CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205572Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205572

COMPLETE RESPONSE

Fresenius Kabi USA, LLC
Attention: Nicole Cage
Senior Regulatory Specialist
Three Corporate Drive
Lake Zurich, IL, 60047

Dear Ms. Cage:

Please refer to your New Drug Application (NDA) dated June 06, 2013, received June 07, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Moxifloxacin Injection 400 mg/250 mL.

We acknowledge receipt of your amendment(s) dated June 25 and November 12, 2013.

We also acknowledge receipt of your amendment dated February 11, 2014, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below, and where possible, our recommendations to address these issues.

Biopharmaceutics:

1. Provide adequate comparative physicochemical property data such as comparison of API solubility, osmolality, and pH of the proposed drug product and the listed product using at least 3 production lots (if available) of the proposed drug product and three commercial lots of the listed drug product. The measurements should be done in triplicate for each lot tested.

2. Provide adequate data/justification demonstrating that the human physiological disposition (i.e., metabolism and excretion) of the proposed drug product and the listed drug product is similar, despite the formulation differences between these drug products. You may include published literature references to support your justification.

Pharmacology-Toxicology:

3. Provide additional toxicity information for each of the three identified leachables (b) (4) and the "related" compounds from nonclinical studies you may have conducted, from studies described in published literature, or from public toxicity databases. Provide a more detailed rationale for your selection of "related" compounds used to determine the Permitted Daily Exposure (PDE) for each of the identified leachables for which no toxicity information is available.

Product Quality:

4. A DMF deficiency letter was sent to the DMF holder on June 24, 2013. Please follow-up with the DMF holder to ensure that the deficiencies have been addressed.

5. Leachable data on one batch at six months is insufficient to justify the exclusion of leachable testing in the drug product specification. Establish tentative acceptance criteria for four leachables, (b) (4) in the drug product specification and provide justification for the proposed acceptance criteria. Include monitoring leachable levels on stability until end of shelf-life for the three ongoing registration stability batches, and for each annual batch as part of post-approval stability protocol. Test the leachable levels in the three registration stability batches and the batch for which the six month leachable data were provided. If data from a sufficient number of commercial scale batches show negligible levels of leachables or data are generated to provide accurate PDE for each leachable you may propose to eliminate the leachable test.

6. The conditions used for extraction testing of 300 mL **free***flex* bags are not adequate to establish appropriate acceptance criteria for leachables in the container closure raw material. Specifically, you did not conduct studies in alcohol and at pH 2 solution, and studies were done only over 1 hour. Using methods that meet or exceed USP, determine total extractables for drug product contact materials (b) (4) in a one-time extraction study in water for injection (WFI), pH 2, pH 8.0, and alcohol. Continue refluxing in the extraction media at hourly intervals until the extractables are exhausted from material and calculate new safety factors for each using these values. Report these data to your type III DMF (b) (4).

7. The proposed drug product specification includes one identification test by HPLC. Per ICH Q6A, identification solely by a single chromatographic retention time is not regarded as being specific. Include a second chromatographic procedure where the separation is based on different principles, or include a combination of tests into a

single procedure (e.g. HPLC/UV diode array, HPLC/MS, etc.). If a single method is used, propose a specific identification test such as infrared spectroscopy.

8. You have indicated that at your drug product formulation pH, moxifloxacin exists as moxifloxacin hydrogen sulfate, not as moxifloxacin HCl, but have not demonstrated that the moxifloxacin hydrogen sulfate salt form is functionally equivalent to Avelox I.V. (moxifloxacin HCl in NaCl injection). In addition to pH and osmolality, the side by side comparison between Moxifloxacin Injection and the listed drug product, Avelox I.V. should include a comparison of sodium content, chloride content, hydrogen sulfate content, and isotonicity calculations.

9. You have indicated that at pH 4.0-6.0, the sulfuric acid is [redacted] (b) (4) moxifloxacin hydrogen sulfate. Provide information on acid base equillibria over the 4.0-6.0 pH range (and in particular over the 4.1-4.6 pH range) to substantiate the above claim.

10. You have indicated that precipitation occurs in the drug product at pH [redacted] (b) (4) or lower, but have specified a pH range of [redacted] (b) (4) for the drug product formulation. The lower limit of the pH range should be revised to pH 4.5 or higher to prevent precipitation. As this could result in a different pH range from that of the listed drug product, additional justification should be provided to support the comparability of your product to the listed product.

11. The exhibit batches show an underage. Provide the target fill volume, target fill weight and formulation density. Provide the target assay for each drug product unit (as a percentage of label claim) and additional clarification on weight loss determination.

12. You have submitted an in-house analytical method [redacted] (b) (4) test for the identification, assay at release, and assay at stability for moxifloxacin and impurities of moxifloxacin in the finished drug product. Provide the complete analytical method with details of the method and any modifications to the use for identification, release and stability. Details such as sampling procedure for release testing, detector sensitivity, flow rate, sample preparation, standard preparation, assay preparation, injection volume, etc. should be included. The limits of detection (LOD) and quantitation (LOQ) should also be described in the method. The LOD and LOQ should be measured with respect to the label. Additionally, the analytical calculations appear to be based on a moxifloxacin hydrochloride conversion factor which may be a less precise determination than with moxifloxacin hydrogen sulfate.

13. Include specifications for specified degradants. Revise the term [redacted] (b) (4) "Any unspecified degradations product", and revise your acceptance criterion for any unspecified degradation product to NMT [redacted] (b) (4) %.

14. Replace the term of [redacted] with "total degradants" and revise your acceptance criterion for total degradation product to NMT [redacted]%. Explain why degradants less than [redacted]% are not included in the total degradant calculation.

15. Revise the acceptance criterion for Extractable Volume in Container to the actual nominal value. The specification should state: NLT [redacted]mL complies with current USP <1> of NLT labeled volume.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Fariba Izadi, Pharm.D., Regulatory Health Project Manager at (301) 796-0563.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUMATHI NAMBIAR
04/04/2014