Clinical Policy Title:	doxycycline
Policy Number:	RxA.4
Drug(s) Applied:	Acticlate®, Doryx®, Doryx® MPC, Oracea®
Original Policy Date:	02/07/2020
Last Review Date:	03/09/2021
Line of Business Policy Applies to:	All lines of business

Background

Doxycycline (Acticlate®, Doryx®, Doryx® MPC, Oracea®) is a tetracycline-class drug. Acticlate® and Doryx®/ Doryx® MPC are indicated for:

- Rickettsial infections
- Sexually transmitted infections
- Respiratory tract infections
- Specific bacterial infections
- Ophthalmic infections
- Anthrax, including inhalational anthrax (post-exposure)
- Alternative treatment for selected infections when penicillin is contraindicated
- Adjunctive therapy in acute intestinal amebiasis and severe acne
- Prophylaxis of malaria

Oracea® is indicated 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.

Limitation(s) of use: This formulation of doxycycline has not been evaluated in the treatment or prevention of infections. Oracea® should not be used for treating bacterial infections, providing antibacterial prophylaxis, or reducing the numbers or eliminating microorganisms associated with any bacterial disease. To reduce the development of drug-resistant bacteria as well as to maintain the effectiveness of other antibacterial drugs, Oracea® should be used only as indicated. Efficacy of Oracea® beyond 16 weeks and safety beyond 9 months have not been established. Oracea® has not been evaluated for the treatment of the erythematous, telangiectatic, or ocular components of rosacea.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
doxycycline hyclate (Acticlate®), doxycycline hyclate delayed release (Doryx®, Doryx® MPC)	All indications listed in the FDA-approved indications section	<u>Acticlate® + Doryx®:</u> • Adults: 200 mg PO on the first day of treatment (administered 100 mg every 12 hours) followed by a maintenance dose of 100 mg PO daily. In the management of more severe infections	200 mg/day Doryx® MPC: 240 mg/day

		(particularly chronic infections of the urinary tract), 100 mg PO every 12 hours is recommended. • For all pediatric patients weighing less than 45 kg with severe or life-threatening infections (e.g., anthrax, Rocky Mountain spotted fever): 2.2 mg per kg of body weight administered every 12 hours PO. • For pediatric patients with less severe disease (greater than 8 years of age and weighing less than 45 kg): 4.4 mg per kg of body weight PO divided into two doses on the first day of treatment, followed by a maintenance dose of 2.2 mg per kg of body weight (given as a single daily dose or divided into two doses) PO. • For pediatric patients weighing over 45 kg: the usual adult dose should be used. <u>Doryx® MPC</u> • Adults: 240 mg PO on the first day of treatment (administered 120 mg every 12 hours) followed by a maintenance dose of 120 mg daily. In the management of more severe infections (particularly chronic infections of the urinary tract), 120 mg every 12 hours PO is recommended. • For all pediatric patients weighing less than 45 kg with severe or life threatening infections (e.g., anthrax, Rocky Mountain spotted fever): 2.6 mg per kg of body weight administered PO every 12 hours. • For pediatric patients with less severe disease (greater than 8 years of age and weighing less than 45 kg): 5.3 mg per kg of body weight divided into two doses on the first day of treatment PO,	

		followed by a maintenance dose of 2.6 mg per kg of body weight (given as a single daily dose or divided into twice daily doses) PO. • For pediatric patients weighing over 45 kg: the usual adult dose should be used.	
doxycycline capsule (Oracea®)	Inflammatory lesions (papules and pustules) of rosacea	40 mg PO once daily	40 mg/day

Dosage Forms

- doxycycline hyclate (Acticlate®):
  - Tablets: 75 mg, 150 mg
  - Capsules: 75 mg
- doxycycline hyclate delayed-release tablets:
  - Doryx® MPC: 120 mg
  - Doryx®: 50 mg, 80 mg, and 200 mg
- doxycycline (Oracea®):
  - Capsules: 40 mg

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

I. Initial Approval Criteria

A. Rosacea (must meet all)**:**

1. Diagnosis of rosacea with inflammatory lesions (papules and pustules);
2. Request is for Oracea®;
3. Age 18 years or older;
4. Medical justification supports inability to use immediate-release doxycycline (e.g., member experienced clinically significant adverse effects or has contraindication(s) to the excipients in immediate-release doxycycline);
5. Failure of at least 4-week trial of one additional preferred oral tetracycline antibiotic, unless contraindicated or clinically significant adverse effects are experienced;
6. Dose does not exceed 40 mg/day (1 capsule/day).

Approval duration

Commercial: 4 months

Medicaid: 4 months

B. Acne Vulgaris (must meet all)**:**

1. Diagnosis of acne vulgaris;
2. Request is for Acticlate®, Doryx® or Doryx®MPC;

3. Medical justification supports inability to use immediate-release doxycycline (e.g., member experienced clinically significant adverse effects or has contraindication(s) to the excipients in immediate-release doxycycline);
4. Failure of at least 4-week trial of one additional preferred oral tetracycline antibiotic, unless clinically significant adverse effects are experienced;
5. Dose does not exceed (one of the following):
   a. Acticlate®, Doryx®: 300 mg/day;
   b. Doryx® MPC: 240 mg/day.

Approval duration
Commercial: 3 months
Medicaid: 3 months

C. Prophylaxis of Malaria (must meet all)**:**
1. Prescribed for malaria prophylaxis;
2. Request is for Acticlate®, Doryx®, or Doryx®MPC;
3. Medical justification supports inability to use immediate-release doxycycline (e.g., member experienced clinically significant adverse effects or has contraindication(s) to the excipients in immediate-release doxycycline);
4. Dose does not exceed (one of the following):
   a. Acticlate®, Doryx®: 100 mg/day;
   b. Doryx® MPC: 120 mg/day.

Approval duration
Commercial: 4 months or duration of travel and up to 4 weeks after member leaves the malarious area, whichever is less
Medicaid: 4 months or duration of travel and up to 4 weeks after member leaves the malarious area, whichever is less

D. FDA-Approved Acute Infection Indications for Acticlate®, Doryx®/ Doryx® MPC (must meet all)**:**
1. Prescribed for the treatment of one of the following conditions or diseases (*refer to Appendix D for conditions or diseases that are applicable*):
   a. Rickettsial infections;
   b. Sexually transmitted infections;
   c. Respiratory tract infections;
   d. Specific bacterial infections;
   e. Ophthalmic infections;
   f. Anthrax, including inhalational anthrax (post-exposure);
   g. Selected infections when penicillin is contraindicated;
   h. Acute intestinal amebiasis;
2. Request is for Acticlate®, Doryx®, or Doryx® MPC;
3. Medical justification supports inability to use immediate-release doxycycline (e.g., member experienced clinically significant adverse effects or has contraindication(s) to the excipients in immediate release doxycycline);
4. Failure of one additional preferred oral tetracycline antibiotic (e.g., immediate-release minocycline), unless clinically significant adverse effects are experienced or the other preferred tetracycline antibiotics are not indicated for the member's diagnosis;

5. Dose does not exceed (one of the following):
   a. Acticlate®, Doryx®: 300 mg/day;
   b. Doryx® MPC: 240 mg/day.

Approval duration
Commercial: 2 months
Medicaid: 2 months

II. Continued Therapy Approval

A. Rosacea (must meet all)**:**

1. Currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
2. Request is for Oracea®;
3. Member is responding positively to therapy;
4. Member has not received Oracea® daily for > 16 weeks;
5. If request is for a dose increase, new dose does not exceed 40 mg/day (1 capsule/day).

Approval duration
Commercial: 4 months
Medicaid: 4 months

B. Acne Vulgaris (must meet all)**:**

1. Currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
2. Request is for Acticlate®, Doryx®/ Doryx® MPC;
3. Member is responding positively to therapy;
4. If request is for a dose increase, new dose does not exceed (one of the following):
   a. Acticlate®, Doryx®: 300 mg/day;
   b. Doryx® MPC: 240 mg/day.

Approval duration
Commercial: 3 months
Medicaid: 3 months

C. Prophylaxis of Malaria and FDA-Approved Acute Infection Indications for Acute Infections:

1. Re-authorization for Acticlate®, Doryx®/ Doryx® MPC is not permitted. Members must meet the initial approval criteria.

Approval duration
Not applicable.

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
FDA: Food and Drug Administration

APPENDIX B: Therapeutic Alternatives
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Maximum Dose
doxycycline (Vibramycin®)	Adults: 200 mg PO on the first day of treatment (administered 100 mg every 12 hours) followed by a maintenance dose of 100 mg/day. See Full Prescribing Information for additional indication specific dosage information. Rosacea: 40 mg or 50 mg PO once daily.	300 mg/day
minocycline (Minocin®)	Adults: 200 mg PO initially, then 100 mg PO every 12 hours. Alternatively, if more frequent oral doses are preferred, 100 to 200 mg PO initially, then 50 mg PO every 6 hours.	300 mg on day 1, then 200 mg/day
tetracycline	Adults: 500 mg PO twice daily or 250 mg four times daily. See Full Prescribing Information for additional indication specific dosage information.	2 gram/day

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Hypersensitivity to doxycycline or other tetracyclines.

- Boxed Warning(s):
  - None reported.

APPENDIX D: General Information

Other FDA-approved acute infection indications for Doryx®/ Doryx® MPC and Acticlate®:

FDA-Approved Indications	Applicable Conditions or Diseases
Rickettsial infections	Rocky Mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsialpox, and tick fevers caused by Rickettsiae

FDA-Approved Indications	Applicable Conditions or Diseases
Sexually transmitted infections	Uncomplicated urethral, endocervical or rectal infections caused by Chlamydia trachomatis Nongonococcal urethritis caused by Ureaplasma urealyticum Lymphogranuloma venereum caused by Chlamydia trachomatis Granuloma inguinale caused by Klebsiella granulomatis Uncomplicated gonorrhea caused by Neisseria gonorrhoeae Chancroid caused by Haemophilus ducreyi
Respiratory tract infections	Respiratory tract infections caused by Mycoplasma pneumoniae Psittacosis (ornithosis) caused by Chlamydophila psittaci Doxycycline is indicated for treatment of infections caused by the following micro- organisms, when bacteriological testing indicates appropriate susceptibility to the drug: Respiratory tract infections caused by Haemophilus influenzae Respiratory tract infections caused by Klebsiella species Upper respiratory infections caused by Streptococcus pneumoniae
Specific bacterial infections	Relapsing fever due to Borrelia recurrentis Plague due to Yersinia pestis Tularemia due to Francisella tularensis Cholera caused by Vibrio cholerae Campylobacter fetus infections caused by Campylobacter fetus
	Brucellosis due to Brucella species (in conjunction with streptomycin) Bartonellosis due to Bartonella bacilliformis Doxycycline is indicated for treatment of infections caused by the following gram- negative microorganisms, when bacteriological testing indicates appropriate susceptibility to the drug: Escherichia coli, Enterobacter aerogenes, Shigella species, Acinetobacter species, urinary tract infections caused by Klebsiella species
Ophthalmic infections	Trachoma caused by Chlamydia trachomatis Inclusion conjunctivitis caused by Chlamydia trachomatis

FDA-Approved Indications	Applicable Conditions or Diseases
Anthrax including inhalational anthrax (post-exposure)	Anthrax due to Bacillus anthracis, including inhalational anthrax (post-exposure)
Alternative treatment for selected infections when penicillin is contraindicated	Syphilis caused by Treponema pallidum Yaws caused by Treponema pallidum subspecies pertenue Vincent's infection caused by Fusobacterium fusiforme Actinomycosis caused by Actinomyces israelii Infections caused by Clostridium species
Adjunctive therapy for acute intestinal amebiasis	Not applicable

References

1. Oracea® Prescribing Information. Fort Worth, TX: Galderma Laboratories, L.P.; August 2017. Available at: www.oracea.com. Accessed February 1, 2021.
2. Doryx® Prescribing Information. Greenville, NC: Mayne Pharma; February 2020. Available at: https://dailymed.nlm.nih.gov/dailymed/. Accessed February 1, 2021.
3. Doryx® MPC Prescribing Information. Greenville, NC: Mayne Pharma; February 2020. Available at: https://dailymed.nlm.nih.gov/dailymed/. Accessed February 1, 2021.
4. Acticlate® Prescribing Information. Exton, PA: Aqua Pharmacueticals; March 2020. Available at: https://dailymed.nlm.nih.gov/dailymed/. Accessed February 1, 2021.
5. Schaller M, Almeida LM, Bewley A, et al. Rosacea treatment update: recommendations from the global ROSacea COnsensus (ROSCO) panel. Br J Dermatol. 2017 Feb;176(2):465-471.
6. Oge LK, Muncie HL, Phillips-Savoy AR. Rosacea: Diagnosis and Treatment. Am Fam Physician. 2015;92(3):187-196.
7. Del Rosso JQ, Thiboutot D, Gallo R. Consensus Recommendations from the American Acne & Rosacea Society on the Management of Rosacea, Part 5: A Guide on the Management of Rosacea. Cutis. 2014 March;93(3):134-138.
8. Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. J Am Acad Dermatol. 2016;74(5):945-973.
9. Arguin PM, Tan KR. Chapter 3. Infectious diseases related to travel. Malaria. In. Centers for Disease Control and Prevention. 2014 Yellow Book - Traveler's Health. Atlanta: U.S. Department of Health and Human Services, Public Health Service. 2014. Available at: http://wwwnc.cdc.gov/travel/yellowbook/2014/chapter-3-infectious-diseases-related-totravel/malaria.
10. Thiboutot D, Anderson R, Cook-Bolden F, et al. Standard management options for rosacea: The 2019 update by the National Rosacea Society Expert Committee. J Am Acad Dermatol. 2020 Jun;82(6):1501-1510. doi: 10.1016/j.jaad.2020.01.077. Epub 2020 Feb 7. PMID: 32035944. Accessed February 1, 2021.

Review/Revision History	Review/Revision Date	P&T Approval Date
Policy was established	01/2020	02/07/2020
2Q2020 P&T Review; No updates, references reviewed and updated	04/2020	05/20/2020
Policy was reviewed: 1. Clinical policy title table was updated.	02/01/2021	03/09/2021

2. Dosing information section was updated to consolidate dosing regimen for Acticlate® and Doryx®. 3. Dosage forms section was updated. 4. Added “one of the following” to maximum dosing criteria in initial and continued therapy criteria. 5. Continued therapy approval criteria II.A.1 was rephrased to “Currently receiving medication that has been authorized by RxAdvance…”. 6. Approval duration sections were updated for initial and continued therapy approval. For I.A, to 4 months from 16 weeks, for I.D to 2 months from 60 days or duration of request, whichever is less, and for II.A, 4 months from up to 16 weeks of treatment (total). 7. Appendix B standard verbiage was updated to “Below are suggested therapeutic alternatives…”. 8. References were updated.		