CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205572Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	(electronic stamp)
From	Balajee Shanmugam Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA #	205572; class 2 resubmission
Applicant Name	Fresenius Kabi USA, LLC
Date of Submission	October 3, 2014
PDUFA Goal Date	April 3, 2015
Established (USAN) Name	Moxifloxacin Injection*
Dosage Forms / Strength	Intravenous Solution, 400 mg/250 mL
Proposed Indications	Acute Bacterial Sinusitis Acute Bacterial Exacerbation of Chronic Bronchitis Complicated Intra-abdominal Infections Complicated and Uncomplicated Skin and Skin Structure Infections Community Acquired Pneumonia
Recommended Action:	Approval

**No proprietary/trade name was proposed for the drug product*

1.0 Introduction

This 505 (b)(2) NDA submitted by Fresenius Kabi, USA, LLC provides for a new injectable formulation of Moxifloxacin to be used for the treatment of the same indications as listed in the drug labeling for Avelox® (moxifloxacin hydrochloride) Injection and provided in the table above. The drug product proposed in this NDA, Moxifloxacin injection, 400 mg/250 mL is a new formulation supplied in a 300 mL **free***flex*® bag. The presented formulation differs from the listed drug in the excipients used in the formulation, specifically, the tonicity and pH adjusters.

2.0 Background

Moxifloxacin hydrochloride is a synthetic fluoroquinolone antibacterial drug administered either orally or intravenously and has been previously approved in a variety of dosage forms. The proposed drug product, Moxifloxacin Injection, 400 mg/250 mL, is a new formulation of moxifloxacin hydrochloride intravenous solution supplied in a 300 mL **free***flex*® bag. The proposed product has the same drug substance, and concentration, dosage form, route of administration, and indications as the listed drug but as discussed above, it differs from the listed drug in the excipients used in the formulation, specifically, the tonicity and pH adjusters. A complete response (CR) letter was issued on April 04, 2014, due to outstanding issues from pharmacology-toxicology, biopharmaceutics, and product quality standpoint. The Applicant submitted the resubmission package in response to the CR on Oct 3, 2014. Since details of the original submission have been adequately covered in the first-cycle reviews, this review will

only cover salient aspects of the reviews related to the responses to the deficiencies cited in the CR. For further details, please refer to the discipline specific reviews, Cross-Discipline Team Leader Review and Division Director Memo filed with the original submission.

The appropriate discipline reviewers have completed evaluation of their respective review portions of the resubmission. For detailed information, please refer to discipline specific reviews.

3.0 Product Quality

The Product Quality reviewer for this application is Milton Sloan, Ph.D.

Moxifloxacin hydrochloride drug substance is manufactured by (b) (4) and all CMC information related to the drug substance is referenced to the Drug Master File (DMF) (b) (4) held by (b) (4) The DMF has been previously reviewed and found adequate to support this NDA.

The proposed drug product Moxifloxacin Injection, 400 mg/250 mL, supplied in 300mL **free***flex*® bags contains moxifloxacin hydrochloride (b) (4) and sodium acetate trihydrate, disodium sulfate, sulfuric acid, and water for injection. All excipients used in the manufacture of the drug product are compendial and meet the requirements of the current USP/NF. DMF (b) (4) was referenced for the **free***flex*® bags. The DMF was found deficient in the first cycle and the DMF holder, as discussed below in this section and in the Pharmacology/Toxicology section, has adequately addressed the deficiencies. The DMF is adequate to support this application.

The drug product is manufactured at the Fresenius Kabi Norge AS facility in Norway. In addition, several other facilities are involved (and are listed in the NDA) in chemical and microbiological testing of the proposed drug product. An overall recommendation of "Acceptable" has been issued by the Office of Process & Facilities for all facilities involved in manufacture of the drug substance and the drug product.

In the first review cycle, Dr. Sloan had recommended that the NDA not be approved from Product Quality perspective as several deficiencies were noted, including deficiencies in the DMF for the container closure, specifically on the issue of extractables and leachables. Dr. Sloan has noted that all the CMC deficiencies listed in the complete response letter dated April 04, 2014, have been adequately addressed. DMF (b) (4) was found adequate to support this NDA. Based on available stability data, including data for leachables, Product Quality recommends granting (b) (4)-month expiration period. All outstanding Product Quality issues have been resolved adequately and Dr. Sloan recommends approval of the NDA from Product Quality Perspective.

4.0 Pharmacology/Toxicology

In the first cycle review, pharmacology/toxicology, reviewed by Terry Miller, PhD, also did not recommend approval of the NDA for lack of adequate safety information related to the leachables (b) (4) based on the 6-month migration study in the **free***flex*® bag.

The resubmission provided updated leachable information on extraction performed on the **free***flex*® bag with (b) (4)% ethanol to determine leachable compounds for up to 24 months. The updated information to address the deficiencies was reviewed by Dr. Miller (issues are discussed in the in the Product Quality section above in this review). Additionally, the amendment also provided toxicological risk assessment for each extractable. The results presented indicate that no new extractables were detected in ethanol extraction. Though the levels of the leachables, (b) (4) were significantly higher, the very large safety margins detected in the migration study encompass the increased levels of each solvent detected in the extraction study. Furthermore, the extraction conditions were far more at extreme conditions considering the formulation is aqueous. The studies on migration of the leachables were performed up to 24 months of storage under different conditions and the observed leachables were evaluated for potential toxicity based on literature survey where possible or additional toxicological studies were performed to determine the permitted daily exposure per ICH Q3C (R5). Animal toxicology studies conducted on the three leachables (b) (4) showed that they were generally well tolerated at concentrations that exceeded levels detected in the drug product.

The applicant also conducted detailed studies to evaluate each leachable for systemic toxicity, potential mutagenicity and determined the No-Observed-Adverse-Effect-Level (NOAEL) for the three leachables. None of the leachables were found to have mutagenic potential. Dr. Miller, based on the evaluation of the data presented, does not expect any significant safety risk from the leachables in the drug product and therefore recommends approval of the NDA from pharmacology/toxicology perspective.

Biopharmaceutics

Biopharmaceutics (reviewed by Kareen Reviere, PhD), in the first cycle review noted that a biowaiver request cannot be granted because of the differences in the formulation of the RLD and the drug product. The applicant was recommended to provide information on: a) a comparison of the drug product to the RLD for osmolality and pH, and b) a justification that the human physiological disposition (i.e. metabolism and excretion) of the proposed and listed products are similar, despite the differences in the inactive ingredients.

Based on the evaluation of the submitted information, Dr. Kolhatkar who reviewed the resubmission has granted waiver for in vivo bioavailability/bioequivalence studies. Dr. Kolhatkar recommends approval of the NDA.

5.0 Clinical Microbiology

The resubmission provides no new clinical microbiology information and therefore no review was conducted by Kalavati Suvarna, PhD. Also, Dr. Suvarna has no changes to the approval recommendation of this application nor to the labeling.

6.0 Clinical Pharmacology

Since the resubmission provides no new no new clinical pharmacology data, no new review was performed by Seong Jang, PhD, the clinical pharmacology reviewer for this application.

7.0 Clinical Efficacy/Safety

The resubmission did not provide new clinical or statistical information. Yuliya Yasinskaya, MD, clinical reviewer for this application recommended adding a warning statement as discussed below. Since the drug product is a new formulation of moxifloxacin injection containing higher levels of sodium (source: sodium acetate trihydrate and disodium sulfate to adjust tonicity) as compared to the RLD (which contains sodium chloride), a warning on high sodium load was proposed by the reviewer for inclusion in the Warnings and Precaution section. In addition, Dr. Yasinskaya recommended adding additional information to the Use in Specific Populations, and Description Sections, and to the MedGuide. The Applicant has accepted all recommended labeling revisions. Dr. Yasinskaya recommends approval of the NDA.

No new statistical review was performed by Christopher Kadoorie, PhD, the statistical reviewer since no new clinical data was provided in the resubmission.

8.0 Labeling

All labeling issues have been adequately resolved based on reviews from several offices including, Office of Prescription Drug Products (OPDP) (reviewed by Puja Shah, PharmD), Division of Medical Policy Programs (DMPP) (reviewed by Shawna Hutchins, MPH, BSN, RN) and the Division of Medication Error Prevention and Analysis (DMEPA) (reviewed by Jacqueline Sheppard, PharmD). The Product Quality reviewer, Dr. Sloan recommended that the applicant includes the following equivalency statement, “Each 250 mL contains 400 mg moxifloxacin equivalent to 437.5 mg of moxifloxacin hydrochloride”. As indicated above, all labeling recommendations were accepted by the Applicant.

9.0 Pediatrics

This NDA does not meet the criteria required under the Pediatric Research and Equity Act (PREA), and is therefore exempt from PREA requirements.

10.0 Other Regulatory Issues

Fresenius Kabi indicates that the two unexpired patents listed in the Orange Book for the reference listed drug, NDA 21277 Avelox® (moxifloxacin hydrochloride) Injection, 400 mg/250 mL, US Patent No. 5,849,752 (Expiry Date: December 5, 2016) and US Patent No. 6,548,079 – (Expiry Date: July 25, 2020) will not be infringed.

Paragraph IV certifications [per 21 CFR 314.50(i)(1)(i)(A)(4)] regarding the two patents are invalid, unenforceable, and/or will not be infringed by the manufacture, use, or sale of Moxifloxacin Injection, 400 mg/250 mL, which is the subject of the current application has been provided by the applicant.

Furthermore, the applicant, per 21 CFR 314.52(b) notified Bayer on August 7, 2013, that they had submitted an NDA under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act along with a certification under Section 505(b)(2)(A)(iv) ("Paragraph IV"), requesting approval to market Moxifloxacin Injection, 400 mg/250 mL. Subsequently, in an amendment dated November 12, 2013, the applicant certified that Bayer Pharmaceuticals had not filed suit against Fresenius Kabi for patent infringement.

This application was not presented to the Anti-Infective Drugs Advisory Committee (AIDAC) as there were no issues requiring input from the AIDAC.

11.0 Recommended Regulatory Action

This reviewer agrees with the recommendations made by the review team that this NDA covered under 505(b)(2) be approved, relying on the Agency's prior findings of safety and effectiveness of the listed drug product Avelox (NDA 21277).

Balajee Shanmugam -S

Digitally signed by Balajee Shanmugam -S
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