CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211226Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review memo

Submission Type	NDA 211226/0001 (505(b)(2)
Applicant	Spectrum Pharmaceuticals, Inc.
Submission Date	12/22/2017
Review Classification	Standard
Generic Name	(b) (4) Levoleucovorin
Brand Name	N/A
Drug Class	Folic acid antagonist
Indication	1. As rescue after high-dose methotrexate therapy in osteosarcoma; 2. To diminish the toxicity (b) (4) of impaired methotrexate elimination and of (b) (4) overdosage of folic acid antagonists; 3. For use in combination chemotherapy with 5-fluorouracil (5-FU) in the (b) (4) treatment of patients with (b) (4) metastatic colorectal cancer
Dosage Regimens	5 mg/m^2 every 6 hours; 50 mg/m^2 every 3 hours; 100 mg/m^2 by slow intravenous injection over 3 minutes
Dosage Form	Solution for Injection
Dosage Strengths	175 mg/vial and 300 mg/vial (new)
Route of Administration	Intravenous
Dosage Strengths	175 mg/vial and 300 mg/vial (new)
OND Division	DOP2
OCP Division	DCPV
OCP Review Team	Brian D. Furmanski, Ph.D. / Hong Zhao, Ph.D.
PDUFA Goal Date	10/22/2018

This NDA submission is intended to support the registration of (b) (4) levoleucovorin solution for intravenous injection via the 505(b)(2) regulatory pathway. Spectrum is pursuing approval of (b) (4) levoleucovorin, 175 mg/vial and 300 mg/vial presentations. This product represents (b) (4) (b) (4) addition of a new strength, 300 mg/vial. Spectrum's drug product (b) (4)

To support approval of (b) (4) Levoleucovorin for Injection, Spectrum is relying upon FDA's finding of safety and effectiveness of the above two approved calcium levoleucovorin or by reliance on published literature. Spectrum requested a waiver for the submission of *in vivo* bioavailability (BA) and/or bioequivalence (BE) data. To support the waiver, Spectrum provided bridging information of the (b) (4) Levoleucovorin compared with Fusilev which includes comparison of qualitative and quantitative composition, comparative physicochemical data and comparative disposition kinetics of (b) (4) levofolinate.

In addition, Spectrum Pharmaceuticals submitted a literature survey and risk-benefit assessment for (b) (4) levofolinate based on recently published studies with levoleucovorin, case reports of serious adverse events, and a Periodic Safety Update Report (PSUR) prepared by (b) (4)

On December 5th through a written response only (WRO) communication, FDA stated that Spectrum's proposal to request a waiver of the requirement for a human in vivo bioavailability study was acceptable. However, FDA's assessment of waiver requests is determined during the NDA review based on the supporting data and information provided in the NDA submission.

The approvability of this product is based on the acceptability of the request for biowaiver of BA/BE study. No clinical pharmacology or biopharmaceutics studies were submitted; therefore, clinical pharmacology review team did not conduct a review of this NDA submission.

Signature:

Hong Zhao, Ph.D.

Team Leader

Division of Clinical Pharmacology V

Cc: OHOP: RPM –Autumn Zack-Taylor; MTL –Martha Donoghue; MO – Sahn Pradhan

DCPV: Deputy DD - B Booth; DD - A Rahman

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/

HONG ZHAO
09/21/2018