CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208723Orig1s000

PHARMACOLOGY REVIEW(S)

MEMORANDUM

Date: August 12, 2016
From: Emily F. Wearne, PhD
Pharmacologist
Division of Hematology Oncology Toxicology for Division of Oncology Products 2
Through: Whitney S. Helms, PhD
Pharmacology Supervisor
Division of Hematology Oncology Toxicology for Division of Oncology Products 2
To: File for NDA 208723
Levoleucovorin Calcium for Injection (b) (4)
Re: Supporting Document (SD) 1, New NDA submitted on December 1, 2015

Actavis LLC submitted a 505(b)(2) application for levoleucovorin calcium for injection relying on the listed drug levoleucovorin (FUSILEV®) for injection marketed by Spectrum Pharmaceuticals. The proposed indications are rescue after high-dose methotrexate therapy for osteosarcoma and diminishing the toxicity (b) (4) methotrexate elimination (b) (4). This application is for a new strength of levoleucovorin (175 mg base/vial) supplied as a sterile lyophilized powder consisting of 175 mg levoleucovorin and 175 mg mannitol per vial. The listed drug is the sterile lyophilized powder formulation of FUSILEV® (50 mg/vial) consisting of 50 mg levoleucovorin and 50 mg mannitol per vial. Levoleucovorin is a folate analog and the levo isomeric form of racemic *d,l*-leucovorin. The Applicant requested a biowaiver stating that the conditions of use, active ingredients, route of administration, and dosage form are related to those of the listed drug FUSILEV® (NDA 020140). The biopharmaceutics review team determined that the biowaiver request was adequately supported.

The Applicant did not submit any new nonclinical data. Rather, the Applicant is relying on FDA's previous findings of nonclinical safety for FUSILEV® and published literature for the listed drug. Impurities are within ICH limits. The label was updated in accordance with the Pregnancy and Lactation Labeling Rule (PLLR) in collaboration with the Maternal Health review team. The Maternal Health review team recommended the addition of information regarding the embryo-fetal toxicity of folate pathway antagonists including methotrexate to Section 8.1 (Pregnancy) and revised Section 8.2 (Lactation) to advise women not to breastfeed during treatment with levoleucovorin when it is given with folic acid antagonist therapy. In addition, the nonclinical team deleted (b) (4) of the label because it was not informative to the prescriber. FDA internal labeling meetings are still ongoing. There are no pharmacology/toxicology issues that would preclude approval of this 505(b)(2) for the proposed indications.

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/s/

EMILY F WEARNE
08/12/2016

WHITNEY S HELMS
08/12/2016

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 208723 **Applicant: Actavis, LLC** **Stamp Date: December 1, 2015**

Drug Name: Levoleucovorin Calcium for Injection **NDA/BLA Type: 505(b)(2)**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?			Not applicable. No pharmacology/toxicology data was submitted.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?			Not applicable. No pharmacology/toxicology data was submitted.
3	Is the pharmacology/toxicology section legible so that substantive review can begin?			Not applicable. No pharmacology/toxicology data was submitted.
4	Are all required and requested IND studies in accord with 505 (b)(1) and (b)(2) including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			Not applicable. No toxicology studies were submitted.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?			Not applicable. No pharmacology/toxicology data was submitted.
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			Not applicable. No pharmacology/toxicology data was submitted.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			Not applicable. There were no pre-submission discussions.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity, degradant, extractable/leachable, etc. issues been addressed? (New toxicity studies may not be needed.)		X	This will be a review issue.
11	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable.
12	If the applicant is entirely or in part supporting the safety of their product by relying on nonclinical information for which they do not have the right to the underlying data (i.e., a 505(b)(2) application referring to a previous finding of the agency and/or literature), have they provided a scientific bridge or rationale to support that reliance? If so, what type of bridge or rationale was provided (e.g., nonclinical, clinical PK, other)?	X		The Applicant requested a biowaver and states that the conditions of use, active ingredients, route of administration, and dosage form are related to those of the listed drug FUSILEV® (levoleucovorin; NDA 020140). A new strength is proposed. The Applicant is relying on FDA's previous findings of nonclinical and clinical safety and efficacy for FUSILEV®, as well as on published nonclinical and clinical literature for the listed drug.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? __Yes___

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None at this time.

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/s/

EMILY F WEARNE
01/15/2016

WHITNEY S HELMS
01/15/2016