BlueCross BlueShield of Alabama

Doxycycline/Minocycline Step Therapy Program Summary

This program applies to Commercial, SourceRx series and Health Insurance Marketplace formularies.

OBJECTIVE

The intent of the Doxycycline/Minocycline Step Therapy (ST) program is to encourage the use of both cost-effective preferred doxycycline and minocycline agents prior to the use of nonpreferred brand or generic doxycycline or minocycline agents and to accommodate for use of brand nonpreferred doxycycline or minocycline agents when the generic agents cannot be used due to previous trial, documented intolerance, FDA labeled contraindication, or hypersensitivity. Requests for nonpreferred doxycycline and minocycline agents will be reviewed when patient-specific documentation has been provided.

TARGET AGENTS

Doxycycline Agents:

Acticlate™ (doxycycline hyclate tablet)
Adoxa® (doxycycline monohydrate tablet, capsule)
Doryx®, Doryx MPC® (doxycycline hyclate delayed-release tablet)[a]
Doxycycline (doxycycline hyclate delayed-release capsule[a], 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, doxycycline monohydrate suspension, doxycycline calcium syrup

Minocycline Agents:

Minocin® (minocycline capsule)
minocycline tablet
Minocycline SR (minocycline extended release tablet)[a]
Solodyn® (minocycline extended-release tablet)[a]
Ximino™ (minocycline extended-release capsule)

a - available as a generic; designated target

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Brand and *Nonpreferred* generic doxycycline and minocycline agents will be approved when BOTH of the following are met:

1. ONE of the following:
   a. The patient's medication history includes use of a preferred generic doxycycline agent in the past 180 days
      OR
   b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to a preferred generic doxycycline agent

   AND
2. ONE of the following:
   a. The patient's medication history includes use of a preferred generic minocycline agent in the past 180 days
      OR

b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to a preferred generic minocycline agent

Length of Approval: 12 months

This pharmacy policy is not an authorization, certification, explanation of benefits or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All pharmacy policies are based on (i) information in FDA approved package inserts (and black box warning, alerts, or other information disseminated by the FDA as applicable); (ii) research of current medical and pharmacy literature; and/or (iii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

The purpose of Blue Cross and Blue Shield of Alabama's pharmacy policies are to provide a guide to coverage. Pharmacy policies are not intended to dictate to physicians how to practice medicine. Physicians should exercise their medical judgment in providing the care they feel is most appropriate for their patients.

Neither this policy, nor the successful adjudication of a pharmacy claim, is guarantee of payment.

FDA APPROVED INDICATIONS AND DOSAGE[1-13,25,26]

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

a – generic equivalents are available

Agent	Indications and Dosing
Minocycline Agents	
Minocin® (minocycline capsule[a]) **minocycline tablet**	• For the treatment of infections due to susceptible strains of microorganisms (see labeling for details) • In *acute intestinal amebiasis*, minocycline may be a useful adjunct to amebicides • For the treatment of asymptomatic carriers of *Neisseria meningitidis* to eliminate meningococci from the nasopharynx • In *severe acne*, minocycline may be useful adjunctive therapy • Labeling does not include dosing recommendations for treatment of acne. Typical dosing is 50-100 mg twice daily.

Agent	Indications and Dosing
Minocycline Agents	
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
Ximino™ (minocycline extended-release capsule)	• To treat only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older • Ximino did not demonstrate any effect on non-inflammatory acne lesions. Safety of Ximino has not been established beyond 12 weeks of use • The recommended dosage of Ximino is approximately 1 mg/kg once daily for 12 weeks

a – generic equivalents are available

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 acne[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.[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.[24]

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 salicyclic acid peels. Intralesional 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.[14]

Rosacea
Because there is no proven natural progression for rosacea, treatment choice is based on the patient's current clinical manifestations and avoidance of known triggers is recommended.[9]

Topical agents are first-line therapy for the treatment of mild to moderate rosacea.[21,22,23] Topical agents have less risk of adverse events, drug interactions and antibiotic resistance compared to systemic therapies.[27] Topical metronidazole, azelaic acid, or brimonidine are recommended for erythema associated with rosacea. Topical ivermectin is recommended for rosacea inflammation with papulopustalar lesions and may be used in combination with topical metronidazole or azelaic acid. Vascular laser therapy, such as pulsed dye laser, intense pulsed light, is also recommended for erythema and telangiectasia.[9]

Combination of topical antibiotics with oral antimicrobials could produce a more rapid response.[23] Metronidazole and azelaic acid are standard topical antimicrobials used to treat the papules and pustules of rosacea; they appear to be about equally effective.[21,23] 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.[23] 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.[22]

Safety
The use of tetracycline agents, 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.[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 $\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.[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."[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]

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]

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