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RESEARCH**

APPLICATION NUMBER:

761045Orig1s000

OTHER ACTION LETTERS



BLA 761045

COMPLETE RESPONSE

Sandoz Inc.
Attention: Jordanis Joy, PharmD
Regulatory Affairs Associate
US Biopharmaceuticals
100 College Road West
Princeton, NJ 08540

Dear Dr. Joy:

Please refer to your Biologics License Application (BLA) dated August 27, 2015, received August 27, 2015, and your amendments, submitted under section 351(k) of the Public Health Service (PHS) Act for LA-EP2006.

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.

CLINICAL PHARMACOLOGY

1. You have not demonstrated PK similarity between LA-EP2006 and US-licensed Neulasta. We recommend that you conduct further root cause analyses to identify factors that may have led to the inability to demonstrate PK similarity.
2. You have not demonstrated PK similarity between LA-EP2006, US-licensed Neulasta, and EU-approved Neulasta. As a result, you have also not established the PK component of the scientific bridge between these products. This bridge is needed to justify the relevance of data from your clinical studies comparing EU-approved Neulasta to LA-EP2006 to support a demonstration of biosimilarity of LA-EP2006 to US-licensed Neulasta. In the absence of an adequate scientific bridge, there is insufficient data to support a demonstration of no clinically meaningful differences between LA-EP2006 and US-licensed Neulasta.
3. Once the root causes that may have led to the inability to demonstrate PK similarity are identified, you should conduct a feasibility assessment to determine whether developing your product as a proposed biosimilar product under section 351(k) of the PHS Act is still a viable option for licensure of LA-EP2006.
4. If the results of the feasibility assessment are supportive of continued development of LA-EP2006 as a proposed biosimilar to US-licensed Neulasta, you should consider conducting an adequately designed study to demonstrate PK and PD similarity of LA-EP2006 and US-

licensed Neulasta in healthy subjects. You should consider a cross-over study with a sample size estimation based on the expected mean AUC and Cmax differences and publicly available PK variability of pegylated G-CSF. In addition, you should consider designing the study as a 3-arm study (LA-EP2006, US-licensed Neulasta, and EU-approved Neulasta) to establish the PK component of the scientific bridge (refer to Clinical Pharmacology comment 2 above).

PRODUCT QUALITY

1. The maximum duration for [REDACTED] (b) (4)
[REDACTED] However, the maximum filling duration has not been validated by media fills. Provide media fill data from three successful runs, which should include representative manipulations and interventions conducted during an LA-EP2006 drug product filling process. Specify the container-closure system used in media fill simulations.
2. Insufficient data were provided to support the requalification strategy for [REDACTED] (b) (4)
[REDACTED]. In your resubmission, you should address the following comments and update section 3.2.P.3.5 of the BLA accordingly.

- a. [REDACTED] (b) (4)
- b. [REDACTED]

3. Insufficient microbial challenge data were provided for [REDACTED] (b) (4) validation studies, which were described in amendment 0024 (Module 1.2, Annex 01). In your resubmission, you should address the following comments and update section 3.2.P.3.5 of the BLA accordingly.

- a. [REDACTED] (b) (4)
- b. [REDACTED]

c.

d.

(b) (4)

4. The method validation study for the dye ingress container closure integrity (CCI) test method is not adequate because a vial instead of a prefilled syringe (PFS) was used as the positive control. Conduct a new CCI qualification study for the LA-EP2006 drug product PFS using a method that is sufficiently sensitive to detect breaches that could allow microbial ingress (<20 µm or smaller) using compromised syringes as positive controls. Routine dye ingress CCI testing should include at least one compromised PFS unit as a system suitability control.
5. Insufficient data from the simulated air transportation study were provided (b) (4)
(b) (4)
In addition, the study parameters were not fully described. Provide summary data demonstrating (b) (4)
(b) (4) during worst-case air transportation conditions. In addition, provide the study protocol, the study report, and justification for the study acceptance criteria.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

CONTAINER LABEL AND CARTON LABELING

We acknowledge receipt of your proposed container label and carton labeling dated August 27, 2015. We reserve comments on the proposed container label and carton labeling until the application is otherwise adequate.

PROPRIETARY NAME

Please refer to correspondence dated, October 30, 2015, which addresses the proposed proprietary name, Ziextenzo. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update. The safety update should include data from all nonclinical and clinical studies of the product under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile and their relevance, if any, to whether there may be clinically meaningful differences between the proposed biosimilar product and the U.S.-licensed reference product.
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 clinical studies for the proposed indication using the same format as the original BLA submission.
 - Present tabulations of the new safety data combined with the original BLA data.
 - Include tables that compare frequencies of adverse events in the original BLA with the retabulated frequencies described in the bullet above.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study 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 BLA data.
6. Provide updated exposure information for the clinical studies (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this product, including adverse events known to be associated with the use of the product and immunogenicity. Include an updated estimate of use for this product marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

Product Quality

1. You propose that differences in purity between clinical lots of LA-EP2006, US-licensed Neulasta, and EU-approved Neulasta may account for much of the observed differences in clinical PK, based on a non-linear relationship between the levels of product-related impurities and PK. To support a risk-based assessment for the potential impact of product-related variants and impurities on clinical PK, we recommend you test your hypothesis experimentally in *in vitro* studies, animal studies, or both (preferentially). The following *in vitro* experiments may be helpful:
 - a. Evaluate whether product-related variant species impact expression or function of the G-CSF receptor.
 - b. Evaluate the potential impact of physiological conditions, such as (but not limited to) the presence of serum or physiologically relevant proteases, on product stability and function. Assess how product-related variants and impurities are affected by these conditions.
2. For the SEC and RP-HPLC identity tests in the Drug Substance and Drug Product release specifications, add quantitative limits for relative peak retention times to the “conforms to reference” acceptance criteria. To ensure consistency across chromatography columns and other sources of variability in peak retention times, define the retention times for the main sample peaks in terms of percent relative retention time compared to the reference standard. Make these limits sufficiently tight to unambiguously distinguish LA-EP2006 from other products in the Drug Substance and Drug Product manufacturing facilities.
3. Include storage under accelerated conditions as part of the annual stability program in your post-approval drug substance and drug product stability commitments.

Pediatric Presentation

Ziextenzo is subject to the Pediatric Research Equity Act (PREA) as a biosimilar product. Thus, your application must include a pediatric assessment, which includes development of an appropriate pediatric presentation. The proposed presentation(s) may need Human Factors studies to demonstrate that users can accurately measure the doses. The proposed pediatric presentation(s) can be developed prior to approval, or you can request a deferral of the pediatric assessment pending development of an appropriate pediatric presentation. If you choose the

latter approach, the development of an appropriate pediatric presentation will be required as a post marketing requirement (PMR).

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 601.3(b). 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 601.3(c). 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.

You may request a meeting or teleconference 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 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 Rachel McMullen, Regulatory Project Manager, at (240) 402-4574.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology 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/

ANN T FARRELL
06/24/2016