CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211226Orig1s000

NON-CLINICAL REVIEW(S)

MEMORANDUM

Date: August 30, 2018
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Through: Whitney S. Helms, PhD
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To: File for NDA 211226
[redacted] Levoleucovorin for Injection
Re: Supporting Document (SD) 1, New NDA submitted on December 22, 2017

Spectrum Pharmaceuticals, Inc. submitted a 505(b)(2) application for [redacted] levoleucovorin for injection (hereafter referred to as levoleucovorin), relying on the listed drugs levoleucovorin calcium for injection (FUSILEV®; NDA 020140), marketed by Spectrum Pharmaceuticals, and Leucovorin calcium for injection (NDA 008107), marketed by Hospira Inc. NDA 008107 was withdrawn from the market, but not for reasons of safety or efficacy. Levoleucovorin is a folate analog and the levo isomeric form of racemic *d,l*-leucovorin. The proposed indications for levoleucovorin are rescue after high-dose methotrexate therapy in patients with osteosarcoma, diminishing the toxicity associated with overdose of folic acid antagonists or impaired methotrexate elimination, and treatment of patients with metastatic colorectal cancer in combination with fluorouracil, the same indications as the listed drugs. The Applicant did not submit any new nonclinical data, but instead is relying on FDA's previous findings of nonclinical safety for FUSILEV® and Leucovorin calcium for Injection, as well as published literature for levoleucovorin to address the nonclinical requirements for an NDA. In addition, the Applicant requested a waiver for submitting in vivo human bioavailability and/or bioequivalence data stating that the admixed dosage, route of administration, drug concentration, and administered volumes are identical for the proposed drug product and listed drug FUSILEV® (NDA 020140), which the FDA biopharmaceutics team reviewed and accepted.

This application introduces a [redacted] new strength of levoleucovorin (300 mg/vial) supplied as a sterile lyophilized powder (see Table 1). The levels of mannitol and sodium hydroxide included in the proposed formulation, while higher than the levels in the listed drugs, are still adequately supported from a safety perspective as higher amounts of these common excipients [redacted] are present in other approved products. In addition, all listed impurities are within ICH limits. [redacted] of the proposed label was deleted despite its inclusion in the current FUSILEV label because it was not informative to the prescriber, consistent with the most recent updates to the leucovorin label. There are no outstanding pharmacology/toxicology issues that would preclude approval of this 505(b)(2) for the proposed indications.

Table 1: Composition of (b) (4) Levoleucovorin for Injection

Ingredients	Composition			Function	Reference to Standard
	Quantity per vial		Percent (%)		
	175 mg	300 mg			
(b) (4)					

(Table excerpted from Applicant's submission)

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/s/

EMILY F WEARNE
08/30/2018

WHITNEY S HELMS
08/31/2018