

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208723Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

### Cross-Discipline Team Leader Review (Addendum)

<b>Date</b>	September 26, 2016
<b>From</b>	Anamitro Banerjee, Ph.D.
<b>Subject</b>	Cross-Discipline Team Leader Review - Addendum
<b>NDA</b>	208723
<b>Type of Application</b>	505(b)(2)
<b>Applicant</b>	Actavis LLC
<b>Date of Receipt</b>	December 01, 2015
<b>PDUFA Goal Date</b>	October 01, 2016
<b>Proposed Proprietary Name</b>	N/A
<b>Established Name</b>	Levoleucovorin for injection (Non Proprietary Name)
<b>Dosage forms / Strength</b>	Lyophilized Powder for Injection 175 mg/vial
<b>Route of Administration</b>	Intravenous
<b>Proposed Indication(s)</b>	<ul style="list-style-type: none"> <li>• Rescue after high-dose methotrexate therapy in osteosarcoma.</li> <li>• Diminishing the toxicity (b) (4) methotrexate elimination (b) (4)</li> </ul>
<b>Recommended:</b>	<b>Approval</b>

This cross-discipline team leader review is based on the primary reviews, memos and documented review input of:

- Drug Product (William Adams); in Panorama, dated August 25, 2016
- Drug Substance (Haripada Sarkar); in Panorama, dated August 25, 2016
- Microbiology (Elizabeth Berr); in Panorama, dated August 25, 2016
- Manufacturing Facilities (Rose Xu); in Panorama, dated August 25, 2016
- Manufacturing Process (Kumar Janoria); in Panorama, dated August 25, 2016
- Quality Biopharmaceutics (Jing Li); in Panorama, dated August 25, 2016
- Clinical (Shan Pradhan); in DARRTS, dated July 29, 2016
- Clinical Pharmacology (Safaa Burns); in DARRTS, dated March 15, 2016
- Pharmacology/Toxicology (Emily Wearne); in DARRTS, dated August 12, 2016
- DMEPA (Otto Townsend); in DARRTS, dated August 10, 2016

- Division of Pediatric and Maternal Health (Donna Snyder); in DARRTS, dated July 29, 2016

## 1. Introduction

Actavis LLC has submitted NDA 208723 for the product Levoleucovorin for injection, for intravenous use, 175 mg/vial. The submission is a 505(b)(2) application, referencing the lyophilized powder formulation, Fusilev® (levoleucovorin) for injection, for intravenous use. The listed drug (LD) Fusilev is available in 50 mg single-dose vials. The active pharmaceutical ingredient (levoleucovorin calcium pentahydrate), excipients (mannitol, sodium hydroxide and hydrochloride acid), formulation for lyophilized powder, dosage form, route of administration, solution for reconstitution (0.9% NaCl), and concentration of the reconstituted solution (10 mg /mL for both active moiety and excipient mannitol) of the proposed drug product are identical to those of the listed drug product. However, the proposed and the listed drug product differ in the strength of levoleucovorin (175 mg/vial vs 50 mg/vial), the quantity of the excipients (mannitol 175 mg/vial vs 50 mg/vial), and the volume of 0.9% NaCl solution for reconstitution (17.7 mL vs 5.3 mL). The applicant provided a bio-waiver request of 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

The current application relies on the Agency's determination of human safety and efficacy for Fusilev® (levoleucovorin) for injection, for intravenous use (Spectrum Pharmaceuticals) which was approved for marketing under NDA 20-140 on March 7, 2008. The applicant is seeking approval of Levoleucovorin for injection, for intravenous use in the strength of 175 mg/vial for the (b) (4) indications (b) (4).

FDA/CDER 505b(2) Clearance Committee has determined that there are no patent/exclusivity infringement issues caused by the proposed drug product by Actavis to the listed drug Fusilev and U.S. Patent No.6,500,829. The official clearance was pending at the time of CDTL review dated September 14, 2016. The review team was notified via email on September 19, 2016 that this application is cleared for action from a 505(b)(2) perspective.

## 14. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

The cross disciplinary team lead recommends an **approval action** for the application from a 505(b)(2) perspective.

- **Risk Benefit Assessment**

Please refer to NDA 020140.

Anamitro Banerjee -S

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## Cross-Discipline Team Leader Review

<b>Date</b>	05-SEP-2016
<b>From</b>	Joyce Z Crich, Ph.D.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA</b>	208-723
<b>Type of Application</b>	505(b)(2)
<b>Applicant</b>	Actavis, LLC
<b>Date of Receipt</b>	01-Dec-2015
<b>PDUFA Goal Date</b>	01-Oct-2016
<b>Proposed Proprietary/Established Name</b>	N/A Levoleucovorin for injection (Non Proprietary Name)
<b>Dosage forms / Strength</b>	Lyophilized powder for Injection / 175 mg/vial
<b>Route of Administration</b>	Intravenous
<b>Proposed Indication(s)</b>	<ul style="list-style-type: none"> <li>• Rescue after high-dose methotrexate therapy in osteosarcoma.</li> <li>• Diminishing the toxicity [REDACTED] (b) (4) [REDACTED] methotrexate elimination [REDACTED] (b) (4)</li> </ul>
<b>Recommended:</b>	<b>Approval</b>

This cross-discipline team leader review is based on the primary reviews, memos and documented review input of:

- ✧ Drug Substance (Haripada Sarker); in SharePoint, dated 10-Aug-2016
- ✧ Drug Product (William Adams); in SharePoint, dated 16-Aug-2016
- ✧ Microbiology (Elizabeth Bearr); in SharePoint, dated 12-Aug-2016
- ✧ Manufacturing Facilities (Rose Xu); in SharePoint, dated 17-Aug-2016
- ✧ Manufacturing Process (Kumar Janoria); in SharePoint, dated 16-Aug-2016
- ✧ Quality Biopharmaceutics (Jing Li); in SharePoint, dated 11-Apr-2016
- ✧ Clinical (Shan Pradhan); in DARRTS, dated 29-JUL-2016
- ✧ Pharmacology/Toxicology (Emily Wearne); in DARRTS, dated 12-Aug-2016
- ✧ DMEPA (Otto Townsend); in DARRTS, dated 10-Aug-2016
- ✧ Clinical Pharmacology (Safaa Burns); in DARRTS, dated 15-MAR-2016
- ✧ Division of Pediatric and Maternal Health (Donna Snyder), in DARRTS, dated 29-JUL-2016

## 1. Introduction

Actavis LLC has submitted NDA 208-723 for the product Levoleucovorin for injection, for intravenous use, 175 mg/vial. The submission is a 505(b)(2) application, referencing the lyophilized powder formulation, Fusilev<sup>®</sup> (levoleucovorin) for injection, for intravenous use. The listed drug (LD) Fusilev is available in 50 mg single-dose vials. The active pharmaceutical ingredient (levoleucovorin calcium pentahydrate), excipients (mannitol, sodium hydroxide and hydrochloric acid), formulation for lyophilized powder, dosage form, route of administration, solution for reconstitution (0.9% NaCl), and concentration of the reconstituted solution (10 mg /mL for both active moiety and excipient mannitol) of the proposed drug product are identical to those of the listed drug product. However, the proposed and the listed drug product differ in the strength of levoleucovorin (175 mg/vial vs 50 mg/vial), the quantity of the excipients (mannitol 175 mg/vial vs 50 mg/vial), and the volume of 0.9% NaCl solution for reconstitution (17.7 mL vs 5.3 mL). The applicant provided a bio-waiver request of 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

The current application relies on the Agency's determination of human safety and efficacy for Fusilev<sup>®</sup> (levoleucovorin) for injection, for intravenous use (Spectrum Pharmaceuticals) which was approved for marketing under NDA 20-140 on March 7, 2008. The applicant is seeking approval of Levoleucovorin for injection, for intravenous use in the strength of 175 mg/vial (b) (4)

These two indications are: (1) for rescue after high-dose methotrexate therapy in osteosarcoma; (2) for diminishing the toxicity (b) (4) methotrexate elimination (b) (4)

The third indication of Fusilev approved on April 29, 2011 in the revised Fusilev labeling\* is not claimed by Actavis in the proposed labeling for the product Levoleucovorin for injection. This third indication is for use in combination chemotherapy with 5-fluorouracil in the palliative treatment of patients with advanced metastatic colorectal cancer, and Fusilev's orphan drug exclusivity (ODE) for the colorectal cancer indication under NDA 20140 is set to expire on April 29, 2018. Therefore this ODE expiration date does not affect the market approvability of the proposed drug product by Actavis because the first two indications claimed by Actavis are not covered by the ODE.

In accordance with 21 CFR 314.52(b) and 21 CFR 314.52(e) Actavis amended the subject application to certify that the requirements stated in 21 CFR 314.52(a) and 21 CFR 314.52(c) have been satisfied. On February 1, 2016, Actavis notified Spectrum Pharmaceuticals, Inc. that Actavis submitted a Paragraph IV certification to U.S. Patent No. 6,500,829. Spectrum Pharmaceuticals, Inc. is the apparent holder of approved New Drug Application ("NDA") No.020-140 for Fusilev<sup>®</sup> (levoleucovorin) for Injection, Eq. 50 mg Base/Vial, according to the records of the U.S. Food and Drug Administration ("FDA"). On February 8, 2016, Actavis notified the University of Strathclyde that Actavis submitted a Paragraph IV certification to U.S. Patent No. 6,500,829. The University of Strathclyde is the record owner of U.S. Patent No. 6,500,829, according to the records of the U.S. Patent and Trademark Office ("PTO"). On April 22, 2016, Actavis submitted a Patent Amendment (eCTD Sequence # 0003) to NDA 208723 to inform the Agency that

Actavis amended the subject application in accordance with the provisions of Section 505(c)(3); 21 CFR §314.52(f), 21 CFR §314.107(f) and 21 CFR §314.107(f)(2), to certify that neither Spectrum Pharmaceuticals, nor University of Strathclyde, the record owner of U.S. Patent No. 6,500,829 have taken any legal action against Actavis within the statutory 45-day period (which was March 24, 2016). Though the patent expiration

date for U.S. Patent No. 6,500,829 is March 7, 2022 which was extended from December 31, 2009, there have been no legal actions from the patent holders against Actavis for the proposed drug product within the statutory 45-day period.

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

\* The revised Fusilev labeling approved on April 29, 2011 contains the following two dosage forms and three strengths:

Fusilev<sup>®</sup> (levoleucovorin) for Injection, Lyophilized Powder for Solution for Intravenous use in strength of 50 mg Base/Vial – approved on March 7, 2008

Fusilev<sup>®</sup> (levoleucovorin) Injection, Solution for Intravenous use in strengths of 175 mg/17.5 mL /Vial and 250 mg/25 mL/Vial – approved on April 29, 2011.

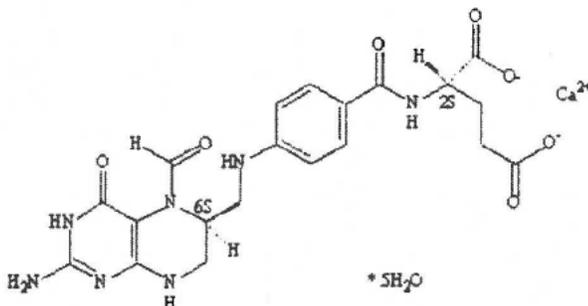
### 3. Chemistry, Manufacturing and Controls (CMC)

#### Drug Substance

The drug substance for NDA 208-723 is levoleucovorin calcium pentahydrate, the calcium salt in a pentahydrate form of levoleucovorin. Since levoleucovorin is a folate analog and the pharmacologically active levo isomer (or S isomer) of d,l-leucovorin, the drug substance is the pharmacologically active diastereoisomer (S isomer) of Leucovorin Calcium.

Labeling and strength designation (b) (4) consistent with the listed drug product, Fusilev, based on the FDA salt nomenclature policy adopted for labeling purpose.

Chemical Name: Calcium (2S)-2-[[4[[[(6S)-2-amino-5-formyl-4-oxo-1,4,5,6,7,8-hexahydropteridin-6-yl]methyl]amino]benzoyl]amino]-pentanedioate. Molecular Structure:



Molecular Formula: C<sub>20</sub>H<sub>21</sub>CaN<sub>7</sub>O<sub>7</sub> · 5H<sub>2</sub>O

Molecular Weight: 601.6 (b) (4)

Levoleucovorin calcium pentahydrate is white or light yellow crystalline hygroscopic powder. It is slightly soluble in water, practically insoluble in acetone and in alcohol.

The drug substance manufacturing process is referenced to DMF (b)(4) and it was found adequate to support the NDA. Though a retest period of (b)(4) months is proposed by the drug substance manufacturer when stored between (b)(4) which is acceptable based on DMF (b)(4) quality review, the applicant proposed a retest period of (b)(4) months stored between (b)(4) for this NDA.

The Drug Substance reviewer concluded that the overall control of the drug substance is satisfactory, and has recommended approval of the application.

#### Drug Product

The drug product is a sterile lyophilized powder in (b)(4) clear colorless glass vial with (b)(4) stopper, containing 175 mg of levoleucovorin (equivalent to 222 mg of levoleucovorin calcium pentahydrate). The drug product also contains mannitol (175 mg /vial) (b)(4) sodium hydroxide and/or hydrochloric acid which are used to adjust pH during manufacturing. The drug product is to be reconstituted with 17.7 mL of sterile 0.9% sodium chloride injection, USP, resulting in a solution of 10 mg/mL levoleucovorin in pH (b)(4) for further dilution prior to intravenous infusion for patient administration.

Except for the difference in solution volume and total drug quantity per vial, the reconstituted drug product is the same as the reconstituted listed drug Fusilev<sup>®</sup> (levoleucovorin) for injection (50 mg/vial), with respect to the concentration of levoleucovorin (and levoleucovorin calcium), excipient mannitol, pH adjusting agents (hydrochloric acid and sodium hydroxide), pH (=8), and reconstitution solution. The Applicant submitted a bio-waiver request which was reviewed by the biopharm reviewer (see the Biopharmaceutics section).

The applicant provided stability data from the three primary drug product batches (no. 4LM001, 4LM002 and 4LN002) up to 12 months at 25°C/60% RH (long term storage condition) and up to 6 months at 40°C/75% RH (accelerated condition) in the proposed commercial container closure system (b)(4). Those stability data reveal no significant trend during the studied period and all the test results meet the acceptance criteria of the proposed regulatory specifications for the drug product.

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

The CMC related comments for Sections 3, 11 and 16 of the proposed labeling were provided to align with current FDA labeling guidances and practice.

The Drug Product reviewer has recommended approval of the NDA.

#### Manufacturing Process

The manufacturing process consists of (b)(4)

(b)(4) The Process reviewer concluded that the risks associated with the drug product quality are adequately mitigated with the manufacturing process and has recommended approval of the NDA.

#### Product Quality Microbiology

(b) (4)

The overall microbiological control is satisfactory, in regarding to the manufacturing process, the manufacturing equipment, the microbiology tests in the proposed regulatory specifications, and the primary container closure system. The Microbiology reviewer has recommended approval of the application.

#### Facilities

(b) (4) (FEI No. (b) (4)) in (b) (4) is the drug substance manufacturer for manufacture, release testing, stability testing and packaging. Actavis Italy SPA (FEI 3001116953) in Nerviano, Italy is the drug product manufacturer for drug product manufacturing, release testing, stability testing, packaging, and labeling. The overall recommendations by the Facility reviewer from OPF/OPQ/CDER are "Acceptable" based on Pre-Approval Inspection for the drug substance manufacturing site and Profile Review for the drug product manufacturing site respectively.

#### Biopharmaceutics

The Actavis requested a bio-waiver for its proposed drug product. Though there is a difference in the total amount of the active ingredient Levoleucovorin (175 mg vs 50 mg) and the lyophilized powder pre vial between the proposed drug product and the listed drug Fusilev, both products after reconstitution with 0.9% sodium chloride achieve the same concentration of 10 mg/mL for levoleucovorin, (b) (4) the same excipients qualitatively (b) (4), and the comparable osmolality values. The waiver request for the in vivo bioequivalence study is granted according to 21CFR 320.22(b), on the basis of the nature of the reconstituted drug product in solution, as it is self-evident for the comparable physical and chemical characteristics of the proposed drug product to the listed drug Fusilev. From a biopharmaceutics perspective, NDA 208723 for Levoleucovorin for Injection 175 mg/vial is recommended for approval.

#### Overall CMC Recommendation

From the overall quality standpoint for chemistry, manufacturing and controls, the Office of Pharmaceutical Quality recommends approval for this NDA. There are no outstanding CMC issues that impact approvability of this NDA.

The following language 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 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).**

#### **4. Pharmacology/Toxicology**

The Applicant did not submit any new nonclinical data. Rather, the Applicant relied on FDA's previous findings of nonclinical safety in the Fusilev labeling (package insert) and published literature for the listed drug. All the impurities in the proposed drug substance and drug product 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. There are no pharmacology/toxicology issues that would preclude approval of this 505(b)(2) for the proposed indications. The Pharmacology/Toxicology reviewer recommended approval of the application.

## 5. Clinical

Actavis did not conduct safety or effectiveness studies to support the application and does not have right of reference to the listed drug Fusilev's data. The applicant relies on FDA's previous findings of efficacy and safety for Fusilev® (levoleucovorin) for injection, for intravenous use (Spectrum Pharmaceuticals, NDA 020140), approved March 7, 2008, for the following clinical indications and limitation (b) (4)

- Rescue after high-dose methotrexate therapy in osteosarcoma.
- Diminishing the toxicity (b) (4) methotrexate elimination (b) (4)
- (b) (4) for pernicious anemia (b) (4) megaloblastic anemias. (b) (4)  
hematologic remission (b) (4)

The applicant also refer red the same Fusilev labeling approved March 7, 2008 as the sole support, including for the Pediatric Use section, of the 505(b)(2) application.

On April 29, 2011, Fusilev's label was expanded to include a new indication, for use in combination chemotherapy with 5-fluorouracil in the palliative treatment of patients with advanced metastatic colorectal cancer. Spectrum Pharmaceuticals was granted orphan exclusivity for Fusilev for the colorectal cancer indication, and the exclusivity is set to expire April 29, 2018. Actavis did not request a colorectal cancer indication in the current application.

Actavis stated that though a vial containing a higher amount of drug product is proposed (175 mg/vial compared to the 50 mg/vial for Fusilev), the dose administered will not result in higher patient exposure to any of the active or inactive ingredients, and that when the same dose is reconstituted for administration, both products contain the same ingredients (b) (4)

The proposed labeling Actavis submitted was based on, (b) (4) the Fusilev labeling, (b) (4)

The clinical review team provided comments to proposed updates through the labeling in various sections to align with current FDA labeling guidances and practice.

The Clinical reviewer has recommended approval of Actavis' application as there are no other pending clinical issues.

## 6. Clinical Pharmacology

This NDA does not contain any clinical or clinical pharmacology studies as the Applicant requests for a biowaiver. The Clinical Pharmacology reviewer provided comments to revise the Section 12 (Clinical Pharmacology) as the following: 1. (b) (4)

2. Revising Sub-section 12.3 Pharmacokinetics this section according to p. 6, C. Subsection 12.3 Pharmacokinetics in *Draft Guidance for Industry: Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format*. Specifically, the pharmacokinetics subsection contains the following headings and subheadings: Absorption, Distribution, Elimination, Metabolism, Excretion, Specific Populations, Drug Interaction Studies, Drug A, Drug B.

## 7. Safety

N/A

## 8. Pediatrics

The Division of Pediatric and Maternal Health (DPMH) was consulted by DOP2 on January 5, 2016 to review the full waiver from the pediatric studies requested by Actavis and to assist the NDA labeling review related to pediatric use.

Since the proposed drug product does not constitute a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration and therefore the Pediatric Research Equity Act (PREA, which requires a pediatric assessment) does not apply. In addition, 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 PREA were not applicable to the original approval.

DPMH recommended the following language for Section 8.4 Pediatric Use of the labeling as the current labeling version does not contain such information, "The safety and effectiveness of levoleucovorin for injection have been established in pediatric patients. Use of levoleucovorin in pediatric patients is supported by open-label clinical trial data in 16 pediatric patients, 6 years of age and older and with additional supporting evidence from literature. [See Clinical Studies (14)]." A more detailed description of the clinical study is included in Section 14 of the labeling.

As stated in the DPMH review, "Methotrexate labeling notes that leucovorin is indicated as rescue to diminish the toxic effects of high doses of methotrexate. Methotrexate is approved for use in pediatric patients of all ages receiving cancer chemotherapy. Although there is no specific data for use of levoleucovorin in pediatric

patients under 6 years of age, mechanistically, the product would be likely to work similarly in patients < 6 years of age. Because of the known, serious adverse consequences of high dose methotrexate therapy without leucovorin rescue, the known benefit of the product outweighs any potential unknown risk for use in patients < 6 years of age”.

## 9. Advisory Committee Meeting

N/A

## 10. Labeling

The cross-discipline review team (including Nonclinical, Clinical, DPMH, Clin Pharm, CMC, and DMEPA) has completed the internal review of the labeling and the Division’s edits were conveyed to the applicant on September 02, 2016, the final completion of the revised labeling is pending on the Applicant’s response requested by September 09, 2016.

## 11. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

The proposed drug product, Levoleucovorin for injection, for intravenous use (175 mg/vial) is (b) (4) to the listed drug, Fusilev® (levoleucovorin) for injection, for intravenous use (50 mg/vial) for (b) (4) active and inactive ingredients except the difference in total amount of drug product in a vial. Both products after reconstitution with 0.9% sodium chloride achieve the same concentration (10 mg/mL), (b) (4) the same ingredients qualitatively and quantitatively (per mL), and the comparable osmolality values. There were no non-clinical or clinical studies conducted to assure nonclinical safety, clinical safety and efficacy, and a bio-waiver request was granted for this 505(b)(2) application. The cross disciplinary team lead recommendation is for APPROVAL to the application, pending on the 505b(2) Clearance Committee’s final determination on any potential patent/exclusivity infringement issues if applicable.

- **Risk Benefit Assessment**

Refer to NDA 20140

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