

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208253Orig1s000**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

Application Type NDA 505 (b)(2)  
Application Number 208253  
Priority or Standard Standard

Submit Date June 26, 2015  
Received Date June 26, 2015  
PDUFA Goal Date April 26, 2016  
Division / Office Division of Anti-Infective Products /  
Office of Antimicrobial Products

Reviewer Name Edward Weinstein, MD, PhD  
Review Completion Date February 26, 2016

Established Name Doxycycline Hyclate  
(Proposed) Trade Name Acticlate<sup>®</sup> CAP  
Therapeutic Class Tetracycline-class antibacterial  
Applicant Aqua Pharmaceuticals

Formulation Capsules, 75 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

<b>1</b>	<b>RECOMMENDATIONS/RISK BENEFIT ASSESSMENT .....</b>	<b>5</b>
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
<b>2</b>	<b>INTRODUCTION AND REGULATORY BACKGROUND.....</b>	<b>5</b>
2.1	Product Information.....	6
2.2	Tables of Currently Available Treatments for Proposed Indications .....	6
2.3	Availability of Proposed Active Ingredient in the United States .....	7
2.4	Important Safety Issues With Consideration to Related Drugs .....	8
2.5	Summary of Presubmission Regulatory Activity Related to Submission .....	8
<b>3</b>	<b>ETHICS AND GOOD CLINICAL PRACTICES.....</b>	<b>8</b>
<b>4</b>	<b>SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES.....</b>	<b>9</b>
4.1	Chemistry Manufacturing and Controls .....	9
4.2	Clinical Microbiology .....	9
4.3	Preclinical Pharmacology/Toxicology.....	9
4.4	Clinical Pharmacology.....	9
	<b>Table 2: Summary Clinical Bioequivalence Studies .....</b>	<b>10</b>
<b>5</b>	<b>SOURCES OF CLINICAL DATA.....</b>	<b>10</b>
<b>6</b>	<b>REVIEW OF EFFICACY.....</b>	<b>10</b>
	Efficacy Summary .....	10
<b>7</b>	<b>REVIEW OF SAFETY .....</b>	<b>10</b>
	Safety Summary.....	10
7.1	Studies 11060201 and 11060202 .....	11
7.2	Database Queries .....	12
<b>8</b>	<b>POSTMARKET EXPERIENCE.....</b>	<b>12</b>
<b>9</b>	<b>APPENDICES .....</b>	<b>12</b>
9.1	Literature Review/References .....	12
9.2	Labeling Recommendations .....	13
9.3	Advisory Committee Meeting.....	13

Clinical Review  
Edward Weinstein, MD, PhD  
NDA 208253, 505 (b)(2)  
Doxycycline Hyclate Capsules, 75 mg

---

## Table of Tables

<b>Table 1: List of Approved Doxycycline Drug Product NDAs .....</b>	<b>7</b>
<b>Table 2: Summary Clinical Bioequivalence Studies .....</b>	<b>10</b>

## Table of Figures

<b>Figure 1: Molecular Structure of Doxycycline.....</b>	<b>6</b>
--	----------

## 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 reference listed drug (RLD).

### 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 capsules relies on FDA's previous findings of safety and effectiveness for the reference drug, Vibramycin<sup>®</sup> (doxycycline hyclate) capsules 100 mg, NDA 050007. The 75 mg strength may be of use for some pediatric patients for whom weight-based dosing is appropriate. No additional safety concerns are expected to be associated with 75 mg capsules.

### 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 RLD is Vibramycin<sup>®</sup> (doxycycline hyclate 100 mg capsules (NDA 050007) manufactured by Pfizer, approved on December 5, 1967.

The proposed drug product provides a new strength of the RLD which is available in 50 mg and 100 mg dosage strengths. Aqua Pharmaceuticals (Aqua) proposes to introduce

dosage strengths of 75 mg which falls within the approved dosing regimens for the approved RLD. The proposed 75 mg capsule would provide appropriate dosing for a pediatric patient weighing (b) (4) to be dosed at 2.2 mg/kg (1 mg/lb) of body weight once or twice daily. All other attributes, such as active ingredient, dosage form, route of administration, conditions of use, indications and dosing regimens are the same as the RLD. In support of this NDA, the applicant has submitted two pharmacokinetic studies demonstrating bioequivalence to the already approved formulation.

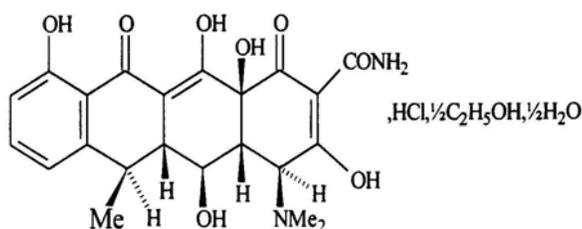
## 2.1 Product Information

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 capsule strength of 75 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. The 75 mg may potentially be used in some children (b) (4) 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's Orange Book of approved doxycycline drug products with infectious disease indications yielded the products listed in Table 1.

**Table 1: List of Approved Doxycycline Drug Product NDAs**

Application Number	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
N205931	Yes	DOXYCYCLINE HYCLATE	TABLET;ORAL	EQ 150MG BASE	ACTICLATE	AQUA PHARMS LLC
N205931	No	DOXYCYCLINE HYCLATE	TABLET;ORAL	EQ 75MG BASE	ACTICLATE	AQUA PHARMS LLC
N050805	Yes	DOXYCYCLINE	CAPSULE;ORAL	40MG	ORACEA	GALDER MA LABS LP
N050795	No	DOXYCYCLINE HYCLATE	TABLET, DELAYED RELEASE;ORAL	EQ 100MG BASE	DORYX	MAYNE PHARMA
N050795	No	DOXYCYCLINE HYCLATE	TABLET, DELAYED RELEASE;ORAL	EQ 150MG BASE	DORYX	MAYNE PHARMA
N050795	Yes	DOXYCYCLINE HYCLATE	TABLET, DELAYED RELEASE;ORAL	EQ 200MG BASE	DORYX	MAYNE PHARMA
N050795	No	DOXYCYCLINE HYCLATE	TABLET, DELAYED RELEASE;ORAL	EQ 75MG BASE	DORYX	MAYNE PHARMA
N050795	No	DOXYCYCLINE HYCLATE	TABLET, DELAYED RELEASE;ORAL	EQ 80MG BASE	DORYX	MAYNE PHARMA
N050795	No	DOXYCYCLINE HYCLATE	TABLET, DELAYED RELEASE;ORAL	EQ 50MG BASE	DOXTERIC	MAYNE PHARMA
N050751	Yes	DOXYCYCLINE HYCLATE	SYSTEM, EXTENDED RELEASE;PERIODONTAL	50MG	ATRIDOX	TOLMAR
N050641	Yes	DOXYCYCLINE	CAPSULE;ORAL	EQ 100MG BASE	MONODOX	AQUA PHARMS
N050641	No	DOXYCYCLINE	CAPSULE;ORAL	EQ 50MG BASE	MONODOX	AQUA PHARMS
N050641	No	DOXYCYCLINE	CAPSULE;ORAL	EQ 75MG BASE	MONODOX	AQUA PHARMS
N050480	Yes	DOXYCYCLINE CALCIUM	SUSPENSION;ORAL	EQ 50MG BASE/5ML	VIBRAMYCIN	PFIZER

Clinical Review  
Edward Weinstein, MD, PhD  
NDA 208253, 505 (b)(2)  
Doxycycline Hyclate Capsules, 75 mg

N050007	Yes	DOXYCYCLINE HYCLATE	CAPSULE;ORAL	EQ 100MG BASE	VIBRAMYCIN	PFIZER
N050006	Yes	DOXYCYCLINE	FOR SUSPENSION;ORAL	EQ 25MG BASE/5ML	VIBRAMYCIN	PFIZER

**MO comment:** *The proposed product in this application is a 75 mg doxycycline hyclate capsule. The Monodox 75 mg capsule (Aqua Pharmaceuticals) listed above is a doxycycline monohydrate formulation. Some doxycycline products have non-infectious disease indications, such as Oracea for the treatment of rosacea and Atridox for periodontal disease. Multiple doxycycline hyclate products have been discontinued, but not for reasons involving safety or efficacy.*

## 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, intracranial hypertension, and antianabolic activity.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

A pre-IND meeting teleconference was held on 12 July 2011 (PIND 111602) to discuss the development of doxycycline hyclate capsules and tablets in dosage strengths of 75 mg and 150 mg. It was agreed that the bioequivalence studies for this new drug application could be conducted on 150 mg strength capsules (b) (4). A request has been included within this application to waive *in vivo* bioequivalence studies of the 75 mg capsules based upon (b) (4) the dissolution profiles of the 75 mg and 150 mg capsules.

The NDA 208253 for Doxycycline Hyclate, 75 mg capsules, was submitted pursuant to section 505(b)(2) on June 26, 2015 and received on June 26, 2015.

## 3 Ethics and Good Clinical Practices

This NDA has been submitted as a 505(b)(2) application and included two 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 VIBRAMYCIN<sup>®</sup> (Doxycycline Hyclate Capsules) labeling for additional information on clinical pharmacology, clinical microbiology, pharmacodynamics and pharmacokinetics of doxycycline<sup>1</sup>.

### **4.1 Chemistry Manufacturing and Controls**

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

### **4.2 Clinical Microbiology**

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

### **4.3 Preclinical Pharmacology/Toxicology**

No pharmacology/toxicology studies were included in this submission. The pharmacology/toxicology reviewer for this product is Dr. Terry Miller. The applicant refers to information found in the labeling for the reference listed drug, Vibramycin<sup>®</sup>, in accordance with regulations found under 21 CFR 314.51(a)(3).

### **4.4 Clinical Pharmacology**

The reader is referred to the clinical pharmacology review by Dr. Dakshina Chilukuri for detailed analysis. In summary, two pharmacokinetic studies were conducted to demonstrate bioequivalence between approved Vibramycin<sup>®</sup> Hyclate (doxycycline hyclate capsules, USP), 100 mg and Aqua's Doxycycline Hyclate Capsules, 150 mg under fasted (Study 11060201) and fed conditions (Study 11060202). Both studies were single-dose, randomized, 2-treatment, 2-way cross over studies in healthy volunteers and are summarized in Table 2. No other clinical pharmacology studies were conducted.

---

<sup>1</sup>[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2015/050007s029lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/050007s029lbl.pdf)

**Table 2: Summary Clinical Bioequivalence Studies**

<b>Study No</b>	<b>Study Objectives</b>	<b>TestProduct(s) Dosing Regimen</b>	<b>Number of Subjects</b>
11060201	Evaluate bioavailability of a new formulation of doxycycline hyclate capsules relative to an equivalent dose of the RLD in healthy adult volunteers under fasted conditions.	Doxycycline Hyclate Capsules, 150 mg Vibramycin® Capsules, 100 mg 300 mg Single Oral Dose (14 Day interval between doses)	26 (22 included in statistical analysis)
11060202	Evaluate bioavailability of a new formulation of doxycycline hyclate capsules 150 mg in healthy adult volunteers under fasted and non-fasted conditions.	Doxycycline Hyclate Capsules, 150 mg 150 mg Single Oral Dose (14 Day interval between doses)	26 (26 included in statistical analysis)

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) two bioavailability/bioequivalence studies conducted by (b) (4), (2) previous findings 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 11060201 and 11060202

No serious adverse events were reported in the two bioequivalence studies.

In study 11060201, Aqua's 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. Of the 26 study participants, four subjects withdrew from due to emesis within four hours of dosing, and 22 subjects completed the study. A total of 16 adverse events (9 Aqua product, 7 Reference product) were reported by 14 of the 26 subjects who participated in this study. All reported adverse events were considered "mild" by the investigator. Fifteen adverse events resolved spontaneously prior to study completion and one, elevated liver enzymes, did not resolve prior to study completion and the subject was lost to follow-up. The most frequently reported adverse event for both the test and reference products was nausea (Aqua product: 5 subjects; Reference product: 4 subjects).

In study 11060202, bioequivalence was compared under fasting and non-fasting conditions for Aqua's 150 mg doxycycline hyclate capsules in 26 healthy adult volunteers. As in the previous study, a randomized, single-dose, two-treatment, two-period, crossover study design was employed. All of the subjects completed the study. Eleven (11) adverse events were reported by 9 of the 26 subjects who participated in the study. Of these events, 3 occurred after receipt of the fed dose and 8 occurred after the fasting dose. All reported adverse events were considered "mild" by the investigator and resolved spontaneously prior to study completion. The most frequently reported adverse event was nausea (fasted conditions: 4 subjects).

### Physical and Laboratory Findings:

In both 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 exception of the LFT elevations noted above.

***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 February 1, 2011 to present.

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 RLD lists several skin adverse reactions that may have bullous manifestations, such as Stevens -Johnson syndrome and toxic epidermal necrolysis.

A case report by Moy and Kapila (2016)<sup>4</sup> describes probable doxycycline-induced pancreatitis in a 51-year-old man on empiric therapy for Lyme disease who required intubation and admission to the intensive care unit. This report triggered a further search for “pancreatitis” and “doxycycline” within Entrez Pubmed. A report was identified from Wachira and colleagues (2013)<sup>5</sup> describing the case of a 21-year-old female with pancreatitis following doxycycline treatment for an upper respiratory infection. Several other reports of doxycycline associated acute pancreatitis have been published in the scientific literature<sup>6-8</sup>. Tetracycline and tigecycline, both tetracycline-class drugs, have been implicated as causes of acute pancreatitis<sup>9-10</sup>. Acute pancreatitis is listed as an adverse reaction in the Minocin® (minocycline) package insert and as a warning in the Tygacil® (tigecycline) package insert. Acute pancreatitis may therefore be a tetracycline-class drug effect, and would be an emerging safety signal for doxycycline.

**MO comment:** *The safety profile of doxycycline has been well characterized over the course of its continuous clinical use over the past 48 years. Nevertheless, the reports of acute pancreatitis will be investigated as an emerging safety signal which may result in future labeling changes. A finding of drug-induced pancreatitis would not significantly alter the risk-benefit profile of the drug.*

## 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
  4. Moy BT, Kapila N. “Probable doxycycline-induced acute pancreatitis.” Am J Health Syst Pharm. 2016 Mar 1;73(5):286-91.
  5. Wachira JK, Jensen CH, Rhone K. “Doxycycline-induced pancreatitis: A rare finding.” S D Med 2013;66(6):227-9.
  6. Inayat F, Virk HU, Yoon DJ, Riaz I. “Drug-induced pancreatitis: A rare manifestation of doxycycline administration.” NAJMS. 2016; 8:117-120.
  7. Ocal S, Selçuk H, Korkmaz M, Unal H, Yilmaz U. “Acute pancreatitis following doxycycline and ornidazole coadministration.” JOP. 2010 Nov 9;11(6):614-6.
  8. Eland IA, van Puijenbroek EP, Sturkenboom MJ, et al. “Drug-associated acute pancreatitis: Twenty-one years of spontaneous reporting in the Netherlands.” Am J Gastroenterol 1999;94(9):2417-22.
  9. Nicolau DP, Mengedoht DE, Kline JJ. “Tetracycline-induced pancreatitis.” Am J Gastroenterol. 1991 Nov;86(11):1669-71
  10. Gilson M, Moachon L, Jeanne L, et al. “Acute pancreatitis related to tigecycline: Case report and review of the literature.” Scand J Infect Dis 2008;40:681-3.

## 9.2 Labeling Recommendations

Draft labeling has been submitted and will be reviewed separately.

## 9.3 Advisory Committee Meeting

No advisory committee was deemed necessary for this NDA submission.

-----  
**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  
02/26/2016

YULIYA I YASINSKAYA  
02/26/2016