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APPLICATION NUMBER:

208253Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

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Date	April 4, 2016
From	Seong Jang, Ph.D.
Subject	Cross Discipline Team Leader Review
NDA #	208-253
Applicant	Aqua Pharmaceuticals
Date of Submission	June 26, 2015
PDUFA Goal Date	April 26, 2016
Proprietary Name / Established (USAN) names	Acticlate® CAP (Doxycycline Hyclate)
Dosage forms / Strength	Capsules, 75 mg
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.
Recommended:	Approval

1. Introduction

Aqua Pharmaceuticals submitted the 505(b)(2) application for Acticlate® CAP (doxycycline hyclate USP), 75 mg capsules. The reference listed drug (RLD) to support the safety and efficacy of the product is Vibramycin® (doxycycline hyclate) capsules 100 mg (NDA 50-007) manufactured by Pfizer, approved in 1967. The proposed 75 mg capsules would provide appropriate dosing mainly for a pediatric patient weighing approximately (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 a Pre-IND meeting (held in July 2011) to discuss the development of the Sponsor’s doxycycline hyclate 75 mg (b) (4)

(b) (4)

As a result, in June 2015, the Sponsor submitted NDA 208253 to seek US marketing approval for the 75 mg strength doxycycline hyclate capsules only

In support of this 505(b)(2) application, the Sponsor conducted two pharmacokinetic (PK) studies (Studies 11060201 and 11060202). Study 11060201 was a bioavailability/bioequivalence (BA/BE) study to bridge the proposed formulation with the RLD. Study 11060202 was conducted to compare BA of the proposed formulation under fasted and non-fasted conditions in healthy volunteers. It should be noted that these PK studies were conducted with the 150 mg capsules and the Sponsor requested a waiver from conducting *in vivo* bioequivalence study to bridge the 75 mg capsules with the 150 mg capsules based on the (b) (4) comparable dissolution profiles of the 75 mg and 150 mg capsules. The waiver request was reviewed and granted by the Biopharmaceutics review team (see Biopharmaceutics Assessment in **3. Quality Assessment** below).

This CDTL review summarizes the findings of the various discipline reviews.

2. Background

Doxycycline is a tetracycline-class antibacterial drug synthetically derived from oxytetracycline. 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. 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.

Doxycycline has been marketed for many decades as the active ingredient in several FDA approved solid oral dosage forms, including the innovator product Vibramycin (doxycycline hyclate, USP) capsules (NDA 050007), as well as several approved generic products. 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 safety- or efficacy-related reasons.

3. Quality Assessment

Drug Substance

Information regarding the chemistry, manufacturing and controls used in production of doxycycline hyclate, USP, is referenced to DMF Type II (b)(4) held by (b)(4), which has been reviewed and found adequate previously. The proposed specification for doxycycline hyclate meets the requirements of the respective USP monograph. The doxycycline hyclate drug substance, USP, supplied by (b)(4) is packaged in a (b)(4)

. The Quality review team agreed that the drug substance section of this NDA is acceptable.

Drug Product

Doxycycline hyclate capsules, 75 mg, are supplied as (b)(4) hard gelatin, navy blue opaque (b)(4) capsules (with a logo: Aqua 101C75) filled with yellow powder. The 75 mg doxycycline hyclate capsule is a size #2 hard gelatin capsule. Each capsule contains 86.6 mg doxycycline hyclate equivalent to 75 mg doxycycline. It should be noted that this NDA includes also some CMC information for 150 mg capsules, which were used in the bioavailability studies (Studies 11060201 and 11060202) conducted by the Sponsor to support the current NDA. Both 75 mg and 150 mg capsules contain microcrystalline cellulose and magnesium stearate. The formulation approach (b)(4) for the two capsule strengths. However, the 150 mg doxycycline hyclate capsules are not proposed for marketing (b)(4).

The drug product specification includes appearance, identification, dissolution, uniformity of dosage units, water, assay, impurities/degradation products and microbial limits. Most of the analytical procedures comply with the USP Monograph. The analytical procedure to be used for identification, assay, and impurities is an HPLC method, developed in-house. The residual solvents are controlled for the drug substance and excipients and no organic solvents are used in the drug product manufacture. The acceptance criteria for assay, water content, dissolution, and one of the impurities (b)(4) have been revised according to the FDA recommendation. The Quality review team agreed that sufficient information was provided for the drug product specification. The drug product specification, as revised, is acceptable.

Manufacturing and Stability

The drug substance manufacturing site proposed via this NDA is (b)(4) the drug product manufacturing facility is (b)(4). There are several other facilities involved in testing and packaging of the proposed drug product and the drug substance. All manufacturing facilities were found acceptable by the Office of Process and Facilities.

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The manufacturing process for the drug product, doxycycline hyclate capsules, 75 mg, is relatively straightforward and includes the following step (b) (4) as described in the submission, have been found acceptable.

The NDA includes (b) (4) manufacturing site for the drug substance. Several revisions recommended by the FDA (b) (4) has been found acceptable.

The proposed container closure systems for the drug product include 60-count HDPE bottles (commercial packaging presentation) and 2-count (b) (4) blisters (physician's samples). Based on the overall stability information submitted in the NDA, the proposed expiration dating of 36 months and 24 months for the proposed drug product, doxycycline hyclate capsules, 75 mg, packaged in HDPE bottles and (b) (4) blisters, respectively, has been found acceptable.

Biopharmaceutics Assessment

BCS Classification: Although the Sponsor did not formally request (and thus, did not officially receive) a BCS-1 designation for the proposed oral capsule, the known characteristics of the drug substance (i.e., high solubility and high permeability) and the observed *in vitro* dissolution profile of the proposed commercial doxycycline hyclate capsule (i.e., NLT (b) (4)% in 15 minutes, see below) suggest behavior consistent with an immediate release oral dosage form containing a BCS-1 compound.

Dissolution Specification: The proposed USP Method for doxycycline hyclate capsules is appropriate for the routine QC of Aqua's proposed commercial 75 mg capsule. The dissolution data provided shows (b) (4) dissolution of Aqua's 75 mg strength capsule (as well as the Listed Drug Vibramycin 100 mg capsule). Therefore, a dissolution acceptance criterion of $Q = (b) (4)\%$ in 15 minutes (instead of (b) (4) minutes) was recommended. The Sponsor agreed to the FDA recommended dissolution acceptance criterion of $Q = (b) (4)\%$ at 15 minutes for Doxycycline Hyclate capsules (75 mg), and to update the Drug Product Specification Table and Stability Protocols accordingly.

Biowaiver Request: In line with 21 CFR 320.22(d)(2), the Sponsor's request to waive the requirement to conduct *in vivo* bioequivalence studies for the 75 mg doxycycline hyclate capsule was considered acceptable because both the Sponsor's 150 mg and 75 mg strength doxycycline hyclate capsules (b) (4)

In summary, the Quality information as provided in the NDA has been found to be adequate to assure the identity, strength, purity, and quality of the drug substance and drug product. In addition, an "Acceptable" site recommendation from the Office of Process and Facilities has been made. Therefore, from the Office of Pharmaceutical Quality (OPQ) perspective, this NDA was recommended for approval. As CDTL, I concur with this assessment.

Refer to the OPQ Integrated Assessment by the Quality review team (dated March 25, 2016) for further information.

4. Nonclinical Pharmacology/Toxicology

No new pharmacology/toxicology data was submitted to this NDA. This NDA was submitted before 6/30/2015 and therefore is not subject to PLLR labeling requirements. Originally, the Sponsor did not propose any changes to the pharmacology/toxicology relevant sections of the labeling. However, the Pharmacology/Toxicology

reviewer, Dr. Miller, found that the product labeling for Oracea (doxycycline hyclate), a low dose (40 mg) tablet of doxycycline indicated for treatment of inflammatory lesions of rosacea (and not for treatment/prevention of infections), contains nonclinical genetic toxicology and carcinogenicity data from animal studies and that those information is not included in the anti-infective product labeling. Accordingly, the information request to revise the labeling in order to reflect the information in the package insert for Oracea® capsules was sent to the Sponsor. In response to the information request, the Sponsor submitted the revised labeling containing changes to Subsection 13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility for their drug product on 1/08/2016.

The Nonclinical Pharmacology/Toxicology reviewer recommended that the proposed changes to Subsection 13.1 be revised for further clarification. As CDTL, I agree with this recommendation. Refer to the Nonclinical Pharmacology/Toxicology Memo to File by Dr. Miller dated January 15, 2016 for further information.

5. Clinical Pharmacology

In support of this 505(b)(2) application, the Sponsor conducted two PK studies (Studies 11060201 and 11060202). Study 11060201 was a BA/BE study to bridge the proposed formulation with the RLD. Study 11060202 was conducted to compare BA of the proposed formulation under fasted and non-fasted conditions in healthy volunteers. As mentioned above, these two PK studies were conducted with Acticlate 150 mg capsules which are not proposed for marketing (b)(4). It was agreed that the results of these studies conducted with Acticlate 150 mg capsules support the BA/BE of Acticlate 75 mg capsules to the RLD and the effect of food intake on the PK of Acticlate 75 mg capsules, because the 150 mg and 75 mg strength doxycycline hyclate capsules (b)(4)

issolution (i.e., $\geq \frac{(b)(4)}{(4)}\%$ of label amount released in 15 minutes) in all four media tested (see 3. Quality Assessment above).

Study 11060201 was a randomized, single-dose, two-treatment, two-period, crossover study to evaluate the relative bioavailability of Acticlate 150 mg capsules (test product, Aqua Pharmaceuticals) compared to Vibramycin 100 mg capsules (reference product, Pfizer Labs) at equal doses (i.e., 300 mg) in healthy volunteers under fasting conditions. The study was conducted with 26 (22 completing) healthy adult subjects. In each period of the study, a single 300 mg dose of doxycycline was administered to subjects following an overnight fast of at least 10 hours. Subjects received the test product as 2 x 150 mg capsules in one of the study periods and the reference product as 3 x 100 mg capsules in the other study period, according to the randomization schedule. The statistical analysis of doxycycline PK parameters showed that the test formulation of Acticlate 150 mg capsules (Aqua Pharmaceuticals) meets the 90% CI criterion (0.80 – 1.25) for log transformed AUC_{0-t} , AUC_{0-inf} , and C_{max} and has therefore shown equivalent bioavailability to a similar dosage of the reference formulation, Vibramycin 100 mg capsules (Pfizer Labs) (Table 1).

Table 1. Geometric Means, Ratio of Means, and 90% Confidence Intervals Based on ANOVA of Ln-Transformed Data: Doxycycline (N = 22) (Study 11060201)

Parameter	Treatment A (test)	Treatment B (reference)	Ratio	CI*	Intra-Subject %CV
AUC_{0-t} (ng·hr/mL)	57155.04	55587.75	1.0282	0.9497 - 1.1132	15.2958
AUC_{0-inf} (ng·hr/mL)	63017.18	61525.97	1.0242	0.9401 - 1.1159	16.5192
C_{max} (ng/mL)	2756.47	2734.26	1.0081	0.9379 - 1.0836	13.8872

* Equivalent if confidence intervals are within 0.80-1.25 limits.

Treatment A (test): 2 x 150 mg Acticalte capsules (AQUA Pharmaceuticals)

Treatment B (reference): 3 x 100 mg Vibramycin (doxycycline hyclate) Capsules (Pfizer Labs)

Study 11060202 was a randomized, single-dose, two-treatment, two-period, crossover study to evaluate the relative bioavailability of Acticlate® doxycycline hyclate capsules, 150 mg under fasted and non-fasted conditions. The study was conducted with 26 healthy, adult subjects. In one period of the study, a single doxycycline hyclate 150 mg capsule was administered after an overnight fast of at least 10 hours. In the other period, a single doxycycline hyclate 150 mg capsule was administered following a standardized high fat breakfast. The comparisons of PK parameters under fasted and non-fasted conditions are summarized in Table 2. When dosing doxycycline hyclate capsule, 150 mg (Aqua Pharmaceuticals) after a high fat breakfast, C_{max} is reduced by approximately 20% compared with the fasted state and T_{max} was extended by about 2 hours. However, there was no change in the extent of overall bioavailability, with the 90% CI for both AUC_{0-t} and AUC_{0-inf} falling within the range 80-125%. As this drug is intended for chronic rather than acute usage, then this decrease in maximum exposure after a single dose is not significant with respect to clinical efficacy. Therefore, it is proposed that doxycycline hyclate capsules, 150 mg (Aqua Pharmaceuticals) can be taken without regard to meals.

Table 2. Geometric Means, Ratio of Means, and 90% Confidence Intervals Based on ANOVA of Ln-Transformed Data: Doxycycline (N = 26) (Study 11060202)

Parameter	Treatment A (fed)	Treatment B (fasted)	Ratio	CI*	Intra-Subject %CV
AUC_{0-t} (ng-hr/mL)	26121.83	28080.14	0.9303	0.8924 - 0.9697	8.7645
AUC_{0-inf} (ng-hr/mL)	28191.58	29757.49	0.9474	0.9040 - 0.9929	9.9060
C_{max} (ng/mL)	1106.38	1386.70	0.7979	0.7462 - 0.8530	14.1644

* Equivalent if confidence intervals are within 0.8000-1.2500 (80.00 to 125.00%) limits.

Treatment A (fed): 1 x 150 mg Doxycycline Hyclate Capsule (AQUA Pharmaceuticals) after high fat breakfast
 Treatment B (fasted): 1 x 150 mg Doxycycline Hyclate Capsule (AQUA Pharmaceuticals) after an overnight fast

The clinical pharmacology information provided by the applicant in support of the 505 (b)(2) application has been found to be acceptable and supports the approval of Doxycycline 75 mg capsules pending the biowaiver review and an agreement on the labeling.

6. Clinical Microbiology

No new clinical microbiology data were submitted with this application. The Microbiology reviewer recommends that the microbiology section of the label be revised to reflect the current CLSI guidelines. As CDTL, I concur with this assessment. Refer to the proposed labeling recommendations in Section 12 and the Clinical Microbiology review by Dr. Grande dated March 22, 2016 for further information.

7. Clinical/Statistical- Efficacy

No new clinical efficacy data were submitted with this application. The Sponsor is relying on the previous findings of efficacy for the reference listed drug, Vibramycin. The Clinical reviewer, Dr. Weinstein, recommends approval of this 505(b)(2) application for doxycycline hyclate for the same indications as the reference listed drug (RLD). Refer to the Clinical review by Dr. Weinstein dated February 26, 2016 for further information.

8. Safety

There were no clinical studies conducted for the purpose of evaluating safety. The Sponsor is relying on previous findings of safety for the listed drug, Vibramycin. The Clinical reviewer, Dr. Weinstein, assessed adverse events reported in the aforementioned PK studies (Studies 11060201 and 11060202). He concluded that the adverse events reported in the PK studies were consistent with the known safety profile of orally administered doxycycline hyclate as detailed in the package inserts. As CDTL, I agree with this assessment.

In addition to assessing adverse events reported in the two PK studies, Dr. Weinstein reviewed published literature describing adverse reactions of doxycycline. There were case reports regarding the incidences of a generalized bullous fixed drug eruption and acute pancreatitis. However, the Clinical reviewer concluded that the findings of these adverse events would not significantly alter the risk-benefit profile of doxycycline hyclate. Refer to the Clinical review by Dr. Weinstein dated February 26, 2016 for further information.

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

Not applicable.

11. Other Relevant Regulatory Issues

No regulatory issues are outstanding for this application.

12. Labeling

The Sponsor has modified the approved labeling for the Actclate tablets (doxycycline hyclate) to include the proposed capsule formulation. Finalization of FDA proposed labeling revisions and labeling negotiations with the Sponsor are ongoing at the time of this CDTL memo.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I concur with the assessments made by the review team and recommend approval of this 505(b)(2) application.

- 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® (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.

- Recommendation for Post-marketing Risk Management Activities

Not applicable.

- Recommendation for other Postmarketing Study Commitments

Not applicable.

- Recommended Comments to Applicant

Not applicable.

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/s/

SEONG H JANG
04/04/2016