CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761148Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761148
PDUFA Goal Date	September 9, 2022
OSE RCM #	2019-2237
Reviewer Name	Donella Fitzgerald, PharmD
Team Leader	Jacqueline Sheppard, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	August 19, 2022
Subject	Evaluation of Need for a REMS
Established Name	Eflapegrastim-xnst
Trade Name	Rolvedon
Name of Applicant	Spectrum Pharmaceuticals, Inc.
Therapeutic Class	Leukocyte growth factor
Formulation(s)	13.2 mg/0.6 ml solution in a single-dose prefilled syringe
Dosing Regimen	13.2 mg administered subcutaneously once per chemotherapy cycle

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1. Introduction

This memorandum by the Division of Risk Management (DRM) pertains to the Biologic Licensing Application (BLA) 761148 submitted on March 11, 2022 by Spectrum Pharmaceuticals, Inc. (Spectrum) and evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Rolvedon (eflapegrastim-xnst) is necessary to ensure the benefits outweigh its risks. Eflapegrastim-xnst received a Complete Response (CR) on August 3, 2021 due to facility inspection deficiencies.[1] Spectrum resubmitted BLA 761148 for the proposed indication to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with clinically significant incidence of febrile neutropenia. During the course of the review, the applicant submitted updated draft labeling indicating use in adults only.

DRM completed a review on September 10, 2020, that concluded a REMS was not needed based on the risk-benefit profile at the time of completion of that review.[2] BLA 761148 is under review in the Division of Non-malignant Hematology (DNH). Spectrum did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Eflapegrastim-xnst (EFG), a new molecular entity (NME), is a leukocyte growth factor, proposed to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with clinically significant incidence of febrile neutropenia. EFG is proposed as an injectable to be given by subcutaneous route with the recommended dose of 13.2 mg (0.6 ml) once per chemotherapy cycle. EFG is not currently approved in any jurisdiction.

2.2. Regulatory History

The following is a summary of the regulatory history for BLA 761148 relevant to this review:

- 10/23/2019: BLA 761148 submission for the proposed indication to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with clinically significant incidence of febrile neutropenia received.
- 08/03/2021: Complete Response (CR) letter sent to the applicant due to facility inspection deficiencies.
- 03/11/2022: BLA 761148 resubmission in response to the 8/3/21 CR letter received.

3. Risk Assessment & Safe-Use Conditions

The safety evaluation for EFG was completed during the first review cycle and identified the risks of serious allergic reactions, splenic rupture, leukocytosis, and fatal sickle cell crisis. In the resubmission, additional trials were not included in the safety database. The applicant submitted interim safety analysis for a new ongoing Phase 1 dosing and Phase 2 pediatric study, however, the studies are not mature and full datasets were not provided with the resubmission. The medical officer stated that the interim analysis did not present new safety issues.[3]

4. Discussion of Need for a REMS

The risks associated with EFG include serious allergic reactions, splenic rupture, leukocytosis, and fatal sickle cell crisis. DRM evaluated these risks in a review dated September 10, 2020 and determined that a REMS was not needed to ensure the benefits of EFG outweigh the risks at the time of that review. The database used to evaluate safety of EFG did not change with the resubmission. At the time of this memorandum, the safety profile of EFG remains unchanged. Serious allergic reactions, splenic rupture, leukocytosis, and use in patients with sickle cell disorders will be communicated in Section 5 Warnings and Precautions of the label. These risks have been reported with other drugs in the leukocyte growth factor class. Oncologists, the likely prescribers, are familiar with these risks as drugs in this class have been on the market for several years.

5. Conclusion & Recommendations

Based on the analysis in the initial REMS review and the absence of new safety data that changes the benefit-risk profile in the resubmission following the Complete Response letter, we maintain our determination that a REMS is not needed to ensure the benefits of EFG outweigh its risks. At the time of this review, labeling is ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

6. Appendices

6.1. References

[1] Division of Hematology Products. Complete Response Letter for eflapegrastim-xnst, BLA 761148, August 3, 2021.

[2] Chen, Mei -Yean. REMS Review for BLA 761148 eflapegrastim-xnst. September 10, 2020.

[3] Lee, Hyon-Zu. Eflapegrastrim-xnst, BLA 761148 Internal Mid-cycle meeting presentation. June 6, 2022.

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Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761148
PDUFA Goal Date	October 24, 2020
OSE RCM #	2019-2237
Reviewer Name(s)	Mei-Yean Chen, Pharm.D.
Team Leader	Naomi Reed, Pharm.D.
Division Deputy Director (acting)	Doris Auth, Pharm.D.
Review Completion Date	September 10, 2020
Subject	Evaluation of Need for a REMS
Established Name	Eflapegrastim-xnst
Trade Name	Rolontis
Name of Applicant	Spectrum Pharmaceuticals, Inc.
Therapeutic Class	A leukocyte growth factor
Formulations	13.2 mg/0.6 ml solution in a single-dose prefilled syringe
Dosing Regimen	13.2 mg administered subcutaneously once per chemotherapy cycle

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Rolontis (eflapegrastim-xnst) is necessary to ensure the benefits outweigh its risks. Spectrum Pharmaceuticals, Inc. submitted a Biologics License Application (BLA) 761148 for the granulocyte colony-stimulating factor (G-CSF) eflapegrastim-xnst with the proposed indication to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with clinically significant incidence of febrile neutropenia. The possible risks associated with eflapegrastim-xnst include serious allergic reactions (including anaphylaxis), fatal splenic rupture, leukocytosis, and fatal sickle cell crises. The applicant did not submit a proposed REMS or risk management plan with this application.

Myelosuppression is major toxicity of chemotherapy and limits optimal clinical benefits. Neutropenia and its complications also lead to therapy delay and/or dose reduction chemotherapy, compromising the effectiveness of treatment. The prophylactic use of granulocyte colony-stimulating factors (G-CSF) improves safety, optimizes treatment intensity, and overall clinical outcome.

The Division of Risk Management (DRM) and the Division of Hematology Products (DHP) agree that a REMS is not needed for eflapegrastim-xnst to ensure the benefits of outweigh its risks. The risks of eflapegrastim-xnst include serious allergic reactions, splenic rupture, leukocytosis, and fatal sickle cell crises and these will be communicated in Section 5 Warnings and Precautions. These risks have been reported with other drugs in this class and oncologists, the likely prescribers, are already familiar with these risks as other G-CSFs have been on the market since 2002.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Rolontis (eflapegrastim-xnst) is necessary to ensure the benefits outweigh its risks. Spectrum Pharmaceuticals, Inc. submitted a Biologics License Application (BLA) 761148 for eflapegrastim-xnst with the proposed indication to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with clinically significant incidence of febrile neutropenia. This application is under review in the Division of Hematology Products (DHP). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Eflapegrastim-xnst, a new molecular entity (NME)[a], is a leukocyte growth factor, proposed to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with clinically significant incidence of febrile neutropenia. Eflapegrastim-xnst proposed as an injectable to be given by

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

subcutaneous route with the recommended dose is 13.2 mg (0.6 ml) once per chemotherapy cycle. Eflapegrastim-xnst is not currently approved in any jurisdiction.

Eflapegrastim-xnst is a long-acting granulocyte colony-stimulating factor (G-CSF) that is a novel biologic and not a biosimilar to any currently marketed G-CSF product. Eflapegrastim-xnst is produced by covalent coupling of a human G-CSF analog and human immunoglobulin G4 Fe fragment, both derived from recombinant Escherichia Coli (E. coli), via a single 3.4 kDa polyethylene glycol.[1]

The mechanism of action of eflapegrastim-xnst is the same as that of filgrastim and pegfilgrastim; by binding to G-CSF receptors on myeloid progenitor cells and neutrophils, eflapegrastim-xnst triggers pathways that control cell survival, proliferation, differentiation, and migration of neutrophil precursors and mature neutrophils. Eflapegrastim-xnst shows similar in vitro activity and pharmacokinetic profile compared with pegfilgrastim.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761148 relevant to this review:

- 12/12/2014: End of phase 2 meeting to discuss clinical development of eflapegrastim-xnst
- 08/21/2018: Pre-BLA meeting.
- 12/21/2018: BLA (b) (4) submitted
- 03/14/2019: The Applicant requested for the withdrawal of BLA (b) (4)
- 10/23/2019: BLA 761148 submitted
- 04/16/2020: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for Eflapegrastim-xnst.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Myelosuppression is major toxicity of chemotherapy and limits its ability to be used on dose schedules that offer optimal clinical benefits. Both the severity of neutropenia and the duration of severe neutropenia have been demonstrated to be correlated with the risk of developing fever, infectious complications, and hospitalization.[b] Neutropenia and its complications also lead to therapy delay and/or dose reduction of critical components of chemotherapy, potentially compromising the effectiveness of treatment.

[b] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Clinical trials have demonstrated that prophylactic use of G-CSF can reduce the incidence and duration of severe neutropenia associated with myelotoxic chemotherapies. Clinical guidelines, such as the National Comprehensive Cancer Network (NCCN) guidelines[2], support the use of myeloid growth factors, especially in early disease settings in which clinical benefit may be derived by achieving a critical level of dose-intensity. The prophylactic use of G-CSF improves safety, optimizes treatment intensity, and improves overall clinical outcome.

There have been multiple short-acting filgrastim approved in the United States (US) following the approval of filgrastim (Neupogen) in 1991. Neulasta,[3] the first long-acting filgrastim, was approved by the FDA in 2002. There are three biosimilars of Neulasta approved by the FDA, Fulphila (pegfilgrastim-jmdb, approved June 2018), Udenyca (pegfilgrastim-cbqv, approved November 2018), and Ziextenzo (pegfilgrastim-bmez, approved November 2019). The labeling of all four long-acting G-CSF products has the same Warnings and Precautions: splenic rupture, acute respiratory distress syndrome, serious allergic reactions, risk of severe and sometimes fatal sickle cell crisis when used in patients with sickle cell disorders, glomerulonephritis, leukocytosis, capillary leak syndrome, and aortitis. None of these products are approved with a Boxed Warning or REMS according to the prescribing information of Neulasta[3], Fulphila[4], Udenyca[5], Ziextenzo[6].

4 Benefit Assessment

The efficacy of eflapegrastim-xnst was evaluated in two randomized, open-label, non-inferiority studies of similar design Study 1 (NCT 02643420) and Study 2 (NCT02953340).[7] Both studies enrolled patients with early stage breast cancer. Docetaxil 75 mg/m^2 and cyclophosphamide 600 mg/m^2 were administered intravenously on day 1 of every 21 days for up to 4 cycles. A fixed dose of eflapegrastim-xnst 13.2 mg/0.6 ml or pegfilgrastim 6 mg/0.6 ml was administered subcutaneously on day 2 of each cycle after chemotherapy. The median age of patients was 60 years (range: 24 to 88), the majority of patients were female (>99%), 77% were White and 12% were Black or African American.

The efficacy for both trials was based on the duration of severe neutropenia (DSN) in cycle 1. Study 1 enrolled 196 patients to the eflapegrastim-xnst arm and 210 patients to the pegfilgrastim arm. Study 2 enrolled 118 patients to the eflapegrastim-xnst arm and 119 patients to the pegfilgrastim arm.

In Study 1, the difference in DSN between the eflapegrastim-xnst arm and the pegfilgrastim arm was -0.148 days and the corresponding 95% confidence interval (CI) was (-0.265, -0.033). Non-inferiority (NI) to pegfilgrastim was demonstrated for the eflapegrastim-xnst arm (upper bound of 95% CI <0.62 days) for the mean DSN. In Study 2, the difference in DSN between the eflapegrastim-xnst arm and the pegfilgrastim arm was -0.073 days and the corresponding 95% CI was (-0.292, 0.129). Non-inferiority (NI) to pegfilgrastim was demonstrated for the eflapegrastim-xnst arm (upper bound of 95% CI <0.62 days).[c] The medical officer concluded that both studies met the non-inferiority criteria for the primary endpoint (DSN in Cycle 1).[8]

[c] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

5 Risk Assessment & Safe-Use Conditions

The safety of eflapegrastim-xnst was evaluated in Study 1 and Study 2. There were no new or unusual adverse events seen in the eflapegrastim-xnst clinical trials that have not been seen with the use of other G-CSF drugs. There were no deaths in the eflapegrastim-xnst arm and there were two deaths in the pegfilgrastim arm, one death was due to cardiac arrest and the other was due to chronic obstructive pulmonary disease.[8]

No cases of splenic rupture, acute respiratory distress syndrome, glomerulonephritis, capillary leak syndrome or aortitis were reported in the eflapegrastim-xnst arm of both Study 1 and Study 2.[8] The following adverse events are communicated in Warnings and Precautions of the eflapegrastim-xnst label, and do not differ from other G-CSF drugs. These adverse events are included to reflect the potential for these adverse events due to the drug class.

5.1 Serious Allergic Reactions

(b) (4)

5.2 Splenic Rupture

Splenic rupture, including fatal cases, (b) (4) left upper abdominal or shoulder pain.

5.3 Leukocytosis

White blood count (b) (4) 100 x 10^9/L have been (b) (4) in patients receiving other drugs in this class. (b) (4) .

5.4 Use in patients with Sickle Cell Disorders

Severe and fatal sickle cell crises can occur in patients with sickle cell disorders receiving (b) (4) if sickle cell crisis occurs.

6 Expected Post market Use

If approved, it is expected that oncologists will be the likely HCPs to prescribe eflapegrastim-xnst in both inpatient and outpatient settings.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for eflapegrastim-xnst beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of eflapegrastim-xnst on the basis of the efficacy and safety information currently available. DRM and DHP agree that a REMS is not necessary to ensure the benefits outweigh its risk.

Myelosuppression is major toxicity of chemotherapy and limits optimal clinical benefits. Both the severity of neutropenia and the duration of severe neutropenia have been demonstrated to be correlated with infection and hospitalization. Neutropenia and its complications also lead to therapy delay and/or dose reduction of critical components of chemotherapy, potentially compromising the effectiveness of treatment. The prophylactic use of G-CSF improves safety, optimizes treatment intensity, and overall clinical outcome.

This reviewer recommends that, if eflapegrastim-xnst is approved, a REMS is not needed to ensure its benefits outweigh its risks. Serious allergic reactions, splenic rupture, leukocytosis, and use in patients with sickle cell disorders will be communicated in Section 5 Warnings and Precautions. These risks have been reported with other drugs in this class. Oncologists, the likely prescribers, are familiar with these drugs as they have been on the market for several years.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for eflapegrastim-xnst to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10Appendices

10.1References

[1] eflapegrastim-xnst Spectrum's submission on 10/24/2019 common technical document summaries, 2.2 Introduction

[2] NCCN Guideline Version 2.2020 Hematopoietic Growth Factors, www.nccn.org, accessed 09/02/2020

[3] Neulasta prescribing information, www.neulasta.com, accessed 09/01/2020

[4] Fulphila prescribing information, www.fulphila.com, accessed 09/01/2020

[5] Udenyca prescribing information, www.udenyca.com, accessed 09/01/2020

[6] Ziextenzo prescribing information, www.ziextenzo.com accessed 09/01/2020

[7] eflapegrastim-xnst draft prescribing information accessed 09/02/2020

[8] eflapegrastim-xnst medical officer Hyon-Zu Lee slide presentation at internal midcycle meeting 03/25/2020

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