Collaborative Clinical, Cross-Discipline Team Leader, and Division Summary Memo of BLA 761045/S-014

Date	See Electronic Stamp Date
From	Juwaria Waheed, MD, Clinical Reviewer (OTBB) Thomas Herndon, MD, CDTL (OTBB) Libero (Louis) Marzella, MD, PhD, Division Director (DIRM)
Subject	351(k) BLA Labeling Prior Approval Supplement - Category B to add the Hematopoietic Subsyndrome of Acute Radiation Syndrome indication
BLA # and Supplement#	761045/S-014
Applicant	Sandoz Inc.
Date of Submission	November 9, 2023
BSUFA Goal Date	March 9, 2024
Product Code Name	LA-EP2006
Nonproprietary name	pegfilgrastim-bmez
Proprietary Name	Ziextenzo
Reference Product	Neulasta (pegfilgrastim)
Applicant Proposed Indication(s)/Population(s)	To increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation)
Applicant Proposed Dosing Regimen(s)	Same as Neulasta for the respective indication
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	To increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation)
Recommended Dosing Regimen(s) (if applicable)	Same as Neulasta for the respective indication

1. Introduction

The Applicant submitted this supplement 014 to expand the indication of Ziextenzo (pegfilgrastim-bmez) to include Hematopoietic Subsyndrome of Acute Radiation ((H-ARS) - to increase survival in patients acutely exposed to myelosuppressive doses of radiation) that was previously under orphan exclusivity. US-Neulasta's H-ARS orphan exclusivity expired on November 13, 2022.

No new clinical information is included nor required for the Applicant's submission. The Pediatric Study Plan addressing the new indication was previously submitted and reviewed by the Agency. The Applicant has provided a scientific justification for extrapolation to H-ARS indication and updated labeling to include the additional indication sought for licensure.

2. Background

Ziextenzo is a leukocyte growth factor. On August 27, 2015, Sandoz Inc submitted BLA 761045 under section 351(k) of the Public Health Service Act for LA-EP20063 as a proposed biosimilar product to US-licensed Neulasta (Amgen Inc). The Applicant received a complete response letter (CRL) on June 24, 2016, because the PK similarity study LA-EP06-101, did not demonstrate PK similarity between LA-EP2006 and US-licensed Neulasta (hereinafter US-Neulasta) and did not establish the PK portion of the scientific bridge between LA-EP2006, US-Neulasta and EU-approved Neulasta (EU-Neulasta). In addition, there were microbiology deficiencies identified in the initial submission. The Applicant resubmitted the application on February 27, 2019, addressing the deficiencies noted in the CRL issued on June 24, 2016.

Ziextenzo was approved as a biosimilar to US-Neulasta on November 04, 2019, under section 351(k) of the Public Health Service Act. Ziextenzo is currently approved for the treatment of:

1. Patients with Cancer Receiving Myelosuppressive Chemotherapy
    - Ziextenzo is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia

In considering the totality of the evidence for the original BLA submission, review of the data submitted by the Applicant showed that Ziextenzo is highly similar to US-Neulasta, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between Ziextenzo and US-Neulasta in terms of the safety, purity, and potency of the product.

Ziextenzo is approved in the following strength and presentation:

- Injection: 6 mg/0.6 mL in a single-dose prefilled syringe for manual use only

3. CMC/Product Quality

No new product quality information was submitted nor required for this sBLA. On January 12, 2024, the Applicant provided a claim for categorical exclusion from environmental assessment (EA) requirements in compliance with the categorical exclusion criteria 21 CFR 25.31(b) for the additional indication being sought in this supplement (S-014). There are no CMC or product quality issues that would preclude approval of the indications sought for licensure.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology/toxicology information was submitted nor required for this sBLA. There are no nonclinical pharmacology/toxicology issues that would preclude approval of the indications sought for licensure.

5. Clinical Pharmacology

No new clinical pharmacology information was submitted nor required for this sBLA. There are no clinical pharmacology issues that would preclude approval of the indications sought for licensure.

6. Clinical/Statistical-Efficacy

Ziextenzo was previously evaluated in two comparative clinical studies (LA-EP06-301 and LA-EP06-302) in 624 women with breast cancer receiving myelosuppressive chemotherapy. The data were previously reviewed and summarized in the clinical and statistical reviews of the original BLA, dated May 18, 2016. No new clinical/statistical efficacy information was submitted nor required for the current sBLA. There are no clinical/statistical efficacy issues that would preclude approval of the indication sought for licensure.

7. Safety

The safety of Ziextenzo was evaluated in four clinical studies, two in healthy subjects (LA-EP06-101 and LA-EP06-104) and two in patients with breast cancer (LA-EP06-301 and LA-EP06-302). The overall safety profile of LA-EP2006 was similar to US-Neulasta and EU-Neulasta. The data were previously reviewed and summarized in the initial clinical review dated May 18, 2016. No new safety data were submitted nor required for this sBLA. There are no clinical safety issues that would preclude approval of the indication sought for licensure.

8. Considerations for Extrapolation of Biosimilarity in Other Conditions of Use

Ziextenzo is a leukocyte growth factor licensed to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. In this supplement, the applicant submitted a scientific justification for extrapolation of the data and information to support licensure of Ziextenzo for the non-studied indication of H-ARS (Increase survival in patients acutely exposed to myelosuppressive doses of radiation). (Also, see Section 9 Pediatrics).

Scientific considerations for the extrapolation of data and information to support licensure for the H-ARS indication are outlined below:

- Biosimilarity has previously been established between Ziextenzo and US-Neulasta. The data supporting its approval included comparative analytical characterization data, and comparative PK, efficacy, safety, and immunogenicity data demonstrating that Ziextenzo is biosimilar to the reference product, US-Neulasta.
- In Supplement 14 and in their response to an Information Request (BLA 761046, SDN 282 *Clinical Overview Addendum v2.0* dated February 15,

2024), the Applicant has provided adequate scientific justification supporting extrapolation of data and information from the original BLA submission that addresses the mechanism of action, PK, immunogenicity, and safety for each non-studied indication for which the applicant is seeking licensure and for which the reference product has been approved.

- The Mechanism of Action, the binding to specific cell surface receptors resulting in the stimulating proliferation, differentiation, and commitment of end cell functional activation is the same in Ziextenzo and US-Neulasta for all indications currently approved for US-Neulasta to the extent that the mechanisms of action are known or can reasonably be determined.
- PK similarity was demonstrated between Ziextenzo and US-Neulasta. There were no product-related attributes that would increase uncertainty that the PK/biodistribution may differ between Ziextenzo and US-Neulasta in the H-ARS indication. A similar PK profile would be expected between Ziextenzo and US-Neulasta in patients being treated for H-ARS.
- Immunogenicity and safety profiles were shown to be similar in Ziextenzo and US-Neulasta. Similar immunogenicity and safety profiles would be expected between Ziextenzo and US-Neulasta in patients being treated for the H-ARS indication.

In conclusion, the totality of evidence and scientific justification discussed above are adequate to justify extrapolating data and information submitted to this BLA to support licensure of Ziextenzo for the indication to increase survival in patients acutely exposed to myelosuppressive doses of radiation.

9. Pediatrics

The Applicant previously submitted (in February 2019) an Agreed initial Pediatric Study Plan (Agreed iPSP) that included the Applicant's plan for addressing Pediatric Research Equity Act (PREA) requirements for the H-ARS indication. The pediatric assessment for the H-ARS indication was based on the Applicant´s proposal to extrapolate pediatric data and information from the reference product US-Neulasta to LA-EP2006 on the basis of a demonstration of biosimilarity between US-Neulasta and LA-EP2006.

Since the Agreed iPSP, the reference product, US-Neulasta, Ziextenzo (LA-EP2006) and other biosimilar programs to US-Neulasta received a Postmarketing Requirement (PMR) to develop a pediatric formulation for pediatric patients who weigh less than 45 kg and require doses that are less than 0.6 mL (6 mg).

As such, Ziextenzo (LA-EP2006) has an outstanding PREA PMR, issued on November 4, 2019, to develop a pediatric formulation as noted below:

> 3734-1 Submit pediatric assessments for Ziextenzo (pegfilgrastim-bmez) as described in section 505B(a)(2)(A) of the FD&C Act, including development of an "appropriate formulation" (presentation) that can be used to directly and accurately administer Ziextenzo (pegfilgrastim-bmez) to pediatric patients who weigh less than 45 kg and require doses that are less than 0.6 mL (6 mg), and conducting any necessary human factors studies to evaluate the ability of healthcare providers and/or caregivers to measure the appropriate doses.

On July 28, 2023, the Agency agreed to a deferral extension for this PMR until 04/2028 because the completion date for the pediatric presentation development for the reference product US-Neulasta has been extended to April 30, 2025.

On February 20, 2024, the Pediatric Review Committee (PeRC) reviewed the agreed iPSP and agreed with the Applicant's proposals. The pediatric assessment was considered complete.

10. Other Relevant Regulatory Issues

None

11. Labeling

The proposed Ziextenzo prescribing information incorporated relevant data and information from the US-Neulasta prescribing information, with appropriate modifications. It was determined that the proposed labeling is consistent with the current FDA labeling practice. The labeling has been agreed upon with the Applicant.

12. Postmarketing Recommendations

There are no new safety or efficacy issues identified in this review that warrant further assessment with a postmarketing requirement or commitment.

13. Risk Evaluation and Mitigation Strategies

The review team did not identify a need for Risk Evaluation and Mitigation Strategies (REMS) to ensure the safe use of Ziextenzo.

14. Recommended Regulatory Action

Approval

15. Division Director Comments

I concur with the team's assessment of the data and information submitted in this supplemental BLA.

No additional data, new PMRs, PMCs, or REMS are required for this supplement.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JUWARIA WAHEED
02/27/2024 02:51:28 PM

THOMAS M HERNDON
02/27/2024 02:54:07 PM

LIBERO L MARZELLA
02/27/2024 05:58:21 PM