CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208723Orig1s000

SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	September 29,2016
From	Joseph E. Gootenberg, M.D.
Subject	Division Director Summary Review
NDA #	208723
Type of Application	505(b)(2)
Applicant	Actavis, LLC
Date of Submission	01-Dec-2015
PDUFA Goal Date	01-Oct-2016
Proprietary Name / Non-Proprietary Name	N/A Levoleucovorin for injection (Non Proprietary Name)
Dosage Form(s) / Strength(s)	Lyophilized powder for Injection / 175 mg/vial
Applicant Proposed Indication(s)/Population(s)	• Rescue after high-dose methotrexate therapy in osteosarcoma. • Diminishing the toxicity (b) (4) methotrexate elimination (b) (4)
Recommended Action	**APPROVAL**

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Shan Pradhan
Pharmacology Toxicology Review	Emily Wearne
Clinical Pharmacology Review	Safaa Burns
OPMH	Donna Snyder
OPQ ATL Review	Joyce Crich
Drug Substance Review	William Adams
Drug Product Review	Haripada Sarker
Manufacturing Facilities Review	Rose Xu
Manufacturing Process Review	Kumar Janoria
Microbiology Review	Elizabeth Bearr
Quality Biopharmaceutics Review	Jing Li
OPDP	Carole Broadnax
OSE/DMEPA	Otto Townsend
CDTL Review	Joyce Crich

1. Introduction

This New Drug Application, NDA 208723, for Levoleucovorin for injection was submitted by Actavis, LLC (Actavis) under the provisions of section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. The application relies on FDA's previous findings of safety and efficacy for the listed drug (LD), Fusilev (Levoleucovorin for injection) manufactured by Spectrum Pharmaceuticals, as well as published literature and additional quality data . The LD, Fusilev, was originally approved on March 7, 2008 under NDA 20140 and is marketed as a lyophilized powder available in sterile single-use vials containing 50 mg levoleucovorin as levoleucovorin calcium. Fusilev is administered by reconstituting and diluting the lyophilized powder with 0.9% NaCl. Actavis's proposed presentation is a lyophilized powder available in sterile single-use vials containing 175 mg levoleucovorin as levoleucovorin calcium, and is reconstituted by dilution with 0.9% NaCl. Although the therapeutic active moiety (levoleucovorin calcium), dosage form, route of administration, and drug content of the proposed drug product (b) (4) the listed drug product, the listed and the proposed drug product differ in strength: 50 mg levoleucovorin for Spectrum's Fusilev and 175 mg levoleucovorin for Actavis's Levoleucovorin for injection. Actavis submitted a bio-waiver request for in-vivo bioavailability/ bioequivalence studies to support the equivalence of the LD and the proposed drug product. No clinical data was submitted in the application

2. Background

Levoleucovorin [(6S)-leucovorin] is the "levo" isomer (actually the 2S,6S-diastereoisomer) of what has been historically known as "*d,l*-leucovorin" or "racemic leucovorin". Leucovorin (folinic acid) is a 5-formyl derivative of tetrahydrofolic acid and as a reduced form of folic acid carries the therapeutic classification of "folate analogue". It is readily converted to other reduced folic acid derivatives (e.g., tetrahydrofolate), and since it does not require the action of dihydrofolate reductase for its conversion, its function is unaffected by inhibition of this enzyme by drugs such as methotrexate, a folate antagonist long used in anti-cancer chemotherapy. Leucovorin allows purine/pyrimidine synthesis to occur in the presence of dihydrofolate reductase inhibition, so normal DNA replication processes can precede, therefore countering the effects of methotrexate and other folate inhibitors. In certain chemotherapy regimens, Leucovorin is administered at an appropriate time following methotrexate with the intention of "rescuing" bone marrow and gastrointestinal mucosa cells from methotrexate and therefore reducing the toxicity associated with its anti-cancer use. Used in proper doses, no apparent significant effect is seen on pre-existing methotrexate-induced cancer cell death or nephrotoxicity. The original FDA approval of leucovorin, known widely as *d,l*- leucovorin (or in common use "racemic leucovorin", a 1:1 mixture of "*d*- and *l*-leucovorin isomers") was in 1952. This FDA approved leucovorin was a mixture of two diastereoisomers: 6R-leucovorin (commonly referred to as *d*-leucovorin), and 6S-leucovorin (commonly referred to as *l*-leucovorin)

Levoleucovorin [(6S)-leucovorin] was discovered to be the pharmacologically active levo isomer (or 6S-diastereoisomer) of *d,l*-leucovorin and was developed to be an alternative to the marketed "*d,l*-leucovorin". The Fusilev (levoleucovorin) for injection application was

originally submitted in 1990 for indications of "rescue after high-dose methotrexate therapy in osteosarcoma" and "diminishing the toxicity (b) (4) of impaired methotrexate elimination (b) (4)
Sponsorship changed hands several times between 1992 and the subsequent resubmission of the application in in 2007. Fusilev was approved on March 7, 2008. Efficacy was based on the demonstration that levoleucovorin prevented the severe toxicity expected to occur in the absence of rescue. Market exclusivity associated with these indications expired in 2015. A third indication for use in combination chemotherapy with 5-fluorouracil in the palliative treatment of patients with advanced metastatic colorectal cancer was approved on April 29, 2011, and Fusilev's orphan drug exclusivity for this indication will expire on April 29, 2018.

In this application, Actavis has only requested the two methotrexate-related indications, and has "carved out" the colorectal cancer indication, in that way avoiding the orphan exclusivity afforded to Fusilev by the colorectal cancer indication that would preclude market approvability of the proposed drug product.

3. Product Quality

I concur with the conclusions reached by the CDTL and Product Quality Lead Joyce Crich that an Approval action is recommended.

The following items were reviewed by Product Quality and found to be adequate:

- The synthesis of the bulk drug substance, Levoleucovorin calcium pentahydrate
- The formulation of the Drug Product
- In-process manufacturing controls
- Drug Product impurity levels
- Drug Product stability, including long-term stability, under real-time and accelerated conditions
- The overall microbiological control and sterility assurance
- Container closure system compatibility with the Drug Product
- The proposed expiratory dating period of 18 months when stored (b) (4) at USP controlled room temperature 20-25ºC (68-77ºF); with excursions permitted to 15-30ºC (59-86ºF).
- Labelling of the product's strength consistent with FDA salt nomenclature policy

The overall recommendations by the Facilities Reviewer are "Acceptable" based on a Pre-Approval Inspection for the drug substance manufacturing site, (b) (4) (FEI No. (b) (4)) in (b) (4), and based on a Profile Review for the drug product manufacturing site, Actavis Italy SPA (FEI 3001116953) in Nerviano, Italy. respectively.

Actavis requested bio-waiver for this drug product. According to 21 CFR 320.22(b), the in vivo bioavailability (BA) or bioequivalence (BE) of certain drug products may be self-evident and the requirement for the submission of in vivo BA/BE data for such drug products can be waived. A drug product's in vivo bioavailability or bioequivalence may be considered self-evident if the drug product meets the following requirements:

- Is a parenteral solution intended solely for administration by injection, and
- Contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.

Actavis's proposed product Levoleucovorin, for Injection 175 mg/vial meets the above requirements for granting the biowaiver request, because:

- It is a lyophilized powder to be reconstituted to a solution for injection.
- It is qualitatively the same as the LD. Though the absolute quantity of the active and inactive ingredient in each vial is different from the LD (175 mg versus 50 mg), the final concentration in the reconstituted solution is the same due to the use of different volumes of the reconstitution liquid (17.7 mL versus 5.3 mL).
- • The pH and osmolality of the proposed reconstituted product are comparable to that of the listed drug.

Therefore the Biopharmaceutics Reviewer recommended approval of the requested bio-waiver for this drug product at the time of approval of the application.

There are no other Product Quality issues that would preclude approval of this Application.

The following is to be included in the approval letter:

Based on the provided stability data, a 18-month expiration dating period is granted for Levoleucovorin for injection (175 mg/vial) when stored (b) (4) **at USP controlled room temperature 20-25ºC (68-77ºF); excursions permitted to 15-30ºC (59-86ºF).**

4. Nonclinical Pharmacology/Toxicology

Actavis did not submit any new nonclinical data. Rather, the application relies on FDA's previous findings of nonclinical safety in the Fusilev labelling and published literature for Fusilev.

During the review, in collaboration with the Pediatric and Maternal Health review team. the label was updated in accordance with the Pregnancy and Lactation Labeling Rule (PLLR). 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)

I concur with the conclusions of the Nonclinical Pharmacology/Toxicology reviewer that there are no nonclinical pharmacology/toxicology issues that would preclude approval of this product.

5. Clinical Pharmacology

Actavis did not submit any new clinical pharmacology studies as the application contains a request for a waiver for the requirement to submit in vivo BA/BE data for the proposed new drug product. The Clinical Pharmacology reviewer provided comments to be used in the revision of the label.

The Clinical Pharmacology Review contained no statement to the effect that clinical pharmacology issues were found that would preclude approval of this product. I concur with the tacit conclusion there are no clinical pharmacology issues that would preclude approval of this product.

6. Clinical Microbiology

See Section 3 "Product Quality".

7. Clinical/Statistical-Efficacy

The application relies on FDA's previous findings of safety and efficacy for the LD, Fusilev. No Clinical/Statistical-Efficacy data were submitted in the Application. The clinical review team provided comments to proposed updates through the labeling in various sections to align with current FDA PLR labeling guidance's and practice. I concur with the conclusions of the clinical reviewer that no clinical issues were identified that would preclude approval.

8. Safety

The application relies on FDA's previous findings of safety and efficacy for the listed drug, Gemzar (Eli Lilly). No safety data were submitted in the Application. I concur with the conclusions of the clinical reviewer that no clinical issues, including safety issues, were identified that would preclude approval.

9. Advisory Committee Meeting

This 505(b)(2) application was not referred to an advisory committee because it has the same active ingredient, same route of administration, (b) (4) as the LD, Fusilev, and relies on FDA's finding of safety and efficacy for the LD, Fusilev.

10. Pediatrics

The Division of Pediatric and Maternal Health (DPMH) was consulted by DOP2 to review Actavis's request for a full waiver from pediatric studies and to assist the NDA labeling review related to pediatric use.

Under the Pediatric Research Equity Act (PREA), any application submitted for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration must submit a pediatric assessment. Actavis's Levoleucovorin for Injection does not constitute a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration and therefore PREA does not apply and no waiver from pediatric studies is necessary. Of note, Fusilev was granted orphan status on August 1, 1991 for use in conjunction with high dose methotrexate in the treatment of osteosarcoma and as a result requirements under the Pediatric Research and Equity Act (PREA) were not applicable to the original 2008 approval.

During review, in consultation with the DPMH, the pediatric information in the labeling was revised to comply with 21 CFR 201.57(c)(9)(iv) "Pregnancy and Lactation Labeling Rule" (PLLR).

11. Other Relevant Regulatory Issues

Patent/Exclusivity Issues

On February 1, 2016, Actavis notified Spectrum, Pharmaceuticals, Inc, the holder of NDA 020140 for Fusilev (levoleucovorin) for Injection, according to the records of the U.S. FDA, that Actavis submitted a Paragraph IV certification to U.S. Patent No. 6,500,829. On February 8, 2016, Actavis notified the University of Strathclyde, the owner of U.S. Patent No. 6,500,829, according to the records of the U.S. Patent and Trademark Office, that Actavis submitted a Paragraph IV certification to U.S. Patent No. 6,500,829. On April 22, 2016, Actavis submitted a Patent Amendment (eCTD Sequence # 0003) to NDA 208723 to inform FDA that neither Spectrum Pharmaceuticals nor the University of Strathclyde had taken any legal action against Actavis within the statutory 45-day period (which expired March 24, 2016). Though the patent expiration date for U.S. Patent No. 6,500,829 is March 7, 2022, there have been no legal actions from the patent holders against Actavis for the proposed drug product within the statutory 45-day period. Therefore Actavis is free to pursue marketing approval for its Levoleucovorin for Injection product.

In addition, the FDA/CDER 505b(2) Clearance Committee has determined that there are no patent/exclusivity infringement issues caused by the drug product proposed by Actavis to the listed drug Fusilev and to U.S. Patent No.6,500,829.

12. Labeling

The cross-discipline review team (including Nonclinical, Clinical, DPMH, Clin Pharm, CMC, and DMEPA) revised the label for brevity, clarity, updated language use to comply with PLR, updated sections to comply with PLLR, replacement of passive voice, transition to command language where appropriate, to remove sections that represented the "current practice of medicine", and to remove "promotional" language.

ORP was consulted pertaining to exclusivity issues regarding the LD, Fusilev.

The labelling review was completed and the revised labeling was sent to Actavis on September 2, 2016.

Actavis accepted all FDA label revisions on September 9, 2016

DMEPA reviewed the carton/container labeling and made recommendations that have been incorporated by Actavis.

13. Decision/Action/Risk Benefit Assessment

- **Regulatory Action: <u>Approval</u>**

1. The requested bio-waiver for this drug product is approved at the time of approval of the application.

2. The following is to be included in the approval letter:

   Based on the provided stability data, a 18-month expiration dating period is granted for Levoleucovorin for injection (175 mg/vial) when stored (b) (4) **at USP controlled room temperature 20-25ºC (68-77ºF); excursions permitted to 15-30ºC (59-86ºF).**

- **Risk Benefit Assessment**

The application relies on FDA's previous findings of safety and efficacy for the listed drug, Fusilev (Spectrum). There are no new efficacy or safety concerns that would preclude approval of this product. This product is nearly identical to the LD, Fusilev, when each product is reconstituted and diluted for administration. No new studies clinical were provided with this submission, as no clinical studies were conducted for this 505(b)(2) application.

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/s/

JOSEPH E GOOTENBERG
09/29/2016