Collaborative Clinical, CDTL, and Division Director Summary Review

Date	See electronic stamp date
From	Michelle Luo, M.D, PhD, Scientific Reviewer (OTBB) N Calvin Han, MD, Clinical Reviewer (DIRM) Louis Marzella, MD, PhD, Division Director (DIRM)
Subject	Collaborative Clinical, Cross-Discipline Team Leader, and Division Summary Review
BLA # and Supplement #	#125553 s-038 (Category D supplement)
Applicant	SANDOZ 100 College Road West Princeton, NJ 08540
Date of Submission	April 24, 2024
BsUFA Goal Date	October 24, 2024
Proprietary Name (Proper Name)	Zarxio (filgrastim-sndz)
Product Code	EP2006
Reference Product Proprietary (Proper Name)	Neupogen (filgrastim)
Dosage Form(s) / Strength	No new proposed dosage forms
Applicant Proposed Indication(s) / Population(s)	Expansion of existing indications to include the following: • Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)
Applicant Proposed Dosing Regimen(S)	Same as reference product dosing regimen
Recommendation on Regulatory Action	Approval

1. Introduction

Sandoz (hereafter referred to as "the Applicant"), submitted a supplemental biologics license application for BLA 125553 (sBLA-038) under section 351(k) of the Public Health Service (PHS) Act to expand the indications for Zarxio (proper name: filgrastim-sndz, product code: EP2006) to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome (H-ARS)). The H-ARS indication was not included in the initial approval for Zarxio because this indication was protected under orphan drug exclusivity which expired March 30, 2022.

No new scientific or clinical data are included for this submission. The Applicant has cross-referenced the original application submission under BLA 125553 and provided the supporting scientific justification for extrapolation for the indication currently sought for licensure. The current submission provided updated labeling including H-ARS indication, and an amended pediatric study plan to address PREA requirement.

2. Background

On March 6, 2015, Zarxio (non-proprietary name: filgrastim-sndz, code name: EP2006) was approved as a biosimilar to US-licensed Neupogen (US-Neupogen) under Section 351(k) of the Public Health Service Act. Zarxio is a 175 amino acid human granulocyte colony-stimulating factor manufactured by recombinant DNA technology and approved for the following indications that are same as US-Neupogen:

- Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever
- Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML)
- Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT)
- Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis
- Reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia

Additionally, US-Neupogen is licensed for the following indication:

- Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)

The original BLA for EP2006 included the following:

- A comprehensive comparative analytical assessment that characterizes the physicochemical attributes and biological function between EP2006, US-licensed Neupogen and EU-approved Neupogen.

- Nonclinical animal studies to evaluate the PD, toxicity, toxicokinetics and local tolerance of EP2006 that compared with EU-approved Neupogen, which includes a 28-day repeat dose toxicology/toxicokinetics study in rats (EP06-006) and a 12-day repeat dose PD study in rats (EP06-004).

- Single dose and/or multiple doses of PK and PD studies by subcutaneous administration (Study EP06-101, EP06-103, EP-06-105 and EP06-109) that evaluating the PK (AUC and Cmax) and PD (absolute neutrophil count and CD34+) similarity, immunogenicity, and safety between EP2006, US-licensed Neupogen and EU-approved Neupogen in healthy subjects.

- A comparative clinical study (EP06-302) to assess efficacy and safety in patients with breast cancer receiving TAC chemotherapy who are randomized to receive EP2006 or US-Neupogen.

- A scientific justification (based on mechanism of action, PK, immunogenicity and toxicity) for extrapolation of data and information submitted in the application to support the licensure of EP2006 for each of the indications for which the Applicant was seeking licensure and for which US-Neupogen has been previously approved.

In considering the totality of the evidence for the assessment of biosimilarity and the original BLA submission, review of the data submitted by the Applicant showed that filgrastim-sndz is highly similar to US-Neupogen, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between filgrastim-sndz and US-Neupogen in terms of the safety, purity, and potency of the product. The Applicant also provided adequate scientific justification for extrapolation of data and information to support licensure of filgrastim-sndz for the non-studied indications sought for approval.

In the original BLA submission, the Applicant did not seek licensure for the indication of H-ARS because of unexpired Orphan Drug Exclusivity for US-Neupogen for the H-ARS indication. In this sBLA, the Applicant has cross-referenced the previously submitted justification for extrapolation of the data and information in support of licensure of filgrastim-sndz for H-ARS indication. The proposed dosing regimen for H-ARS is same as the reference product, US-Neupogen.

Zarxio (filgrastim-sndz) is approved for the same strength, dosage form, and route of administration as those approved for US-Neupogen:

Vial

- Injection: 300mcg/mL in a single-dose vial
- Injection: 480 mcg/1.6mL (300mcg/mL) in a single dose vial

Prefilled Syringe

- Injection: 300mcg/mL in a single-dose prefilled syringe with BD UltraSafe Passive Needle Guard
- Injection: 480 mcg/1.6mL (300mcg/mL) in a single dose prefilled syringe with BD UltraSafe Passive Needle Guard

Additionally, the condition(s) of use for which Zarxio is licensed have been previously approved for US-Neupogen.

3. CMC/Product Quality

For sBLA-038, no new product quality information was submitted nor required. There are no CMC or product quality issues that would preclude approval of the indication sought for licensure.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology/toxicology information was submitted nor required for this supplemental BLA.

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 indication sought for licensure.

6. Clinical/Statistical-Efficacy

Zarxio was previously studied in the comparative clinical study in patients with breast cancer (EP06-302). The data were previously reviewed in the clinical and statistical reviews of the original BLA by DNH. No new clinical/statistical efficacy information was submitted nor required for this sBLA. There are no clinical/statistical efficacy issues that would preclude approval of the indication sought for licensure.

7. Safety

There are no clinical safety issues that would preclude approval of the indication sought for licensure.

8. Extrapolation

In this supplement, the Applicant referenced the original BLA application and the scientific justification that was provided for extrapolation of the data and information to support licensure of Zarxio to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome (H-ARS)).

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 Zarxio and US-Neupogen. The data supporting its approval included comparative analytical characterization, comparative PK, efficacy, safety, and immunogenicity demonstrating that Zarxio is biosimilar to US-Neupogen.
- In Supplement 038, the Applicant referenced the scientific justification provided in the original application. The Applicant has provided adequate scientific justification supporting the 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 US-Neupogen has been approved.
- The mechanism of action, relevant to decreasing the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever (the studied population) is also relevant to H-ARS.
- PK similarity was demonstrated between Zarxio and US-Neupogen. There were no product-related attributes that would increase uncertainty that the PK/biodistribution may differ between Zarxio and US-Neupogen in the H-ARS indication. A similar PK profile would be expected between Zarxio and US-Neupogen in patients being treated for H-ARS.

- Immunogenicity and safety profiles were shown to be similar in Zarxio and US-Neupogen. Similar immunogenicity and safety profiles would be expected between Zarxio and US-Neupogen 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 sBLA to support licensure of Zarxio for the indication to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome (H-ARS).

9. Pediatrics

Under the Pediatric Research Equity Act (PREA) (section 505B of the FD&C Act), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable. Section 505B(l) of the FD&C Act provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a “new active ingredient” for purposes of PREA, and a pediatric assessment is generally required unless waived or deferred or inapplicable.

To address PREA requirement for the indication of H-ARS, the Applicant submitted an amended agreed pediatric study plan (iPSP) with a request for extrapolation for pediatric patients for H-ARS indication. The Applicant proposed to fulfil the PREA requirements for pediatric patients for H-ARS indication by satisfying the statutory requirements for demonstrating biosimilarity and providing an adequate scientific justification for extrapolating the pediatric information from US-Neupogen to the biosimilar product Zarxio. On September 10, 2024, The Pediatric Review Committee (PeRC) agreed with the Applicant’s approach for the H-ARS indication.

The Applicant has fully addressed PREA, and, at this time, no additional pediatric studies are required.

10. Other Relevant Regulatory Issues

None

11. Labeling

Prescribing Information

In this application labeling for Zarxio was updated to include the indication of H-ARS.

Labeling consultants, including Office of Therapeutic Biologics and Biosimilar (OTBB)-labeling, Office of Biotechnology Products (OBP)-labeling, and the Office of Prescription Drug Promotion (OPDP) reviewed the proposed labeling. The final label will be included in the approval letter.

12. Post-Marketing Recommendation

None.

13. Risk Evaluation and Mitigation Strategies

None.

14. Regulatory Action

Approval.

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/s/

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