CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211226Orig1s000

CLINICAL REVIEW(S)

FROM: Shan Pradhan, Medical Officer, DOP2
THROUGH: Martha Donoghue, Team Leader, DOP2
TO: File
SUBJECT: NDA 211226 SDN 1
SUBMIT DATE: December 22, 2017
PRODUCT: [redacted] levoleucovorin for injection, 175 mg/vial and 300 mg/vial
APPLICANT: Spectrum Pharmaceuticals

Spectrum Pharmaceuticals (Spectrum) submitted this application for [redacted] levoleucovorin for injection under the 505(b)(2) regulatory pathway. Spectrum referenced two reference listed drugs, Fusilev (levoleucovorin) under Spectrum NDA 20140 and levoleucovorin calcium for injection under Hospira NDA 8107 (withdrawn for reasons unrelated to safety or efficacy concerns). Spectrum did not conduct clinical safety or effectiveness studies to support the application.

A Type B Pre-NDA meeting was held June 28, 2017, and Type C Meeting Written Responses issued December 5, 2017, regarding development of [redacted] levoleucovorin; meeting minutes can be found under IND 108407.

Spectrum's application relies on FDA's previous findings of safety and effectiveness under referenced NDAs 20140 and 8107. Fusilev is the calcium salt of levoleucovorin and is approved under NDA 20140 for the following indications:

- Rescue after high-dose methotrexate therapy in osteosarcoma
- Diminishing the toxicity and counteracting the effects of impaired methotrexate elimination and inadvertent overdosage of folic acid antagonists
- Use in combination chemotherapy with 5-fluorouracil in the palliative treatment of patients with advanced metastatic colorectal cancer

The Fusilev label includes a limitation of use as follows: "Fusilev is not approved for pernicious anemia and megaloblastic anemias. Improper use may cause a hematologic remission while neurologic manifestations continue to progress."

Fusilev is supplied as Fusilev for Injection (50 mg single-use vial containing sterile lyophilized powder) and Fusilev Injection (175 mg/17.5 mL and 250 mg/25 mL single use vials).

Spectrum stated in the cover letter that the product represents a [redacted] addition of a new strength, the 300 mg/vial.

The proposed labeling Spectrum submitted with the application was based on Fusilev's approved labeling (including the same indications, listed above) 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:

- Removal of [redacted] (b) (4)
- Deletion of the following from Warnings and Precautions [redacted] (b) (4))
- Deletion of [redacted] (b) (4)
- Revised strength information.

FDA proposed updates throughout the label to align with current FDA labeling guidances and practice. Spectrum proposed revisions in Section 2.4 (which describes dosing for the colorectal cancer indication) changing [redacted] (b) (4) Spectrum reverted to the "followed by" language from the Fusilev labeling, [redacted] (b) (4) At the time of this review, labeling negotiations with Spectrum are ongoing and this proposal is under review.

The application included a request for full waiver of pediatric studies. The initial Pediatric Study Plan (iPSP) containing the proposal for this request was submitted to IND 108407 onNovember 9, 2017, and was under review when NDA 211226 was submitted; however, because NDA 211226 was submitted, the PSP submission under IND 108407 was administratively closed. Refer to the February 5, 2018 PSP Closure Form under IND 108407. FDA agrees with a full waiver of pediatric studies for all the proposed indications; refer to the Oncology Center of Excellence (OCE) Subcommittee of the Pediatric Review Committee (PeRC) January 31, 2018 Meeting Minutes under IND 108407.

Other than the labeling issues described above, there are no clinical issues that would preclude approval of NDA 211226. The clinical review team recommends approval of this NDA once agreement on product labeling has been reached.

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/

SHAN PRADHAN
09/26/2018

MARTHA B DONOGHUE
09/28/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

MEMORANDUM

Date: September 19, 2018

From: Autumn Zack-Taylor, M.S., Regulatory Health Project Manager
DOP2/OHOP/CDER

Subject: Financial Disclosure

Financial disclosures were not required for the review of this application because there were no new clinical studies submitted supporting the application.