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RESEARCH**

APPLICATION NUMBER:

205931Orig1s000

SUMMARY REVIEW

Division Director Decisional Memo

Date	(electronic stamp)
From	Sumathi Nambiar MD MPH
Subject	Division Director Decisional Memo
NDA #	205931
Applicant Name	Aqua Pharmaceuticals
Date of Submission	September 25, 2013
PDUFA Goal Date	July 25, 2014
Established (USAN) Name	Doxycycline hyclate
Proprietary Name	Acticlate Tablets
Dosage Forms / Strength	75 and ^{(b) (4)} mg tablets
Proposed Indications	All approved indications for doxycycline
Recommended Action:	Approval

Material Reviewed/Consulted	Names of Discipline Reviewers
Action Package including:	
Pharmacology Toxicology Review	Wendelyn Schmidt PhD
Chemistry Manufacturing and Controls Review	Shrikant Pagay PhD
Biopharmaceutics Review	Minerva Hughes PhD
Cross-Discipline Team Leader Review	Angelica Dorantes PhD
Medical Officer Review	Edward Weinstein MD PhD
Statistical Review	Mushfiqur Rashid PhD
Product Quality Review	Jessica Cole PhD
Microbiology Review	Kerian Grande-Roche PhD
Clinical Pharmacology Review	Ryan Owen PhD
Division of Medication Error Prevention and Analysis	Aleksander Winiarski Pharm D
Labeling Review	Carrie Newcomer PharmD

1.0 Introduction

NDA 205931, Doxycycline hyclate 75 mg and 150 mg tablets was submitted by Aqua Pharmaceuticals LLC on September 25, 2013. This NDA was submitted as a 505(b)(2) application and the listed drug is Vibra-Tabs (doxycycline hyclate, 100 mg) , manufactured by Pfizer (NDA 50533). Pfizer has discontinued marketing of this product. As noted in a memorandum in DARRTS, dated July 16, 2014, it has been determined that Vibra-Tabs was not withdrawn from sale for reasons of safety or effectiveness. Doxycycline hyclate 100 mg tablets (ANDA 65095, West-Ward Pharmaceuticals Corp), is the reference list drug (RLD) and was used for the bioequivalence study conducted to support this NDA.

Doxycycline is approved for the treatment of the following indications:

- 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

2.0 Background

The proposed 75 mg tablet product is unscored and the 150 mg tablet is a dual-scored product. The proposed new strengths are intended to provide flexibility and ease of dosing and fall within the approved dosing regimens for the listed drug. The applicant is seeking approval of the 75 mg and 150 mg dosage strengths for the same indications that are currently labeled in the approved doxycycline products. The applicant has submitted results of one study to demonstrate the bioavailability/bioequivalence of the proposed drug product to the listed drug and the results of one food-effect study to support this NDA.

The review team has completed their reviews of this application. For a detailed discussion of NDA 205931, please refer to discipline specific reviews and the Cross-Discipline Team Leader review.

3.0 Chemistry Manufacturing and Controls (CMC)

The CMC reviewer for this NDA is Shrikant Pagay, PhD and the product quality microbiology reviewer is Jessica Cole, PhD. For CMC information regarding doxycycline hyclate, reference is made to DMF (b) (4). A Letter of Authorization was provided. The drug substance is manufactured in (b) (4). The DMF was last reviewed on 9/30/2013 and found to be adequate. Doxycycline hyclate is a yellow, crystalline hygroscopic powder. The starting material, process related impurities, known degradants, and potential impurities are well characterized. The residual solvents are controlled under the GMP process.

The proposed 75 mg tablet contains (b) (4) doxycycline hyclate and is a round, light teal (b) (4) tablet debossed with “75” on one side and “AQ101” on the other side. The proposed 150 mg tablet contains (b) (4) doxycycline hyclate and is an oblong capsule-shaped, mossy-green tablet with two parallel score lines on both upper and lower side to provide flexible dosing of 50 and 100 mg. Each 50 mg split portion is debossed with “A” on one side while the other side is unmarked. The tablets contain microcrystalline cellulose, sodium lauryl sulfate, croscarmellose sodium and magnesium stearate. The tablets are film coated with a commercially available (b) (4) formulation (b) (4) for 75 mg and (b) (4) green for 150 mg tablets). All excipients are compendial and commonly used in tablet formulations. Upon splitting, the scored tablets meet the quality requirements for content uniformity, loss of mass, friability, dissolution, (b) (4) and assay for each split portion of the tablet. The split tablets are stable when stored at room temperature for up to 90 days.

The drug product shelf life granted for the commercial tablet in HDPE (60 tablets/bottle) is 18 months and for Physician sample in (b) (4) blisters 12 months when stored at 20°C to 25°C.

In a review dated 6/19/14, Dr. Pagay notes that from the product quality perspective, the application is satisfactory to assure the identity, strength, purity and quality of the drug product. All product quality issues have been satisfactorily resolved. As the Office of Compliance has not yet made an overall recommendation for the manufacturing and testing facilities, Dr. Pagay does not recommend approval of the NDA until an overall acceptable recommendation is received from the Office of Compliance.

The drug substance manufacturing facility is (b) (4) and the drug product manufacturing facility is Catalent Pharma Solutions LLC, Winchester, New York. Other facilities listed for this NDA include, a drug product packaging facility, (b) (4) and a testing facility, (b) (4). On 7/21/14, the Office of Compliance has made an overall recommendation of ‘Acceptable’ for all the manufacturing and testing facilities.

In an addendum dated 07/24/14, Dr. Pagay recommends approval of the NDA.

From a product quality microbiology standpoint, Dr. Cole found the application to be adequate and recommended approval.

4.0 Pharmacology/Toxicology

The pharmacology/toxicology reviewer for this application is Wendelyn Schmidt PhD. Dr. Schmidt noted that the excipient profile and labeling for this product are acceptable. Dr. Schmidt recommends approval of the NDA.

5.0 Biopharmaceutics

Minerva Hughes, PhD, is the biopharmaceutics reviewer for this application. The applicant completed three pharmacokinetic studies (Studies 11060203, 11060204, and 11060201). Study 11060203 was a pivotal bioavailability/bioequivalence study comparing 300 mg (two 150 mg tablets) of the proposed drug product to 300 mg (three 100 mg doxycycline hyclate tablets, ANDA 65095). Primary review of this study was conducted by Dr. Hughes. The food effect study (Study 11060204) was reviewed by Dr. Owen from the Office of Clinical Pharmacology. This study was submitted in support of a request to waive bioavailability/bioequivalence studies for the 75 mg and 150 mg dual-scored tablets given that the pivotal bioequivalence study was completed using unscored 150 mg tablets. This NDA is only seeking approval of the tablet formulation.

Dr. Hughes notes that results of Study 11060203 demonstrated acceptable bioequivalence between the 150 mg unscored tablets and the reference listed drug, doxycycline hyclate tablets, ANDA 65095. Dr. Hughes granted a waiver for the requirement for bioavailability /bioequivalence data to support approval of the proposed 75 mg tablets and dual-scored 150 mg tablet. Dr. Hughes found the proposed dissolution method and acceptance criterion acceptable and recommends approval of the NDA from a biopharmaceutics perspective.

6.0 Clinical 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 of the NDA with labeling revisions.

7.0 Clinical Pharmacology

Ryan Owen, PhD, is the clinical pharmacology reviewer for this application. Of the three studies submitted by the applicant to support the NDA, one of the studies (Study 11060204), was a food-effect study and was reviewed by Dr. Owen. This study compared the relative bioavailability of doxycycline hyclate 150 mg tablets under fasted and non-fasted conditions. Using a cross-over design, a single dose of 150 mg doxycycline hyclate tablet was administered to subjects in a fed

and fasted state. When given with food, the lower bound of the 90% confidence interval fell below 80% for C_{max}, AUC_{0-t}, and AUC_{0-inf}. Dr. Owen notes that the clinical significance of this decrease is not known.

Dr. Owen recommends that this information be included in Section 12.3 of labeling and that labeling cannot state that this product can be given without regard to food.

Dr. Owen recommends approval of the NDA.

8.0 Clinical Efficacy/Safety

Edward Weinstein, MD PhD, is the clinical reviewer for this application. No new clinical studies were conducted to support efficacy. Safety data from the Studies 11060203, 11060204, and 11060201 were reviewed. The most common adverse reactions were related to the gastrointestinal system (nausea, emesis, abdominal discomfort). All reported adverse reactions are included in the approved labeling for doxycycline products. No new safety signals were identified in these studies or in a review of the literature. Dr. Weinstein has provided labeling recommendations to the Warnings section of the package insert regarding intracranial hypertension. Dr. Weinstein recommends approval of the NDA.

Mushfiqur Rashid, PhD, is the statistical reviewer for this application. No new clinical data were submitted with this application. Dr. Rashid noted that a statistical review was not needed as no clinical data were submitted.

9.0 Labeling

Aleksander Winiarski, PharmD, from the Division of Medication Error Prevention and Analysis (DMEPA) has provided a review of the proposed labeling. Dr. Winiarski's recommendations for labeling have been communicated to the applicant and incorporated in labeling. The proposed proprietary name, Acticlate was found acceptable by DMEPA.

Carrie Newcomer, PharmD, from the Office of Prescription Drug promotion (OPDP) has provided labeling recommendations that have been incorporated in the labeling proposed by the Division.

10.0 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.

11.0 Other Regulatory Issues

The Division of Bioequivalence and GLP Compliance (DBGLPC) conducted inspections of the clinical and analytical portions of Study 11060203 and recommend that the data are acceptable for Agency review.

This application was not presented to the Anti-Infective Drugs Advisory Committee (AIDAC) as there were no issues requiring input from the AIDAC. There are no other relevant regulatory issues for this application.

12.0 Recommended Regulatory Action

I agree with the recommendations made by the review team that this NDA be approved, under 505(b)(2), relying on the Agency's prior findings of safety and effectiveness of the listed drug product, Vibra-Tabs (NDA 50533). As Vibra-Tabs is no longer marketed, the applicant has provided adequate data to support the bioequivalence of doxycycline hyclate, 75 mg and 150 mg tablets to the reference listed drug, ANDA 65095, doxycycline hyclate tablets, 100 mg.

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/s/

SUMATHI NAMBIAR
07/25/2014