CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205645Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205645

TENTATIVE APPROVAL

Fresenius Kabi, USA, LLC
Attention: Kurt Pearl, MChE
Regulatory Specialist
Three Corporate Drive
Lake Zurich, IL 60047

Dear Mr. Pearl:

Please refer to your New Drug Application (NDA) dated July 31, 2013, received August 1, 2013 submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Tigecycline for Injection.

The May 29, 2015, submission constituted a complete response to our May 30, 2014, action letter.

This NDA provides for the use of Tigecycline for Injection for the following indications:

- Complicated Skin and Skin Structure Infections
- Complicated Intra-abdominal Infections
- Community-Acquired Bacterial Pneumonia

We have completed our review of this application, as amended. It is tentatively approved under 21 CFR 314.105 for use as recommended in the agreed-upon enclosed labeling text for the package insert, carton and immediate container labels. This determination is based upon information available to the Agency at this time, [i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product]. This determination is subject to change on the basis of any new information that may come to our attention.

The listed drug upon which your application relies is subject to a period of patent protection and therefore final approval of your application under section 505(c)(3) of the Act [21 U.S.C. 355(c)(3)] may not be made effective until the period has expired.

Your application contains certifications to each of the patents under section 505(b)(2)(A)(iv) of the Act stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of, this drug product under this application ("Paragraph IV certifications").

Section 505(c)(3)(C) of the Act provides that approval of a new drug application submitted pursuant to section 505(b)(2) of the Act shall be made effective immediately, unless an action is brought for infringement of one or more of the patents that were the subject of the paragraph IV certifications. This action must be taken prior to the expiration of forty-five days from the date the notice provided under section 505(b)(3) is received by the patent owner/approved application holder. You notified us that you complied with the requirements of section 505(b)(3) of the Act.

In addition, you have notified the Agency that the patent owner and/or approved application holder has initiated a patent infringement suit against you with respect to patents 40,183, 7,879,828 and 8,372,995 in the United States District Court for the District of Delaware (Pfizer Inc, Wyeth LLC, Pfizer Pharmaceuticals LLC, PF Prism C.V. Pfizer Manufacturing Holdings LLC, Wyeth Holdings LLC, and Wyeth Holdings Corporations, Plantiff, v. Fresnius Kabi USA, LLC Defendant. Therefore, final approval cannot be granted until:

1. a. expiration of the 30-month period provided for in Section 505(c)(3)(C) beginning on the date of receipt of the 45-day notice required under Section 505(b)(3),unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or
   b. the date the court decides that the patents are invalid or not infringed as described in section 505(c)(3)(C)(i), (ii), (iii,) or (iv) of the Act, or,
   c. the listed patents have expired, and
2. we are assured there is no new information that would affect whether final approval should be granted.

To obtain final approval of this application, submit an amendment two or six months prior to the: 1.) expiration of the patent(s) or 2.) date you believe that your NDA will be eligible for final approval, as appropriate. In your cover letter, clearly identify your amendment as "REQUEST FOR FINAL APPROVAL". This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of any relevant court order or judgment settlement, or licensing agreement, as appropriate. In addition to a safety update, the amendment should also identify changes, if any, in the conditions under which your product was tentatively approved, i.e., updated labeling; chemistry, manufacturing, and controls data; and risk evaluation and mitigation strategy (REMS). If there are no changes, clearly state so in your cover letter. Any changes require our review before final approval and the goal date for our review will be set accordingly.

Until we issue a final approval letter, this NDA is <u>not</u> deemed approved.

Please note that this drug product may not be marketed in the United States without final agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under Section 501 of the Act and 21 U.S.C. 331(d).

PROPRIETARY NAME

If you intend to have a proprietary name for this product, the name and its use in the labels must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit a request for a proposed proprietary name review. See the guidance for industry titled, "Contents of a Complete Submission for the Evaluation of Proprietary Names", at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075068.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".

If you have any questions, call Carmen DeBellas, Regulatory Project Manager, at (301) 796-1203.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURES:
Content of Labeling
Carton and Container Labeling

34 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/ TS) immediately following this page

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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
11/25/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205645

COMPLETE RESPONSE

Fresenius Kabi, USA, LLC
Attention: Jeremy Rybicki
Manager, Regulatory Affairs
Three Corporate Drive
Lake Zurich, IL 60047

Dear Mr. Rybicki:

Please refer to your New Drug Application (NDA) dated July 31, 2013, received August 1, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Tigecycline for Injection, 50 mg/vial.

We acknowledge receipt of your amendments dated August 19, November 8, 14 and 27, 2013, and January 16, February 27, March 25, April 4(2), and April 17, 2014.

We also acknowledge receipt of your amendment dated May 30, 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, as amended, 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.

Product Quality:

1. During a recent inspection of the Fresenius Kabi USA, LLC, Grand Island, NY, manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

2. The [redacted] (b) (4) contains a structural alert for mutagenicity. The mutagenic potential of [redacted] (b) (4) needs to be evaluated and results submitted to the NDA. If [redacted] (b) (4) is confirmed to be mutagenic, propose an appropriate control strategy for [redacted] (b) (4) impurity in the drug product.

3. In Section 2.4 of the proposed package insert, the drug product is stated to be compatible with several other drugs. To support this statement, for each drug listed, provide physical and chemical compatibility data with the proposed drug product, Tigecycline for Injection, including tests for appearance, description (color, visible particulates, turbidity), sub-visible particulates (i.e., USP <788> compliance), and assay.

In addition, the following outstanding issue should also be addressed:

1. Provide results of the extractable and leachable studies for the proposed (b) (4) rubber stopper using suitable solvents and the reconstituted solutions of the proposed drug product, Tigecycline for Injection, with the proposed reconstitution diluents.

Labeling:

We reserve comment on the proposed package insert 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.

Please submit draft carton and container labeling revised as follows.

A. Vial Labels
   1. The Principal Display Panel (PDP) contains the I.V. abbreviation, which is listed on Institute for Safe Medication Practices' (ISMP) list of error-prone abbreviations. Replace the I.V. abbreviation with the word "Intravenous" for clarity.
   2. For consistency with the insert labeling, revise the statement (b) (4) to "Single Dose Vial" and relocate it to appear directly under the "For Intravenous Infusion Only" statement for increased prominence.
   3. To improve prominence of important use information, relocate the statement "Discard Unused Portion" from the side panel to under the "Single Dose Vial" statement.
   4. The Statement "Not Made with Natural Rubber Latex" should be removed from the side panel.
   5. To improve readability, revise the letter case of the established name "TIGECYCLINE FOR INJECTION" from all capitals to title case to read "Tigecycline for Injection.

B. Carton Labeling
   1. See A2, A3 and A5 above
   2. To improve readability revise the letter case of the statement (b) (4) from all capitals to title case to read: (b) (4)
   3. Currently, the Usual Dosage statement: (b) (4) provides one of the recommended dosage regimens. To help ensure correct dosing revise the Usual Dosage statement to read "Dosage and Administration: See package insert".

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.

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations that support any proposed changes.

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 Carmen DeBellas, Regulatory Project Manager, at (301) 796-1203.

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
05/30/2014