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APPLICATION NUMBER:

211226Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	10/19/2018
From	Nina Ni, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA	211226
Type of Application	505(b)(2)
Applicant	Spectrum Pharmaceuticals, Inc. (Spectrum)
Date of Receipt	12/22/2017
PDUFA Goal Date	10/22/2018
Proposed Proprietary Name	Levoleucovorin for injection
Dosage forms / Strength	For Injection, 175 mg/vial and 300 mg/vial
Route of Administration	Intravenous administration
Proposed Indication(s)	• Rescue after high-dose methotrexate therapy in patients with osteosarcoma. • Diminishing the toxicity associated with over-dosage of folic acid antagonists or impaired methotrexate elimination. • Treatment of patients with metastatic colorectal cancer in combination with fluorouracil.
Recommended:	**APPROVAL**

This cross-discipline team leader review is based on the primary reviews, memos, and documented review input of:

- Drug Substance (Gaetan Ladouceur, Ph.D.); in Panorama, dated August 03, 2018
- Drug Product (William Adams, Ph.D.); in Panorama, dated September 10, 2018
- CMC Labeling (William Adams, Ph.D. and Nina Ni, Ph.D.); in Panorama, dated September 24, 2018 and October 18, 2018
- Drug Product BC Memo (Anamitro Banerjee, Ph.D.); in Panorama, dated September 06, 2018
- Microbiology (Hemlata Tamta, Ph.D.); in Panorama, dated September 21, 2018
- Manufacturing Facilities (David Anderson, Ph.D.); in Panorama, dated August 30, 2018
- Manufacturing Process (David Anderson, Ph.D.); in Panorama, dated August 30, 2018
- Quality Biopharmaceutics (Akm Khairuzzaman, Ph.D.); in Panorama, dated August 30, 2018

- Clinical (Shan Pradhan, M.D.); in DARRTS, dated September 28, 2018
- Clinical Pharmacology (Hong Zhao, Ph.D.); in DARRTS, dated September 21, 2018
- Pharmacology/Toxicology (Emily Wearne, Ph.D.); in DARRTS, dated August 31, 2018
- PeRC (Christine Lincoln); in DARRTS, dated September 24, 2018
- DMEPA (Colleen Little, Pharm.D.); in DARRTS, dated April 27, 2018, August 10, 2018, September 07, 2018, and October 11, 2018 for proprietary name review; May 16, 2018 and August 09, 2018 for labeling review; and October 17, 2018 for carton/container review
- OPDP (Carole Broadnax, Regulatory Review Officer); in DARRTS, dated August 01, 2018; and October 17, 2018 for carton/container review

1. Introduction

Spectrum submitted NDA 211226 on 12/22/2017 to pursue approval of (b) (4) levoleucovorin for injection, 175 mg/vial and 300 mg/vial, under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the Act) (b) (4) and includes the addition of a new strength, 300 mg/vial. The proposed drug product, levoleucovorin for injection is a lyophilized product containing 175 mg or 300 mg of levofolinic acid per vial. The drug product is reconstituted with sterile 0.9% saline to 50 mg/mL levoleucovorin. The reconstituted colorless to slightly yellow solution is either injected or further admixed prior to injection. The 300 mg/vial strength is supplied in a 20-mL (b) (4) clear glass vial closed with a 20-mm grey (b) (4) stopper. The 175 mg/vial strength is supplied in 10-mL (b) (4) clear glass vial closed with a same stopper.

This NDA relies on the FDA's determination of safety and efficacy for Spectrum's Fusilev® (levoleucovorin) lyophilized and ready-to-use drug products approved under NDA 020140, and Hospira Inc.'s leucovorin calcium for injection approved under NDA 008107. The applicant is seeking approval of a lyophilized powder form of levoleucovorin for the same indications granted for Fusilev.

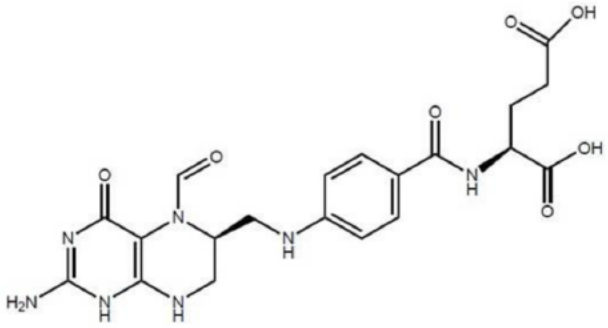
2. Background

Spectrum's NDA relies on two drugs: Spectrum's Fusilev® (levoleucovorin) lyophilized and ready-to-use drug products approved under NDA 020140 by cross-reference, and Hospira Inc.'s leucovorin calcium for injection approved under NDA 008107 (which was withdrawn not due to safety or efficacy concerns) as listed drug (LD). Spectrum's cross-referenced drug product and Hospira's listed drug product are the calcium salt of leucovorin. Upon reconstitution, Spectrum's proposed drug is claimed to contain (b) (4) levoleucovorin for injection which is composed of the active moiety l-isomer of folinic acid; the same active moiety in Spectrum's approved drug, Fusilev. Therefore, the indications to be filed in this 505(b)(2) NDA for levoleucovorin for injection are identical to those approved for Fusilev. Fusilev is approved for rescue after high-dose methotrexate therapy in patients with osteosarcoma; for diminishing the toxicity associated with over-dosage of

folic acid antagonists or impaired methotrexate elimination; and for treatment of patients with metastatic colorectal cancer in combination with fluorouracil.

3. Chemistry, Manufacturing, and Controls (CMC)

The drug substance, levoleucovorin is a folate analog and the pharmacologically active levo-stereoisomer of leucovorin free acid. Labeling and strength designation is based on the levoleucovorin free acid which is consistent with the cross-referenced drug product, Fusilev, and the FDA salt nomenclature policy adopted for labeling purpose.



(2S)-2-[[4-[[(6S)-2-amino-5-formyl-4-oxo-1,6,7,8-tetrahydropteridin-6-yl] methylamino] benzoyl] amino] pentanedioate

Molecular Formula: $C_{20}H_{23}N_7O_7$
Molecular Weight: 473.5 g/mole

Levoleucovorin possesses the (6S) absolute configuration at carbon 6 of the pteridine nucleus and the natural "L" configuration in the glutamate side chain. Levoleucovorin is soluble in DMSO, and insoluble in acetone and water.

The drug substance, levoleucovorin (b) (4) CMC information for characterization, manufacture, control, and stability is provided by cross-referencing to (b) (4) (b) (4) DMFs (b) (4) and (b) (4) Release testing is conducted by (b) (4) DMF (b) (4) was last reviewed and found adequate on 04/28/2018. DMF (b) (4) was last reviewed and found adequate on 06/13/2018. The drug substance which is stored at (b) (4) °C in a (b) (4) is stable for (b) (4) (b) (4)

The proposed drug substance is crystalline powder of levoleucovorin free acid. The proposed drug product is claimed to be levoleucovorin (b) (4) which is (b) (4) (b) (4) Therefore, the applicant was advised to revise the product name from to levoleucovorin (see labeling section).

The proposed drug product is a white to pale yellow lyophilized powder formulated to contain 175 mg or 300 mg levofolinic acid in a single-dose vial which is to be stored at USP controlled room temperature. The commercial presentations are a 10-mL (175 mg) or a 20-mL (300 mg) (b) (4) clear glass vial closed with a 20-mm grey (b) (4) stopper and a (b) (4) aluminum over seal. The primary container is enclosed in a single vial carton.

The proposed drug product is intended to be reconstituted with 3.6 mL or 6.2 mL sterile normal saline (0.9% sodium chloride for injection, USP) to obtain a colorless to slightly yellow solution containing 50 mg/mL levoleucovorin. Reconstituted solution is either injected directly or further diluted with sterile normal saline or sterile D5W (5% dextrose for injection, USP) for intravenous (IV) infusion as a solution containing 0.5 - 5.0 mg/mL levoleucovorin.

Unit formulation is levoleucovorin (b) (4) with mannitol, USP and sodium hydroxide, USP formulated with water for injection, USP which is removed during lyophilization. Sodium hydroxide and hydrochloric acid are used to adjust pH in the (b) (4). Excipients are shown to be BSE/TSE/melamine-free and none are of human or animal origin. No excipient is novel. All excipients meet USP/NF monograph requirements for acceptance.

Drug product is manufactured at (b) (4); release and stability tested at (b) (4); labeled and secondary packaged at (b) (4) and distributed by (b) (4)

The drug product may be granted an expiry dating period of 24 months when stored at USP controlled room temperature.

All the manufacturing and testing facilities for both drug substance and drug product were found acceptable either based on profile or per pre-approval inspection.

The applicant is requesting categorical exclusion for EA as per 21 CFR 25.21 which is granted based on the calculated EIC-aquatic.

Biopharmaceutics
The biopharmaceutics review assessed the adequacy of the Applicant's biowaiver request for the proposed drug product, levoleucovorin for injection. Per 21 CFR 320.24(b)(6), the supporting data and information for the biowaiver request were evaluated and found to adequately support bridging of the proposed drug product to the cross-referenced and listed drugs. The Biopharmaceutics reviewer recommends approval of this NDA.

Overall CMC recommendation
The drug substance, drug product, biopharmaceutics, process, microbiology, and facility reviewers recommended approval for this NDA. Thus, the Office of Pharmaceutical Quality review team recommends approval of this NDA.

4. Clinical Pharmacology

No clinical pharmacology or biopharmaceutics studies were submitted; therefore, clinical pharmacology review team did not conduct a review of this NDA submission.

5. Non-Clinical Pharmacology/Toxicology

The Applicant did not submit any new nonclinical data, but instead is relying on FDA's previous findings of nonclinical safety for Spectrum's Fusilev and Hospira's leucovorin calcium for injection, as well as published literature for levoleucovorin to address the nonclinical requirements for an NDA. This application introduces a (b) (4) new strength of levoleucovorin (300 mg/vial) supplied as a sterile lyophilized powder. The levels of mannitol and sodium hydroxide included in the proposed formulation, while higher than the levels in the cross-referenced and listed drugs, are still adequately supported from a safety perspective as higher amounts of these common excipients/buffers are present in other approved products. In addition, all listed impurities are within ICH limits. There are no outstanding pharmacology/toxicology issues that would preclude approval of this 505(b)(2) for the proposed indications.

The non-clinical pharmacology/toxicology review team recommends approval of this NDA.

6. Clinical/Statistical-Efficacy

Spectrum relied on FDA's previous findings of safety and efficacy for two drugs, cross-referenced Fusilev (levoleucovorin) under Spectrum NDA 020140 and the listed drug leucovorin calcium for injection under Hospira NDA 008107 (withdrawn not due to safety or efficacy concerns). Spectrum did not conduct clinical safety or effectiveness studies to support the application and relies on FDA's previous findings of safety and effectiveness under NDAs 020140 and 008107.

The clinical team recommends approval of this NDA.

7. Safety N/A

8. Advisory Committee Meeting N/A

9. Pediatrics

The application included a request for full waiver of pediatric studies. The Initial Pediatric Study Plan (iPSP) was submitted under IND 108407, with FDA's agreement on January 31, 2018. At its September 24, 2018 meeting, a full waiver of pediatric studies was also granted by the Pediatric Review Committee (PeRC). This information will be communicated to the applicant at the time of final approval.

10. Other Relevant Regulatory Issues N/A

11. Labeling

The labeling review was performed by DMEPA, OPDP, Clinical, Non-Clinical, and CMC. The following comments have been satisfactorily resolved.

CMC Recommendations:

1. The proposed draft labeling for [redacted] levoleucovorin does not include section 2.2 from the Fusilev (cross-referenced drug) product labeling. Provide the rationale for, and justification regarding the safety of, the proposed removal of section 2.2.
2. The application should be evaluated as levoleucovorin which is formulated into a lyophilized powder as [redacted], not as [redacted] levoleucovorin in solution as proposed. Therefore, the established name for the proposed drug product should be revised to Levoleucovorin for Injection as approved for the cross-referenced and listed products; and the drug strength presented on the product labels and in the calculation for assay should be revised to reflect content of levoleucovorin [redacted]

[redacted]

Clinical Recommendations:

1. The proposed labeling Spectrum submitted with the application was based on that for Fusilev and not the most recently approved levoleucovorin product (Actavis). Section 1.14.3.1 of the application contained an annotated comparison with the Fusilev package insert. Changes Spectrum proposed compared to the Fusilev labeling included:
   a. Removal of [redacted])
   b. Deletion of the following from Warnings and Precautions [redacted]
   c. Deletion of [redacted]
   d. Revised strength information
2. FDA proposed updates throughout the label to align with current FDA labeling guidance and practice. Spectrum proposed revisions in Section 2.4 (which describes dosing for the colorectal cancer indication) [redacted]

OPDP Recommendations:

1. The FPI section 5.2 states, "… increased treatment failure and morbidity." OPDP recommends adding this language consistent with the FPI.

2. Recommend listing in decreasing order of frequency consistent with the incidences in the FPI Table 3 (i.e., stomatitis (72%), diarrhea (70%), and nausea (62%).
3. OPDP has no comments on carton and container labels.

DMEPA Recommendations:

A. General Comments (Container labels & Carton Labeling)
   1. Revise the established name to read "(Levoleucovorin) for Injection" and remove the [redacted] (b) (4)
   2. Revise the strength expression to read "175 mg/vial" and "300 mg/vial" on the principal display panel (PDP) for consistency with the proposed PI submitted on March 9, 2018. [redacted] (b) (4).
   3. Revise the container labels and carton labeling to include the use of different colors, boxing, or some other means to provide adequate differentiation between the different strengths to mitigate the risk of wrong strength selection or dosing errors. As currently proposed, there is inadequate strength differentiation between the 175 mg and 300 mg strengths, which are [redacted] (b) (4)
   4. Revise the product code in the NDC numbers to ensure the middle 3 or 4 digits are different and non-sequential between strengths. [redacted] (b) (4) The similarity of the product code numbers has led to selecting and dispensing of the wrong strength and wrong drug. The middle digits are traditionally used by healthcare providers to check the correct product, strength, and formulation.
   5. Ensure the lot number and expiration date are clearly differentiated from one another and are not located in close proximity to other numbers where the numbers can be mistaken as the lot number.
   6. Consider revising the storage and handling statement from "...excursions from 15-30° C (59-86 °F)" to "...excursion from 15 °C - 30 °C (59 °F - 86 °F)" to include the unit of measurement after each numerical temperature value.
   7. Revise package type term from [redacted] (b) (4) to "Single-dose vial- Discard Unused Portion."
   8. Change the statement, "Usual Dosage [redacted] (b) (4)." to read, "Usual Dosage: See Prescribing information."
   9. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you wish to use. We recommend using a format such as MMMYYY (e.g. JAN2019) or MMMDDYYY (e.g. JAN312019).
   10. As proposed, mannitol is expressed as "mg/mL" on container labels and carton labeling but expressed as "mg" in PI (Section 11). Clarify which expression you intend to use across all labels and labeling (container labels, carton labeling, and PI) for consistency.

B. Container Labels
   11. FDA notes the presence of the barcode placeholder, but please submit updated container labels with the actual linear barcode instead of the placeholder for our review.

C. Carton Labeling
   12. Decrease the prominence of statement "Rx Only" as this information appears more prominent than the established name on the principal display panel.

D. Proprietary Name

DMEPA denied Spectrum's proposed proprietary names of (b) (4) for the following reasons:

(b) (4)

Spectrum proposed an alternate proprietary name of Khapzory which was received on September 18, 2018 and the team found Khapzory is acceptable on October 11, 2018.

Overall Labeling Recommendation:

The labeling for the proposed levoleucovorin for injection is acceptable.

12. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

This product relies on the safety and efficacy of two products, Spectrum's Fusilev® (levoleucovorin) lyophilized and ready-to-use drug product approved under NDA 020140 by cross-reference, and the listed drug Hospira Inc.'s leucovorin calcium for injection approved under NDA 008107 (which was withdrawn not due to safety or efficacy concerns). No new clinical or nonclinical data were provided with this submission, as no other studies were conducted for this 505(b)(2) application. The cross disciplinary team lead recommends **APPROVAL** of this submission.

- **Risk Benefit Assessment**

Please refer to NDAs 020140 and 008107.

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

/s/

NINA NI
10/19/2018

JOSEPH E GOOTENBERG
10/19/2018
I agree with the conclusions reached by the CDTL, as embodied in this review, that no issues preclude full approval of this NDA. I recommend that this NDA be issued an APPROVAL