

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205931Orig1s000**

**MICROBIOLOGY / VIROLOGY REVIEW(S)**

DIVISION OF ANTI-INFECTIVE PRODUCTS  
CLINICAL MICROBIOLOGY REVIEW

NDA 205931 Doxycycline Date review completed: 6-24-14

Date Company Submitted Document: 9-25-13  
Received for Review: 9-25-13  
Date Assigned: 9-25-13

CDER Date Received: 9-25-13  
Reviewer: Kerian Grande Roche

**NAME AND ADDRESS OF SPONSOR**

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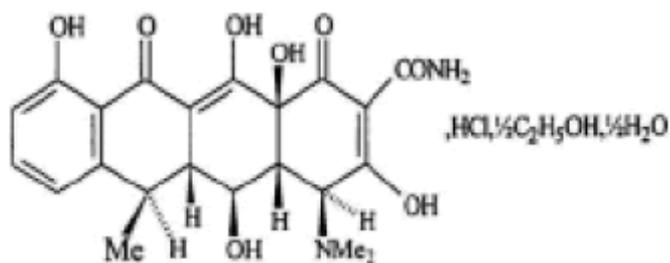
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**DRUG PRODUCT NAME**

Proprietary Name: Acticlate is the proposed name which is under review  
Established Name/Code Name(s): Doxycycline Hyclate Tablets,  
USP

Chemical Name: [4S(4aR,5S,5aR,6R,12aS)]-4-(dimethylamino)-  
1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6methyl-  
1,11-deoxonaphhtacene-2-carboxamide monohydrochloride

Chemical Formulae and Chemical Structure:



**DRUG CATEGORY:**

Antibiotic

**PROPOSED INDICATION(S)**

To reduce the development of drug-resistant bacteria and maintain the effectiveness of TRADENAME and other antibacterial drugs, TRADENAME should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.

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Doxycycline is a tetracycline-class antimicrobial indicated in the following conditions or diseases:

- 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

**PROPOSED DOSAGE FORM, DOSAGE, ROUTE OF ADMINISTRATION, STRENGTH AND DURATION OF TREATMENT**

Dosage Form: Tablets

Route of Administration: oral

Strength: 75 mg and 150 mg tablets

Dosage and Duration of Treatment:

Adults: the usual dose of oral doxycycline is 200 mg on the first day of treatment (administered 100 mg every 12 hours) followed by a maintenance dose of 100 mg daily. In the management of more severe infections (particularly chronic infections of the urinary tract), 100 mg every 12 hours is recommended.

For children above eight years of age: The recommended dosage schedule for children weighing 45 kg or less is 4.4 mg per kg of body weight divided into two doses on the first day of treatment, followed by 2.2 mg per kg of body weight given as a single daily dose or divided into two doses on subsequent days. For more severe infections, up to 4.4 mg per kg of body weight may be used. For children over 45 kg, the usual adult dose should be used.

**DISPENSED:**

Rx

**RELATED DOCUMENTS:**

ANDA 065095 Doxycycline Hyclate Tablets USP

NDA 50533 Vibramycin

**REMARKS**

This product is for doxycycline new strengths in an immediate release tablet. The strengths fall within the approved strengths and the same indications will be used as the approved product. No new micro studies were proposed, and they will rely on previous findings of efficacy. They are seeking a biowaiver.

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**CONCLUSIONS**

From a clinical microbiology perspective this product may be approved, with updates to the label as recommended below. Additionally, the name *Calymmatobacterium granulomatis* is old taxonomy that should be replaced with the new taxonomy *Klebsiella granulomatis* in the indications and usage section and list of organisms, since the bacteria has been renamed. Updates to Quality control have been made to agree with recent Clinical and Laboratory Standards Institute documents (M100-S24). Updates to the interpretive criteria for tetracycline and doxycycline for *Streptococcus pneumoniae* were made in order to eliminate the need for some clinical microbiology laboratories to attach a footnote to their tetracycline susceptibility results indicating that tetracycline was used to represent doxycycline. Additionally, studies have been undertaken over the past two years to develop specific interpretive breakpoints for doxycycline and to re-evaluate the tetracycline breakpoints when testing *S. pneumoniae*. Those studies have been reviewed and are also in agreement with the current thinking of CLSI and EUCAST. The Applicant's annotated indications and usage section may be found in the appendix of this review.

**Agency's Proposed Labeling (Only sections 12.4 Microbiology and Section 15 References, are shown)**

**1.1 Microbiology**

**Mechanism of Action**

Doxycycline inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit. Doxycycline has bacteriostatic activity against a broad range of Gram-positive and Gram-negative bacteria. Cross resistance with other tetracyclines is common.

Doxycycline has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section of the package insert for TRADENAME [see *Indications and Usage (Error! Reference source not found.)*].

**Gram-Negative Bacteria**

*Acinetobacter* species  
*Bartonella bacilliformis*  
*Brucella* species  
*Campylobacter fetus*  
*Enterobacter aerogenes*  
*Escherichia coli*  
*Francisella tularensis*  
*Haemophilus ducreyi*  
*Haemophilus influenzae*  
*Klebsiella granulomatis*  
*Klebsiella* species  
*Neisseria gonorrhoeae*  
*Shigella* species

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*Vibrio cholerae*

*Yersinia pestis*

**Gram-Positive Bacteria**

*Bacillus anthracis*

*Streptococcus pneumoniae*

**Anaerobic Bacteria**

*Clostridium* species

*Fusobacterium fusiforme*

*Propionibacterium acnes*

**Other Bacteria**

*Nocardiae* and other aerobic *Actinomyces* species

*Borrelia recurrentis*

*Chlamydophila psittaci*

*Chlamydia trachomatis*

*Mycoplasma pneumoniae*

*Rickettsiae* species

*Treponema pallidum*

*Treponema* (b) (4) *pallidum* subspecies *pertenue*

*Ureaplasma urealyticum*

**Parasites**

*Balantidium coli*

*Entamoeba* species

*Plasmodium falciparum*\*

\*Doxycycline has been found to be active against the asexual erythrocytic forms of *Plasmodium falciparum*, but not against the gametocytes of *P. falciparum*. The precise mechanism of action of the drug is not known.

Susceptibility Testing Methods

When available, the clinical microbiology laboratory should provide the results of *in vitro* susceptibility test results for antibacterial drugs used in resident hospitals to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antibacterial.

Dilution techniques

Quantitative methods are used to determine antibacterial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antibacterial compounds. The MICs should be determined using a standardized test method <sup>5,6,7,8,9</sup> (broth and/or agar). The MIC values should be interpreted according to criteria provided in Table 1.

Diffusion techniques

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Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to antibacterial compounds. The zone size provides an estimate of the susceptibility of bacteria to antibacterial compounds.

The zone size should be determined using a standardized test method<sup>5,7,710</sup>. This procedure uses paper disks impregnated with 30 mcg doxycycline to test the susceptibility of microorganisms to doxycycline. The disk diffusion interpretive criteria are provided in [Table 1](#).

Anaerobic Techniques

For anaerobic bacteria, the susceptibility to doxycycline can be determined by a standardized test method<sup>111</sup>. The MIC values obtained should be interpreted according to the criteria provided in [Table 1](#).

**Table 1: Susceptibility Test Interpretive Criteria for Doxycycline and Tetracycline**

(b) (4) Pathogen*	Minimal Inhibitory Concentration (mcg per mL)			Zone Diameter (mm)			Agar Dilution (mcg per mL)		
	S	I	R	S	I	R	S	I	R
<i>Acinetobacter spp.</i>									
Doxycycline	≤4	8	≥16	≥13	10 - 12	≤9	-	-	-
Tetracycline	≤4	8	≥16	≥15	12 - 14	≤11	-	-	-
Anaerobes									
Tetracycline	-	-	-	-	-	-	≤4	8	≥16
<i>Bacillus anthracis</i> †									
Doxycycline	≤1	-	-	-	-	-	-	-	-
Tetracycline	≤1	-	-	-	-	-	-	-	-
<i>Brucella species</i> †									
Doxycycline	≤1	-	-	-	-	-	-	-	-
Tetracycline	≤1	-	-	-	-	-	-	-	-
<i>Enterobacteriaceae</i>									
Doxycycline	≤4	8	≥16	≥14	11 - 13	≤10	-	-	-
Tetracycline	≤4	8	≥16	≥15	12 - 14	≤11	-	-	-
<i>Francisella tularensis</i> †									
Doxycycline	≤4	-	-	-	-	-	-	-	-
Tetracycline	≤4	-	-	-	-	-	-	-	-
<i>Haemophilus influenzae</i>									
Tetracycline	≤2	4	≥8	≥29	26 - 28	≤25	-	-	-
<i>Mycoplasma pneumoniae</i> †									
Tetracycline	-	-	-	-	-	-	≤2	-	-
<i>Nocardiae</i> and other aerobic <i>Actinomyces species</i> †									
Doxycycline	≤1	2-4	≥8	-	-	-	-	-	-
<i>Neisseria gonorrhoeae</i> ‡									
Tetracycline	-	-	-	≥38	31 - 37	≤30	≤0.25	0.5 - 1	≥ 2
<i>Streptococcus pneumoniae</i>									
Doxycycline	≤0.25	0.5	≥1	≥ 28	25-27	≤24	-	-	-
Tetracycline	≤ 1	2	≥ 4	≥ 28	25-27	≤24	-	-	-
<i>Vibrio cholerae</i>									
Doxycycline	≤4	8	≥16	-	-	-	-	-	-
Tetracycline	≤4	8	≥16	-	-	-	-	-	-

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**Table 1: Susceptibility Test Interpretive Criteria for Doxycycline and Tetracycline**

(b) (4) Pathogen*	Minimal Inhibitory Concentration (mcg per mL)			Zone Diameter (mm)			Agar Dilution (mcg per mL)		
	S	I	R	S	I	R	S	I	R
<i>Yersinia pestis</i>									
Doxycycline	≤4	8	≥16	-	-	-	-	-	-
Tetracycline	≤4	8	≥16	-	-	-	-	-	-
<i>Ureaplasma urealyticum</i>									
Tetracycline	-	-	-	-	-	-	≤ 1	-	≥ 2

- \* Organisms susceptible to tetracycline are also considered susceptible to doxycycline. However, some organisms that are intermediate or resistant to tetracycline may be susceptible to doxycycline.
- † The current absence of resistance isolates precludes defining any results other than "Susceptible". If isolates yielding MIC results other than susceptible, they should be submitted to a reference laboratory for further testing.
- ‡ Gonococci with 30 mcg tetracycline disk zone diameters of less than 19 mm usually indicate a plasmid-mediated tetracycline resistant *Neisseria gonorrhoeae* isolate. Resistance in these strains should be confirmed by a dilution test (MIC ≥ 16 mcg per mL).

A report of *Susceptible* (S) indicates that the antibacterial is likely to inhibit growth of the pathogen if the antibacterial compound reaches the concentrations at the infection site necessary to inhibit growth of the pathogen. A report of *Intermediate* (I) indicates that the result should be considered equivocal, and, if the bacteria is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug product is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of *Resistant* (R) indicates that the antibacterial is not likely to inhibit growth of the pathogen if the antibacterial compound reaches the concentrations usually achievable at the infection site; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of the supplies and reagents used in the assay, and the techniques of the individuals performing the test<sup>5,6,7,8,9,10,11</sup>. Standard doxycycline and tetracycline powders should provide the following range of MIC values noted in Table 2. For the diffusion technique using the 30 mcg doxycycline disk the criteria noted in Table 2 should be achieved.

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**Table 2: Acceptable Quality Control Ranges for Susceptibility Testing for Doxycycline and Tetracycline**

QC Strain	Minimal Inhibitory Concentration (mcg per mL)	Zone Diameter (mm)	Agar Dilution <sup>b</sup> (mcg per mL)
<i>Enterococcus faecalis</i> ATCC <sup>a</sup> 29212 Doxycycline Tetracycline	2 - 8 8 - 32	- -	- -
<i>Escherichia coli</i> ATCC 25922 Doxycycline Tetracycline	0.5 - 2 0.5- 2	18 - 24 18 to 25	- -
<i>Eubacterium lentum</i> ATCC 43055 Doxycycline	2-16	-	-
<i>Haemophilus influenzae</i> ATCC 49247 Tetracycline	4 - 32	14 - 22	-
<i>Neisseria gonorrhoeae</i> ATCC 49226 Tetracycline	-	30 - 42	0.25 - 1
<i>Staphylococcus aureus</i> ATCC 25923 Doxycycline Tetracycline	- -	23 - 29 24 - 30	- -
<i>Staphylococcus aureus</i> ATCC 29213 Doxycycline Tetracycline	0.12 - 0.5 0.12 - 1	- -	- -
<i>Streptococcus pneumoniae</i> ATCC 49619 Doxycycline Tetracycline	0.015 - 0.12 0.06 - 0.5	25 - 34 27 - 31	- -
<i>Bacteroides fragilis</i> ATCC 25285 Tetracycline	-	-	0.125 - 0.5
<i>Bacteroides thetaiotaomicron</i> ATCC 29741 Doxycycline Tetracycline	2-8 -	- -	- 8 - 32
<i>Mycoplasma hominis</i> ATCC 23114 Tetracycline	-	-	0.12-1
<i>Mycoplasma pneumoniae</i> ATCC 29342 Tetracycline	0.06 - 5	-	0.06 - 0.5
<i>Ureaplasma urealyticum</i> ATCC 33175 Tetracycline	-	-	≥8

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<sup>a</sup> ATCC is the American Type Culture Collection

<sup>b</sup> For four-dilution ranges, results at the extremes of the acceptable ranges should be suspect. Verify with data from other control strains.

## 15 REFERENCES

1. Friedman JM, Polifka JE. *Teratogenic Effects of Drugs. A Resource for Clinicians (TERIS)*. Baltimore, MD: The Johns Hopkins University Press: 2000: 149-195.
2. Cziezel AE and Rockenbauer M. Teratogenic study of doxycycline. *Obstet Gynecol* 1997; 89: 524-528.
3. Horne HW Jr. and Kundsinn RB. The role of mycoplasma among 81 consecutive pregnancies: a prospective study. *Int J Fertil* 1980; 25: 315-317.
4. Hale T. *Medications and Mothers Milk*. 9th edition. Amarillo, TX: Pharmasoft Publishing 2000; 225-226.
5. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-third fourth Informational Supplement*, CLSI document M100-S234. CLSI document M100-S234, Clinical Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 20134.
6. Clinical and Laboratory Standards Institute (CLSI). *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard – Ninth Edition*. CLSI document M07-A9, Clinical Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2012.
7. Clinical and Laboratory Standards Institute (CLSI). *Methods for Antimicrobial Dilution and Disk Susceptibility Testing of Infrequently Isolated or Fastidious Bacteria; Approved Guideline – Second Edition*. CLSI document M45-A2, Clinical Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2010.
8. Clinical and Laboratory Standards Institute (CLSI). *Methods for Mycobacteria, Nocardiae, and Other Aerobic Actinomycetes; Approved Standard – Second Edition*. CLSI document M24-A2, Clinical Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2011.
9. Clinical and Laboratory Standards Institute (CLSI). *Methods for Antimicrobial Susceptibility Testing for Human Mycoplasmas; Approved Guideline*. CLSI document M43-A, Clinical Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2011.

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10. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Disk Diffusion Susceptibility Tests; Approved Standard – Eleventh Edition*. CLSI document M02-A11, Clinical Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2012.
11. Clinical and Laboratory Standards Institute (CLSI). *Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard – Eighth Edition*. CLSI document M11-A8, Clinical Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2012.

**Applicant’s Proposed Labeling (Only sections 12.4 Microbiology and Section 15 References, are shown)**

**15.1 Microbiology**

**Mechanism of Action**

Doxycycline inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit. Doxycycline has bacteriostatic activity against a broad range of Gram-positive and Gram-negative bacteria. Cross resistance with other tetracyclines is common.

Doxycycline has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section of the package insert for TRADENAME [see *Indications and Usage* (**Error! Reference source not found.**)].

**Gram-Negative Bacteria**

*Acinetobacter* species

*Bartonella bacilliformis*

*Brucella* species

(b) (4)

*Campylobacter fetus*

*Enterobacter aerogenes*

*Escherichia coli*

*Francisella tularensis*

*Haemophilus ducreyi*

*Haemophilus influenzae*

*Klebsiella* species

*Neisseria gonorrhoeae*

*Shigella* species

*Vibrio cholerae*

*Yersinia pestis*

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**Gram-Positive Bacteria**

*Bacillus anthracis*

*Streptococcus pneumoniae*

**Anaerobic Bacteria**

*Clostridium* species

*Fusobacterium fusiforme*

*Propionibacterium acnes*

**Other Bacteria**

*Nocardiae* and other aerobic *Actinomyces* species

*Borrelia recurrentis*

*Chlamydophila psittaci*

*Chlamydia trachomatis*

*Mycoplasma pneumoniae*

*Rickettsiae*

*Treponema pallidum*

*Treponema pertenu*

*Ureaplasma urealyticum*

**Parasites**

*Balantidium coli*

*Entamoeba* species

*Plasmodium falciparum*\*

\*Doxycycline has been found to be active against the asexual erythrocytic forms of *Plasmodium falciparum*, but not against the gametocytes of *P. falciparum*. The precise mechanism of action of the drug is not known.

Susceptibility Testing Methods

When available, the clinical microbiology laboratory should provide the results of *in vitro* susceptibility test results for antibacterial drugs used in resident hospitals to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antibacterial.

Dilution techniques

Quantitative methods are used to determine antibacterial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antibacterial compounds. The MICs should be determined using a standardized test method <sup>5,6,7</sup> (broth and/or agar). The MIC values should be interpreted according to criteria provided in [Table 1](#).

Diffusion techniques

Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to antibacterial compounds. The zone size provides an estimate of the susceptibility of bacteria to antibacterial compounds.

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The zone size should be determined using a standardized test method<sup>5,7,7</sup>. This procedure uses paper disks impregnated with 30 mcg doxycycline to test the susceptibility of microorganisms to doxycycline. The disk diffusion interpretive criteria are provided in [Table 1](#).

Anaerobic Techniques

For anaerobic bacteria, the susceptibility to doxycycline can be determined by a standardized test method<sup>11</sup>. The MIC values obtained should be interpreted according to the criteria provided in [Table 1](#).

**Table 3: Susceptibility Test Interpretive Criteria for Doxycycline and Tetracycline**

(b) (4) *	Minimal Inhibitory Concentration (mcg per mL)			Zone Diameter (mm)			Agar Dilution (mcg per mL)		
	S	I	R	S	I	R	S	I	R
<i>Acinetobacter spp.</i>									
Doxycycline	≤4	8	≥16	≥13	10 - 12	≤9	-	-	-
Tetracycline	≤4	8	≥16	≥15	12 - 14	≤11	-	-	-
Anaerobes									
Tetracycline	-	-	-	-	-	-	≤4	8	≥16
<i>Bacillus anthracis</i> †									
Doxycycline	≤1	-	-	-	-	-	-	-	-
Tetracycline	≤1	-	-	-	-	-	-	-	-
<i>Brucella species</i> †									
Doxycycline	≤1	-	-	-	-	-	-	-	-
Tetracycline	≤1	-	-	-	-	-	-	-	-
<i>Enterobacteriaceae</i>									
Doxycycline	≤4	8	≥16	≥14	11 - 13	≤10	-	-	-
Tetracycline	≤4	8	≥16	≥15	12 - 14	≤11	-	-	-
<i>Franciscella tularensis</i> †									
Doxycycline	≤4	-	-	-	-	-	-	-	-
Tetracycline	≤4	-	-	-	-	-	-	-	-
<i>Haemophilus influenzae</i>									
Tetracycline	≤2	4	≥8	≥29	26 - 28	≤25	-	-	-
<i>Mycoplasma pneumoniae</i> †									
Tetracycline	-	-	-	-	-	-	≤2	-	-
<i>Nocardia</i> and other aerobic <i>Actinomyces</i> species†									
Doxycycline	≤1	2-4	≥8	-	-	-	-	-	-
<i>Neisseria gonorrhoeae</i> ‡									
Tetracycline	-	-	-	≥38	31 - 37	≤30	≤0.25	0.5 - 1	≥2

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**Table 3: Susceptibility Test Interpretive Criteria for Doxycycline and Tetracycline**

(b) (4) *	Minimal Inhibitory Concentration (mcg per mL)			Zone Diameter (mm)			Agar Dilution (mcg per mL)		
	S	I	R	S	I	R	S	I	R
<i>Streptococcus pneumoniae</i> Tetracycline	(b) (4)						-	-	-
<i>Vibrio cholerae</i> Doxycycline	≤4	8	≥16	-	-	-	-	-	-
<i>Vibrio cholerae</i> Tetracycline	≤4	8	≥16	-	-	-	-	-	-
<i>Yersinia pestis</i> Doxycycline	≤4	8	≥16	-	-	-	-	-	-
<i>Yersinia pestis</i> Tetracycline	≤4	8	≥16	-	-	-	-	-	-
<i>Ureaplasma urealyticum</i> Tetracycline	-	-	-	-	-	-	≤1	-	≥2

\* Organisms susceptible to tetracycline are also considered susceptible to doxycycline. However, some organisms that are intermediate or resistant to tetracycline may be susceptible to doxycycline.

† The current absence of resistance isolates precludes defining any results other than "Susceptible". If isolates yielding MIC results other than susceptible, they should be submitted to a reference laboratory for further testing.

‡ Gonococci with 30 mcg tetracycline disk zone diameters of less than 19 mm usually indicate a plasmid-mediated tetracycline resistant *Neisseria gonorrhoeae* isolate. Resistance in these strains should be confirmed by a dilution test (MIC ≥ 16 mcg per mL).

A report of *Susceptible* (S) indicates that the antibacterial is likely to inhibit growth of the pathogen if the antibacterial compound reaches the concentrations at the infection site necessary to inhibit growth of the pathogen. A report of *Intermediate* (I) indicates that the result should be considered equivocal, and, if the bacteria is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug product is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of *Resistant* (R) indicates that the antibacterial is not likely to inhibit growth of the pathogen if the antibacterial compound reaches the concentrations usually achievable at the infection site; other therapy should be selected.

**Quality Control**

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of the supplies and reagents used in the assay, and the techniques of the individuals performing the test<sup>5,6,7,7,11,8,9</sup>.

Standard doxycycline and tetracycline powders should provide the following range of MIC values noted in Table 2. For the diffusion technique using the 30 mcg doxycycline disk the criteria noted in Table 2 should be achieved.

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**Table 4: Acceptable Quality Control Ranges for Susceptibility Testing for Doxycycline and Tetracycline**

QC Strain	Minimal Inhibitory Concentration (mcg per mL)	Zone Diameter (mm)	Agar Dilution (mcg per mL)
<i>Enterococcus faecalis</i> ATCC 29212			
Doxycycline	2 - 8	-	-
Tetracycline	8 - 32	-	-
<i>Escherichia coli</i> ATCC 25922			
Doxycycline	0.5 - 2	18 - 24	-
Tetracycline	0.5- 2	18 to 25	-
<i>Haemophilus influenzae</i> ATCC 49247			
Tetracycline	4 - 32	14 - 22	-
<i>Neisseria gonorrhoeae</i> ATCC 49226			
Tetracycline	-	30 - 42	0.25 - 1
<i>Staphylococcus aureus</i> ATCC 25923			
Doxycycline	-	23 - 29	-
Tetracycline	-	24 - 30	-
<i>Staphylococcus aureus</i> ATCC 29213			
Doxycycline	0.12 - 0.5	-	-
Tetracycline	0.12 - 1	-	-
<i>Streptococcus pneumoniae</i> ATCC 49619			
Doxycycline	0.015 - 0.12	25 - 34	-
Tetracycline	0.06 - 0.5	27 - 31	-
<i>Bacteroides fragilis</i> ATCC 25285			
Tetracycline	-	-	0.125 - 0.5
<i>Bacteroides thetaiotaomicron</i>			

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NDA 205931 Doxycycline Date review completed: 6-24-14

**Table 4: Acceptable Quality Control Ranges for Susceptibility Testing for Doxycycline and Tetracycline**

QC Strain	Minimal Inhibitory Concentration (mcg per mL)	Zone Diameter (mm)	Agar Dilution (mcg per mL)
ATCC 29741 Tetracycline	-	-	8 - 32
<i>Mycoplasma pneumoniae</i> ATCC 29342 Tetracycline	0.06 - 5	-	0.06 - 0.5

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NDA 205931 Doxycycline Date review completed: 6-24-14

(b)(4)

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**Appendix: Annotated label for doxycycline hyclate (only indications and usage section shown)**

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(b) (4)	Change Code	Doxycycline Hyclate Tablets USP
<b>FULL PRESCRIBING INFORMATION</b>		<b>FULL OF PRESCRIBING INFORMATION</b>
<p><b>1 INDICATIONS AND USAGE</b></p> <p>To reduce the development of drug-resistant bacteria and maintain the effectiveness of (b) (4) and other antibacterial drugs, (b) (4) should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.</p> <p>Doxycycline is a tetracycline-class (b) (4) indicated in the following conditions or diseases:</p> <p><b>1.1 Rickettsial infections</b> Rocky Mountain spotted fever, typhus fever and the typhus group, rickettsialpox, and tick fevers caused by <i>Rickettsia</i>.</p> <p><b>1.2 Sexually transmitted infections</b> Uncomplicated urethral, endocervical or rectal infections caused by <i>Chlamydia trachomatis</i>. Nongonococcal urethritis caused by <i>Ureaplasma urealyticum</i>. Lymphogranuloma venereum caused by <i>Chlamydia trachomatis</i>. Granuloma inguinale caused by (b) (4) <i>granulomatis</i>. Uncomplicated gonorrhea caused by <i>Neisseria gonorrhoeae</i>. Chancroid caused by <i>Haemophilus ducreyi</i>.</p>	<p>1</p> <p>4</p>	<p><b>1 INDICATIONS AND USAGE</b></p> <p>To reduce the development of drug-resistant bacteria and maintain the effectiveness of <b>TRADENAME</b> and other antibacterial drugs, <b>TRADENAME</b> should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.</p> <p>Doxycycline is a tetracycline-class <b>antibacterial</b> indicated in the following conditions or diseases:</p> <p><b>1.1 Rickettsial infections</b> Rocky Mountain spotted fever, typhus fever and the typhus group, rickettsialpox, and tick fevers caused by <i>Rickettsia</i>.</p> <p><b>1.2 Sexually transmitted infections</b> Uncomplicated urethral, endocervical or rectal infections caused by <i>Chlamydia trachomatis</i>. Nongonococcal urethritis caused by <i>Ureaplasma urealyticum</i>. Lymphogranuloma venereum caused by <i>Chlamydia trachomatis</i>. Granuloma inguinale caused by (b) (4) <i>granulomatis</i>. Uncomplicated gonorrhea caused by <i>Neisseria gonorrhoeae</i>. Chancroid caused by <i>Haemophilus ducreyi</i>.</p>

(b) (4)	Change Code	Doxycycline Hyclate Tablets USP
<p><b>1.3 Respiratory tract infections</b> Respiratory tract infections caused by <i>Mycoplasma pneumoniae</i>. Psittacosis (ornithosis) caused by <i>Chlamydia psittaci</i>. Because many strains of the following groups of microorganisms have been shown to be resistant to doxycycline, culture and susceptibility testing are recommended. Doxycycline is indicated for treatment of infections caused by the microorganisms, when bacteriological testing indicates appropriate susceptibility to the drug. Respiratory tract infections caused by <i>Haemophilus influenzae</i>. Respiratory tract infections caused by <i>Klebsiella species</i>. Upper respiratory infections caused by <i>Streptococcus pneumoniae</i>.</p> <p><b>1.4 Specific bacterial infections</b> Relapsing fever due to <i>Borrelia recurrentis</i>. Plague due to <i>Yersinia pestis</i>. Tularemia due to <i>Francisella tularensis</i>. Cholera caused by <i>Vibrio cholerae</i>. Campylobacter fetus infections caused by <i>Campylobacter fetus</i>. Brucellosis due to <i>Brucella species</i> (in conjunction with streptomycin). Bartonellosis due to <i>Bartonella bacilliformis</i>.</p>		<p><b>1.3 Respiratory tract infections</b> Respiratory tract infections caused by <i>Mycoplasma pneumoniae</i>. Psittacosis (ornithosis) caused by <i>Chlamydia psittaci</i>. Because many strains of the following groups of microorganisms have been shown to be resistant to doxycycline, culture and susceptibility testing are recommended. Doxycycline is indicated for treatment of infections caused by the microorganisms, when bacteriological testing indicates appropriate susceptibility to the drug. Respiratory tract infections caused by <i>Haemophilus influenzae</i>. Respiratory tract infections caused by <i>Klebsiella species</i>. Upper respiratory infections caused by <i>Streptococcus pneumoniae</i>.</p> <p><b>1.4 Specific bacterial infections</b> Relapsing fever due to <i>Borrelia recurrentis</i>. Plague due to <i>Yersinia pestis</i>. Tularemia due to <i>Francisella tularensis</i>. Cholera caused by <i>Vibrio cholerae</i>. Campylobacter fetus infections caused by <i>Campylobacter fetus</i>. Brucellosis due to <i>Brucella species</i> (in conjunction with streptomycin). Bartonellosis due to <i>Bartonella bacilliformis</i>.</p>

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(b) (4)	Change Code	Doxycycline Hyclate Tablets USP
<p>Because many strains of the following groups of microorganisms have been shown to be resistant to doxycycline, culture and susceptibility testing are recommended.</p> <p>Doxycycline is indicated for treatment of infections caused by the following gram-negative microorganisms, when bacteriological testing indicates appropriate susceptibility to the drug:</p> <p><i>Escherichia coli</i> <i>Enterobacter aerogenes</i> <i>Shigella</i> species <i>Acinetobacter</i> species</p> <p>Urinary tract infections caused by <i>Klebsiella</i> species.</p> <p><b>1.5 Ophthalmic infections</b> Trachoma caused by <i>Chlamydia trachomatis</i>, although the infectious agent is not always eliminated as judged by immunofluorescence. Inclusion conjunctivitis caused by <i>Chlamydia trachomatis</i>.</p> <p><b>1.6 Anthrax including inhalational anthrax (post-exposure)</b> Anthrax due to <i>Bacillus anthracis</i>, including inhalational anthrax (post-exposure): to reduce the incidence or progression of disease following exposure to aerosolized <i>Bacillus anthracis</i>.</p>		<p>Because many strains of the following groups of microorganisms have been shown to be resistant to doxycycline, culture and susceptibility testing are recommended.</p> <p>Doxycycline is indicated for treatment of infections caused by the following gram-negative microorganisms, when bacteriological testing indicates appropriate susceptibility to the drug:</p> <p><i>Escherichia coli</i> <i>Enterobacter aerogenes</i> <i>Shigella</i> species <i>Acinetobacter</i> species</p> <p>Urinary tract infections caused by <i>Klebsiella</i> species.</p> <p><b>1.5 Ophthalmic infections</b> Trachoma caused by <i>Chlamydia trachomatis</i>, although the infectious agent is not always eliminated as judged by immunofluorescence. Inclusion conjunctivitis caused by <i>Chlamydia trachomatis</i>.</p> <p><b>1.6 Anthrax including inhalational anthrax (post-exposure)</b> Anthrax due to <i>Bacillus anthracis</i>, including inhalational anthrax (post-exposure): to reduce the incidence or progression of disease following exposure to aerosolized <i>Bacillus anthracis</i>.</p>

(b) (4)	Change Code	Doxycycline Hyclate Tablets USP
<p><b>1.7 Alternative treatment for selected infections when penicillin is contraindicated</b> When penicillin is contraindicated, doxycycline is an alternative drug in the treatment of the following infections: Syphilis caused by <i>Treponema pallidum</i>. Yaws caused by <i>Treponema pertenu</i>.</p> <p>Vincent's infection caused by <i>Fusobacterium fusiforme</i>. Actinomycosis caused by <i>Actinomyces israelii</i>. Infections caused by <i>Clostridium</i> species.</p> <p><b>1.8 Adjunctive therapy for acute intestinal amebiasis and severe acne</b> In acute intestinal amebiasis, doxycycline may be a useful adjunct to amebicides. In severe acne, doxycycline may be useful adjunctive therapy.</p> <p><b>1.9 Prophylaxis of malaria</b> Doxycycline is indicated for the prophylaxis of malaria due to <i>Plasmodium falciparum</i> in short-term travelers (less than 4 months) to areas with chloroquine and/or pyrimethamine-sulfadoxine resistant strains [see <i>Dosage and Administration</i> (2.2) and <i>Patient Counseling Information</i> (17)].</p>	2.f	<p><b>1.7 Alternative treatment for selected infections when penicillin is contraindicated</b> When penicillin is contraindicated, doxycycline is an alternative drug in the treatment of the following infections: Syphilis caused by <i>Treponema pallidum</i>. Yaws caused by <i>Treponema pertenu</i>. <b>Listeriosis due to <i>Listeria monocytogenes</i>.</b></p> <p>Vincent's infection caused by <i>Fusobacterium fusiforme</i>. Actinomycosis caused by <i>Actinomyces israelii</i>. Infections caused by <i>Clostridium</i> species.</p> <p><b>1.8 Adjunctive therapy for acute intestinal amebiasis and severe acne</b> In acute intestinal amebiasis, doxycycline may be a useful adjunct to amebicides. In severe acne, doxycycline may be useful adjunctive therapy.</p> <p><b>1.9 Prophylaxis of malaria</b> Doxycycline is indicated for the prophylaxis of malaria due to <i>Plasmodium falciparum</i> in short-term travelers (less than 4 months) to areas with chloroquine and/or pyrimethamine-sulfadoxine resistant strains [see <i>Dosage and Administration</i> (2.2) and <i>Patient Counseling Information</i> (17)].</p>

Kerian Grande Roche, Ph.D.  
Clinical Microbiology Reviewer

Kerry Snow, MS, MT(ASCP)  
Clinical Microbiology Team Leader  
18 June 2014

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KERIAN K GRANDE ROCHE  
07/25/2014

KERRY SNOW  
07/26/2014

DIVISION OF ANTI-INFECTIVE PRODUCTS  
CLINICAL MICROBIOLOGY REVIEW

NDA 205931 Doxycycline Date review completed: 6-19-14

Date Company Submitted Document: 9-25-13  
Received for Review: 9-25-13  
Date Assigned: 9-25-13

CDER Date Received: 9-25-13  
Reviewer: Kerian Grande Roche

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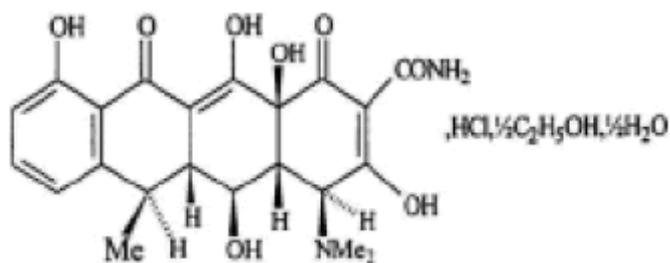
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**DRUG PRODUCT NAME**

Proprietary Name: Acticlate is the proposed name which is under review  
Established Name/Code Name(s): Doxycycline Hyclate Tablets,  
USP

Chemical Name: [4S(4aR,5S,5aR,6R,12aS)]-4-(dimethylamino)-  
1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6methyl-  
1,11-deoxonaphhtacene-2-carboxamide monohydrochloride

Chemical Formulae and Chemical Structure:



**DRUG CATEGORY:**

Antibiotic

**PROPOSED INDICATION(S)**

To reduce the development of drug-resistant bacteria and maintain the effectiveness of TRADENAME and other antibacterial drugs, TRADENAME should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.

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Doxycycline is a tetracycline-class antimicrobial indicated in the following conditions or diseases:

- 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

**PROPOSED DOSAGE FORM, DOSAGE, ROUTE OF ADMINISTRATION, STRENGTH AND DURATION OF TREATMENT**

Dosage Form: Tablets

Route of Administration: oral

Strength: 75 mg and 150 mg tablets

Dosage and Duration of Treatment:

Adults: the usual dose of oral doxycycline is 200 mg on the first day of treatment (administered 100 mg every 12 hours) followed by a maintenance dose of 100 mg daily. In the management of more severe infections (particularly chronic infections of the urinary tract), 100 mg every 12 hours is recommended.

For children above eight years of age: The recommended dosage schedule for children weighing 45 kg or less is 4.4 mg per kg of body weight divided into two doses on the first day of treatment, followed by 2.2 mg per kg of body weight given as a single daily dose or divided into two doses on subsequent days. For more severe infections, up to 4.4 mg per kg of body weight may be used. For children over 45 kg, the usual adult dose should be used.

**DISPENSED:**

Rx

**RELATED DOCUMENTS:**

ANDA 065095 Doxycycline Hyclate Tablets USP

NDA 50533 Vibramycin

**REMARKS**

This product is for doxycycline new strengths in an immediate release tablet. The strengths fall within the approved strengths and the same indications will be used as the approved product. No new micro studies were proposed, and they will rely on previous findings of efficacy. They are seeking a biowaiver.

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**CONCLUSIONS**

From a clinical microbiology perspective this product may be approved, with updates to the label as recommended below. Additionally, the name *Calymmatobacterium granulomatis* is old taxonomy that should be associated with the new taxonomy *Klebsiella granulomatis* in the indications and usage section and list of organisms, since the bacteria has been renamed. Updates to Quality control have been made to agree with recent Clinical and Laboratory Standards Institute documents (M100-S24). The Applicant's annotated indications and usage section may be found in the appendix of this review.

**Agency's Proposed Labeling (Only sections 12.4 Microbiology and Section 15 References, are shown)**

**1.1 Microbiology**

**Mechanism of Action**

Doxycycline inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit. Doxycycline has bacteriostatic activity against a broad range of Gram-positive and Gram-negative bacteria. Cross resistance with other tetracyclines is common.

Doxycycline has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section of the package insert for TRADENAME [see *Indications and Usage (Error! Reference source not found.)*].

**Gram-Negative Bacteria**

*Acinetobacter* species

*Bartonella bacilliformis*

*Brucella* species

*Klebsiella granulomatis*

(b) (4)

*Campylobacter fetus*

*Enterobacter aerogenes*

*Escherichia coli*

*Francisella tularensis*

*Haemophilus ducreyi*

*Haemophilus influenzae*

*Klebsiella* species

*Neisseria gonorrhoeae*

*Shigella* species

*Vibrio cholerae*

*Yersinia pestis*

**Gram-Positive Bacteria**

*Bacillus anthracis*

*Streptococcus pneumoniae*

**Anaerobic Bacteria**

*Clostridium* species  
*Fusobacterium fusiforme*  
*Propionibacterium acnes*

**Other Bacteria**

*Nocardiae* and other aerobic *Actinomyces* species  
*Borrelia recurrentis*  
*Chlamydophila psittaci*  
*Chlamydia trachomatis*  
*Mycoplasma pneumoniae*  
*Rickettsiae* species  
*Treponema pallidum*  
*Treponema pertenue*  
*Ureaplasma urealyticum*

**Parasites**

*Balantidium coli*  
*Entamoeba* species  
*Plasmodium falciparum*\*

\*Doxycycline has been found to be active against the asexual erythrocytic forms of *Plasmodium falciparum*, but not against the gametocytes of *P. falciparum*. The precise mechanism of action of the drug is not known.

Susceptibility Testing Methods

When available, the clinical microbiology laboratory should provide the results of *in vitro* susceptibility test results for antibacterial drugs used in resident hospitals to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antibacterial.

Dilution techniques

Quantitative methods are used to determine antibacterial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antibacterial compounds. The MICs should be determined using a standardized test method<sup>5,6,7,8,9</sup> (broth and/or agar). The MIC values should be interpreted according to criteria provided in [Table 1](#).

Diffusion techniques

Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to antibacterial compounds. The zone size provides an estimate of the susceptibility of bacteria to antibacterial compounds.

The zone size should be determined using a standardized test method<sup>5,7,10</sup>. This procedure uses paper disks impregnated with 30 mcg doxycycline to test the susceptibility of microorganisms to doxycycline. The disk diffusion interpretive criteria are provided in [Table 1](#).

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Anaerobic Techniques

For anaerobic bacteria, the susceptibility to doxycycline can be determined by a standardized test method<sup>†††</sup>. The MIC values obtained should be interpreted according to the criteria provided in [Table 1](#).

**Table 1: Susceptibility Test Interpretive Criteria for Doxycycline and Tetracycline**

(b) (4) Pathogen*	Minimal Inhibitory Concentration (mcg per mL)			Zone Diameter (mm)			Agar Dilution (mcg per mL)		
	S	I	R	S	I	R	S	I	R
<i>Acinetobacter spp.</i>									
Doxycycline	≤4	8	≥16	≥13	10 - 12	≤9	-	-	-
Tetracycline	≤4	8	≥16	≥15	12 - 14	≤11	-	-	-
Anaerobes									
Tetracycline	-	-	-	-	-	-	≤4	8	≥16
<i>Bacillus anthracis</i> †									
Doxycycline	≤1	-	-	-	-	-	-	-	-
Tetracycline	≤1	-	-	-	-	-	-	-	-
<i>Brucella species</i> †									
Doxycycline	≤1	-	-	-	-	-	-	-	-
Tetracycline	≤1	-	-	-	-	-	-	-	-
<i>Enterobacteriaceae</i>									
Doxycycline	≤4	8	≥16	≥14	11 - 13	≤10	-	-	-
Tetracycline	≤4	8	≥16	≥15	12 - 14	≤11	-	-	-
<i>Francisella tularensis</i> †									
Doxycycline	≤4	-	-	-	-	-	-	-	-
Tetracycline	≤4	-	-	-	-	-	-	-	-
<i>Haemophilus influenzae</i>									
Tetracycline	≤2	4	≥8	≥29	26 - 28	≤25	-	-	-
<i>Mycoplasma pneumoniae</i> †									
Tetracycline	-	-	-	-	-	-	≤2	-	-
<i>Nocardia</i> and other aerobic <i>Actinomyces species</i> †									
Doxycycline	≤1	2-4	≥8	-	-	-	-	-	-
<i>Neisseria gonorrhoeae</i> ‡									
Tetracycline	-	-	-	≥38	31 - 37	≤30	≤0.25	0.5 - 1	≥ 2
<i>Streptococcus pneumoniae</i>									
Tetracycline	≤ 2	4	≥ 8	≥ 23	19 -- 22	≤18	-	-	-
<i>Vibrio cholerae</i>									
Doxycycline	≤4	8	≥16	-	-	-	-	-	-
Tetracycline	≤4	8	≥16	-	-	-	-	-	-
<i>Yersinia pestis</i>									
Doxycycline	≤4	8	≥16	-	-	-	-	-	-
Tetracycline	≤4	8	≥16	-	-	-	-	-	-
<i>Ureaplasma urealyticum</i>									
Tetracycline	-	-	-	-	-	-	≤ 1	-	≥ 2

\* Organisms susceptible to tetracycline are also considered susceptible to doxycycline. However, some organisms that are intermediate or resistant to tetracycline may be susceptible to doxycycline.

† The current absence of resistance isolates precludes defining any results other than "Susceptible". If isolates yielding MIC results other than susceptible, they should be submitted to a reference laboratory for further testing.

‡ Gonococci with 30 mcg tetracycline disk zone diameters of less than 19 mm usually indicate a plasmid-mediated tetracycline resistant *Neisseria gonorrhoeae* isolate. Resistance in these strains should be confirmed by a dilution test (MIC ≥ 16 mcg per mL).

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A report of *Susceptible* (S) indicates that the antibacterial is likely to inhibit growth of the pathogen if the antibacterial compound reaches the concentrations at the infection site necessary to inhibit growth of the pathogen. A report of *Intermediate* (I) indicates that the result should be considered equivocal, and, if the bacteria is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug product is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of *Resistant* (R) indicates that the antibacterial is not likely to inhibit growth of the pathogen if the antibacterial compound reaches the concentrations usually achievable at the infection site; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of the supplies and reagents used in the assay, and the techniques of the individuals performing the test<sup>5,6,7,8,9,10,11</sup>. Standard doxycycline and tetracycline powders should provide the following range of MIC values noted in [Table 2](#). For the diffusion technique using the 30 mcg doxycycline disk the criteria noted in [Table 2](#) should be achieved.

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**Table 2: Acceptable Quality Control Ranges for Susceptibility Testing for Doxycycline and Tetracycline**

QC Strain	Minimal Inhibitory Concentration (mcg per mL)	Zone Diameter (mm)	Agar Dilution <sup>b</sup> (mcg per mL)
<i>Enterococcus faecalis</i> ATCC <sup>a</sup> 29212			
Doxycycline	2 - 8	-	-
Tetracycline	8 - 32	-	-
<i>Escherichia coli</i> ATCC 25922			
Doxycycline	0.5 - 2	18 - 24	-
Tetracycline	0.5 - 2	18 to 25	-
<i>Eubacterium lentum</i> ATCC 43055			
Doxycycline	2-16	-	-
<i>Haemophilus influenzae</i> ATCC 49247			
Tetracycline	4 - 32	14 - 22	-
<i>Neisseria gonorrhoeae</i> ATCC 49226			
Tetracycline	-	30 - 42	0.25 - 1
<i>Staphylococcus aureus</i> ATCC 25923			
Doxycycline	-	23 - 29	-
Tetracycline	-	24 - 30	-
<i>Staphylococcus aureus</i> ATCC 29213			
Doxycycline	0.12 - 0.5	-	-
Tetracycline	0.12 - 1	-	-
<i>Streptococcus pneumoniae</i> ATCC 49619			
Doxycycline	0.015 - 0.12	25 - 34	-
Tetracycline	0.06 - 0.5	27 - 31	-
<i>Bacteroides fragilis</i> ATCC 25285			
Tetracycline	-	-	0.125 - 0.5
<i>Bacteroides thetaiotaomicron</i> ATCC 29741			
Doxycycline	2-8	-	-
Tetracycline	-	-	8 - 32
<i>Mycoplasma hominis</i> ATCC 23114			
Tetracycline	-	-	0.12-1
<i>Mycoplasma pneumoniae</i> ATCC 29342			
Tetracycline	0.06 - 5	-	0.06 - 0.5
<i>Ureaplasma urealyticum</i> ATCC 33175			
Tetracycline	-	-	≥8

<sup>a</sup> ATCC is the American Type Culture Collection

<sup>b</sup> For four-dilution ranges, results at the extremes of the acceptable ranges should be suspect. Verify with data from other control strains.

## 15 REFERENCES

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2. Cziezel AE and Rockenbauer M. Teratogenic study of doxycycline. *Obstet Gynecol* 1997; 89: 524-528.

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**Applicant's Proposed Labeling (Only sections 12.4 Microbiology and Section 15 References, are shown)**

(b) (4)

**Microbiology**

**Mechanism of Action**

Doxycycline inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit. Doxycycline has bacteriostatic activity against a broad range of Gram-positive and Gram-negative bacteria. Cross resistance with other tetracyclines is common.

Doxycycline has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section of the package insert for TRADENAME [see *Indications and Usage* (**Error! Reference source not found.**)].

**Gram-Negative Bacteria**

*Acinetobacter* species

*Bartonella bacilliformis*

*Brucella* species

(b) (4)

*Campylobacter fetus*

*Enterobacter aerogenes*

*Escherichia coli*

*Francisella tularensis*

*Haemophilus ducreyi*

*Haemophilus influenzae*

*Klebsiella* species

*Neisseria gonorrhoeae*

*Shigella* species

*Vibrio cholerae*

*Yersinia pestis*

**Gram-Positive Bacteria**

*Bacillus anthracis*

*Streptococcus pneumoniae*

**Anaerobic Bacteria**

*Clostridium* species

*Fusobacterium fusiforme*

*Propionibacterium acnes*

**Other Bacteria**

*Nocardiae* and other aerobic *Actinomyces* species

*Borrelia recurrentis*

*Chlamydophila psittaci*

*Chlamydia trachomatis*

*Mycoplasma pneumoniae*

*Rickettsiae*

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*Treponema pallidum*

*Treponema pertenue*

*Ureaplasma urealyticum*

#### **Parasites**

*Balantidium coli*

*Entamoeba* species

*Plasmodium falciparum*\*

\*Doxycycline has been found to be active against the asexual erythrocytic forms of *Plasmodium falciparum*, but not against the gametocytes of *P. falciparum*. The precise mechanism of action of the drug is not known.

#### Susceptibility Testing Methods

When available, the clinical microbiology laboratory should provide the results of *in vitro* susceptibility test results for antibacterial drugs used in resident hospitals to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antibacterial.

#### Dilution techniques

Quantitative methods are used to determine antibacterial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antibacterial compounds. The MICs should be determined using a standardized test method<sup>5,6,7</sup> (broth and/or agar). The MIC values should be interpreted according to criteria provided in [Table 1](#).

#### Diffusion techniques

Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to antibacterial compounds. The zone size provides an estimate of the susceptibility of bacteria to antibacterial compounds.

The zone size should be determined using a standardized test method<sup>5,7,7</sup>. This procedure uses paper disks impregnated with 30 mcg doxycycline to test the susceptibility of microorganisms to doxycycline. The disk diffusion interpretive criteria are provided in [Table 1](#).

#### Anaerobic Techniques

For anaerobic bacteria, the susceptibility to doxycycline can be determined by a standardized test method<sup>11</sup>. The MIC values obtained should be interpreted according to the criteria provided in [Table 1](#).

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**Table (b) (4) Susceptibility Test Interpretive Criteria for Doxycycline and Tetracycline**

(b) (4) *	Minimal Inhibitory Concentration (mcg per mL)			Zone Diameter (mm)			Agar Dilution (mcg per mL)		
	S	I	R	S	I	R	S	I	R
<i>Acinetobacter spp.</i>									
Doxycycline	≤4	8	≥16	≥13	10 - 12	≤9	-	-	-
Tetracycline	≤4	8	≥16	≥15	12 - 14	≤11	-	-	-
Anaerobes									
Tetracycline	-	-	-	-	-	-	≤4	8	≥16
<i>Bacillus anthracis</i> †									
Doxycycline	≤1	-	-	-	-	-	-	-	-
Tetracycline	≤1	-	-	-	-	-	-	-	-
<i>Brucella species</i> †									
Doxycycline	≤1	-	-	-	-	-	-	-	-
Tetracycline	≤1	-	-	-	-	-	-	-	-
<i>Enterobacteriaceae</i>									
Doxycycline	≤4	8	≥16	≥14	11 - 13	≤10	-	-	-
Tetracycline	≤4	8	≥16	≥15	12 - 14	≤11	-	-	-
<i>Francisella tularensis</i> †									
Doxycycline	≤4	-	-	-	-	-	-	-	-
Tetracycline	≤4	-	-	-	-	-	-	-	-
<i>Haemophilus influenzae</i>									
Tetracycline	≤2	4	≥8	≥29	26 - 28	≤25	-	-	-
<i>Mycoplasma pneumoniae</i> †									
Tetracycline	-	-	-	-	-	-	≤2	-	-
<i>Nocardia</i> and other aerobic <i>Actinomyces</i> species†									
Doxycycline	≤1	2-4	≥8	-	-	-	-	-	-
<i>Neisseria gonorrhoeae</i> ‡									
Tetracycline	-	-	-	≥38	31 - 37	≤30	≤0.25	0.5 - 1	≥2
<i>Streptococcus pneumoniae</i>									
Tetracycline	(b) (4)						-	-	-
<i>Vibrio cholerae</i>									
Doxycycline	≤4	8	≥16	-	-	-	-	-	-
Tetracycline	≤4	8	≥16	-	-	-	-	-	-
<i>Yersinia pestis</i>									
Doxycycline	≤4	8	≥16	-	-	-	-	-	-
Tetracycline	≤4	8	≥16	-	-	-	-	-	-
<i>Ureaplasma urealyticum</i>									
Tetracycline	-	-	-	-	-	-	≤1	-	≥2

\* Organisms susceptible to tetracycline are also considered susceptible to doxycycline. However, some organisms that are intermediate or resistant to tetracycline may be susceptible to doxycycline.

† The current absence of resistance isolates precludes defining any results other than "Susceptible". If isolates yielding MIC results other than susceptible, they should be submitted to a reference laboratory for further testing.

‡ Gonococci with 30 mcg tetracycline disk zone diameters of less than 19 mm usually indicate a plasmid-mediated tetracycline resistant *Neisseria gonorrhoeae* isolate. Resistance in these strains should be confirmed by a dilution test (MIC ≥ 16 mcg per mL).

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A report of *Susceptible* (S) indicates that the antibacterial is likely to inhibit growth of the pathogen if the antibacterial compound reaches the concentrations at the infection site necessary to inhibit growth of the pathogen. A report of *Intermediate* (I) indicates that the result should be considered equivocal, and, if the bacteria is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug product is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of *Resistant* (R) indicates that the antibacterial is not likely to inhibit growth of the pathogen if the antibacterial compound reaches the concentrations usually achievable at the infection site; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of the supplies and reagents used in the assay, and the techniques of the individuals performing the test<sup>5,6,7,7,11,8,9</sup>.

Standard doxycycline and tetracycline powders should provide the following range of MIC values noted in [Table 2](#). For the diffusion technique using the 30 mcg doxycycline disk the criteria noted in [Table 2](#) should be achieved.

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Table (b) (4) Acceptable Quality Control Ranges for Susceptibility Testing for Doxycycline and Tetracycline

QC Strain	Minimal Inhibitory Concentration (mcg per mL)	Zone Diameter (mm)	Agar Dilution (mcg per mL)
<i>Enterococcus faecalis</i> ATCC 29212			
Doxycycline	2 - 8	-	-
Tetracycline	8 - 32	-	-
<i>Escherichia coli</i> ATCC 25922			
Doxycycline	0.5 - 2	18 - 24	-
Tetracycline	0.5- 2	18 to 25	-
<i>Haemophilus influenzae</i> ATCC 49247			
Tetracycline	4 - 32	14 - 22	-
<i>Neisseria gonorrhoeae</i> ATCC 49226			
Tetracycline	-	30 - 42	0.25 - 1
<i>Staphylococcus aureus</i> ATCC 25923			
Doxycycline	-	23 - 29	-
Tetracycline	-	24 - 30	-
<i>Staphylococcus aureus</i> ATCC 29213			
Doxycycline	0.12 - 0.5	-	-
Tetracycline	0.12 - 1	-	-
<i>Streptococcus pneumoniae</i> ATCC 49619			
Doxycycline	0.015 - 0.12	25 - 34	-
Tetracycline	0.06 - 0.5	27 - 31	-
<i>Bacteroides fragilis</i> ATCC 25285			
Tetracycline	-	-	0.125 - 0.5
<i>Bacteroides thetaiotaomicron</i> ATCC 29741			
Tetracycline	-	-	8 - 32
<i>Mycoplasma pneumoniae</i> ATCC 29342			
Tetracycline	0.06 - 5	-	0.06 - 0.5

(b) (4) REFERENCES

- (b) (4) Friedman JM, Polifka JE. *Teratogenic Effects of Drugs. A Resource for Clinicians (TERIS)*. Baltimore, MD: The Johns Hopkins University Press: 2000: 149-195.
- Cziesel AE and Rockenbauer M. Teratogenic study of doxycycline. *Obstet Gynecol* 1997; 89: 524-528.
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Clinical and Laboratory Standards Institute (CLSI). *Methods for Mycobacteria, Nocardiae, and Other Aerobic Actinomycetes; Approved Standard – Second Edition*. CLSI document M24-A2, Clinical Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne Pennsylvania 19087, USA, 2011.

Clinical and Laboratory Standards Institute (CLSI). *Methods for Antimicrobial Susceptibility Testing for Human Mycoplasmas; Approved Guideline*. CLSI document M43-A, Clinical Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne Pennsylvania 19087, USA, 2011.

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**Appendix: Annotated label for doxycycline hyclate (only indications and usage section shown)**

(b) (4)	Change Code	Doxycycline Hyclate Tablets USP
<b>FULL PRESCRIBING INFORMATION</b>		<b>FULL OF PRESCRIBING INFORMATION</b>
<p><b>1 INDICATIONS AND USAGE</b></p> <p>To reduce the development of drug-resistant bacteria and maintain the effectiveness of (b) (4) and other antibacterial drugs, (b) (4) should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.</p> <p>Doxycycline is a tetracycline-class (b) (4) indicated in the following conditions or diseases:</p> <p><b>1.1 Rickettsial infections</b> Rocky Mountain spotted fever, typhus fever and the typhus group, rickettsialpox, and tick fevers caused by <i>Rickettsiae</i>.</p> <p><b>1.2 Sexually transmitted infections</b> Uncomplicated urethral, endocervical or rectal infections caused by <i>Chlamydia trachomatis</i>. Nongonococcal urethritis caused by <i>Ureaplasma urealyticum</i>. Lymphogranuloma venereum caused by <i>Chlamydia trachomatis</i>. Granuloma inguinale caused by (b) (4) <i>granulomatis</i>. Uncomplicated gonorrhea caused by <i>Neisseria gonorrhoeae</i>. Chancroid caused by <i>Haemophilus ducreyi</i>.</p>	<p>1</p> <p>4</p>	<p><b>1 INDICATIONS AND USAGE</b></p> <p>To reduce the development of drug-resistant bacteria and maintain the effectiveness of <b>TRADENAME</b> and other antibacterial drugs, <b>TRADENAME</b> should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.</p> <p>Doxycycline is a tetracycline-class <b>antibacterial</b> indicated in the following conditions or diseases:</p> <p><b>1.1 Rickettsial infections</b> Rocky Mountain spotted fever, typhus fever and the typhus group, rickettsialpox, and tick fevers caused by <i>Rickettsiae</i>.</p> <p><b>1.2 Sexually transmitted infections</b> Uncomplicated urethral, endocervical or rectal infections caused by <i>Chlamydia trachomatis</i>. Nongonococcal urethritis caused by <i>Ureaplasma urealyticum</i>. Lymphogranuloma venereum caused by <i>Chlamydia trachomatis</i>. Granuloma inguinale caused by (b) (4) <i>granulomatis</i>. Uncomplicated gonorrhea caused by <i>Neisseria gonorrhoeae</i>. Chancroid caused by <i>Haemophilus ducreyi</i>.</p>

(b) (4)	Change Code	Doxycycline Hyclate Tablets USP
<p><b>1.3 Respiratory tract infections</b> Respiratory tract infections caused by <i>Mycoplasma pneumoniae</i>. Psittacosis (ornithosis) caused by <i>Chlamydophila psittaci</i>. Because many strains of the following groups of microorganisms have been shown to be resistant to doxycycline, culture and susceptibility testing are recommended. Doxycycline is indicated for treatment of infections caused by the microorganisms, when bacteriological testing indicates appropriate susceptibility to the drug: Respiratory tract infections caused by <i>Haemophilus influenzae</i>. Respiratory tract infections caused by <i>Klebsiella species</i>. Upper respiratory infections caused by <i>Streptococcus pneumoniae</i>.</p> <p><b>1.4 Specific bacterial infections</b> Relapsing fever due to <i>Borrelia recurrentis</i>. Plague due to <i>Yersinia pestis</i>. Tularemia due to <i>Francisella tularensis</i>. Cholera caused by <i>Vibrio cholerae</i>. Campylobacter fetus infections caused by <i>Campylobacter fetus</i>. Brucellosis due to <i>Brucella species</i> (in conjunction with streptomycin). Bartonellosis due to <i>Bartonella bacilliformis</i>.</p>		<p><b>1.3 Respiratory tract infections</b> Respiratory tract infections caused by <i>Mycoplasma pneumoniae</i>. Psittacosis (ornithosis) caused by <i>Chlamydophila psittaci</i>. Because many strains of the following groups of microorganisms have been shown to be resistant to doxycycline, culture and susceptibility testing are recommended. Doxycycline is indicated for treatment of infections caused by the microorganisms, when bacteriological testing indicates appropriate susceptibility to the drug: Respiratory tract infections caused by <i>Haemophilus influenzae</i>. Respiratory tract infections caused by <i>Klebsiella species</i>. Upper respiratory infections caused by <i>Streptococcus pneumoniae</i>.</p> <p><b>1.4 Specific bacterial infections</b> Relapsing fever due to <i>Borrelia recurrentis</i>. Plague due to <i>Yersinia pestis</i>. Tularemia due to <i>Francisella tularensis</i>. Cholera caused by <i>Vibrio cholerae</i>. Campylobacter fetus infections caused by <i>Campylobacter fetus</i>. Brucellosis due to <i>Brucella species</i> (in conjunction with streptomycin). Bartonellosis due to <i>Bartonella bacilliformis</i>.</p>

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1	(b) (4)	Change Code	Doxycycline Hyclate Tablets USP
	<p>Because many strains of the following groups of microorganisms have been shown to be resistant to doxycycline, culture and susceptibility testing are recommended.</p> <p>Doxycycline is indicated for treatment of infections caused by the following gram-negative microorganisms, when bacteriological testing indicates appropriate susceptibility to the drug:</p> <p><i>Escherichia coli</i> <i>Enterobacter aerogenes</i> <i>Shigella</i> species <i>Acinetobacter</i> species</p> <p>Urinary tract infections caused by <i>Klebsiella</i> species.</p> <p><b>1.5 Ophthalmic infections</b> Trachoma caused by <i>Chlamydia trachomatis</i>, although the infectious agent is not always eliminated as judged by immunofluorescence. Inclusion conjunctivitis caused by <i>Chlamydia trachomatis</i>.</p> <p><b>1.6 Anthrax including inhalational anthrax (post-exposure)</b> Anthrax due to <i>Bacillus anthracis</i>, including inhalational anthrax (post-exposure): to reduce the incidence or progression of disease following exposure to aerosolized <i>Bacillus anthracis</i>.</p>		<p>Because many strains of the following groups of microorganisms have been shown to be resistant to doxycycline, culture and susceptibility testing are recommended.</p> <p>Doxycycline is indicated for treatment of infections caused by the following gram-negative microorganisms, when bacteriological testing indicates appropriate susceptibility to the drug:</p> <p><i>Escherichia coli</i> <i>Enterobacter aerogenes</i> <i>Shigella</i> species <i>Acinetobacter</i> species</p> <p>Urinary tract infections caused by <i>Klebsiella</i> species.</p> <p><b>1.5 Ophthalmic infections</b> Trachoma caused by <i>Chlamydia trachomatis</i>, although the infectious agent is not always eliminated as judged by immunofluorescence. Inclusion conjunctivitis caused by <i>Chlamydia trachomatis</i>.</p> <p><b>1.6 Anthrax including inhalational anthrax (post-exposure)</b> Anthrax due to <i>Bacillus anthracis</i>, including inhalational anthrax (post-exposure): to reduce the incidence or progression of disease following exposure to aerosolized <i>Bacillus anthracis</i>.</p>

1	(b) (4)	Change Code	Doxycycline Hyclate Tablets USP
	<p><b>1.7 Alternative treatment for selected infections when penicillin is contraindicated</b> When penicillin is contraindicated, doxycycline is an alternative drug in the treatment of the following infections: Syphilis caused by <i>Treponema pallidum</i>. Yaws caused by <i>Treponema pertenu</i>.</p> <p>Vincent's infection caused by <i>Fusobacterium fusiforme</i>. Actinomycosis caused by <i>Actinomyces israelii</i>. Infections caused by <i>Clostridium</i> species.</p> <p><b>1.8 Adjunctive therapy for acute intestinal amebiasis and severe acne</b> In acute intestinal amebiasis, doxycycline may be a useful adjunct to amebicides. In severe acne, doxycycline may be useful adjunctive therapy.</p> <p><b>1.9 Prophylaxis of malaria</b> Doxycycline is indicated for the prophylaxis of malaria due to <i>Plasmodium falciparum</i> in short-term travelers (less than 4 months) to areas with chloroquine and/or pyrimethamine-sulfadoxine resistant strains [see <i>Dosage and Administration</i> (2.2) and <i>Patient Counseling Information</i> (17)].</p>	2.f	<p><b>1.7 Alternative treatment for selected infections when penicillin is contraindicated</b> When penicillin is contraindicated, doxycycline is an alternative drug in the treatment of the following infections: Syphilis caused by <i>Treponema pallidum</i>. Yaws caused by <i>Treponema pertenu</i>. <b>Listeriosis due to <i>Listeria monocytogenes</i>.</b></p> <p>Vincent's infection caused by <i>Fusobacterium fusiforme</i>. Actinomycosis caused by <i>Actinomyces israelii</i>. Infections caused by <i>Clostridium</i> species.</p> <p><b>1.8 Adjunctive therapy for acute intestinal amebiasis and severe acne</b> In acute intestinal amebiasis, doxycycline may be a useful adjunct to amebicides. In severe acne, doxycycline may be useful adjunctive therapy.</p> <p><b>1.9 Prophylaxis of malaria</b> Doxycycline is indicated for the prophylaxis of malaria due to <i>Plasmodium falciparum</i> in short-term travelers (less than 4 months) to areas with chloroquine and/or pyrimethamine-sulfadoxine resistant strains [see <i>Dosage and Administration</i> (2.2) and <i>Patient Counseling Information</i> (17)].</p>

Kerian Grande Roche, Ph.D.  
Clinical Microbiology Reviewer

Kerry Snow, MS, MT(ASCP)  
Clinical Microbiology Team Leader  
18 June 2014

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/s/  
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KERIAN K GRANDE ROCHE  
06/19/2014

KERRY SNOW  
06/19/2014

MEMORANDUM



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**DATE:** 25 November 2013

**TO:** NDA 205931

**FROM:** Jessica G. Cole, PhD  
Review Microbiologist  
CDER/OPS/New Drug Microbiology Staff  
(301) 796-5148

**THROUGH:** Bryan Riley, PhD  
Microbiology Team Leader  
CDER/OPS/New Drug Microbiology Staff

**cc:** Carmen DeBellis  
CDER/OND/OAP/DAIP

**SUBJECT:** Product Quality Microbiology assessment of Microbial Limits for Doxycycline Hyclate Tablets, USP [Submission Date: 25 September 2013]

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**The Microbial Limits specification for Doxycycline Hyclate Tablets, USP is acceptable from a Product Quality Microbiology perspective. Therefore, this submission is recommended for approval from the standpoint of product quality microbiology.**

Doxycycline Hyclate Tablets, USP are for oral administration and will be manufactured at Catalent Winchester, KY. The composition is shown in Table 1.

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/s/  
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JESSICA COLE  
11/25/2013

BRYAN S RILEY  
11/25/2013  
I concur.