CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208253Orig1s000

SUMMARY REVIEW

Division Director Decisional Memo

Date	(electronic stamp)
From	Sumathi Nambiar MD MPH
Subject	Division Director Decisional Memo
NDA #	208253
Applicant Name	Aqua Pharmaceuticals
Date of Submission	June 26, 2015
PDUFA Goal Date	April 26, 2016
Established (USAN) Name	Doxycycline hyclate
Dosage Forms / Strength	Capsules 75 mg
Proposed Indications	All approved indications for the listed drug, Vibramycin
Recommended Action:	Approval

Material Reviewed/Consulted Action Package including:	**Names of Discipline Reviewers**
Pharmacology Toxicology Review	Terry Miller PhD
Product Quality Application Technical Lead	Dorota Matecka PhD
Cross-Discipline Team Leader Review	Seong Jang PhD
Medical Officer Review	Edward Weinstein MD PhD
Statistical Review	Christopher Kadoorie PhD
Clinical Microbiology Review	Kerian Grande Roche PhD
Clinical Pharmacology Review	Dakshina Chilukuri PhD
Division of Medication Error Prevention and Analysis	Sevan Kolejian Pharm D
Office of Prescription Drug Promotion	Adam George Pharm D
Division of Medical Policy Programs	Nyedra Booker, PharmD MPH

1.0 Introduction

Aqua Pharmaceuticals submitted NDA 208253 under Section 505(b)(2) of the Food Drug and Cosmetic Act for doxycycline hyclate, 75 mg capsules (Acticlate CAP). The listed drug to support the safety and efficacy of the product is Vibramycin (doxycycline hyclate) capsules 100 mg (NDA 50007). All other attributes of the drug product, such as active ingredient, dosage form, route of administration, conditions of use, indications and dosing regimens are the same as the listed drug. Acticlate tablets 75 mg and 150 mg are currently approved products.

In support of this NDA, the Applicant 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 listed drug. Study 11060202 was conducted to compare the bioavailability of the proposed formulation under fasted and non-fasted conditions in healthy volunteers.

For a detailed discussion of NDA 208253, please refer to discipline specific reviews and the Cross-Discipline Team Leader Review.

2.0 Product Quality

Information regarding the chemistry, manufacturing and controls used in the production of doxycycline hyclate, USP, is referenced to DMF Type II (b) (4) held by (b) (4) which has been reviewed previously and found to be adequate. The drug product, doxycycline hyclate capsules, 75 mg, is supplied as (b) (4) navy blue opaque (b) (4) capsules filled with yellow powder. The drug product specifications include appearance, identification, dissolution, uniformity of dosage units, water, assay, impurities/degradation products and microbial limits. The Applicant revised the acceptance criteria for assay, water content, dissolution, and one of the impurities ((b) (4)) based on the recommendations from the review team.

The drug substance manufacturing site is (b) (4) and 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. The Applicant also submitted a comparability protocol that proposes a post-approval submission (via a manufacturing supplement) of the (b) (4) facility as an additional manufacturing site for the drug substance. Revisions recommended by the review team were accepted by the Applicant and the revised protocol is 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, is acceptable.

The Biopharmaceutics reviewer for this NDA is Gerlie Gieser, PhD. Under 21 CFR 320.22(d)(2), the Applicant requested a waiver from conducting in vivo bioequivalence studies for the 75 mg doxycycline hyclate capsules. Dr. Geiser considered this request to be acceptable as the Applicant's (b) (4) 75 mg strength doxycycline hyclate capsules (b) (4) in all four media tested. Dr. Geiser also notes (b) (4)

(b) (4)

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The overall recommendation from the Office of Pharmaceutical Quality review team is approval. I concur with the team's assessment.

3.0 Microbiology

Kerian Grande Roche, PhD, is the clinical microbiology reviewer for this application. No new clinical microbiology information was submitted in this application. Dr. Grande Roche recommends approval from a clinical microbiology perspective. Labeling revisions proposed by Dr. Grande Roche are incorporated in labeling.

4.0 Pharmacology-Toxicology

Terry Miller, PhD, is the pharmacology-toxicology reviewer for this application. No new pharmacology/toxicology data were submitted in this NDA. As the NDA was submitted before 6/30/2015, it was not subject to PLLR labeling requirements. Dr. Miller recommended labeling changes to Subsection 13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility of the package insert. Labeling has been updated to reflect Dr. Miller's recommendations.

5.0 Clinical Pharmacology

Dakshina Chilukuri, PhD, is the clinical pharmacology reviewer for this application. The Applicant conducted two studies (Studies 11060201 and 11060202). Study 11060201 was a Bioavailability (BA)/Bioequivalence (BE) study and Study 11060202 was conducted to compare the BA of the proposed formulation under fasted and non-fasted conditions in healthy volunteers. These two studies were conducted with Acticlate 150 mg capsules. Results of these studies conducted with Acticlate 150 mg capsules were found to be acceptable to support the BE of Acticlate 75 mg capsules to the listed drug and to assess food effect as the 150 mg and 75 mg strength doxycycline hyclate capsules (b) (4) dissolution (i.e., ≥ (b) (4) % of label amount released in 15 minutes) in all four media tested.

Study 11060202 was a randomized, single-dose, two-treatment, two-period, crossover study to evaluate the relative bioavailability of Acticlate, 150 mg under fasted and non-fasted conditions. When dosing doxycycline hyclate capsule, 150 mg 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%. Therefore, doxycycline hyclate capsules, 150 mg (Aqua Pharmaceuticals) can be taken without regard to meals.

Dr. Chilukuri notes that the clinical pharmacology information provided by the Applicant is acceptable and supports approval of the NDA pending review of the biowaiver request and agreement on labeling.

6.0 Clinical Efficacy/Safety

Edward Weinstein, MD PhD, is the clinical reviewer for this application. No new efficacy studies were submitted in this NDA. Dr. Weinstein performed a safety review of the data from the PK studies and the reported adverse events were consistent with the known safety profile of doxycycline. Dr. Weinstein also performed a literature review and identified case reports of acute pancreatitis associated with doxycycline use. Acute pancreatitis is listed as an adverse reaction in the minocycline package insert and as a warning in the tigecycline labeling. This will need to be evaluated further and labeling updates might be needed if an association is identified. Dr. Weinstein notes that the 75 mg formulation is of limited clinical utility as the dosing regimen for adults and children > 45 kgs is 100 mg twice a day and might be potentially useful in the pediatric population. Dr. Weinstein recommends approval of this NDA and I concur with this assessment.

Christopher Kadoorie, PhD, is the statistics reviewer for this application. As no clinical data were submitted there are no comments from Dr. Kadoorie for this NDA.

7.0 Labeling

Labeling recommendations provided by Adam George, PharmD, from the Office of Prescription Drug Promotion have been incorporated in labeling. Nyedra Booker, PharmD from the Division of Medical Policy Programs has provided labeling recommendations for patient labeling and these have been incorporated in labeling. Sevan Kolejian, PharmD, from DMEPA provided labeling revisions to the package insert, physician sample pack, and the carton. These revisions have been incorporated in labeling. Dr. Kolejian also notes that the proprietary name, Acticlate CAP is acceptable.

8.0 Pediatrics

Under the Pediatric Research and Equity Act (PREA), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless the requirement is waived, deferred or inapplicable. As none of these criteria are applicable, this NDA is exempt from PREA requirements.

9.0 Other Regulatory Issues

Nicola Fenty-Stewart, PhD, from the Division of New Drug Bioequivalence Evaluation in the Office of Study Integrity and Surveillance recommended that the data from the NDA be accepted without an on-site inspection as the two sites listed had been recently inspected and the outcome was classified as No Action Indicated.

The Applicant has certified that they had not entered into any financial agreement with the listed clinical investigators.

10.0 Recommended Regulatory Action

I agree with the recommendations made by the review team and the cross-discipline team leader that NDA 208253, covered under 505(b)(2), be approved, relying on the Agency's prior findings of safety and effectiveness of the listed drug product, Vibramycin (NDA 50007).

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/s/

SUMATHI NAMBIAR
04/21/2016