Clinical Policy: Doxycycline Hyclate (Acticlate, Doryx), Doxycline (Oracea)

Reference Number: PA.CP.PMN.79
Effective Date: 01/18
Last Review Date: 04/19

Coding Implications
Revision Log

Description
Doxycycline (Acticlate, Doryx®, Doryx® MPC, Oracea®) is a tetracycline-class drug.

FDA approved indication
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.

Limitations 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.

Policy/Criteria
Provider must submit documentation (including office chart notes and lab results) supporting that member has met all approval criteria

It is the policy of Pennsylvania Health and Wellness® that Acticlate, Doryx, Doryx MPC, or Oracea is **medically necessary** when the following criteria are met:

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;

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 ≥ 4-week trial of one additional PDL oral tetracycline antibiotic, unless clinically significant adverse effects are experienced;
6. Dose does not exceed 40 mg/day (1 capsule/day).

Approval duration: 16 weeks

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 ≥ 4 week trial of one additional PDL oral tetracycline antibiotic, unless clinically significant adverse effects are experienced;
5. Dose does not exceed:
    a. Acticlate, Doryx: 300 mg/day;
    b. Doryx MPC: 240 mg/day.

Approval duration: 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. No documentation of hypersensitivity to tetracyclines;
5. Dose does not exceed:
    a. Acticlate, Doryx: 100 mg/day;
    b. Doryx MPC: 120 mg/day.

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

D. FDA-Approved Acute Infeection 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 PDL oral tetracycline antibiotic (e.g., immediate-release minocycline), unless clinically significant adverse effects are experienced *or* the other PDL tetracycline antibiotics are not indicated for the member's diagnosis;
5. Dose does not exceed:
   a. Acticlate, Doryx: 300 mg/day;
   b. Doryx MPC: 240 mg/day.

Approval duration: 60 days or duration of request (whichever is less)

E. Other diagnoses/indications
1. Refer to PA.CP.PMN.53 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. Rosacea (must meet all)**:**
1. Currently receiving medication via Pennsylvania Health and Wellness benefit or member has previously met initial approval criteria or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
2. Request is for Oracea;
3. Member is responding positively to therapy;
4. Member has not received Oracea daily for $\geq$ 16 weeks;
5. Dose does not exceed 40 mg/day (1 capsule/day).

Approval duration: up to 16 weeks of treatment (total)

B. Acne Vulgaris (must meet all)**:**
1. Request is for Acticlate, Doryx/Doryx MPC;
2. Currently receiving medication via Pennsylvania Health and Wellness benefit or member has previously met initial approval criteria or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
3. Member is responding positively to therapy.
4. If request is for a dose increase, new dose does not exceed:
   a. Acticlate, Doryx: 300 mg/day;
   b. Doryx MPC: 240 mg/day.

Approval duration: 3 months

C. Prophylaxis of Malaria and FDA-Apporved Acute Infection Indications:
1. Re-authorization for Acticlate, Doryx/Doryx MPC is not permitted. Members must meet the initial approval criteria.

Approval duration: N/A

D. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via Pennsylvania Health and Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.LTSS.PHAR.01) applies; or
2. Refer to PA.CP.PMN.53 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

Approval duration: 3 months or duration of request (whichever is less)

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policy – PA.CP.PMN.53 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key
FDA: Food and Drug Administration
PDL: preferred drug list
N/A: not applicable

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ 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 <u>Rosacea:</u> 40 mg or 50 mg PO QD	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 See Full Prescribing Information for additional indication specific dosage information	300 mg on day 1, then 200 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
tetracycline	Adults: 500 mg PO BID or 250 mg QID 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: 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
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

FDA-approved indications	Applicable conditions or diseases
	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
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	Adjunct to amebicides in acute intestinal amebiasis.

V. Dosage and Administration

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</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 (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*	200 mg/day Doryx MPC: 240 mg/day

Drug Name	Indication	Dosing Regimen	Maximum Dose
		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</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 (particularly chronic infections of the urinary tract), 100 mg every 12 hours PO is recommended. *For children above eight years of age:* The recommended dosage schedule for children weighing 45 kg or less is 4.4 mg/kg of body weight PO divided into two doses on the first day of treatment, followed by 2.2 mg/kg of body weight given as a single daily dose or divided into two doses PO on subsequent days. For more severe infections up to 4.4 mg/kg of body weight may be used. For children over 45 kg, the usual adult dose should be used.	

Drug Name	Indication	Dosing Regimen	Maximum Dose
		Doryx MPC *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 QD	40 mg/day

VI. Product Availability

Doxycycline hyclate (Acticlate)	Tablets: 75 mg, 150 mg

Doxycycline hyclate delayed-release tablets (Doryx, Doryx MPC)	Delayed-release tablets: 50 mg, 200 mg Delayed-release tablets (MPC): 120 mg Generic: 50 mg, 75 mg, 100 mg, 150 mg, 200 mg
Doxycycline (Oracea)	Capsules: 40 mg

VII. References

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Reviews, Revisions, and Approvals	Date	P&T Approval Date
2Q 2018 annual review: added Acticlate to the policy; Removed criteria related to hypersensitivity to tetracyclines per safety guidance; Rosacea: added age requirement; removed criteria related to topical treatments; Acne vulgaris: removed criteria related to topical treatments; added max dose; Other FDA approved indications: added max dose. References reviewed and updated.	1.29.18	
2Q 2019 annual review: added contraindications; references reviewed and updated.	4.17.19	