expected to be ineffective or cause harm
   OR
   e. BOTH of the following:
      A. The prescriber has stated that the patient has tried preferred oral generic minocycline agent
      AND
      B. The preferred oral generic minocycline agent was discontinued due to lack of effectiveness or an adverse event
   OR
   f. The prescriber has provided documentation that ALL preferred oral generic minocycline agents cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm

**Length of Approval:** 12 months