CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205572Orig1s000

SUMMARY REVIEW

Division Director Decisional Memo

Date	(electronic stamp)
From	Sumathi Nambiar MD MPH
Subject	Division Director Decisional Memo
NDA #	205572; class 2 resubmisison
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

Material Reviewed/Consulted Action Package including:	**Names of Discipline Reviewers**
Pharmacology Toxicology Review	Terry Miller PhD
Chemistry Manufacturing and Controls Review	Milton Sloan PhD
Biopharmaceutics Review	Vidula R. Kolhatkar PhD
Cross-Discipline Team Leader Review	Balajee Shanmugam PhD
Medical Officer Review	Yuliya Yasinskaya MD
Statistical Review	Christopher Kadoorie PhD
Microbiology Review	Kalavati Suvarna PhD
Division of Medication Error Prevention and Analysis	Jacqueline Sheppard PharmD
Clinical Pharmacology Review	Seong Jang PhD
Labeling Review	Shawna Hutchins BSN, MPH, RN Puja Shah PharmD

1.0 Introduction

NDA 205572, Moxifloxacin Injection 400 mg/250 mL, submitted by Fresenius Kabi, USA, LLC provides for a new formulation of injectable moxifloxacin to be used for the treatment of the same indications as listed in the drug labeling for Avelox® (moxifloxacin hydrochloride) Injection. This NDA was submitted as a 505(b)(2) application and the listed drug is Avelox® (moxifloxacin hydrochloride) Injection, 400 mg/250 mL (NDA 21277), held by Bayer HealthCare Pharmaceutical. Avelox® (moxifloxacin hydrochloride) Injection is approved for the treatment of the following infections:

- Acute Bacterial Sinusitis
- Acute Bacterial Exacerbation of Chronic Bronchitis
- Community Acquired Pneumonia
- Uncomplicated Skin and Skin Structure Infections
- Complicated Skin and Skin Structure Infections
- Complicated Intra-abdominal Infections

2.0 Background

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 drug product differs from the listed drug in the excipients used in the formulation, specifically, the tonicity and pH adjusters. A complete response letter was issued on April 04, 2014, due to outstanding issues regarding pharmacology-toxicology, biopharmaceutics, and product quality. On August 29, 2014, the Applicant submitted a complete response. On September 12, 2014, a letter was sent to the Applicant notifying them that their submission was not considered a complete response as the Drug Master File (DMF) deficiencies had not been addressed. The Applicant resubmitted a complete response on October 03, 2014. This memo will only cover key aspects of the reviews related to the resubmission. For further details, please refer to the discipline specific reviews, Cross-Discipline Team Leader Review and Division Director memo filed with the original submission.

All reviewers have completed their reviews of the relevant sections of the resubmission. For detailed information, please refer to discipline specific reviews and the Cross-Discipline Team Leader review.

3.0 Product Quality

The Chemistry, Manufacturing and Controls (CMC) reviewer for this application is Milton Sloan, Ph.D.

Moxifloxacin hydrochloride drug substance is manufactured (b) (4) For all drug substance information, reference is made to DMF (b) (4) held by (b) (4) The DMF has been previously reviewed and is adequate to support this NDA.

The proposed drug product Moxifloxacin Injection, 400 mg/250 mL, supplied in 300 mL **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 meet the requirements of the current USP/NF. The components and component manufacturing methods for the container closure system are provided in the referenced type III DMF (b) (4).

An overall recommendation of "Acceptable" has been issued by the Office of Process and Facilities.

In the first review cycle, Dr. Sloan had recommended that the NDA not be approved as there were several deficiencies from a product quality standpoint, including deficiencies in DMF (b) (4) Dr. Sloan has noted that all the CMC deficiencies listed in the complete response letter dated April 04, 2014, have been adequately addressed. Dr. Sloan recommends approval of the NDA. I agree with his recommendation.

4.0 Pharmacology/Toxicology

The pharmacology/toxicology reviewer for this application is Terry Miller, PhD. During the first review cycle, Dr. Miller did not recommend approval of the NDA, as adequate safety information was not provided regarding three leachables (b) (4) identified in 6-month migration studies with moxifloxacin in the proposed **free***flex*® bag.

In this review cycle, Dr. Miller reviewed only the updated information provided regarding the extraction studies of the **free***flex*® bag with (b) (4)% ethanol, the extended migration/stability studies to determine leachable compounds up to 24 months, and the Applicant's updated toxicological risk assessment for each extractable. No new extractables were detected in ethanol compared to water for injection tested previously. Dr. Miller noted that although the concentrations of (b) (4) were detected at significantly greater levels in the extraction study of (b) (4) in ethanol compared to the levels in the migration studies, the very large safety margins detected in the migration study encompass the increased levels of each solvent detected in the extraction study.

The migration studies examined the stability of the drug product for up to 24 months under various storage conditions at different time intervals. All packaging materials (b) (4) were considered in these studies.

The Applicant conducted a toxicologic evaluation of the leachables/extractables detected using literature and public toxicology databases. When no toxicology data for an extractable/leachable were available, the Applicant conducted new toxicology study(ies) with the unqualified leachable and/or examined "related" compounds (i.e. parent compound or individual components of a complex compound) for which toxicology data were available. The permitted daily exposure (PDE) for each extractable was calculated as described in ICH Q3C(R5) Impurities: Guideline on Residual Solvents.

The three leachables of unknown toxicologic risk for which the Applicant conducted additional toxicology studies were (b) (4) Animal toxicology studies conducted with these three leachables showed that they were generally well tolerated at concentrations that exceeded levels detected in the drug product.

Repeated daily oral administration of (b) (4) (in 0.5% carboxymethyl-cellulose/0.1% Tween-80) for 90 days up to 100 mg/kg/day showed minimal effects. A slight accumulation of foamy cells of unknown cause or toxicological consequence in the lung alveoli was seen at 100 mg/kg/day. The No-Observed-Adverse-Effect-Level (NOAEL) for this study was determined to be 30 mg/kg/day. Systemic drug levels of (b) (4) were not estimated. Systemic absorption of at least 50% of the administered dose was assumed due to dose related changes in liver weights and histology of the liver. The PDE level was estimated to be (b) (4) mg (or (b) (4) mg assuming 50% oral absorption), providing a safety margin of approximately 12.5 times the maximum daily exposure of (b) (4) detected in the migration studies. No mutagenic potential was seen in the AMES assay. Dr. Miller found the toxicological risk assessment for (b) (4) adequate and does not expect any significant safety risk from (b) (4) as a leachable in the drug product.

Repeated daily intravenous administration of (b) (4) in 0.9% saline for 4 weeks for up to (b) (4) mg/kg/day showed minimal effects and no significant clinical observations or systemic toxicity were reported. The primary toxicity was observed at the injection site in 4 animals at (b) (4) mg/kg/day. Erythema and reddening along with histological evidence of vascular irritation was seen in a few animals. A slight decrease in body weight gain was noted in females at the highest dose and increased monocyte and platelet counts were observed in males at the

highest dose. These findings were seen in only one sex, lacked dose dependence, or did not have histological correlates. The NOAEL for this study was determined to be (b) (4) mg/kg/day and the PDE value was calculated to be (b) (4) mg (safety margin of approximately (b) (4)). (b) (4) showed no mutagenic potential in the AMES assay. Dr. Miller found the toxicological risk assessment for (b) (4) adequate, and does not expect any significant safety risk from this leachable in the drug product.

The risk assessment for (b) (4) included an evaluation of (b) (4) and its two hydrolysis products, (b) (4). A search of the various toxicology databases showed that (b) (4) were well tolerated in rat feed studies up to 90 days and 225 days, with reported NOEL doses determined to be 200 mg/kg and 50 mg/kg respectively. In addition, neither degradants was found to have mutagenic potential in multiple in vitro and in vivo genotoxicity studies. The calculated PDE values of 40 mg and 25 mg showed the PDE to be (b) (4) and (b) (4) times greater than the potential maximum daily exposure, respectively. Dr. Miller found the toxicological risk assessments for (b) (4) adequate, and expects no significant safety risk from these potential leachables in the drug product.

Repeated intravenous administration of (b) (4) (in 10% DMSO in 1% HP-β-CD) for 4 weeks for up to 25 mg/kg/day showed injection site toxicity on the lateral tail vein of most animals at all doses, including the vehicle control. DMSO is a well-known vascular toxicant, and injection site toxicity can occur with repeated IV administration. Saline control animals did not show tail vein toxicity. In addition, adverse effects on the tail observed at 15 and 25 mg/kg/day appeared to be exacerbated by (b) (4), leading to unscheduled euthanization of all high dose animals on Study Day 15. At a dose of 25 mg/kg/day, a decrease in RBC counts and hemoglobin, associated with a significant increase in reticulocyte count and histological evidence of extramedullary splenic hematopoiesis (EH) was seen. It is not clear if (b) (4) is directly toxic to RBCs. WBC and lymphocyte counts also increased in a dose dependent fashion. Dr. Miller notes that increased platelet counts and EH noted in animals at 25 mg/kg/day are often associated with inflammation and infection. (b) (4) was generally well tolerated at 7.5 and 15 mg/kg/day and the NOAEL was determined to be 7.5 mg/kg/day. The PDE value was calculated at (b) (4) mg (safety margin of approximately (b) (4) No mutagenic potential has been reported in several AMES assays. Dr. Miller found the toxicological risk assessment for (b) (4) adequate and does not expect any significant safety risk from this leachable in the drug product.

In Dr. Miller's assessment, none of the leachables detected in long-term stability studies with Moxifloxacin for Injection in the **free***flex*® bag likely pose any significant safety risk. Dr. Miller recommends approval of this NDA from a pharmacology/toxicology perspective. I agree with Dr. Miller's assessment.

5.0 Biopharmaceutics

Kareen Reviere, PhD, was the biopharmaceutics reviewer for this application in the first review cycle. The applicant had requested a waiver of the requirement for submission of data from an in vivo bioequivalence study. Dr. Riviere had concluded that the biowaiver request could not be granted and recommended that the applicant provide the following information:

1. A side-by-side comparison of the osmolality and pH values for the proposed and listed products.

2. 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.

Vidula Kolhatkar, PhD, is the biopharmaceutics reviewer for this submission. In the resubmission, the Applicant provided a side-by-side comparison of osmolality and pH values for the proposed drug and listed drug products and a justification that the human physiological disposition of the proposed drug product does not differ from that of the listed drug product. Dr. Kolhatkar has granted the waiver for in vivo bioavailability/bioequivalence studies for Moxifloxacin Injection, 400 mg/250 mL and recommends approval of the NDA.

I agree with Dr. Kolhatkar's recommendation to approve the NDA.

6.0 Clinical Microbiology

Kalavati Suvarna, PhD, is the clinical microbiology reviewer for this resubmission. No new clinical microbiology information was submitted in the resubmission. Dr. Suvarna stated that no recommendation is made regarding approval of this application and no labeling changes are proposed at this time.

7.0 Clinical Pharmacology

Seong Jang, PhD, is the clinical pharmacology reviewer for this application. A clinical pharmacology review was not performed as no new clinical pharmacology data were submitted with this application.

8.0 Clinical Efficacy/Safety

Yuliya Yasinskaya, MD, is the clinical reviewer for this application. No new clinical or statistical information was submitted in this NDA. The proposed formulation of Moxifloxacin Intravenous Injection 400 mg/250 mL contains sodium acetate trihydrate and disodium sulfate to adjust tonicity and sulfuric acid to adjust pH, while the Reference Listed Drug (RLD) contains sodium chloride to adjust tonicity and hydrochloric acid and/or sodium hydroxide to adjust pH.

The proposed formulation in a single 60 minute daily infusion dose delivers 52.5 mEq (1207 mg) of sodium, whereas the RLD delivers 34.2 mEq (787 mg). The American Heart Association (AHA) recommended daily sodium intake for an elderly person is 1500 mg and for a healthy young adult is 2300 mg. This high sodium load poses a safety risk in certain patient populations, for example, in the elderly, patients with congestive heart failure, and chronic kidney disease. Dr. Yasinskaya proposed the addition of a new Warning on high sodium load in the Warnings and Precautions section of the package insert. Dr. Yasinskaya also recommended that additional information be added to the Use in Specific Populations, and Description Sections of the package insert and to the Medication Guide. These labeling revisions have been accepted by the Applicant.

Dr. Yasinskaya recommends approval of the NDA pending CMC, Biopharmaceutics and Pharmacology-toxicology reviews and an agreed to label. I agree with Dr. Yasinskaya's recommendation.

Christopher Kadoorie, PhD, is the statistical reviewer for this application. No new clinical data were submitted with this application. Dr. Kadoorie deferred a decision on this application to other review disciplines.

9.0 Labeling

Puja Shah, PharmD, from the Office of Prescription Drug Promotion (OPDP) provided labeling recommendations and Shawna Hutchins, MPH, BSN, RN from the Division of Medical Policy Programs (DMPP) performed a focused review of the Medication Guide. Jacqueline Sheppard, PharmD, from the Division of Medication Error Prevention and Analysis (DMEPA) provided a review of the labeling. The proposed labeling recommendations were accepted by the Applicant.

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 RLD, NDA 21277 Avelox® (moxifloxacin hydrochloride) Injection, 400 mg/250 mL, has the following unexpired patents listed in the Orange Book:

- US Patent No. 5,849,752 - Expiry Date: December 5, 2016

- US Patent No. 6,548,079 - Expiry Date: July 25, 2020

Fresenius Kabi submitted Paragraph IV certifications [per 21 CFR 314.50(i)(1)(i)(A)(4)] regarding the two patents (No. 5,8497,52 and No. 6,5480,79) stating that they 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.

To comply with 21 CFR 314.52(b), Fresenius Kabi notified Bayer Pharmaceuticals 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. 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.

12.0 Recommended Regulatory Action

I agree with the recommendations made by the review team and the cross-discipline team leader 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).

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/s/

SUMATHI NAMBIAR
04/03/2015