

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208253Orig1s000

MICROBIOLOGY/VIROLOGY REVIEW(S)

DIVISION OF ANTI-INFECTIVE PRODUCTS
CLINICAL MICROBIOLOGY REVIEW

NDA 208253 Doxycycline Hyclate, 75mg Date review completed: 2-27-16

Date Company Submitted Document: 6-26-15 CDER Date Received: 6-26-15
Received for Review: 6-26-15 Reviewer: Kerian Grande Roche
Date Assigned: 6-26-15

NAME OF APPLICANT

Aqua Pharmaceuticals

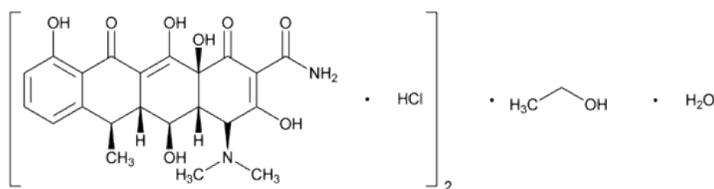
CONTACT PERSON

Kimberley Forbes-McKean, Ph.D.
Vice President Research and Development

DRUG PRODUCT NAME

Established Name/Code Name(s): Doxycycline Hyclate Capsules, 75 mg
Chemical Name: 4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide monohydrochloride
Molecular Formulae: $(C_{22}H_{24}N_2O_8 \cdot HCl)_2 \cdot C_2H_6O \cdot H_2O$, compound with ethyl alcohol (2:1), monohydrate.

Chemical Structure:



DRUG CATEGORY:

Antibiotic

PROPOSED INDICATION(S)

- 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

See labeling for specific organisms listed for the above indications.

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

Dosage Form: capsules

Route of Administration: oral

Strength: 75 mg

Dosage and Duration of Treatment: See labeling for additional information.

DISPENSED:

Rx

RELATED DOCUMENTS:

NDA 50007 Vibramycin

REMARKS

This submission is a New Drug Application for Doxycycline Hyclate Capsules, 75 mg. It is for a new strength of the listed drug, Vibramycin® (doxycycline hyclate) capsules. No new micro studies were proposed, and the indications being sought are the same as the approved listed drug.

CONCLUSIONS

From a clinical microbiology perspective this product may be approved, with updates to the label as recommended below.

1. Susceptibility Testing and Quality Control parameters that were not specific to doxycycline were deleted from the labeling.
2. References were updated to the most current versions of the Clinical and Laboratory Standards Institute.
3. *Lysteria monocytogenes* was added to the list of organisms because it is in the indications.
4. The following statement was added under the table for susceptibility test interpretive criteria: "Doxycycline susceptibility testing interpretive criteria for anaerobes, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Neisseria gonorrhoeae*, and *Ureaplasma urealyticum* have not been established. Isolates of these species that are susceptible to tetracycline are also considered susceptible to doxycycline."⁵
5. Modified the label in accordance with FDA draft guidance document: "Guidance for Industry-Microbiological Data for Systemic Antibacterial Drug Products-Development, Analysis and Presentation".

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

12.4 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.

Resistance

Cross resistance with other tetracyclines is common.

Antimicrobial Activity

Doxycycline has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections (b) (4)

[redacted] see *Indications and Usage* (**Error! Reference source not found.**)].

Gram-n^(b)₍₄₎egative 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
- Vibrio cholerae*
- Yersinia pestis*

Gram-p^(b)₍₄₎ositive Bacteria

- Bacillus anthracis*
- Listeria monocytogenes*
- Streptococcus pneumoniae*

Anaerobic Bacteria

- Clostridium* species
- Fusobacterium fusiforme*

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Propionibacterium acnes

Other Bacteria

Nocardiae and other aerobic *Actinomyces* species

Borrelia recurrentis

Chlamydophila psittaci

Chlamydia trachomatis

Mycoplasma pneumoniae

Rickettsiae species

Treponema pallidum

Treponema 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 **cumulative reports of** (b) (4) *in vitro* susceptibility test results for antibacterial drugs used in (b) (4) **local hospitals and practice areas** 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 an (b) (4) antibacterial **drug for treatment**.

Dilution techniques

Quantitative methods are used to determine antibacterial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to (b) (4) **antimicrobial** compounds. The MICs should be determined using a standardized test method^{5,5,7,8,9} (broth and/or agar). The MIC values should be interpreted according to criteria provided in Table 3.

Diffusion techniques

Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to (b) (4) **antimicrobial** compounds. (b) (4)

The zone size should be determined using a standardized test method^{5,7,10}. This procedure uses paper disks impregnated with 30 mcg doxycycline to test the susceptibility of (b) (4) **bacteria** to doxycycline. The disk diffusion interpretive criteria are provided in Table (b) (4)

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Anaerobic Techniques

For anaerobic bacteria, the susceptibility to doxycycline can be determined by a standardized test method^{5,11}. The MIC values obtained should be interpreted according to the criteria provided in Table (b) (4)

Table 1: Susceptibility Test Interpretive Criteria for Doxycycline (b) (4)

Pathogen [±]	Minimal Inhibitory Concentration (mcg / mL) (b) (4)	(b) (4)
(b) (4)		

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(b) (4)

Table 1: Susceptibility Test Interpretive Criteria for Doxycycline

Pathogen ¹	Minimal Inhibitory Concentrations (mcg/mL)			Disk Diffusion Zone Diameters (mm)		
	≤4	8	≥16	≥13	10 - 12	≤9
<i>Acinetobacter spp.</i>	≤4	8	≥16	≥13	10 - 12	≤9
<i>Bacillus anthracis</i> ²	≤1	-	-	-	-	-
<i>Brucella</i> species ^{2,3}	≤1	-	-	-	-	-
<i>Enterobacteriaceae</i>	≤4	8	≥16	≥14	11 - 13	≤10
<i>Franciscella tularensis</i> ²	≤4	-	-	-	-	-
<i>Nocardiae</i> and other aerobic <i>Actinomyces</i> species ²	≤1	2 - 4	≥8	-	-	-
<i>Streptococcus pneumoniae</i>	≤0.25	0.5	≥1	≥28	25 - 27	≤24
<i>Vibrio cholerae</i>	≤4	8	≥16	-	-	-
<i>Yersinia pestis</i>	≤4	8	≥16	-	-	-

¹ 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.

² 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.

³ Incubation in 5% CO₂ may be required for growth of some strains of *Brucella* spp., especially *B. abortus*. Incubation of broth MIC tests in CO₂ may decrease the MIC of tetracyclines, usually by one doubling dilution.⁷

Doxycycline susceptibility testing interpretive criteria for anaerobes, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Neisseria gonorrhoeae*, and *Ureaplasma urealyticum* have not been established. Isolates of these species that are susceptible to tetracycline are also considered susceptible to doxycycline.⁵

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A report of *Susceptible (S)* indicates that the (b) (4) antimicrobial drug is likely to inhibit growth of the pathogen if the (b) (4) antimicrobial drug reaches the concentrations achievable at the (b) (4) site of infection.

(b) (4) –A report of *Intermediate (I)* indicates that the result should be considered equivocal, and, if the (b) (4) microorganism 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 (b) (4) antimicrobial drug is not likely to inhibit growth of the pathogen if the (b) (4) antimicrobial drug reaches the concentration (b) (4) 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^{5,5,7,8,9,10,11}.

Standard doxycycline and tetracycline powders should provide the following range of MIC values noted in Table 4. For the diffusion technique using the 30 mcg doxycycline disk the criteria noted in Table 4 should be achieved.

(b) (4)

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(b) (4)



Table 2: Acceptable Quality Control Ranges for Doxycycline

QC Strain	Minimal Inhibitory Concentration (mcg per mL)	Zone Diameter (mm)
<i>Enterococcus faecalis</i> ATCC ^a 29212	2 - 8	-
<i>Escherichia coli</i> ATCC 25922	0.5 - 2	18 - 24
<i>Eggerthella lenta</i> ATCC 43055	2 - 16	-
<i>Staphylococcus aureus</i> ATCC 25923	-	23 - 29
<i>Staphylococcus aureus</i> ATCC 29213	0.12 - 0.5	-
<i>Streptococcus pneumoniae</i> ATCC 49619	0.015 - 0.12	25-34
<i>Bacteroides thetaiotaomicron</i> ATCC 29741	2 - 8	-

^a ATCC is the American Type Culture Collection

15 REFERENCES

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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. Drugs and Lactation Database (LactMed) [Internet]. Bethesda (MD): National Library of Medicine (US); [Last Revision Date 2015 March 10; cited 2016 Jan]. Doxycycline; LactMed Record Number: 100; [about 3 screens]. Available from: <http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm>.
5. **Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-sixth Edition*. CLSI Supplement M100S. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2016.**
6. Clinical and Laboratory Standards Institute (CLSI). *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard – ^{(b) (4)}Tenth Edition*. CLSI document M07-A ^{(b) (4)}0, Clinical Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 20 ^{(b) (4)}5.
7. Clinical and Laboratory Standards Institute (CLSI). *Methods for Antimicrobial Dilution and Disk Susceptibility Testing of Infrequently Isolated or Fastidious Bacteria*. ^{(b) (4)} *Third* ^{(b) (4)} Edition. CLSI **Guideline M45** ^{(b) (4)} Clinical Laboratory Standards Institute, 9 ^{(b) (4)}0 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015 ^{(b) (4)}.
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 – Twelfth* ^{(b) (4)} Edition. CLSI document M02-A1 ^{(b) (4)} Clinical Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015 ^{(b) (4)}
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)

12.4 Microbiology

Mechanism of Action



(b) (4)

8 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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(b) (4)



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/s/

KERIAN K GRANDE ROCHE
03/02/2016