

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205931Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type NDA 505 (b)(2)
Application Number 205931
Priority or Standard Standard

Submit Date September 25, 2013
Received Date September 25, 2013
PDUFA Goal Date July 25, 2014
Division / Office Division of Anti-Infective Products /
Office of Antimicrobial Products

Reviewer Name Edward Weinstein, MD, PhD
Review Completion Date May 16, 2014

Established Name Doxycycline Hyclate
(Proposed) Trade Name Acticlate
Therapeutic Class Tetracycline-class antibacterial
Applicant Aqua Pharmaceuticals

Formulation Tablets, 75 mg and 150 mg
Dosing Regimen Multiple
Indications Multiple antibacterial indications
Intended Population Adults and children > 8 years of
age; may be used in younger
children for some indications

Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	5
1.1	Recommendation on Regulatory Action	5
1.2	Risk Benefit Assessment.....	5
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies ...	5
1.4	Recommendations for Postmarket Requirements and Commitments	5
2	INTRODUCTION AND REGULATORY BACKGROUND	5
2.1	Product Information	6
2.2	Tables of Currently Available Treatments for Proposed Indications	7
2.3	Availability of Proposed Active Ingredient in the United States	7
	Table 1: Approved drug products with Doxycycline Hyclate	8
2.4	Important Safety Issues With Consideration to Related Drugs.....	10
2.5	Summary of Presubmission Regulatory Activity Related to Submission	10
3	ETHICS AND GOOD CLINICAL PRACTICES.....	10
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	10
4.1	Chemistry Manufacturing and Controls	10
4.2	Clinical Microbiology.....	10
4.3	Preclinical Pharmacology/Toxicology	11
4.4	Clinical Pharmacology	11
5	SOURCES OF CLINICAL DATA.....	12
6	REVIEW OF EFFICACY	12
	Efficacy Summary.....	12
7	REVIEW OF SAFETY.....	12
	Safety Summary	12
7.1	Studies 11060203, 11060204, and 11060201	12
7.2	Database Queries.....	13
8	POSTMARKET EXPERIENCE.....	14
9	APPENDICES	14
9.1	Literature Review/References	14
9.2	Labeling Recommendations	14
9.3	Advisory Committee Meeting.....	15

Table of Tables

Table 1: Approved drug products with Doxycycline Hyclate	8
Table 2: Summary Clinical Bioequivalence Studies.....	11

Table of Figures

Figure 1: Molecular Structure of Doxycycline	6
---	----------

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The reviewer recommends approval of this 505 (b)(2) application for doxycycline hyclate for the same indications as the listed drug (LD).

1.2 Risk Benefit Assessment

Doxycycline is effective for the approved indications and remains a preferred treatment option against pathogens such as *Chlamydia*, *Rickettsia*, *Vibrio* and *Mycoplasma* species. The doxycycline label adequately informs providers on risks and benefits associated with doxycycline use.

This 505(b)(2) NDA application for doxycycline hyclate 75 mg and dual scored 150 mg tablets relies on FDA's previous findings of safety and effectiveness for the reference drug, Vibra-Tabs (doxycycline hyclate tablets 100 mg). No additional safety concerns are expected to be associated with 75 mg and 150 mg tablets.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

None

2 Introduction and Regulatory Background

This new drug application (NDA) is submitted by Aqua Pharmaceuticals in accordance with Section 505 (b)(2) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355) to seek marketing clearance for doxycycline hyclate. The LD is Vibra-Tabs (doxycycline hyclate 100 mg oral tablets (NDA 50533) manufactured by Pfizer, approved on January 15, 1980. This product was discontinued for reasons not involving safety or efficacy, and a number of presently marketed doxycycline hyclate tablets rely upon the Vibra-Tabs NDA 50533 as the LD. As a result, West-ward Pharmaceuticals doxycycline hyclate 100 mg tablets (ANDA 065095), approved by the Agency on July 2, 2003 is used as a reference for bioequivalence in this application. The initial approval for

Vibramycin®, Doxycycline Hyclate (NDA 50007) was granted to Pfizer, Inc. December 5, 1967.

The proposed drug product provides new strengths of the LD. Aqua Pharmaceuticals (Aqua) proposes to introduce dosage strengths of 75 mg and dual scored 150 mg tablets to provide flexibility and ease of dosing. The 75 mg and 150 mg dosage strengths fall within the approved dosing regimens for the approved LD. All other attributes, such as active ingredient, dosage form, route of administration, conditions of use, indications and dosing regimens are the same as the LD. In support of this NDA, the applicant has submitted three pharmacokinetic studies demonstrating bioequivalence to the already approved tablet formulation.

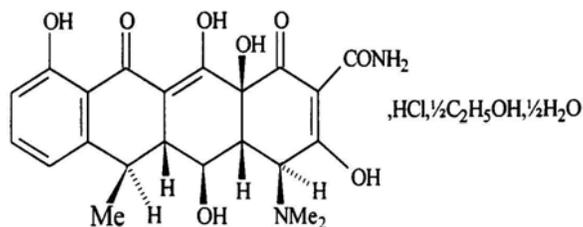
2.1 Product Information

Doxycycline is a tetracycline-class antibacterial drug and is generally considered bacteriostatic.

Tetracycline-class antibacterials inhibit protein synthesis in bacteria by binding to the 30S ribosomal subunit and blocking entry of amino-acyl tRNA molecules into the A site of the ribosome. This prevents incorporation of amino acid residues into elongating peptide chains.

Molecular structure of doxycycline is presented in *Figure 1*.

Figure 1: Molecular Structure of Doxycycline



The antibacterial spectrum of doxycycline includes Gram-positive and Gram-negative organisms (including aerobic and anaerobic species), including methicillin-resistant *Staphylococcus aureus* (MRSA), and some Mycobacteria. Cross-resistance of these organisms to tetracycline is common.

2.2 Tables of Currently Available Treatments for Proposed Indications

Not applicable.

MO comment: The proposed tablet strengths of 75 mg and 150 mg may be of limited use because the dosing regimen for most indications in adults and in children weighing over 45 kg is 100 mg twice daily. In adults the 150 mg tablet may potentially be used in an alternative treatment regimen for gonorrhea consisting of two 300 mg doses administered one hour apart although this regimen is rarely utilized. The 75 mg tablet and a 50 mg portion of the dual scored 150 tablet may potentially be used in some children weighing 45 kg or less who are dosed at 2.2 mg/kg once or twice daily.

2.3 Availability of Proposed Active Ingredient in the United States

A query of the Agency orange book of approved drug products using the search term "Doxycycline Hyclate" yielded the following result in Table 1.

Table 1: Approved drug products with Doxycycline Hyclate

Appl No	RLD	Dosage Form; Route	Strength	Proprietary Name	Applicant
A065281	Yes	CAPSULE, DELAYED RELEASE;ORAL	EQ 100MG BASE	DOXYCYCLINE HYCLATE	MEDICIS
A065281	No	CAPSULE, DELAYED RELEASE;ORAL	EQ 75MG BASE	DOXYCYCLINE HYCLATE	MEDICIS
A062500	No	CAPSULE;ORAL	EQ 100MG BASE	DOXYCYCLINE HYCLATE	CHARTWELL LIFE SCI
A062500	No	CAPSULE;ORAL	EQ 50MG BASE	DOXYCYCLINE HYCLATE	CHARTWELL LIFE SCI
A062396	No	CAPSULE;ORAL	EQ 100MG BASE	DOXYCYCLINE HYCLATE	HIKMA PHARMS
A062396	No	CAPSULE;ORAL	EQ 50MG BASE	DOXYCYCLINE HYCLATE	HIKMA PHARMS
A065103	Yes	CAPSULE;ORAL	EQ 20MG BASE	DOXYCYCLINE HYCLATE	HIKMA PHARMS LLC
A062676	No	CAPSULE;ORAL	EQ 100MG BASE	DOXYCYCLINE HYCLATE	MUTUAL PHARM
A062675	No	CAPSULE;ORAL	EQ 50MG BASE	DOXYCYCLINE HYCLATE	MUTUAL PHARM
A062031	No	CAPSULE;ORAL	EQ 100MG BASE	DOXYCYCLINE HYCLATE	WATSON LABS FLORIDA
A062031	No	CAPSULE;ORAL	EQ 50MG BASE	DOXYCYCLINE HYCLATE	WATSON LABS FLORIDA
N050007	Yes	CAPSULE;ORAL	EQ 100MG BASE	VIBRAMYCIN	PFIZER
N050007	No	CAPSULE;ORAL	EQ 50MG BASE	VIBRAMYCIN	PFIZER
A062475	Yes	INJECTABLE;INJECTION	EQ 100MG BASE/VIAL	DOXY 100	FRESENIUS KABI USA
A062475	Yes	INJECTABLE;INJECTION	EQ 200MG BASE/VIAL	DOXY 200	FRESENIUS KABI USA
A091406	No	INJECTABLE;INJECTION	EQ 100MG BASE/VIAL	DOXYCYCLINE	AGILA SPECLTS
A062569	Yes	INJECTABLE;INJECTION	EQ 100MG BASE/VIAL	DOXYCYCLINE	BEDFORD
N050751	Yes	SYSTEM, EXTENDED RELEASE;PERIODONTAL	50MG	ATRIDOX	TOLMAR
N050795	No	TABLET, DELAYED RELEASE;ORAL	EQ 100MG BASE	DORYX	MAYNE PHARMA
N050795	No	TABLET, DELAYED RELEASE;ORAL	EQ 150MG BASE	DORYX	MAYNE PHARMA
N050795	Yes	TABLET, DELAYED RELEASE;ORAL	EQ 200MG BASE	DORYX	MAYNE PHARMA
N050795	No	TABLET, DELAYED RELEASE;ORAL	EQ 75MG BASE	DORYX	MAYNE PHARMA
N050795	No	TABLET, DELAYED RELEASE;ORAL	EQ 80MG BASE	DORYX	MAYNE PHARMA
A090134	No	TABLET, DELAYED RELEASE;ORAL	EQ 100MG BASE	DOXYCYCLINE HYCLATE	ACTAVIS ELIZABETH

Clinical Review
Edward Weinstein, MD, PhD
NDA 205931, 505 (b)(2)
Doxycycline Hyclate Tablets, 75 mg and 150 mg

A090134	No	TABLET, DELAYED RELEASE;ORAL	EQ 75MG BASE	DOXYCYCLINE HYCLATE	ACTAVIS ELIZABETH
A200856	No	TABLET, DELAYED RELEASE;ORAL	EQ 100MG BASE	DOXYCYCLINE HYCLATE	HERITAGE PHARMS INC
A200856	No	TABLET, DELAYED RELEASE;ORAL	EQ 150MG BASE	DOXYCYCLINE HYCLATE	HERITAGE PHARMS INC
A200856	No	TABLET, DELAYED RELEASE;ORAL	EQ 75MG BASE	DOXYCYCLINE HYCLATE	HERITAGE PHARMS INC
A090505	No	TABLET, DELAYED RELEASE;ORAL	EQ 100MG BASE	DOXYCYCLINE HYCLATE	IMPAX LABS INC
A090505	No	TABLET, DELAYED RELEASE;ORAL	EQ 75MG BASE	DOXYCYCLINE HYCLATE	IMPAX LABS INC
A090431	No	TABLET, DELAYED RELEASE;ORAL	EQ 100MG BASE	DOXYCYCLINE HYCLATE	MYLAN
A090431	No	TABLET, DELAYED RELEASE;ORAL	EQ 75MG BASE	DOXYCYCLINE HYCLATE	MYLAN
A091052	No	TABLET, DELAYED RELEASE;ORAL	EQ 150MG BASE	DOXYCYCLINE HYCLATE	MYLAN PHARMS INC
A062269	No	TABLET;ORAL	EQ 100MG BASE	DOXYCYCLINE HYCLATE	BLU CARIBE INC
A062505	No	TABLET;ORAL	EQ 100MG BASE	DOXYCYCLINE HYCLATE	CHARTWELL LIFE SCI
A065182	No	TABLET;ORAL	EQ 20MG BASE	DOXYCYCLINE HYCLATE	COREPHARMA
A065095	Yes	TABLET;ORAL	EQ 100MG BASE	DOXYCYCLINE HYCLATE	HIKMA PHARMS
A065163	No	TABLET;ORAL	EQ 20MG BASE	DOXYCYCLINE HYCLATE	IVAX SUB TEVA PHARMS
A065277	No	TABLET;ORAL	EQ 20MG BASE	DOXYCYCLINE HYCLATE	LANNETT
A065287	No	TABLET;ORAL	EQ 20MG BASE	DOXYCYCLINE HYCLATE	LARKEN LABS
A062677	No	TABLET;ORAL	EQ 100MG BASE	DOXYCYCLINE HYCLATE	MUTUAL PHARM
A065134	No	TABLET;ORAL	EQ 20MG BASE	DOXYCYCLINE HYCLATE	MUTUAL PHARMA
A062538	No	TABLET;ORAL	EQ 100MG BASE	DOXYCYCLINE HYCLATE	VINTAGE PHARMS
A062421	No	TABLET;ORAL	EQ 100MG BASE	DOXYCYCLINE HYCLATE	WATSON LABS INC FL
N050783	Yes	TABLET;ORAL	EQ 20MG BASE	PERIOSTAT	GALDERMA LABS LP

Multiple Doxycycline Hyclate products were discontinued, but not for safety or efficacy reasons. Doxycycline, the active pharmaceutical ingredient, is also available in a calcium salt formulation by a variety of manufacturers

2.4 Important Safety Issues With Consideration to Related Drugs

Doxycycline has a safety profile that is similar to other tetracyclines whose major safety issues include permanent discoloration of the teeth and bone if administered during development, the development of *Clostridium difficile* associated diarrhea, photosensitivity, overgrowth of non-susceptible organisms, benign intracranial hypertension, and antianabolic activity

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The NDA 205931 for Doxycycline Hyclate, 75 mg and dual scored 150 mg oral tablets, was submitted pursuant to section 505(b)(2) on September 25, 2013 and received on September 25, 2013. There had been no other presubmission regulatory activity related to this NDA.

3 Ethics and Good Clinical Practices

This NDA has been submitted as a 505(b)(2) application and included three bioequivalence/bioavailability studies which did not raise any ethical concerns.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

The reader is referred to DORYX® (Doxycycline Hyclate Delayed-Release Tablets) labeling for additional information on clinical pharmacology, clinical microbiology, pharmacodynamics and pharmacokinetics of doxycycline¹.

4.1 Chemistry Manufacturing and Controls

The reader is referred to the chemistry manufacturing and controls (CMC) review by Dr. Dorota Matecka.

4.2 Clinical Microbiology

The reader is referred to the microbiology review by Dr. Kerian Grande Roche, for additional details.

¹ http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/050795s010lbl.pdf

4.3 Preclinical Pharmacology/Toxicology

No pharmacology/toxicology studies were included in this submission. The pharmacology/toxicology review for this product was written by Dr. Wendelyn Schmidt, PhD. The applicant refers to information found in the labeling for the reference listed drug, Vibra-Tabs[®], in accordance with regulations found under 21 CFR 314.51(a)(3).

4.4 Clinical Pharmacology

The clinical pharmacology review was written by Dr. Ryan Owen, PhD. In summary, two pharmacokinetic studies were conducted to demonstrate bioequivalence between the approved Doxycycline Hyclate Tablet USP, 100 mg (West-ward Pharmaceuticals) and Aqua's unscored Doxycycline Hyclate Tablets USP, 150 mg (Study 11060203) and the effect of food on Aqua's unscored Doxycycline Hyclate Tablets USP, 150 mg (Study 11060204). In addition, Study 11060201 was conducted to demonstrate bioequivalence between (b) (4) Doxycycline Hyclate Capsules, 150 mg and Vibramycin[®] capsules, 100 mg; this study was submitted in support of a request for a waiver from conducting *in vivo* bioequivalence studies for the 75 mg and dual-scored 150 mg tablets. All three studies were single-center, randomized, 2-treatment, 2-way cross over studies and are summarized in Table 2. No other clinical pharmacology studies were conducted.

Table 2: Summary Clinical Bioequivalence Studies

Study No.	Study Objectives	Test Product(s) Dosing Regimen Route of Administration	Number of Subjects	Treatment Duration
11060203	Evaluate bioavailability of a new dosage strength of drug product relative to an equivalent dose of the RLD under fasted conditions.	Doxycycline Hyclate Tablets, 150 mg (unscored) 300 mg Dose Oral	26 (24 included in statistical analysis)	Single Dose
11060204	Evaluate bioavailability of a new dosage strength of drug product under fasted and non-fasted conditions.	Doxycycline Hyclate Tablets, 150 mg (unscored) 150 mg Dose Oral	26 (25 included in statistical analysis)	Single Dose
(b) (4)				

The clinical pharmacology information provided by the Applicant was found to be acceptable and it was concluded that the proposed formulation met the bioequivalence criteria.

5 Sources of Clinical Data

The Applicant is relying on (1) three bioavailability/bioequivalence studies conducted by Novum Pharmaceutical Research Services, (2) previous finding of safety and efficacy for the reference listed drug (RLD). The application did not utilize any published literature as a source of clinical data.

6 Review of Efficacy

Efficacy Summary

There were no clinical studies conducted for the purpose of evaluating efficacy. Aqua is relying on previous findings of efficacy for the listed drug.

7 Review of Safety

Safety Summary

There were no clinical studies conducted for the purpose of evaluating safety. Aqua is relying on previous findings of safety for the listed drug.

However, safety assessments of adverse events were made for three pharmacokinetic studies conducted to demonstrate bioequivalence of Aqua's Doxycycline Hyclate to listed drugs. Case report forms were reviewed. There were no deaths or serious adverse events reported in these limited studies.

7.1 Studies 11060203, 11060204, and (b) (4)

In study 11060203, single doses of 300 mg of doxycycline hyclate were given to 26 healthy volunteers in a randomized, two-period, two-sequence, crossover design. No serious adverse events were reported, but 61 adverse events were recorded for 21 of the 26 subjects. Sixty (60) adverse events resolved spontaneously prior to study completion and one (elevated blood glucose) did not resolve prior to study completion. The most frequently reported adverse event for both the test and reference products was nausea (Test A: 12 subjects; Reference B: 9 subjects). Two subjects experienced

emesis within 4 hours of drug ingestion and withdrew from further study participation per protocol.

In study 11060204, doxycycline hyclate tablets USP, 150 mg were studied in 26 healthy volunteers in a randomized, single-dose, two-treatment, two-period, two-sequence, crossover study. In one period of the study, a single Doxycycline Hyclate Tablet USP, 150 mg was administered after an overnight fast of at least 10 hours. In the other period, a single Doxycycline Hyclate Tablet USP, 150 mg was administered following a standardized high fat breakfast.

No serious adverse events were recorded. Twelve (12) adverse events were reported by 9 of the 26 subjects who participated in this study. All reported adverse events were considered “mild”. Eleven (11) adverse events resolved spontaneously prior to study completion and one (elevated bilirubin) had not resolved prior to study completion. The most frequently reported adverse events were abdominal discomfort and nausea.

In study 11060201, (b) (4) doxycycline hyclate capsules, 150 mg was compared to Vibramycin® (doxycycline hyclate) capsules (Pfizer Labs) in 26 healthy volunteers using a randomized, single-dose, two-treatment, two-period, crossover design under fasting conditions. No serious adverse events were recorded. A total of 16 adverse events (9 Test A, 7 Reference B) were reported by 14 of the 26 subjects who participated in this study. All reported adverse events were considered “mild”. Fifteen (15) adverse events resolved spontaneously prior to study completion and one (elevated liver enzymes) had not resolved prior to study completion. The most frequently reported adverse event for both the test and reference products was nausea (Test A: 5 subjects; Reference B: 4 subjects).

Physical and Laboratory Findings:

In all 3 studies, vital signs (blood pressure and heart rate) were measured prior to dosing and upon completion of the study drug. There were no clinically significant changes in the measured vital signs. Blood samples were collected at the time of the last pharmacokinetic blood sample collection of the study for post-study hematology and chemistry. All values were within 20% of the normal range, with the exceptions noted.

MO comment: The reported adverse events were consistent with the known safety profile of orally administered doxycycline hyclate as detailed in package inserts.

7.2 Database Queries

A search of the Entrez PubMed database was conducted with the terms “doxycycline” and “adverse reaction” for the period from May 14, 2012 to May 12, 2014.

The Entrez PubMed search identified a case report and a comparative analysis of adverse drug reactions attributed to tetracycline class antibiotics in France between 1985 and 2007. The case report described a generalized bullous fixed drug eruption [1], and the analysis of tetracyclines did not identify any new or unexpected adverse reactions [2]. The fixed drug eruption is a known rare adverse reaction associated with tetracycline use [3]. The package insert for the LD lists several skin adverse reactions that may have bullous manifestations, such as Stevens -Johnson syndrome and toxic epidermal necrolysis.

MO comments: Doxycycline has been in continuous clinical use for over 40 years. No unexpected safety findings for doxycycline have been identified from periodic safety updates or a review of recently published literature.

8 Postmarket Experience

Not applicable.

9 Appendices

9.1 Literature Review/References

1. Nitya S, Deepa K, Mangaiarkkarasi A, Karthikeyan K, “Doxycycline induced generalized bullous fixed drug eruption - A case report.” J Young Pharm. 2013 Dec;5(4):195-6.
2. Lebrun-Vignes B, Kreft-Jais C, Castot A, Chosidow O; French Network of Regional Centers of Pharmacovigilance, “Comparative analysis of adverse drug reactions to tetracyclines: results of a French national survey and review of the literature.” Br J Dermatol. 2012 Jun;166(6):1333-41.
3. Pasricha, JS “Drugs causing fixed eruptions.” Br J Dermatol. 1979 Jul;100:183–185

9.2 Labeling Recommendations

A draft labeling has been submitted and will be reviewed separately. Labeling changes related to the Microbiology subsection may be provided. These recommendations will also be relevant to the RLD and will be discussed at a later point during the review cycle.

In addition, the Warning in section 5.5 regarding Intracranial Hypertension should be modified to read as follows:

(b) (4)



(b) (4)



Since intracranial pressure can remain elevated for weeks after drug cessation patients should be monitored until they stabilize. Concomitant use of isotretinoin and doxycycline should be avoided because isotretinoin, a systemic retinoid, is also known to cause pseudotumor cerebri.

9.3 Advisory Committee Meeting

No advisory committee was deemed necessary for this NDA resubmission.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

EDWARD A WEINSTEIN
06/04/2014

JOHN J ALEXANDER
06/12/2014