CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205572Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

NDA # :	205572
Submission Type:	505(b)(2)
Drug Name:	Moxifloxacin Injection (400 mg/250 mL)
Indication(s):	Acute Bacterial Sinusitis, Acute Bacterial Exacerbation of Chronic Bronchitis, Community Acquired Pneumonia, Complicated/Uncomplicated Skin and Skin Structure Infections, Complicated Intra-Abdominal Infections
Applicant:	Fresenius Kabi
Stamp Date:	October 3, 2014
PDUFA Goal Date:	April 3, 2015
Reviewer Completion Date:	March 17, 2015
Biometrics Division:	Division of Biometrics IV
Medical Division:	Division of Anti-Infective Products (DAIP)
Statistical Reviewer:	Christopher Kadoorie, Ph.D.
Concurring Reviewer:	Thamban Valappil, Ph.D.
Clinical Reviewer:	Yuliya Yasinskaya, M.D.
Clinical Team Leader:	John Alexander, M.D., M.P.H
Project Manager:	Fariba Izadi, Pharm.D.

Background

The Applicant, Fresenius Kabi, has submitted a 505(b)(2) New Drug Application (NDA) resubmission for Moxifloxacin Injection 400 mg/250 mL relying on findings of safety and efficacy for Avelox®, the reference listed drug (RLD). Therefore no clinical data or information was submitted. The Applicant has also submitted the proposed labeling for their product which is mostly based on the PLR labeling for Avelox®.

The original NDA submission of June 6, 2013 was not approved by the Agency due to the lack of adequate information to support a waiver of *in vivo* bioequivalence studies. Therefore, a Complete Response letter was issued by the Agency on April 4, 2014. In response to this letter, the Applicant resubmitted the NDA on August 29, 2014 to address the deficiencies identified. However, the Agency did not consider this response to be adequate because the DMF deficiency letter dated June 24, 2013 was not addressed. In the current submission, the Applicant has addressed this issue by confirming that the DMF holder has amended DMF 026696 in response to the DMF deficiency letter.

Product Labeling

As stated above, labeling for this product mostly followed the PLR labeling for Avelox®. However, some text relevant only to the oral formulation of moxifloxacin was removed. In addition, there were other changes in the labeling proposed by the review team which arose from the substantially higher sodium levels in a single 60 minute daily infusion for the proposed formulation (1207 mg) compared to the RLD (787 mg). As noted by the Clinical Reviewer, Dr. Yuliya Yasinskaya, an abrupt high sodium load from a single moxifloxacin dose delivered over 1 hour and as well as persistent additional high sodium exposure over the course of treatment (up to 21 days) constitutes a safety concern for individuals with sodium sensitivity: elderly, patients with underlying comorbidities, such as congestive heart failure, high blood pressure, metabolic syndrome, and chronic kidney disease, leading to vascular volume overload.

For further details regarding the new language about high sodium load and additional safety language to the Warnings and Precautions, Use in Specific Populations, and Description Sections of the label, as well as to the MedGuide, refer to the clinical review.

Conclusions

There were no clinical data or information submitted on this NDA. Therefore, there were no statistical issues identified in this NDA. There were also no statistical issues identified in reviewing the product labeling. The decision on this application is deferred to other disciplines.

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/s/

CHRISTOPHER E KADOORIE
03/17/2015

THAMBAN I VALAPPIL
03/17/2015

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Indication(s):	Acute Bacterial Sinusitis, Acute Bacterial Exacerbation of Chronic Bronchitis, Community Acquired Pneumonia, Complicated/Uncomplicated Skin and Skin Structure Infections, Complicated Intra-Abdominal Infections
Applicant:	Fresenius Kabi
Stamp Date:	June 6, 2013
PDUFA Goal Date:	April 7, 2014
Reviewer Completion Date:	March 15, 2014
Biometrics Division:	Division of Biometrics IV
Medical Division:	Division of Anti-Infective Products (DAIP)
Documents Reviewed:	NDA 205572
Statistical Reviewer:	Christopher Kadoorie, Ph.D.
Concurring Reviewer:	Thamban Valappil, Ph.D.
Clinical Reviewer:	Yuliya Yasinskaya, M.D.
Clinical Team Leader:	John Alexander, M.D., M.P.H
Project Manager:	Fariba Izadi, Pharm.D.

Background

The Applicant, Fresenius Kabi, has submitted a 505(b)(2) New Drug Application for Moxifloxacin Injection 400 mg/250 mL. The reference listed drug (RLD) for this application is Avelox®, NDA 21,277 held by Bayer Healthcare. The application also included a request for the waiver of *in vivo* bioequivalence studies. A comparison between the generic drug and the RLD is outlined below:

Comparison Between Generic Drug and RLD

Conditions of Use: The conditions of use, prescribed, recommended or suggested in the labelling proposed for Moxifloxacin Injection have been previously approved for the reference listed drug (RLD) Avelox®.

Active Ingredients: The active pharmaceutical ingredient (API) of the proposed drug product is Moxifloxacin Hydrochloride which is the same as the RLD except the FK uses (b) (4) and the RLD uses the (b) (4) of the API, Moxifloxacin Hydrochloride.

Inactive Ingredients: The inactive ingredients of the proposed drug product differ from those listed in the RLD package insert. FK uses sodium acetate instead of sodium chloride which is used by the RLD. Also, FK uses disodium sulfate (b) (4) which is not listed in the RLD package insert.

Route of Administration, Dosage Form and Strength: The route of administration, dosage form and strength of the proposed drug product are the same as those of the reference listed drug. The proposed drug product is a sterile solution containing 1.6 mg/mL of Moxifloxacin Hydrochloride (b) (4) which is intended for administration by intravenous infusion.

Table 1.12.12- 1 Side-by-Side Comparison of the Reference Listed and Proposed Drugs

	Reference Listed Drug	Proposed Drug Product
Name	Avelox ®	Moxifloxacin Injection
Conditions of Use (Indications)	It is indicated for treatment of infections.	It is indicated for treatment of infections.
Dosage Form	Sterile Liquid	Sterile Liquid
Route of Administration	Intravenous Infusion	Intravenous Infusion
Active Ingredient	Moxifloxacin Hydrochloride (b) (4)	Moxifloxacin Hydrochloride (b) (4)
Strength	160 mg/100 mL (1.6 mg/mL)	400 mg/250 mL (1.6 mg/mL)
Excipients (per mL)	**per mL**	**per mL**
Sodium Acetate Trihydrate, USP	(b) (4)	
Sodium Chloride, USP		
Disodium Sulfate , USP (b) (4)		
Sodium Hydroxide		
Hydrochloric Acid		
Sulphuric Acid, NF		
Water for Injections, USP		
Bioequivalence	Refer to SECTION 1.12.15	Refer to SECTION 1.12.15
Labeling	Refer to Section 1.14	Refer to Section 1.14

* The RLD does not list Water for Injection on the labeling, however it must be employed in the compounding of the drug product.

Conclusions:

There were no clinical data or information submitted on this NDA. Therefore, from a statistical perspective, there were no issues to report for this application.
The decision on this application is deferred to other disciplines.

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03/19/2014

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