CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761148Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 9, 2022
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	BLA 761148
Product Name and Strength:	Rolvedon (eflapegrastim-xnst) Injection, 13.2 mg/0.6 mL
Applicant/Sponsor Name:	Spectrum Pharmaceuticals (Spectrum)
OSE RCM #:	2019-2236-4
DMEPA 2 Safety Evaluator:	Devin Kane, PharmD
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Spectrum Pharmaceuticals (Spectrum) submitted revised carton labeling and blister tray label on September 2, 2022 for Rolvedon (eflapegrastim-xnst) injection. We reviewed the revised carton labeling and blister tray label for Rolvedon (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations made by Office of Biotechnology Products (OBP) labeling via email on September 2, 2022.

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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/s/

DEVIN R KANE
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HINA S MEHTA
09/12/2022 10:48:17 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	August 10, 2022
To:	May Zuwannin Regulatory Project Manager **Division of Non-Malignant Hematology (DNH)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Melissa Khashei, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	ROLVEDON (eflapegrastim-xnst)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	BLA 761148
Applicant:	Spectrum Pharmaceuticals, Inc.

1 INTRODUCTION

On March 11, 2022, Spectrum Pharmaceuticals, Inc. resubmitted for the Agency's review an original Biologics License Application (BLA) 761148 for ROLVEDON (eflapegrastim-xnst) injection, in response to the Agency Complete Response Letter dated August 2, 2021. The proposed indication for ROLVEDON (eflapegrastim-xnst) injection is to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive antic-cancer drugs associated with clinically significant incidence of febrile neutropenia.

The Applicant proposed the proprietary name Rolontis in the previous review cycle; however, it was found unacceptable on November 15, 2021 due to confusion with another product that was also under review at the time. The Division of Medication Error and Prevention and Analysis 2 (DMEPA 2) found the proprietary name ROLONTIS conditionally acceptable on 5/26/22. On May 20, 2022 DMEPA 2 found the suffix -xnst and recommended the use of the nonproprietary name eflapegrastim-xnst be used throughout the labels and labeling.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Nonmalignant Hematology (DNH) on April 18, 2022 and April 19, 2022, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for ROLVEDON (eflapegrastim) injection.

2 MATERIAL REVIEWED

- Draft ROLVEDON (eflapegrastim-xnst) injection PPI received on March 11, 2022, and received by DMPP on August 1, 2022.
- Draft ROLVEDON (eflapegrastim-xnst) injection Prescribing Information (PI) received on March 11, 2022, revised by the Review Division throughout the review cycle, and received by DMPP on August 1, 2022.
- Approved US-licensed NEULASTA (pegfilagrastim) injection comparator labeling dated January 5, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

SHARON R MILLS
08/10/2022 12:09:26 PM

MELISSA KHASHEI
08/10/2022 12:38:18 PM

LASHAWN M GRIFFITHS
08/10/2022 12:38:57 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: August 10, 2022

To: May Zuwannin, Regulatory Project Manager, Division of Nonmalignant Hematology (DNH)

Virginia Kwitkowski, MS, ACNP-BC, Associate Director for Labeling, (DNH)

From: Melissa Khashei, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jina Kwak, PharmD, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for ROLVEDON™ (eflapegrastim-xnst) injection, for subcutaneous use

BLA: 761148

In response to DNH's consult request dated April 19, 2022, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI) and carton and container labeling for the original BLA submission for ROLVEDON™ (eflapegrastim-xnst) injection, for subcutaneous use.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DNH (May Zuwannin) on August 1, 2022, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on March 11, 2022, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Melissa Khashei at (301) 796-7818 or melissa.khashei@fda.hhs.gov.

14 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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MELISSA KHASHEI
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Division of Nonmalignant Hematology
Associate Director for Labeling Review of the Prescribing Information

Product Title	ROVLEDON (eflapegrastim-xnst) injection, for subcutaneous use
Applicant	Spectrum Pharmaceuticals
Application/Supplement Number	BLA 761148
Is Proposed Labeling in Old Format? (Y/N)	N
Is Labeling Being Converted to PLR? (Y/N)	N
Is Labeling Being Converted to PLLR? (Y/N)	N
Approved Indication(s)	Rolvedon is a leukocyte growth factor indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in adult patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with clinically significant incidence of febrile neutropenia. (1) Limitations of Use Rolvedon is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation. (1)
Date FDA Received Application	03/11/2022
Review Classification (Priority/Standard)	Resubmission (6 mo clock)
Action Goal Date	09/11/2022
Review Date	08/01/2022
Reviewer	Virginia Kwitkowski, MS, ACNP-BC

This Associate Director for Labeling (ADL) review provides recommendations on the content and format of the prescribing information (PI) to help ensure that PI:

- Is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) requirements[1]
- Is consistent with labeling guidance recommendations[3] and with CDER/OND best labeling practices and policies
- Conveys the essential scientific information needed for safe and effective use of the product
- Is clinically meaningful and scientifically accurate
- Is a useful communication tool for health care providers
- Is consistent with other PI with the same active moiety, drug class, or similar indication

[1] See *January 2006 Physician Labeling Rule*; 21 CFR 201.56 and 201.57; and *December 2014 Pregnancy and Lactation Labeling Rule* (the PLLR amended the PLR regulations). For applications with labeling in non-PLR "old" format, see 21 CFR 201.56(e) and 201.80.

[3] See *PLR Requirements for PI* website for PLR labeling guidances.

Background: Rolvedon (eflapegrastim-xnst) is a leukocyte growth factor. The application was initially submitted on 10/24/2019. This application is a resubmission after a Complete Response action due to facilities issues. Labeling was nearly finalized on 10/08/2020, during the previous review cycle.

Review:
Most of the edits are described in labeling comments, however, significant revision of the adverse reactions section of labeling were made.
The adverse reactions section as proposed by the Applicant, contains adverse reactions that are not likely to be caused by the study drug or control (they are known adverse reactions for the background chemotherapy that the patients were receiving during the trial). Per the Adverse Reactions Guidance, "the definition of adverse reactions does not include all adverse events observed during use of drug. It is limited to those events for which there is some basis to believe there is a causal relationship between the occurrence of an adverse event and the use of a drug. Decisions on whether there is some basis to believe there is a causal relationship are a matter of judgment and are based on factors such as: (1) the frequency of reporting,
(2) whether the adverse event rate for the drug exceeds the placebo rate,
(3) the extent of dose-response,
(4) the extent to which the adverse event is consistent with the pharmacology of the drug,
(5) the timing of the event relative to the time of drug exposure,
(6) existence of challenge and dechallenge experience, and
(7) whether the adverse event is known to be caused by related drugs."

Therefore, the approach to determining the adverse reactions for eflapegrastim should be:
1. Create a list of the most frequent adverse events (all events in the AE list) for eflapegrastim, without regards to the rate in the control arm. Select a frequency cutoff of ≥20% for this list.
2. Review the list for events that are consistent with the pharmacology of the drug.
3. Review the list for events that are known to be caused by other drugs in the "leukocyte growth factor" class.
   <u>NEULASTA</u>
   USPI has 'bone pain' and 'pain in exremity' in the main AR table with leukocytosis listed in the less common ARs below the table. The postmarketing safety section describes other adverse reactions (below).

   - Splenic rupture and splenomegaly (enlarged spleen) *[see Warnings and Precautions (5.1)]*
   - Acute respiratory distress syndrome (ARDS) *[see Warnings and Precautions (5.2)]*
   - Allergic reactions/hypersensitivity, including anaphylaxis, skin rash, urticaria, generalized erythema, and flushing *[see Warnings and Precautions (5.3)]*
   - Sickle cell crisis *[see Warnings and Precautions (5.5)]*
   - Glomerulonephritis *[see Warnings and Precautions (5.6)]*
   - Leukocytosis *[see Warnings and Precautions (5.7)]*
   - Thrombocytopenia *[see Warnings and Precautions (5.8)]*
   - Capillary Leak Syndrome *[see Warnings and Precautions (5.9)]*

- Injection site reactions
- Sweet's syndrome (acute febrile neutrophilic dermatosis), cutaneous vasculitis
- Application site reactions (including events such as application site hemorrhage, application site pain, application site discomfort, application site bruise, and application site erythema) have been reported with the use of the on-body injector for Neulasta.
- Contact dermatitis and local skin reactions such as rash, pruritus, and urticaria have been reported with the use of the on-body injector for Neulasta, possibly indicating a hypersensitivity reaction to the adhesive.
- Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) in patients with breast and lung cancer receiving chemotherapy and/or radiotherapy *[see Warnings and Precautions (5.11)]*
- Aortitis *[see Warnings and Precautions (5.13)]*
- Alveolar hemorrhage

NEUPOGEN

USPI has AR data presented in a few disease areas.

First, Table 2 includes data from two placebo-controlled trials of patients with cancer receiving myelosuppressive chemotherapy. This table contained a longer list of adverse reactions including thrombocytopenia, nausea, pyrexia, chest pain, pain, fatigue, back pain, arthralgia, bone pain, pain in extremity, dizziness, cough, dyspnea, rash, LDH increased, and alkaline phosphatase increased. Beneath the table, this label lists AEs with at least 5% higher incidence compared to placebo and associated with the sequelae of the underlying malignancy or cytotoxic chemotherapy delivered included anemia, constipation, diarrhea, oral pain, vomiting, asthenia, malaise, edema peripheral, hemoglobin decreased, decreased appetite, oropharyngeal pain, and alopecia.

A non-tabular description of the ARs in patients with Acute Myeloid Leukemia (also a placebo-controlled trial) was provided. The list included "epistaxis, back pain, pain in extremity, erythema, and rash maculo-papular". This section also listed the ARs that were associated with the malignancy and chemotherapy; "diarrhea, constipation, and transfusion reaction".

Adverse reactions were provided in list form for the patients with cancer undergoing bone marrow transplantation. There was one controlled study (control included no treatment or placebo). The ARs listed that were at least 5% higher in the Neupogen arm were rash and hypersensitivity. There was another list of ARs in patients receiving intensive chemotherapy followed by autologous BMT which included thrombocytopenia, anemia, hypertension, sepsis, bronchitis, and insomnia.

Reviewer Comment: The Neupogen labeling was initially approved in 1991, so the approaches used to identify the adverse reactions were not entirely consistent with the AR guidance (published after the labeling was approved).

I recommend that the Adverse Reactions table in the USPI be revised to remove terms that are not mechanistically plausible and more likely to be an effect of the underlying disease or chemotherapy treatment.

That leaves fatigue, nausea, diarrhea, bone pain, headache, pyrexia, anemia, rash, myalgia, arthralgia, back pain, decreased appetite, edema peripheral, abdominal pain, dizziness, dyspnea, thrombocytopenia, cough, pain, pain in extremity, local administration reactions, and flushing. These adverse reactions appear to be mechanistically-related as well as known class effects of leukocyte growth factors.

In addition, many of the class warnings/precautions were omitted from the submitted labeling. The Warnings that are relevant to the class were added back in.

Regulatory Recommendation:

Attachments: Revised labeling with track changes edits and bubble comments explaining the revisions. This version has completed multi-disciplinary review but is pending DMPP, OPDP, and DMEPA review. The reader is referred to their reviews for their labeling recommendations.

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/s/

VIRGINIA E KWITKOWSKI
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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	June 17, 2022
Requesting Office or Division:	Division of Nonmalignant Hematology (DNH)
Application Type and Number:	BLA 761148
Product Name, Dosage Form, and Strength:	Rolvedon (eflapegrastim-xnst) Injection, 13.2 mg/0.6 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Spectrum Pharmaceuticals (Spectrum)
FDA Received Date:	July 22, 2020 and March 11, 2022
OSE RCM #:	2019-2236-3
DMEPA 2 Safety Evaluator:	Devin Kane, PharmD
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

Spectrum Pharmaceuticals (Spectrum) submitted a Class 2 Resubmission for BLA 761148 for Rolvedon (eflapegrastim-xnst) Injection on March 11, 2022. Rolvedon is a recombinant human granulocyte 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. We evaluated the proposed Prescribing Information (PI), syringe container label, carton labeling, blister tray label, and Patient Information (PPI) for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND OR REGULATORY HISTORY

On November 30, 2017, Spectrum requested a Type C meeting under IND 103461. As part of the meeting package, Spectrum requested that "the requirement to conduct a Human Factors (HF) study for the eflapegrastim drug product be waived as the planned combination product is a prefilled syringe, will be administered by a trained health care professional, and the product design does not introduce or incorporate any new or novel design mechanisms". In our comments to the Sponsor, we recommended that they conduct a comprehensive use-related risk analysis (URRA) to determine if a HF validation study would be necessary for the proposed product.[a]

On April 30, 2018, Spectrum submitted the requested URRA and concluded that an HF validation study is not necessary for the proposed product. Based on our review of the Sponsor's URRA, MAUDE analysis, and product comparison, as well as our postmarket experience with similar products, we agreed with the Sponsor's justification for not providing a HF validation study to support the marketing application for eflapegrastim Injection was reasonable.[b]

BLA 761148 received a Complete Response (CR) Letter on August 3, 2021 due to facility inspection issues.[c] We previously reviewed the label and labeling (see Appendix B).

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

[a] Meeting Preliminary Comments: https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af8047688a&_afrRedirect=1716581318811819

[b] Rahimi, L. Use-Related Risk Analysis Review for eflapegrastim injection (IND 103461). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUL 25. Panorama No. 2018-922.

[c] Garr-Colon, B. Complete Response Letter. 2020 AUG 03. Available at: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8060859a

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed prescribing information (PI), syringe container label, carton labeling, blister tray label, and patient information (PPI) for Rolvedon to determine whether there are deficiencies that may lead to medication errors and other areas of improvement.

We note that all previous label and labeling recommendations that were communicated to Spectrum have been accepted and implemented. Additionally, we note the PI, syringe container label, carton labeling, blister tray label, and PPI have been updated to reflect the conditionally acceptable proprietary name and proper name, Rolvedon (eflapegrastim-xnst). Our evaluation of the proposed PI, syringe container label, carton labeling, blister tray label and PPI for Rolvedon did not identify any unique areas of vulnerability that may lead to medications errors. Thus, we have no concerns or additional recommendations at this time.

4 CONCLUSION & RECOMMENDATIONS

Our evaluation of the proposed Rolvedon prescribing information (PI), syringe container label, carton labeling, blister tray label, and patient information (PPI) did not identify areas of vulnerability that may lead to medication errors. We have no recommendations at this time for the proposed Rolvedon PI, syringe container label, carton labeling, blister tray label or the PPI.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Rolvedon received on March 11, 2022 from Spectrum Pharmaceuticals.

Table 2. Relevant Product Information for Rolvedon	
Initial Approval Date	N/A
Nonproprietary Name	eflapegrastim-xnst
Indication	Rolvedon is a leukocyte growth factor 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 clinically significant incidence of febrile neutropenia.
Route of Administration	Subcutaneous
Dosage Form	Injection
Strength	13.2 mg/0.6 mL
Dose and Frequency	The recommended dosage of Rolvedon is a single subcutaneous injection of 13.2 mg administered once per chemotherapy cycle. Administer approximately 24 hours after cytotoxic chemotherapy. Do not administer within the period from 14 days before to 24 hours after administration of cytotoxic chemotherapy.
How Supplied	Rolvedon (eflapegrastim-xnst) injection is a clear, colorless solution supplied in a single-dose prefilled syringe (b) (4) containing 13.2 mg of eflapegrastim-xnst in 0.6 mL solution, with 29-gauge 1/2 inch pre-attached (staked) needle with a needle guard. Rolvedon is provided in a dispensing pack containing one sterile 13.2 mg/0.6 mL prefilled syringe (NDC 76961 101-01).
Storage	Store refrigerated at 36°F to 46°F (2°C to 8°C) in the carton to protect from light. Do not shake. Discard syringes stored at room temperature for more than 12 hours. Do not freeze; discard syringe if frozen.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On April 21, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, BLA 761148. Our search identified 3 previous reviews[d,e,f], and we confirmed that our previous recommendations were implemented.

[d] DeGraw, S. Label and Labeling Review for Rolontis (BLA 761148). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAY 07. RCM No.: 2019-2236.

[e] DeGraw, S. Label and Labeling Review for Rolontis (BLA 761148). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUN 11. RCM No.: 2019-2236-1.

[f] DeGraw, S. Label and Labeling Review for Rolontis (BLA 761148). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUL 28. RCM No.: 2019-2236-2.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[g] along with postmarket medication error data, we reviewed the following Rolvedon labels and labeling submitted by Spectrum Pharmaceuticals.

- Syringe Container Label received on March 11, 2022
- Carton Labeling received on March 11, 2022
- Blister Tray Label received on March 11, 2022
- Prescribing Information (Image not shown) received on March 11, 2022, available from \\CDSESUB1\evsprod\bla761148\0064\m1\us\114-labeling\draft\labeling\m1-14-1-3-rolvedon-package-insert.docx
- Patient Information (Image not shown) received on March 11, 2022, available from \\CDSESUB1\evsprod\bla761148\0064\m1\us\114-labeling\draft\labeling\m1-14-1-3-rolvedon-patient-info.docx

G.2 Label and Labeling Images

- Syringe Container Label

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[g] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

DEVIN R KANE
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HINA S MEHTA
06/17/2022 02:53:33 PM

Division of Nonmalignant Hematology Products
Associate Director for Labeling Review of the Prescribing Information

Product Title	ROLONTIS (eflapegrastim-xnst) injection, for subcutaneous use
Applicant	Spectrum Pharmaceuticals, Inc.
Application/Supplement Number	BLA 761148
Is Proposed Labeling in Old Format? (Y/N)	N
Is Labeling Being Converted to PLR? (Y/N)	N
Is Labeling Being Converted to PLLR? (Y/N)	M
Approved Indication(s)	None, NME
Date FDA Received Application	10/24/2020
Review Classification (Priority/Standard)	Standard
Action Goal Date	10/24/2020
Review Date	09/28/2020
Reviewer	Virginia Kwitkowski, MS, ACNP-BC

This Associate Director for Labeling (ADL) review provides recommendations on the content and format of the Warnings and Precautions section of the prescribing information (PI) to help ensure that PI:

- Is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) requirements[1]
- Is consistent with labeling guidance recommendations[3] and with CDER/OND best labeling practices and policies
- Conveys the essential scientific information needed for safe and effective use of the product
- Is clinically meaningful and scientifically accurate
- Is a useful communication tool for health care providers
- Is consistent with other PI with the same active moiety, drug class, or similar indication

Background: This application represents a new molecular entity (eflapegrastim-xnst) with a proposed indication of "to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs".

Reviewer Comments: DNH held 4 multidisciplinary labeling meetings to revise and discuss the labeling documents. We sent revised labeling to the Applicant on 08/12/2020 and requested that they return labeling by 8/21/2020. The Applicant submitted their revised labeling on 08/21/2020. DNH revised the labeling and sent it back to the Applicant on 8/31/2020. The Applicant returned revised

[1] See *January 2006 Physician Labeling Rule*; 21 CFR 201.56 and 201.57; and *December 2014 Pregnancy and Lactation Labeling Rule* (the PLLR amended the PLR regulations). For applications with labeling in non-PLR "old" format, see 21 CFR 201.56(e) and 201.80.
[3] See *PLR Requirements for PI* website for PLR labeling guidances.

labeling on 9/4/2020. We are preparing to return labeling to the Applicant again today. Labeling negotiations are nearly complete at this time.

Regulatory Recommendation: This BLA is recommended for approval upon completion of labeling negotiations.

Attachments: Revised labeling (USPI and Patient Labeling) with track changes edits and bubble comments explaining the revisions. This is a later version of labeling with few comments remaining.

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/s/

VIRGINIA E KWITKOWSKI
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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE:	August 28, 2020
Date of Consult Request:	July 21, 2020
From:	CAPT Anissa Davis-Williams, RN, MSN, MPH, Regulatory Health Project Manager, Division of Pediatrics and Maternal Health (DPMH)
To:	Elizabeth Godwin, MSHS, CCRP, RAC, GWCPM Senior Regulatory Health Project Manager, Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN)
BLA Number:	BLA 761148
Drug:	SPI-2012 (eflapegrastim)
Applicant:	Spectrum Pharmaceuticals, Inc.
Indication:	To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anticancer drugs.

DPMH was consulted by OCHEN on July 21, 2020, to review and provide feedback regarding their proposed post marketing requirements (PMRs) and participate in the Late Cycle Meeting that was scheduled for August 5, 2020.

DPMH provided feedback regarding the proposed PMR language and participated in the Late Cycle Meeting with the Applicant on August 5, 2020 and an internal meeting on August 6, 2020.

OCHEN issued advice to the Applicant regarding the PMRs in PMR/PMC/General Correspondence on August 14, 2020, and also issued the official Late Cycle Meeting minutes to the Applicant on August 27, 2020. The official minutes and the PMR/PMC/General Correspondence represent the Agency's current thinking and DPMH's input accordingly. DPMH has no further comment at this time.

DPMH RPM- CAPT Anissa Davis-Williams, RN, B.S.N., M.P.H.
DPMH Supervisory, Consumer Safety Officer-George Greeley, M.S., M.B.A.
DPMH Pediatrics MO Reviewer- CDR Erica Radden, M.D.

DPMH Pediatrics Team Leader- Mona Khurana, M.D.
DPMH Deputy Director- John Alexander, M.D., M.P.H.

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/s/

ANISSA A DAVIS
09/01/2020 08:52:10 AM

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM – PRE-FILLED SYRINGES

Date	8/4/2020
To:	Elizabeth Godwin Elizabeth.Godwin@fda.hhs.gov CDER/OND/OCHEN/DDLDO
From	LCDR Michael Simpson OPEQ/OHT3/DHT3C
Through (Team)	Rumi Young, Team Lead, Injection Devices Team OPEQ/OHT3/DHT3C
Through (Division) *Optional	CAPT Alan Stevens, Assistant Director OPEQ/OHT3/DHT3C
Subject	**ICCR:** 00014270, https://force-dsc.my.salesforce.com/500t000000ONFUf **ICC:** ICC1900993 **Submission:** BLA761148 **Sponsor:** (b) (4) **Drug/Biologic:** Eflapegrastim **Indications for Use:** To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs; Eflapegrastim is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs.
Recommendation	**Final Recommendation:** ☑ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with the following Post-Market Requirements/Commitments, ☐ Device Constituent Parts of the Combination Product are Not Approvable with the following CR Deficiencies
	Comments to Review Team: N/A
	PMC/PMR or CR Deficiencies: N/A

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)
James M. Simpson Jr -S7 2020.08.04 12:11:49 -04'00'	Rumi Young -S Rumi Young -S c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rumi Young -S, 0.9.2342.19200300.100.1.1=2002467913 2020.08.04 12:56:37 -04'00'	

1. PURPOSE

Spectrum has submitted an original 351(a) BLA 761148 for SPI-2012 (proposed name Rolontis (eflapegrastim). DHP requests CDRH review the prefilled biologic delivery device/system.

This review provides an assessment of the syringe device constituent part of the prefilled syringe product.

This review will cover the following review areas:

☒ Device performance
☒ Stability – device performance on stability
☒ Essential Performance Requirements (EPR) Control strategy

☒ CDRH Quality Systems Assessment / Facilities consult not required

It was determined that a device quality systems / facilities assessment is not required for this product because the product is not an emergency (i.e., life-saving and essential[1]) treatment that are administered by non-health care professionals.

Important Dates	
Filing	12/23/2019
74-Day Letter	01/06/2020
Midcycle Meeting/IRs due	03/24/2020
Final Lead Device Review Memo Due	06/24/2020
PDUFA Date	10/24/2020

2. DEVICE DESCRIPTION

2.1. Picture of Final Device Presentation

The primary container closure system for eflapegrastim Drug Product consists of a 1 mL glass syringe with a staked needle, elastomeric needle cap, elastomeric plunger, and plunger rod. This primary container system is inserted into the passive needle guard accessory.

The components of the proposed container/closure system comply with USP <660> and USP <381> requirements for glass containers and elastomeric closures for injections, respectively.

[1] Examples of emergency, life-saving and essential treatments include those used for conditions such as anaphylaxis or cardiac arrest and others in which failure of drug delivery may expose the patient to the reasonable likelihood of serious injury or death.

Sources and descriptions of the components of the primary container closure system to be used for commercial supplies of eflapegrastim Drug Product are provided in Table 1. The letters of authorization to reference the Type III/V DMFs associated with the syringe and stopper, and the 510(k) for the passive needle guard and matching plunger are provided in Section 1.4.1.

Container Closure Component	Manufacturer	Material(s) of Construction	DMF or 510(k)
(b) (4) syringe (b) (4) syringe with 29g staked needle)	(b) (4)		
Needle shield			
Plunger			
(b) (4) Plunger rod[1]			
(b) (4) passive needle accessory[2]			

(b) (4)

[redacted]

2.2. Design Requirements

Syringe Description

Requirement	Describe
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	Healthcare professionals
Injection Site	Subcutaneously not specified
Injection tissue and depth of injection	Subcutaneously
Needle connection (e.g. luer, slip tip, staked)	Staked
Syringe Volume	1 mL glass syringe
Delivered Dose Volume	0.6 mL

Additional Devices

Requirement	Describe
Hypodermic Needle: (length, gauge)	29g, ½"
Safety Features (e.g. Needle safety component/device)	Needle guard

3. DEVICE PERFORMANCE REVIEW

Performance Requirement	Specification	Verification Method Acceptable (Y/N)	Validation (Y/N)	Stability Module 3.2.P.8 (Y/N)	Shipping/ Transportation (Y/N)
Dose Accuracy	[redacted] g	Y	Y	N	N
Break loose Force	[redacted] mm/min	Y	Y	N	N
Glide Force	[redacted] mm/min	Y	Y	N	N
Cap Removal Force	[redacted] N	Y	Y	n/a	n/a
Needle Safety Activation Force	[redacted] N	Y	Y	n/a	n/a

Pull-Off Force of the Tip Cap

Testing was performed per ISO 11040-4:2015, Section 6.5.3.7, Annex G.6. The test assesses the removal force of the tip cap of a sterilized, subassembled syringe ready for filling. The syringes were placed vertically in the test fixture with the needle-end oriented upward. Sub-set of samples three groups (10 syringes per group) were tested using crosshead speeds of 100 mm/min, 500 mm/min and 1,000 mm/min, respectively. The test is complete once the syringe tip cap was removed. The peak load during the test was recorded. Table 16 summarizes the results from this test.

Table 16 Pull-Off Force of the Tip Cap Test Results

Number of Samples Tested	Crosshead Speed (mm/min)	Minimum Force (N)	Maximum Force (N)	Average Peak Force (N)	Std. Dev.
10	100	6.66	12.20	10.37	1.54
10	500	13.57	16.57	14.78	0.94
10	1000	15.12	17.71	16.25	0.81

Reviewer Comments

Eflapegrastim Drug Product is stored 5 ± 3°C in 1 mL long syringe. Based on long term stability data, the sponsor has set the "shelf life" at (b)(4) months.

The sponsor only provided stability data for 12 months. Although results did meet EPRs the sponsor should provide testing for (b)(4) months or accelerated aging representing (b)(4) months.

Testing of empty and filled syringes was performed for both Break Loose and Gliding Force as well as Delivered Volume in section 3.2.P.7 Container Closure System, specifically pages 21-25. However, it was not specified if the EPRs with the reconstituted drug/biologics at release, stability / shelf life testing and shipping studies. The to-be-marketed version of the combination product must demonstrated that the EPRs are maintained up to the labeled date of expiry and after actual and/or simulated shipping. IR#1 added. Sponsor provided adequate accelerated aging testing for 24 months and simulated shipping validation studies with Realtime aged devices at 24 months. (b)(4)

The provided activation force of the needle safety guard was higher than one would expect. IR#2 issued.

Acceptance criteria for cap removal force not provided. IR#4 issued.

4. CONTROL STRATEGY REVIEW

The Sponsor provided the following control strategy information regarding the EPRs of the device constituents:

Essential Performance Requirements Control Strategy Table

** The proposed acceptance criteria for the EPR may be tighter than the design input and should be assessed for adequate quality control)/ Sampling Plan (Sampling plan may be review issue depending on the product (e.g. emergency-use)*

Essential Performance Requirements	Control Strategy Description - The Sponsor provided the following description of how the essential performance requirements of the combination product are controlled through incoming acceptance, in-process control, and/or release testing activities:	Acceptable (Y/N/NA)
Dose Accuracy	Release and stability testing	Y
Break loose Force	Release and stability testing	Y
Glide Force	Release and stability testing	Y
Needle Safety Activation Force	Release and stability testing	Y

Reviewer Comments

The sponsor will control the essential performance requirements through release testing. This is an acceptable control strategy to prevent inadequate devices from being released.

It is not clear if needle safety activation force testing is also performed at release testing. IR#3 issued.

<<END OF REVIEW>>

5. APPENDIX A (INFORMATION REQUESTS)

(b) (4)

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/s/

ELIZABETH R GODWIN
08/26/2020 12:14:23 PM
Signed on behalf of LCDR Michael Simpson OPEQ/OHT3/DHT3C

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	July 28, 2020
Requesting Office or Division:	Division of Nonmalignant Hematology (DNH)
Application Type and Number:	BLA 761148
Product Name and Strength:	Rolontis (eflapegrastim-xnst) injection 13.2 mg/0.6 mL
Applicant/Sponsor Name:	Spectrum Pharmaceuticals (Spectrum)
FDA Received Date:	July 22, 2020
OSE RCM #:	2019-2236-2
DMEPA Safety Evaluator:	Stephanie DeGraw, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Spectrum submitted a revised container label and carton labeling for Rolontis (eflapegrastim-xnst) on July 22, 2020 (Appendix A). The revisions are in response to recommendations that we made during a previous label and labeling review[a], label and labeling review memo[b], and information request.[c] We reviewed the revised labels to determine if they are acceptable from a medication error perspective.

2 DISCUSSION AND CONCLUSION

We note that our previous recommendations were implemented (i.e., the font color for the proper name and dosage form was changed from light blue to black, the font size for the strength was increased, and the conditionally acceptable proper name was added). We conclude the revised container label and carton labeling are acceptable from a medication error perspective. We have no additional recommendations at this time.

[a] DeGraw, S. Label and Labeling Review for Rolontis (eflapegrastim-xxxx) BLA 761148. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAY 07. RCM No.: 2019-2236.
[b] DeGraw, S. Label and Labeling Review Memo for Rolontis (eflapegrastim-xxxx) BLA 761148. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUN 11. RCM No.: 2019-2236-1.
[c] Godwin, E. Information Request. BLA 761148. 2020 JUL 16. Available at: https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af8057d785&_afrRedirect=2203120915925853

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/s/

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07/28/2020 02:57:24 PM

HINA S MEHTA
07/28/2020 05:46:22 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: June 16, 2020

To: Hyon-Zu Lee, Pharm.D., Clinical Reviewer
Division of Nonmalignant Hematology (DNH)

Elizabeth Godwin, MSHS, CCRP, RAC, GWCPM, Senior Regulatory Health Project Manager, (on behalf of DNH)

Virginia Kwitkowski, MS, ACNP-BC, Associate Director for Labeling, (DNH)

From: Rebecca Falter, PharmD, BCACP, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for Rolontis (eflapegrastim-xxxx) injection, for subcutaneous use

BLA: 761148

In response to DNH's consult request dated November 6, 2019, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original BLA submission for Rolontis.

PI and PPI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DNH (Elizabeth Godwin) on June 5, 2020, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover on June 12, 2020.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on May 28, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Rebecca Falter at (301) 837-7107 or Rebecca.Falter@fda.hhs.gov.

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/s/

REBECCA A FALTER
06/16/2020 11:06:30 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	June 12, 2020
To:	Liz Godwin, MSHS, CCRP Senior Regulatory Project Manager **Division of Non-Malignant Hematology (DNH)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Rebecca Falter, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	[SPI-2012] ROLONTIS (eflapegrastim-xxxx)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	BLA 761148
Applicant:	Spectrum Pharmaceuticals, Inc.

1 INTRODUCTION

On October 24, 2019, Spectrum Pharmaceuticals, Inc. re-submitted for the Agency's review an Original Biologics License Application (BLA) for [SPI-2012] ROLONTIS (eflapegrastim-xxxx) injection. The Applicant originally submitted their BLA on December 21, 2018 and subsequently withdrew the proposed application on March 14, 2019. The Applicant proposes the following indication for [SPI-201] ROLONTIS (eflapegrastim-xxxx) injection: to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs. On January 21, 2020, the Division of Medication and Prevention Analysis notified the Applicant that their proposed proprietary name, ROLONTIS, is conditionally acceptable.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Non-Malignant Hematology (DNH) on November 6, 2019, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for [SPI-2012] ROLONTIS (eflapegrastim-xxxx) injection.

2 MATERIAL REVIEWED

- Draft [SPI-2012] ROLONTIS (eflapegrastim-xxxx) injection PPI received on October 24, 2019 revised by the Review Division throughout the review cycle, and received by DMPP on June 5, 2020.
- Draft [SPI-2012] ROLONTIS (eflapegrastim-xxxx) injection Prescribing Information (PI) received on October 24, 2019, revised by the Review Division throughout the review cycle, and received by DMPP on June 5, 2020.
- Approved Neulasta (pegfilgrastim) injection labeling (PI and PPI) dated June 8, 2018 and January 6, 2020.
- Approved Fulphila (pegfilgrastim-jmdb) injection labeling dated May 29, 2019.
- Approved Ziextendo (pegfilgrastim-bmez) injection November 4, 2019.
- Approved UDENYCA (pegfilgrastim-cbqv) injection labeling dated February 12, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using

fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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REBECCA A FALTER
06/12/2020 02:54:32 PM

LASHAWN M GRIFFITHS
06/12/2020 03:44:12 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 11, 2020
Requesting Office or Division:	Division of Nonmalignant Hematology (DNH)
Application Type and Number:	BLA 761148
Product Name and Strength:	Rolontis (eflapegrastim-xxxx)[a] injection 13.2 mg/0.6 mL
Applicant/Sponsor Name:	Spectrum Pharmaceuticals (Spectrum)
FDA Received Date:	May 28, 2020
OSE RCM #:	2019-2236-1
DMEPA Safety Evaluator:	Stephanie DeGraw, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Spectrum submitted revised carton labeling and container label for Rolontis (eflapegrastim-xxxx) on May 28, 2020 (Appendix A). The revisions are in response to recommendations that we made during a previous label and labeling review.[b]

2 DISCUSSION

We reviewed the revised labels to determine if they are acceptable from a medication error perspective. We note that our previous recommendations were accepted where possible. However, we note that Spectrum also made additional changes to the container label and carton labeling including new NDC numbers, revised design elements, and new font colors.

[a] The nonproprietary name for this BLA has not yet been determined; therefore, the placeholder "eflapegrastim-xxxx" is used throughout this memo to refer to the nonproprietary name for this product. The proprietary name Rolontis has been found conditionally acceptable for this product.

[b] DeGraw, S. Label and Labeling Review for Rolontis (eflapegrastim-xxxx) BLA 761148. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAY 07. RCM No.: 2019-2236.

3 CONCLUSION

The revised container label and carton labeling is unacceptable from a medication error perspective. We provide recommendations below for the Sponsor.

3.1 RECOMMENDATIONS FOR SPECTRUM PHARMACEUTICALS

We recommend the following be implemented prior to approval of this BLA:

A. General Comments for All Labels and Labeling

1. We note that the font color for the proper name and dosage form, (eflapegrastim-xxxx) injection, was changed from black [(b) (4)] The color contrast of the [(b) (4)] text on the white background appears difficult to read. Low contrast is a common cause of unreadable text. Therefore, we recommend revising the font color to improve the contrast and readability of the proper name and dosage form.

B. Carton Labeling – Blister Tray and Outer Carton

1. We note that the font color for the strength statement, 13.2 mg/0.6 mL, was changed from black to [(b) (4)] and the [(b) (4)] was removed. As such, the strength now appears less prominent and may be overlooked. Therefore, we recommend increasing the prominence of the strength by enlarging the font size.

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STEPHANIE L DEGRAW
06/11/2020 11:21:52 AM

HINA S MEHTA
06/11/2020 01:33:31 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: June 8, 2020 **Date Consulted:** December 3, 2019

From: Jeanine Best, MSN, RN, PNP, Senior Clinical Analyst, Maternal Health
Division of Pediatric and Maternal Health

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, Division Director
Division of Pediatric and Maternal Health

To: Division of Non-Malignant Hematology (DNH)

Drug: Rolontis (eflapegrastim) injection

BLA: 761148

Applicant: Spectrum Pharmaceuticals

Subject: Pregnancy and Lactation Labeling

Indication: "to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs"

Materials Reviewed:

- Applicants Proposed labeling, 10/24/2019
- Applicant's Summary of Clinical Safety, 10/24/2019

Consult Question: "DHP requests a review of the proposed PLLR Language and supporting information for this application by DPMH."

INTRODUCTION AND BACKGROUND

On October 24, 2019, Spectrum Pharmaceuticals submitted an original BLA for Rolontis (eflapegrastim) injection, to seek approval to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs. The Division of Non-Malignant Hematology (DNH) consulted the Division of Pediatric and Maternal Health (DPMH) on December 3, 2019, to assist with the Pregnancy and Lactation subsections of labeling.

Regulatory History

- 4/9/2009 – IND 103461 submitted for HM 10460A, a long-acting rhG-CSF analog for the indication to reduce the duration of febrile neutropenia in patients with malignancies receiving myelosuppressive anti-cancer drugs).
- 12/21/2018 – (b) (4) submitted for Rolontis (eflapegrastim) injection; BLA withdrawn 3/14/2019 due to CMC filing issues
- There are no previous DPMH consult reviews for eflapegrastim; however, DPMH provided a PLLR consult review for Neupogen (BLA 103353) and Neulasta (BLA 125031) on 5/14/2018; DARRTS Reference ID 4262426.[1]

Eflapegrastim Drug Characteristics[2]

- A long-acting granulocyte-colony stimulating factor (G-CSF) (a leukocyte growth factor) produced by covalent coupling of a human G-CSF analog and an Fc fragment of human immunoglobulin G4 (IgG4), both derived from E-coli via a single 3.4 kDa polyethylene glycol linker. The recombinant G-CSF domain is a variant of human G-CSF with two serine substitutions at positions 17 and 65, and no additional N-terminal methionine.
- Molecular weight ~72 kDa.
- Mechanism of action: stimulates cellular proliferation and neutrophil function by specific binding to G-CSF receptors on myeloid progenitor cells and neutrophils, triggering signaling pathways that control cell differentiation, proliferation, migration, and survival. Eflapegrastim contains an Fc moiety that is known to increase the serum half-life of protein therapeutic biologics. Based on preclinical studies, the Fc moiety is believed to increase the uptake of eflapegrastim into bone marrow by FcRn-mediated transport.
- Pharmacodynamics: elevates neutrophil counts in healthy subjects and cancer patients.
- Pharmacokinetics: nonlinear with exposures increased with increasing doses in a greater than dose proportional manner. No excretion through the kidneys. Clearance decreased with increasing doses, suggesting target-mediated clearance by neutrophils.
- Not genotoxic; carcinogenicity studies not done.
- Immunogenicity showed no impact on pharmacokinetics, safety, or efficacy.
- Serious adverse reactions include serious allergic reactions, splenic rupture, leukocytosis.

[1] This review was part of the materials reviewed but was not a source relied upon for labeling recommendations.
[2] Refer to applicant proposed labeling, 10/24/2019

Proposed Rolontis PLLR Labeling[3]

- No Boxed Warning or Warning and Precaution for embryofetal toxicity;
- No pregnancy or lactation contraindication;
- No human pregnancy or lactation data;
- No nonclinical pregnancy or lactation data; however, animal reproduction studies (not required for this product) were submitted with the application;
- (b) (4) [redacted].

REVIEW

***Disclaimer** Pregnancy and lactation related literature relied upon for this review and labeling recommendations is not specific to a particular drug or biological product. Pregnancy and lactation related literature discussed below that is specific to a particular drug or biological product is for informational purposes only and was not relied upon for this review or for labeling recommendations.*

Pregnancy

Granulocyte - Colony Stimulating Factor (G-CSF) and Pregnancy

Human granulocyte - colony stimulating factor (G-CSF) is a natural cytokine regulating neutrophil production and deployment and is produced in the body by cells such as fibroblasts, monocytes, macrophages, endothelial cells, stromal cells, and bone marrow cells. G-CSF also plays a role in pregnancy success by affecting embryo implantation, ovarian function, promoting endometrial thickening, and improves the pathophysiology of endometriosis, all of which lead to a reduction in pregnancy loss. Recombinant human G-CSF (rhG-CSF) may also have a beneficial outcome after assisted reproduction technology and in women with recurrent spontaneous abortions; however, studies are needed to investigate and confirm the effects of rhG-CSF on these outcomes.[4]

Recombinant human granulocyte-colony stimulating factor (rhG-CSF) therapy can reduce the incidence of febrile neutropenia associated with chemotherapy and some chemotherapy regimens require primary prophylaxis with a rhG-CSF product for this reason. Therapy with a rhG-CSF product is sometimes withheld in pregnant women with cancer undergoing chemotherapy due to a lack of safety studies in pregnant women.[5] Cardonick, et al. (2012)[6,7] identified 176 pregnant women from the Cancer and Pregnancy Registry maintained by Cooper University Hospital and queried whether a rh-GCF product was prescribed when necessary, was not necessary, or was withheld due to pregnancy. Of 176 reported pregnancies in women with cancer undergoing chemotherapy, 34/176 received treatment with Neupogen/Neulasta and 142/176 received no

[3] Refer to applicant proposed labeling, 8/28/2019

[4] Eftekhar M, Naghshineh E, Khani P. Role of granulocyte colony-stimulating factor in human production. *J Res Med Sci*, 2018: 23:7

[5] Loibl S, Schmidt A, et al. Breast cancer diagnosed during pregnancy: adapting recent advances in breast cancer care for pregnant patients. *JAMA Oncology*, 2015;1(8):1145-1153

[6] Cardonick E, Irfan F, Torres N. The use of Neupogen (filgrastim) or Neulasta (pegfilgrastim) during pregnancy when chemotherapy is indicated for maternal cancer treatment. *J of Cancer Ther*, 2012;3:157-161

[7] Disclaimer: This article was used for informational purposes only and was not relied upon for the review or labeling of eflapegrastim.

Neupogen/Neulasta treatment. Of the 142 pregnancies with no rhG-CSF treatment, 98/142 did not report a reason for no Neupogen/Neulasta treatment, 40/142 reported no need for Neupogen/Neulasta treatment, and treatment was withheld due to pregnancy in 4/142 pregnancies. Birth outcomes, white blood cell count at birth, and pediatric health were compared between pregnant women exposed to Neupogen/Neulasta and not exposed. No statistically significant difference in gestational age at birth, congenital anomalies, birthweight, incidence of long-term health issues, mean WBC or neutropenia at birth between newborns exposed to a rhG-CSF with chemotherapy and newborns exposed to chemotherapy alone.

Recombinant human granulocyte-colony stimulating factor (rhG-CSF) has been used in the treatment of women with chronic neutropenia during pregnancy. Boxer, et al. (2015)[8] conducted an observational study in women of reproductive age with congenital, cyclic, idiopathic, or autoimmune neutropenia enrolled in the Severe Chronic Neutropenia International Registry to determine pregnancy outcomes with and without rhG-CSF therapy. Of 224 pregnancies reported in 107 women, 124/224 pregnancies reported no use of rhG-CSF and 100/224 pregnancies reported chronic rhG-CSF use. There were no significant differences reported in adverse outcomes between the rh-GCS exposed and unexposed pregnancies. Spontaneous abortions were reported in 27/124 unexposed pregnancies and in 13/100 in exposed pregnancies; however, the sample size was too small to detect a difference in this outcome (at least 300 women per group would be needed to detect this event with an 80% statistical power [alpha=0.05]).

Nonclinical Experience[9]

Although not required for this BLA, animal reproduction studies were conducted in rats and rabbits. No adverse outcomes were observed in rats with subcutaneous administration of eflapegrastim did not from organogenesis throughout lactation at doses that produced maternal exposures up to 7 times the exposure at the recommended clinical dose. Embryofetal lethality and reduced fetal weight was observed in rats with subcutaneous administration of eflapegrastim during organogenesis doses that produced exposures approximately 6 times the exposure at the clinical dose.

Eflapegrastim showed no evidence of genotoxicity in nonclinical studies.

Clinical Experience

Rolontis (eflapegrastim) injection, has only been used in the applicant's clinical trials and is not currently approved in any country. The applicant provided a Summary Of Clinical Safety in their October 24, 2019 BLA submission and reports that no pregnancy cases were found. There is no published information on the use of Rolontis (eflapegrastim) in pregnant women.

REPROTOX[10] reports that human granulocyte-colony stimulating factor (G-CSF) is a glycoprotein cytokine that induces the proliferation and differentiation of granulocyte precursors

[8] Boxer LA, Bolyard AA, Dale DC. Use of granulocyte colony-stimulating factor during pregnancy in women with chronic neutropenia. Obstetr Gynecol, 2015,; 125(1):197-203

[9] Refer to the final Nonclinical Review

[10]https://www micromedexsolutions.com/micromedex2/librarian/CS/D29AD9/ND_PR/evidencexpert/ND_P/evidencexpert/DUPLICATIONSHIELDSYNC/3AE32A/ND_PG/evidencexpert/ND_B/evidencexpert/ND_AppProduct/evidencexpert/ND_T/evidencexpert/PFActionId/evidencexpert.IntermediateToDocumentLink?docId=3452&contentSet

and activates mature neutrophils. G-CSF is normally present during pregnancy and is produced by human placental and decidual tissues and is found in umbilical cord blood at term. In addition, because of placental drug transfer, prenatal administration of recombinant human G-CSF was investigated as a prophylactic to reduce bacterial infections in premature neonates; however, further study was not pursued due to concerns with the development of leukemia due to prolonged administration of a rhG-CSF product in both mother and baby.

Lactation

Nonclinical Experience[11]

Milk levels of eflapegrastim were not measured in animals.

Clinical Experience

Rolontis (eflapegrastim) has only been used in the applicant's clinical trials and is not currently approved in any country. The applicant provided a Summary of Clinical Safety in their October 24, 2019 BLA submission and reports that no lactation cases were found. There is no published information on the use of Rolontis (eflapegrastim) in lactating women.

The use of recombinant human granulocyte-colony stimulating factor (rhG-CSF) products during lactation is described in LactMed, and Hale's *Medications & Mother's Milk.*

Hale[12] reports that small levels of filgrastim, another rhG-CSF product, was detected in the breastmilk of two women (stem cell donors) at low levels; however, the drug is unlikely to be orally absorbed by a breastfed infant. Hale[13] also reports that there is no lactation data with pegfilgrastim.

LactMed[14] reports that limited data with filgrastim and lenograstim (rhG-CSF products) are poorly excreted into breastmilk and are undetectable by 3 days after an injection. LactMed also reports that filgrastim has been safely given orally to neonates and was not orally absorbed by neonates.

Calhoun, et al. conducted several studies regarding the presence of G-CSF in breastmilk and effects in breastfed neonates:

- Calhoun[15] et al. (1999), report that G-CSF is a normal component of breastmilk and that specific receptors for G-CSF are expressed on the villous enterocytes of neonates; therefore, endogenous G-CSF present in breastmilk is biologically available to the neonate.

Id=35&title=GRANULOCYTE COLONY-STIMULATING FACTOR&servicesTitle=GRANULOCYTE COLONY-STIMULATING FACTOR&navResults=clinicalRefTox, accessed 2/28/2020

[11] Refer to the Final Nonclinical Review

[12] https://www.halesmeds.com/monographs/62104?q=filgrastim, accessed 3/4/2020

[13] https://www.halesmeds.com/monographs/61605?q=pefilgrastim, accessed 3/4/2020

[14] https://www.ncbi.nlm.nih.gov/books/NBK501373/, accessed 3/4/2020

[15] Calhoun DA et al. Concentrations of granulocyte colony-stimulating factor in human milk after in vitro simulations of digestion. Pediatr Res. 1999. Dec; 46(6):767-71.

- Calhoun[16] et al. (2000), quantified G-CSF in the milk samples of 126 healthy lactating women and those with intra-amniotic infection and identified the presence of functional G-CSF receptors (G-CSF-R) in fetal/neonatal intestinal villi enterocytes and specific proteins associated with G-CSF-R signaling are present in these enterocytes. Breastmilk contains substantial quantities of G-CSF, especially during the first 2 days postpartum and remains measurable for the first 4 weeks postpartum. Milk levels of G-CSF were significantly higher in lactating women with infection.

- Calhoun, et al. (2003)[17] report that granulocyte colony-stimulating factor (G-CSF) is present in fluids swallowed by the fetus and neonate; specifically, amniotic fluid, colostrum, and breastmilk. The swallowed G-CSF has local effects on enteric cells, which express the G-CSF receptor. The authors assessed the possibility that some of the swallowed G-CSF may have systemic effects, such as stimulating neutrophil production. A single-center, prospective, blinded, randomized, 2 x 2 cross-over study was conducted in 20 neonates to determine if circulating G-CSF concentration increases after enteral administration of recombinant human granulocyte colony-stimulating factor (rhG-CSF). Each neonate received a dose of rhG-CSF (100 microgram/kg) and one dose of placebo. Plasma G-CSF concentrations were measured at 2 and 4 hours after enteral admistration of study drug with no significant change measured in plasma G-CSF concentration. The authors concluded that the G-CSF swallowed by the fetus and neonate has local effects on the developing gastrointestinal tract but not systemic effects.

Females and Males of Reproductive Potential

Nonclinical Experience[18]

Eflapegrastim did not affect reproductive performance or fertility in male or female rats at weekly doses up to 7 times clinical exposure at maximum recommended dose of 13.2 mg.

Clinical Experience

Rolontis (eflapegrastim) injection has only been used in the applicant's clinical trials and is not currently approved in any country. The applicant provided a Summary Of Clinical Safety in their October 24, 2019 BLA submission and does not report on fertility effects in females or males of reproductive potential. There is no published information on the use of Rolontis (eflapegrastim) and fertility effects in females or males of reproductive potential.

Reviewer Comment: The proposed indication for Rolontis is limited for use in patients receiving myelosuppressive anti-cancer drugs, drugs that are known to have adverse fertility effects in both females and males of reproductive potential.

[16] Calhoun DA *et al*. Granulocyte colony-stimulating factor is present in human milk and its receptor is present in human fetal intestine. Pediatrics. 2000 Jan; 105 (1):e7.
[17] Calhoun DA, Maheshwari A, Christensen RD. Recombinant granulocyte colony-stimulating factor administered enterally to neonates is not absorbed. *Pediatrics*, 2003; 112(2):421-423; only able to access abstract
[18] Refer to the final Nonclinical review.

DISCUSSION AND CONCLUSIONS

Pregnancy

Human granulocyte colony-stimulating factor (G-CSF) is a natural cytokine regulating neutrophil production and deployment and is produced in the body by cells such as fibroblasts, monocytes, macrophages, endothelial cells, stromal cells, and bone marrow cells. G-CSF is a normal component of amniotic fluid. There are no data with the use of Rolontis (eflapegrastim), a long-acting recombinant human granulocyte colony-stimulating factor (rhG-CSF) in pregnant women; however, limited data from studies with the use of other rhG-CSF products in pregnant women have not identified a drug-associated risk for major birth defects, miscarriage, or adverse maternal, or fetal outcomes. In animal reproduction studies, subcutaneous administration of eflapegrastim to pregnant rats and rabbits at doses producing exposures up to 7 and 6 times, respectively, the exposure at the clinical dose resulted in no observed adverse outcomes in rats and embryofetal lethality and reduced fetal weight in rabbits.

Pregnancy labeling should include rhG-CSF class information and contain the Pregnancy and Lactation Labeling Rule background risk statement.

Rolontis will be used in females of reproductive function; however, a postmarketing pregnancy safety study is not warranted at this time because the product is only indicated for use in patients receiving myelosuppressive anti-cancer drugs, drugs that are associated with adverse pregnancy and fetal outcomes due to cytotoxic effects. If the applicant pursues any non-cancer indication(s) in the future, a postmarketing pregnancy study may be warranted at that time.

Lactation

There are no data on the presence of eflapegrastim in breastmilk; however, due to its large molecular weight (72 kDa), any transfer into breastmilk would likely be very low. Other recombinant human granulocyte colony-stimulating factor (rhG-CSF) products with lower molecular weights are poorly secreted into human milk. Breastmilk contains substantial quantities of endogenous G-CSF, especially during the first 2 days postpartum and remains measurable for the first 4 weeks postpartum. G-CSF is thought to exert local enteral action, as fetuses and neonates have specific receptors for G-CSF that are expressed on intestinal villous enterocytes. Additionally, oral administration of an rhG-CSF product to neonates did not change their G-CSF plasma levels.[19]

Lactation labeling should reflect lactation knowledge with the rhG-CSF drug class. The existing published data with both rhG-CSF products and endogenous G-CSF are supportive of the safety of breastfeeding with use rhG-CSF products. The standard lactation benefit/risk statement should be placed in Rolontis lactation labeling.

A lactation study is not recommended for Rolontis at this time because breastfeeding is not recommended in the indicated population due to the potential serious adverse reactions in a breastfed infant from exposure to the concomitant myelosuppressive anti-cancer drugs. If the applicant pursues any additional non-cancer indication(s) in the future, a lactation study may be warranted at that time.

[19] Calhoun DA *et al*. Granulocyte colony-stimulating factor is present in human milk and its receptor is present in human fetal intestine. Pediatrics. 2000 Jan; 105 (1):e7.

Females and Males of Reproductive Potential

There are no human fertility data with Rolontis; however, no adverse fertility findings were observed in animal fertility studies with eflapegrastim. There are no pregnancy testing recommendations, contraception recommendations, or infertility information to convey in Rolontis labeling. (b) (4)

RECOMMENDATIONS

Labeling

DPMH revised subsections 8.1 and 8.2 of labeling for compliance with the PLLR. DPMH discussed our labeling recommendations with the Division on June 3, 2020. The following language was agreed upon for subsections 8.1 and 8.2. DPMH refers to the final BLA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

(b) (4)

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/s/

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TAMARA N JOHNSON
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LYNNE P YAO
06/08/2020 03:26:56 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	May 7, 2020
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	BLA 761148
Product Name, Dosage Form, and Strength:	Rolontis (eflapegrastim-xxxx)* injection 13.2 mg/0.6 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Spectrum Pharmaceuticals (Spectrum)
FDA Received Date:	October 24, 2019
OSE RCM #:	2019-2236
DMEPA Safety Evaluator:	Stephanie DeGraw, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

*The non-proprietary name for this BLA has not yet been determined; therefore, the placeholder "eflapegrastim-xxxx" is used throughout this review to refer to the non-proprietary name for this product. The proprietary name Rolontis has been found conditionally acceptable for this product.

1. REASON FOR REVIEW

Spectrum Pharmaceuticals submitted BLA 761128 Rolontis (eflapegrastim-xxxx) injection on October 24, 2019. Rolontis is a recombinant human granulocyte 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. We evaluated the proposed container label, carton labeling, and Prescribing Information (PI) for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

On November 30, 2017, Spectrum requested a Type C meeting under IND 103461. As part of the meeting package, Spectrum requested that "the requirement to conduct a Human Factors (HF) study for the eflapegrastim drug product be waived as the planned combination product is a prefilled syringe, will be administered by a trained health care professional, and the product design does not introduce or incorporate any new or novel design mechanisms". In our comments to the Sponsor, we recommended that they conduct a comprehensive use-related risk analysis (URRA) to determine if a HF validation study would be necessary for the proposed product.[a]

On April 30, 2018, Spectrum submitted the requested URRA and concluded that an HF validation study is not necessary for the proposed product. Based on our review of the Sponsor's URRA, MAUDE analysis, and product comparison, as well as our postmarket experience with similar products, we agreed with the Sponsor's justification for not providing a HF validation study to support the marketing application for eflapegrastim Injection was reasonable.[b]

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A

[a] Meeting Preliminary Comments: https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af8047688a&_afrRedirect=1716581318811819

[b] Rahimi, L. Use-Related Risk Analysis Review for eflapegrastim injection (IND 103461). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUL 25. Panorama No. 2018-922.

Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP newsletters for our label and labeling reviews unless we are aware of medication errors through our routine post-market safety surveillance

3. OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container label, carton labeling, and PI for Rolontis (eflapegrastim-xxxx) to identify deficiencies that may lead to medication errors and other areas of improvement.

On January 14, 2020, we sent an information request (IR) for samples of the proposed syringe and associated packaging.[c] We note there are discrepancies between the labeling submitted on October 24, 2019 and the samples received in January 2020 (e.g., the sample container label includes a lot number and expiration date which is not indicated on the submitted container label PDF). We address discrepancies and provide labeling recommendations in section 4.2 below.

Our review of the PI, container label, and carton labeling identified areas that can be modified to improve the clarity of the information presented.

4. CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed PI and labels can be improved to increase clarity of important information to promote the safe use of the product. We provide recommendations for the division in Section 4.1 and recommendations for Spectrum in Section 4.2 below.

4.1 RECOMMENDATIONS FOR THE DIVISION

Prescribing Information

A. Highlights of Prescribing Information
    1. Dosage Forms and Strengths
        a. To reduce the risk of dosing errors, we recommend revising the dosage statement to state the dose in milligrams rather than (b) (4) Additionally, we recommend removing (b) (4) from the dosage statement. For example, revise to read: "13.2 mg administered subcutaneously once per chemotherapy cycle".

B. Dosage and Administration [2]
    1. Recommended Dosage [2.1]
        a. To reduce the risk of dosing errors, we recommend revising the dosage statement to only state the dose in milligrams and to remove (b) (4) . For example, revise to read: "The

[c] Godwin, L. Email – Information Request. 14 JAN 2020. Available at: https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af805377ab&_afrRedirect=1114043259800932

recommended dosage of [redacted] is a single subcutaneous injection of 13.2 mg administered once per chemotherapy cycle."

2. Administration [2.2]
    a. We recommend including the minimum length of time needed to bring the syringe to room temperature. For example, "Prior to use, remove the carton from the refrigerator [redacted] allow the [redacted] to reach room temperature [redacted]

C. Dosage Forms and Strengths [3]
    1. We recommend including a description of the solution in the dosage form statement. For example, "Injection: 13.2 mg/0.6 mL clear, colorless, preservative-free solution in a single-dose prefilled syringe [redacted]."

D. [redacted]
    1. We recommend moving the statement "The [redacted] prefilled syringe does not bear graduation marks and is intended only to deliver the entire contents of the syringe (13.2 mg/0.6 mL) for direct administration" to *Section 2.2 Administration* as this includes administration information.

4.2 RECOMMENDATIONS FOR SPECTRUM PHARMACEUTICALS

A. Container Label
    1. As currently presented, the color contrast of the text on the clear background of the syringe label sample appears difficult to read, especially the magenta text for the proprietary name [redacted]. Low contrast is a common cause of unreadable text. We recommend revising the label background color (e.g., white) and consider bolding text to improve the contrast and readability of the proprietary and non-proprietary names.

    2. We request you add the product's linear barcode to the individual container (syringe) label as required per 21CFR 201.25 and 21 CFR 610.67. The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature. The barcode should be surrounded by sufficient white space to allow scanners to read the barcode properly and should be placed in an area where it will not be damaged because it appears at a point of label separation. Additionally, the barcode should be oriented in a vertical position. Barcodes placed in a horizontal position may not scan due to syringe curvature.[d]

    3. We note that the lot number and expiration date is not included on the container label submitted on October 24, 2019; however, the lot number and

[d] Neuenschwander M. et al. Practical guide to bar coding for patient medication safety. Am J Health Syst Pharm. 2003 Apr 15;60(8):768-79.

expiration date are printed on the container label on the provided syringe sample. Please confirm that the location of the lot number and expiration date will be the same on the marketed container label.

4. The format for the expiration date on the container (syringe) label on the syringe sample is (b) (4); however, the format for the expiration date on the blister tray label and carton labeling samples is "DD/MMM/YYYY". We recommend using the same expiration date format for all labels and labeling.

5. Consider adding the NDC and "Rx Only" statement to the principal display panel if space will allow.

B. Carton Labeling – Blister Tray

1. We recommend revising (b) (4) to read "For subcutaneous injection by a healthcare provider only" to help alert patients and healthcare providers that patients should not self-administer, but should take the prefilled syringe to their healthcare provider for administration.

2. We request you add the product's linear barcode, in addition to the 2D data matrix barcode, to the individual blister tray label as required per 21CFR 201.25 and 21 CFR 610.67. The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature The barcode should be surrounded by sufficient white space to allow scanners to read the barcode properly and should be placed in an area where it will not be damaged because it appears at a point of label separation.

3. Consider revising the storage information to present the temperature statement in Fahrenheit before Celsius to align with the storage statement in Section 16 of the Prescribing Information. Revise to read, "Store refrigerated at 36°F to 46°F (2°C to 8°C) in original carton to Protect from Light. Do Not Freeze. Do Not Shake."

C. Carton Labeling – Outer Carton

1. We recommend revising (b) (4) to read "For subcutaneous injection by a healthcare provider only" to help alert patients and healthcare providers that patients should not self-administer, but should take the prefilled syringe to their healthcare provider for administration.

2. We request you add the product's linear barcode, in addition to the 2D data matrix barcode, to the individual carton labeling as required per 21CFR 201.25 and 21 CFR 610.67. The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature. The barcode should be surrounded by sufficient white space to

allow scanners to read the barcode properly and should be placed in an area where it will not be damaged because it appears at a point of label separation.

3. We note that a human-readable and machine-readable product identifier, including the NDC or GTIN, serial number, lot number and expiration date, is not included on the carton labeling submitted on October 24, 2019; however, this information is printed on the side panel of the carton labeling on the provided sample. Please confirm that the location and format of this information will be the same on the marketed carton labeling. Please refer to recommendation A-4 regarding the format for the expiration date.

4. Consider revising the storage information to present the temperature statement in Fahrenheit before Celsius to align with the storage statement in Section 16 of the Prescribing Information. Revise to read, "Store refrigerated at 36°F to 46°F (2°C to 8°C) in original carton to Protect from Light. Do Not Freeze. Do Not shake."

APPENDICES: METHODS & RESULTS FOR MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Rolontis received on October 24, 2019 from Spectrum Pharmaceuticals.

Table 2. Relevant Product Information for Rolontis	
Initial Approval Date	N/A
Active Ingredient	eflapegrastim-xxxx
Indication	decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs
Route of Administration	subcutaneous
Dosage Form	injection
Strength	13.2 mg/0.6 mL
Dose and Frequency	13.2 mg/0.6 mL administered once per chemotherapy cycle approximately 24 hours after cytotoxic chemotherapy. Rolontis is administered subcutaneously via a single-dose prefilled syringe by a healthcare professional. Note: Safety and efficacy in pediatric patients have not been established
How Supplied	Clear, colorless solution supplied in a prefilled single-dose syringe (b) (4) containing 0.6 mL dose of eflapegrastim-xxxx in solution, supplied with 29-gauge ½-inch pre-attached (staked) needle with a needle guard. Dispensing pack containing one sterile 13.2 mg/0.6 mL prefilled syringe (NDC (b) (4)).
Storage	Store refrigerated between 36°F to 46°F (2°C to 8°C) in the carton to protect from light. Do not shake. Discard syringes stored at room temperature for more than 12 hours. Avoid freezing; discard syringe if frozen.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On February 20, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, "Rolontis" and "eflapegrastim". Our search identified 1 previous review, and we considered our previous recommendations to see if they are applicable for this current review.

Reviewer	Document Title	Application	Date	RCM No.
Rahimi, L.	Use-Related Risk Analysis Review for eflapegrastim injection	IND 103461	2018 JUL 25	2018-922

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05/13/2020 03:12:50 PM

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: March 17, 2020

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Clinical Analyst
Division of Cardiology and Nephrology

To: Elizabeth Godwin, RPM
DHP

Subject: QT Consult to BLA 761148 (SDN 001)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 11/13/2019 regarding the sponsor's QT cardiac safety report. We reviewed the following materials:

- Previous IRT review for IND 103461 dated 08/14/2018 in DARRTS;
- Study SPI-GCF-301-PK report and ECG cardiac safety report (Submission 0000);
- Proposed label (Submission 0000);
- Investigator's brochure (Submission 0000).

1 Internal Comments to the Division

1) The available ECG and cardiac safety data do not suggest an unexpected effect on the QTc interval. The findings in Study SPI-GCF-301-PK are consistent with our prior experience for large targeted proteins which have low likelihood of direct interaction with cardiac ion channels.
2) The sponsor did not propose any QT-related language on the proposed product label. This is consistent with the IRT's practice for other monoclonal antibodies and large proteins for which a dedicated QT study is usually not conducted.

2 BACKGROUND

Rolontis (eflapegrastim, 72 kDa) is a recombinant human granulocyte growth factor indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-

myeloid malignancies receiving myelosuppressive anti-cancer drugs. The proposed therapeutic dose is 0.6 mL (13.2 mg) dose administered subcutaneously once per chemotherapy cycle (one single dose pre-filled syringe), administered approximately 24 hours after cytotoxic chemotherapy.

Previously the sponsor proposed to conduct concentration-QTc analysis and statistical analysis (i.e., central tendency analysis, outlier analysis, and morphological analysis) using data from Study SPI-GCF-301-PK. Even though Study SPI-GCF-301-PK would not be adequate to support a thorough evaluation of eflapegrastim effect on the QT/QTc interval, the IRT did not consider that a TQT study would be needed based on the molecular properties of this drug and available non-clinical and clinical data in accordance with ICH E14 Q&A (R3) 6.3).

3 QT Analysis in Study SPI-GCF-301-PK

In the current submission, the sponsor submitted the ECG cardiac safety report based on Study SPI-GCF-301-PK. This was a Phase 1 PK study in a total of 26 early stage breast cancer patients taking eflapegrastim treatment (13.2 mg/0.6 mL fixed dose eflapegrastim) on Day 2 of each cycle. Patients had 12-lead ECGs in triplicate, performed locally prior to the first dose of study drug and at 10 hours and 24 hours post-dose in Cycle 1, and at the End of Treatment Visit (3 ECGs 5 minutes apart). Digital ECGs from 21 patients and paper ECGs from 5 patients were centrally analyzed for QT assessment. A summary of the sponsor's findings is provided below.

Central Tendency (By-Time) Analysis

Table 1 displays the mean change from baseline in ECG measurements. The largest measured mean ΔQTcF was 8.3 msec with upper bound of 90% CI being 11.5 msec. No large significant QT prolongation effect was observed in the study.

Table 1: Time-Point [1] Change from Baseline on Cycle 1 Day 2 (Sponsor's Results)

	Eflapegrastim C1D2 10 Hours Post	Eflapegrastim C1D2 24 Hours Post
Total number of patients (N)	**26**	**26**
Heart Rate in bpm (mean change from baseline)	1.6	7.2
PR in ms (mean change from baseline)	-3.6	-3.4
QRS in ms (mean change from baseline)	1.1	-0.3
QT in ms (mean change from baseline)	5.7	-8.0
QTcF in ms (mean change from baseline)	8.3 [uci=11.5]	4.0 [uci=9.7]
QTcB in ms (mean change from baseline)	9.8	11.0

Bpm = beats per minute; ms = milliseconds; QTcB = Bazett correction; QTcF = Fridericia correction; uci= upper confidence interval; "new" means not present at baseline (i.e. pre-dose on Cycle 1 Day 2), and only seen post baseline.

[1] Time-point results are based on the Replicate mean of the ECGs at baseline (Cycle 1 Day 2 Predose) and on the replicate means obtained at C1D2 10 hours post dose and C1D3 24 hours post dose.

Source: the sponsor's cardiac safety report, Table 3-1, page 15

Categorical Analysis

Table 2 lists the categorical analysis results for mean change from baseline in ECG measurements and morphology findings. No subject had QTcF >500 msec or mean change from baseline in QTcF (ΔQTcF) >60 msec.

Table 2: New Outliers[1,2] and Morphology[3] Findings on Cycle 1 Day 2 (Sponsor's Results)

	Eflapegrastim on C1D2 (Greatest value at either hour 10 or 24 post dose)
Total Number of Patient (N)	26
Heart Rate Bradycardic Outliers, N (%)	0
Heart Rate Tachycardic Outliers, N (%)	0
PR Outliers, N (%)	0
QRS Outliers, N (%)	0
QT new >500 ms, N (%)	0
QTcF new >500 ms, N (%)	0
QTcF new >480 ms, N (%)	2 (8%)
QTcF >30-60 ms, N (%)	2 (8%)
QTcF >60 ms, N (%)	0
QTcB new >500 ms, N (%)	1 (4%)
QTcB new >480 ms, N (%)	0
QTcB >30-60 ms, N (%)	4 (15%)
QTcB >60 ms, N (%)	0
New atrial fibrillation N (%)	0
New ST segment depression changes, N (%)	1 (4%)
New ST segment elevation changes, N (%)	0
New T wave inverted, N (%)	1 (4%)
New 2nd and 3rd Degree Heart Block, N (%)	0
New AF, N (%)	0
New Complete RBBB & LBBB, N (%)	0
New MI, N (%)	0
Abnormal U waves	0

Bpm = beats per minute; ms = milliseconds; QTcB = Bazett correction; QTcF = Fridericia correction; RBBB = right bundle branch block; LBBB = left bundle branch block; AF = atrial flutter; uci= upper confidence interval; "new" means not present at baseline i.e. pre-dose on Cycle 1 Day 2), and only seen post baseline.

[1] Maximum hourly post-dose QTcF(or QTcB) change is categorized as: no increase, >0 to 30 msec, >30 to 60 msec, and >60 msec.
[2] A subject had an outlier event if the maximum hourly post-dose QTcF (or QTcB) is >500 (or 480 or 450, separately) msec with a baseline of <=500 (or 480 or 450, separately) msec.
[3] Abnormalities seen after baseline are considered treatment-emergent if they were not seen on any of the baseline ECGs. For morphological analyses, baseline is defined as Cycle 1 Day 2 Predose ECGs.

Source: the sponsor's cardiac safety report, Table 3-2, page 16

Concentration-QTc analysis

The sponsor applied linear mixed effect modeling to evaluate the relationship between serum concentrations of eflapegrastim with time-matched, change from baseline in QTcF. The model included serum concentration, time (categorical), and a baseline adjustment (baseline value), with random subject effects on the intercept. The model does not suggest a positive exposure-response relationship between eflapegrastim exposure and ΔQTcF. The predicted mean effect at mean Cmax (193.7 ng/mL) is 6.2 ms (90% CI: 3.4-9.1 ms).

Reviewer's comments:

1) *The reviewers agree with the sponsor's selection of the primary endpoint (QTcF) because available data do not appear to suggest significant heart rate effect.*
2) *The reviewers did not conduct independent analyses.*

4 Cardiac Safety in Study SPI-GCF-301-PK

No patient died. SAEs occurred in 4 (15%) patients. None of the SAEs were cardiac related. One patient discontinued before completing all 4 cycles of treatment because of a non-cardiac TEAEs.

Two patients (Patient (b) (6) and Patient (b) (6)) had nonspecific ST and T wave changes from Baseline, which were of unknown clinical relevance.

- Patient (b) (6) reported no cardiac AEs.
- Patient (b) (6), a 55-year old White female with a history of depression and obesity since (b) (6) and taking lorazepam, sertraline, and propranolol for depression and taking Ritalin and topiramate for obesity. This patient had ST-T wave changes from Baseline and had self-limiting events of dizziness 2 times, chest discomfort and a syncopal episode with stable vital signs at each event. The association between the non-specific ST-T wave ECG changes and these events can't be established. In addition, lorazepam, sertraline, propranolol, Ritalin, and topiramate all have side effects of dizziness listed in their package inserts. Sertraline also has syncope listed in the package insert.

Reviewer's comment: *There was no imbalance of TEAEs in the SOC "cardiac disorders" in pooled analysis of studies SPI-GCF-301 and SPI-GCF-302 which contained an active control group (ISS Table 4.1.3.1.2b). None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., significant ventricular arrhythmias or sudden cardiac death) occurred in these studies. Syncope events were balanced between treatment groups.*

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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CLINICAL INSPECTION SUMMARY

Date	March 6, 2020
From	Anthony Orencia M.D., F.A.C.P., Medical Officer Cynthia Kleppinger, M.D., Acting Team Leader *for* Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Hyon-Zu Lee Pharm.D., Clinical Analyst Kathy Robie Suh, M.D., Ph.D., Clinical Team Leader Ann Farrell, M.D., Director Elizabeth Goodwin, Project Manager Division of Non-Malignant Hematology
BLA	761148
Applicant	Spectrum Pharmaceuticals Inc.
Drug	Eflapegrastim
NME	Yes
Division Classification	Anti-Neutropenia (modified Granulocyte Colony Stimulating Factor [G-CSF])
Proposed Indication	Treatment of patients with solid tumor chemotherapy-induced febrile neutropenia
CDER Memo Issuance Date	December 17, 2019
Summary Goal Date	March 25, 2020
Action Goal Date	April 24, 2020
PDUFA Date	October 24, 2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The sponsor was inspected for Study SPI-GCF-301 and Study SPI-GCF-302 in support of BLA 761148 as part of FDA's review of this application, formerly submitted under BLA (b) (4).

The inspection of the sponsor found regulatory deficiencies with oversight and monitoring of the trials, but the findings are not considered significant. Based on the inspection, data from the two studies appear reliable in support of the proposed drug indication.

II. BACKGROUND

Filgrastim, pegfilgrastim, and tbo-filgrastim are Granulocyte-Colony Stimulating Factors (G-CSFs) approved by the US FDA for the prevention of chemotherapy-induced neutropenia. For this application submission, the sponsor proposes a long-acting form of G-CSF, SPI-2012 (also known as (b) (4), eflapegrastim, HM10460A, Long Acting Protein/Peptide Discovery Platform Technology-G-CSF [LAPS-G-CSF]). This therapeutic biologic (b) (4), proposed for the indication of the reduction in the (b) (4), and incidence of infection, as manifested by febrile neutropenia.

Two studies, SPI-GCF-301 and SPI-GCF-302, respectively, will form the basis for the regulatory decision-making process for this application.

Previous submission:
The sponsor's BLA for eflapegrastim was previously submitted under BLA (b) (4). The application was withdrawn due to chemistry, manufacturing and pharmaceutical product quality issues. The following three clinical study sites were inspected with the corresponding final regulatory classifications: Dr. Istvan Lang Site 826002 (No Action Indicated) and Dr. Klara Mezei Site 642003 (No Action Indicated) in Study SPI-GCF-302, and Dr. Richy Agajanian Site 616003 (Voluntary Action Indicated) in Study SPI-GCF-301.

The current submission, under BLA 761148, does not contain any new studies; that is, no new data or clinical study sites were incorporated. This BLA resubmission was received containing Study SPI-GCF-301 and Study SPI-GCF-302, as described in detail below.

The application submission receipt date to the Agency was October 24, 2019. A complaint was received by the Agency, subsequently during the application review timeframe, alleging some of the following concerns:

a) Protocol deviations were not collected or tracked.
b) Protocol deviations captured for the BLA submission were manually collected from monitoring reports without any quality control/verification.
c) Subject diaries were never monitored.
d) Self-reported adverse events were not captured in the adverse event (AE) logs. Specifically, there were dozens of self-reported febrile neutropenia cases not captured in the AE logs.
e) Study coordinators across the US and Canadian sites informed the complainant that they were never trained to report AEs from patient diaries.
f) Source data verification (SDV) was not done on a regular basis as defined in the Monitoring Plan; the Monitoring Plan required "100% SDV" of data.
g) Clinical investigator financial disclosures were not captured.
h) Clinical Research Associates did not follow the monitoring plan with respect to the frequency of monitoring visits.

This clinical inspection summary covers a PDUFA surveillance inspection with a for-cause component.

Study SPI-GCF-301

Study SPI-GCF-301 was a Phase 3, randomized, open-label, active-controlled, multicenter study that compared the efficacy and safety of eflapegrastim (SPI-2012) with pegfilgrastim in early-stage breast cancer (operable Stage 1 to Stage 3A) patients treated with docetaxel with cyclophosphamide chemotherapy. The primary study objective was to compare the efficacy of a single dose of eflapegrastim (SPI-2012) with pegfilgrastim in patients with early-stage breast cancer receiving docetaxel and cyclophosphamide (TC), as measured by the Duration of Severe Neutropenia (DSN) in Cycle 1.

The start of study treatment was defined as the initiation of docetaxel and cyclophosphamide chemotherapy. The dosage groups included the following: Treatment Arm 1: SPI-2012 (13.2 mg/0.6 mL fixed dose SPI-2012 (b) (4) and Treatment Arm 2: pegfilgrastim (6 mg/0.6 mL).

The primary efficacy endpoint was duration of severe neutropenia (DSN in Cycle 1), defined as the number of days of severe neutropenia (i.e., absolute neutrophil count [ANC] less than 0.5×109/L) from the first occurrence of an ANC below the threshold. The secondary clinical efficacy endpoint was febrile neutropenia.

This multi-center, multi-national study was conducted at 82 active sites in the United States, Canada, and South Korea. A total of 406 study subjects were randomized: 210 subjects in the pegfilgrastim (comparative) arm and 196 subjects in the eflapegrastim (investigative) arm. The study period was from January 19, 2016 to October 31, 2018.

Study SPI-GCF-302

SPI-GCF-302 was a parallel study similar to SPI-GCF-301. SPI-GCF-302 was a Phase 3, randomized, open-label, active-controlled, multicenter study to compare the efficacy and safety of eflapegrastim (SPI-2012) with pegfilgrastim in breast cancer (operable Stage 1 to Stage 3A) patients treated with docetaxel and cyclophosphamide chemotherapy. The primary study objective was to compare the efficacy of a single dose of eflapegrastim (SPI-2012) with pegfilgrastim in patients with early-stage breast cancer receiving docetaxel and cyclophosphamide (TC), as measured by the DSN in Cycle 1.

The start of study treatment was defined as the initiation of eflapegrastim (SPI-2012) or pegfilgrastim. The dosage groups included the following: Treatment Arm 1: SPI-2012 (13.2 mg/0.6 mL fixed dose SPI-2012 (b) (4) and Treatment Arm 2: pegfilgrastim (6 mg/0.6 mL).

The primary efficacy endpoint was duration of severe neutropenia in Cycle 1, defined as the number of days of severe neutropenia (ANC less than 0.5×109/L) from the first occurrence of an ANC below the threshold. The assessment of absolute neutrophil counts was performed on Day1 and Days 4-15 in Cycle 1. For patients who did not meet severe neutropenia criteria, the endpoint measurement was defined as DSN=0. The secondary clinical efficacy endpoint was febrile neutropenia.

Study SPI-GCF-302 was a multi-center, multi-national study that was conducted at 74 sites in the US, Canada, Hungary, Poland, India, and Korea. A total of 118 subjects were treated in the eflapegrastim (investigative) arm and 119 subjects were treated in the pegfilgrastim arm. The study period was from July 10, 2017 to May 6, 2019.

III. RESULTS

Spectrum Pharmaceuticals, Inc.
157 Technology Drive
Irvine, CA 92618

Sponsor inspection dates: January 27 to February 12, 2020

This inspection evaluated compliance with the sponsor's responsibilities concerning the conduct of Study SPI-GCF-301 and Study SPI-GCF-302. The inspection included review of organizational charts, vendor list, vendor oversight, transfer of obligations, investigator agreements, institutional review board (IRB) approvals, training records, financial disclosures, monitoring plans, monitoring reports, monitor qualifications, safety reports, adverse events (AEs), protocol deviations, standard operating procedures, electronic records and validations, and drug accountability records. The inspection also addressed the complaint allegations.

The firm was originally incorporated as NeoTherapeutics in the state of Delaware in 1987. In 2002, the firm assumed its current name. The firm maintains offices in Irvine, CA, and most recently, Cambridge, MA. The firm maintains subsidiaries in India, Canada, Cayman Islands, Netherlands, and England/Wales. All the global subsidiaries, excepting India, do not occupy offices but are in place for tax purposes. Spectrum divested all their commercial products on 3/1/19.

Monitoring in the U.S. and Canada was conducted by in-house clinical research associates (CRAs) and by contract research organizations (CROs) at other sites. The monitors and site staff were trained on the protocol. The study protocols which were reviewed during the site audit, documented that febrile neutropenia was considered an adverse event. The sites were required to review each subject's diary at the end of each treatment cycle to ensure that high temperatures were reported. Site Monitoring Visit Reports documented diary review by the site monitors and febrile neutropenia AEs and listed missing diaries or fever AEs as protocol deviations and action item. Subjects' temperatures were not captured in the electronic data capture (EDC) system unless there was fever AE. There were no copies of diaries at Spectrum.

CRAs captured protocol deviations on the Site Monitoring Visit Reports and follow-up letters; they were extracted and listed on an Excel spread sheet. Missed laboratory analyses and out-of-window visits were captured by review of the EDC and the laboratory portal. Besides the CRAs, the Clinical Trial Assistant, Biostatistics team, and Data Management were responsible for capturing protocol deviations. All protocol deviations were put on one Excel spread sheet and

reviewed by the Medical Monitor. At the end of the trial, each clinical investigator was given a list of every protocol deviation at their site and the clinical investigator signed as acknowledgement. These were reviewed during the inspection.

Based on the Monitoring Plans, site monitoring visit frequencies were adequately performed. The Monitoring Plans did not dictate 100% source data verification (SDV). However, a complete verification of source data was mentioned in the CRAs' training slides. Sponsor staff was unable to explain why the training slides were not consistent with the Monitoring Plans. Some monitoring reports stated 100% SDV, some monitoring reports did not state 100% SDV, and some monitoring reports recorded that 100% SDV was not performed at times due to incomplete medical records.

Records for five clinical sites for each study were reviewed. For Study SPI-GCF-301, site records for US Sites 008, 023, 033, 059, and 109 were reviewed. For Study SPI-GCF-302, site records for Hungary Site 005 and US Sites 042, 022, 071, and 015 were reviewed.

The monitoring frequencies of the 10 sites reviewed were adequate and conducted within the parameters of the Monitoring Plans, which allowed for flexibility in frequency. No clinical study sites were closed. The sponsor appropriately put Site 023 (Study SPI-GCF-301) on enrollment hold and brought the site promptly into compliance. The sponsor's actions for Site 033 (Study SPI-GCF-301) and Site 042 (Study SPI-GCF-302) were not sufficient in bringing the two sites into prompt compliance. *See later discussion below.*

The safety oversight appeared adequate. All AEs were evaluated by the Medical Monitors. Protocol deviations were captured. There were eight Clinical Trial Managers during the running of Study SPI-GCF-301, which may have contributed to some lapses in oversight. The high turnover was due to personnel leaving for personal and professional reasons, not terminations.

At the inspection close-out, the FDA inspectors discussed with the sponsor the following items regarding financial disclosure information:

1. For both studies, the sponsor used the wrong financial disclosure form (Form FDA 3455) for clinical investigator financial disclosure reporting. In addition to using the wrong form, there was no commitment by the investigators to update changes in their financial status.

2. For Study (b) (4), financial disclosure forms were not obtained from investigators prior to the start of the study. Four clinical sub-investigators at Site (b) (4), (b) (6) and four investigators at Site (b) (4), (b) (6) signed financial disclosures forms after study start dates of their participation in the study. One sub-investigator at Site (b) (4), (b) (6) never signed a disclosure form.

Reviewer Comment: Although the wrong form was used, the sponsor did obtain clinical investigator financial disclosure reporting for the vast majority of those that were required to submit the information. Despite delay in reporting, there is no indication that these investigators and sub-investigators may have influenced patient safety or outcomes of the study. The eight that

eventually signed had nothing to disclose. The primary study endpoint was based upon a quantifiable study endpoint (duration of severe neutropenia). (b) (4) a clinical investigator that conducted both studies, disclosed a financial interest and Spectrum submitted this information in their BLA. No investigator had received reportable payments from the sponsor during the study.

A Form FDA 483 (Inspectional Observations) was issued at the end of the inspection for not promptly bringing into compliance an investigator who did not comply with the signed agreement and the general investigational plan. Specifically:

1. Study SPI-GCF-301 Site 033 incurred 144 protocol deviations throughout the study, which included missed study procedures from November 2016 to January 2018. Site 033 did not promptly respond to open action items listed on the Site Monitoring Visit (SMV) reports. For example, on visit date January 25, 2018, there were 26 open Action Items and 648 unresolved queries still open from a previous visit. These protocol deviations were previously submitted to the BLA.

2. Study SPI-GCF-302 Site 042 incurred 52 protocol deviations throughout the study, which included 16 major deviations and missed study procedures from June 2017 to November 2018. Action Items were not closed for months or years after being opened. There were no supporting documents of the meetings and discussions that supposedly took place between sponsor staff and the clinical investigator. These protocol deviations were previously submitted to the BLA.

3. The electronic case report form completion guidelines for both studies required that the forms be completed within 5 business days after each subject visit. Several sites did not comply with these guidelines, with entries often weeks late.

The Form FDA 483 observations and discussion items were not disputed by the sponsor.

The sponsor's management was cooperative and had already started corrective actions prior to the inspection, such as revising their standard operating procedures. They provided two revised SOPs during the inspection regarding financial disclosure and management of clinical site noncompliance. A Clinical Trial Management System, which can track protocol deviations and action items, has been implemented for all current studies, as of 4/20/2019. SOP-CL-010 (Identification and Management of Clinical Site Non-Compliance) was recently updated. The sponsor staff will add "repeated late data entry" as an additional example of a significant protocol deviation, and it will warrant escalation.

In general, the complaint was not substantiated. Regulatory deficiencies were observed during the inspection; however, in general, these were not considered significant. These findings did not appear to have an impact on data integrity or reliability.

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