

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208723Orig1s000**

**OTHER REVIEW(S)**

**505(b)(2) ASSESSMENT**  
**Complete 2 months prior to action date**

<b>Application Information</b>		
NDA # 208723	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: NA Established/Proper Name: Levoleucovorin for Injection, 175mg base/vial Dosage Form: Powder for Injection Strengths: 175mg base/vial		
Applicant: Actavis L.L.C.		
Date of Receipt: December 1, 2015		
PDUFA Goal Date: October 1, 2016		Action Goal Date (if different):
RPM: Rebecca Cohen		
Proposed Indication(s): Rescue after high-dose methotrexate therapy in osteosarcoma. • To diminish the toxicity [REDACTED] <sup>(b)(4)</sup> methotrexate elimination [REDACTED] <sup>(b)(4)</sup>		

**GENERAL INFORMATION**

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES  NO

*If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*



**INFORMATION PROVIDED VIA RELIANCE  
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Published Data	Nonclinical toxicology, Clinical Pharmacodynamics and Mechanism of Action, Pharmacokinetics-ADME, Pharmacokinetics DDI, Pharmacokinetics in Special Populations 13.
NDA 020140- "Fusilev"	All FDA's previous finding of safety and effectiveness (clinical and nonclinical)

\*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature<sup>1</sup>. [See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.](#)

21 CFR 320.24(b)(6)

The listed drug for the proposed 505(b)(2) Fusilev for injection is Levoleucovorin Calcium- NDA 020140 marketed. Both products contain the same active moiety, but differ in the product quantity in the vial. Fusilev contains 50 mg base/vial. The product for the proposed product contains 175mg base/vial.

**RELIANCE ON PUBLISHED LITERATURE**

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES  NO

*If "NO," proceed to question #5.*

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES  NO

*If "NO", proceed to question #5.*

*If "YES", list the listed drug(s) identified by name and answer question #4(c)*

Fusilev.

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

<sup>1</sup>For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

YES  NO

APPEARS THIS WAY ON ORIGINAL

<sup>1</sup>For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

**RELIANCE ON LISTED DRUG(S)**

*Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.*

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES  NO

*If "NO," proceed to question #10.*

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Fusilev	NDA 020140	Yes

*✓Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A  YES  NO

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".*

*If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved via the DESI process:

- c) Described in a final OTC drug monograph?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES  NO

If "YES", please list which drug(s) and answer question d) i. below.  
If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing: Fusilev

i) Were the products discontinued for reasons related to safety or effectiveness?

YES  NO

*(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)*

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides a new quantity of drug per vial.

*The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.*

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms intended for the same route of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES  NO

If "NO" to (a) proceed to question #11.  
If "YES" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES  NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent? N/A  YES  NO

If this application relies only on non product-specific published literature, answer "N/A"  
If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES  NO

If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES  NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)? N/A  YES  NO

If this application relies only on non product-specific published literature, answer "N/A"  
If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in

*the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

**PATENT CERTIFICATION/STATEMENTS**

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): 6500829

No patents listed  *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES  NO

*If "NO", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s): 6,500,829

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the*

*NDA holder/patent owner, proceed to question #15.*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s): 6500829

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): 6500829

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES  NO

*If "NO", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES  NO

*If "NO", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): 2/1/2016 and 2/8/2016

*Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information UNLESS the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES  NO  Patent owner(s) consent(s) to an immediate effective date of approval

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/s/  
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REBECCA L COHEN  
09/23/2016

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

**Memorandum**

**Date:** September 14, 2016

**To:** Rebecca Cohen, Regulatory Project Manager  
Division of Oncology Products 2  
Office of Hematology Oncology Products

**From:** Carole Broadnax, Pharm D  
Regulatory Review Officer  
Office of Prescription Drug Promotion

**Subject:** **LEVOLEUCOVORIN for injection, for intravenous use  
NDA 208723  
Comment(s) on proposed product labeling (PI and  
carton/container)**

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In response to the Division of Oncology Product 2's January 6, 2016, consult request, OPDP has reviewed the draft Prescribing Information (PI) and Carton/Container Labeling for Levoleucovorin for injection, for intravenous use.

Comment(s) on the proposed PI are based on the clean version dated September 2, 2016, entitled "NDA 208723 9.2.2016 FDA Proposed Edit CLEAN.docx." Please note that OPDP's comment on the proposed PI is provided directly on the marked version below.

OPDP does not have comments for the proposed carton/container labels at this time.

If you have any questions, please contact Carole Broadnax at 301-796-0575 or [Carole.Broadnax@fda.hhs.gov](mailto:Carole.Broadnax@fda.hhs.gov).

Thank you for the opportunity to provide comments on these proposed materials.

11 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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CAROLE C BROADNAX  
09/14/2016



**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

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Food and Drug Administration  
Office of New Drugs – ODE IV  
Division of Pediatric and Maternal Health  
Silver Spring, MD 20993  
Telephone 301-796-2200

**MEMORANDUM AND PEDIATRIC LABELING REVIEW**

**From:** Donna Snyder, MD, Medical Officer  
Division of Pediatric and Maternal Health (DPMH)

**Through:** Hari Cheryl Sachs, MD, Pediatric Team Leader,  
Lynne Yao, MD, Director, DPMH

**To:** Division of Oncology Products 2 (DOP2)

**NDA:** 208723

**Drug:** Levoleucovorin Calcium for Injection

**Sponsor:** Actavis LLC

**Proposed Indication:** -As rescue after high-dose methotrexate therapy  
-To diminish the toxicity (b) (4)  
methotrexate elimination (b) (4)

**Consult request:** To assist the Division in the review of the this  
505(b)(2) NDA application and with labeling

**Materials Reviewed:**

- Draft Labeling submitted by the sponsor to NDA 208723 on December 1, 2015
- Medical Review for Fusilev (levoleucovorin calcium, NDA 20140) dated February 27, 2008

- Request for Full Waiver of Pediatric Studies submitted with NDA 208723 on December 1, 2015
- Fusilev® (levoleucovorin) for injection labeling, dated April 29, 2011 from Drugs@FDA
- Methotrexate (methotrexate sodium injection, powder, lyophilized, for solution), dated May 2014, accessed July 1, 2016, <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=6cf2e15a-6286-41f7-aa7d-3968d735c864>

### **Introduction:**

On December 1, 2015, Actavis, LLC submitted a 505(b)(2) application under NDA 208723, for Levoleucovorin Calcium for Injection. Levoleucovorin Calcium for Injection relies on the previous findings of safety and effectiveness for Fusilev (levoleucovorin) for injection, powder, lyophilized, solution for intravenous use (Spectrum Pharms, application number NDA 020140), as well as published literature, and additional quality data. Levoleucovorin Calcium for Injection is a lyophilized, solution for intravenous use with 175 mg/vial compared to Fusilev with 50 mg/vial. Both products are reconstituted with 0.9% sodium chloride to result in a concentration of 10 mg/mL. Both products contain the same active and inactive ingredients. The applicant has not conducted any clinical studies and had requested a bio-waiver of in-vivo bioavailability/bioequivalence studies.

The Fusilev (levoleucovorin) for injection application was originally submitted in 1990 and was issued a non-approvable letter in 1992 because of chemistry and labeling deficiencies. Sponsorship changed hands several times between 1992 and the subsequent resubmission of the application in in 2007. Fusilev was approved on March 7, 2008.

Levoleucovorin is the pharmacologically active isomer of leucovorin [(6-S)-leucovorin] an active chemically reduced derivative of folic acid. Levoleucovorin does not require reduction by the enzyme dihydrofolate reductase in order to participate in reactions utilizing folates. Administration of levoleucovorin can counteract the therapeutic and toxic effects of folic acid antagonists such as methotrexate, which act by inhibiting dihydrofolate reductase. Levoleucovorin Calcium for Injection is indicated as rescue after high-dose methotrexate therapy in osteosarcoma and to diminish the toxicity and counteracting the effects of impaired methotrexate elimination and of inadvertent overdosage of folic acid antagonists. Labeling contains a limitation of use stating that the product is not approved for pernicious anemia and megaloblastic anemias because improper use may cause a hematologic remission while allowing neurologic manifestations to progress.

### **Background:**

Primary osteosarcoma (OS) is the most common bone malignancy in pediatric patients and young adults, accounting for approximately 3% of all tumors. Patients generally present during the adolescent growth spurt with OS being exceedingly uncommon in patients less than 5 years of age.<sup>1</sup> The most common locations for the tumor are in the

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<sup>1</sup> Jackson, T et al. Pediatric Malignant Bone Tumors: A Review and Update on Current Challenges, and

distal femur, proximal tibia or proximal humerus. The patient often presents with pain and swelling with a minimal history of trauma. The classic X-ray presentation is a sunburst pattern on plain films. If the tumor has not metastasized, the 5 year survival, after excision and treatment with chemotherapy, is 65-75%. Typical multi-dose chemotherapy includes methotrexate, doxorubicin, cisplatin and ifosfamide.<sup>2</sup>

High-dose methotrexate exposure in chemotherapy protocols has been associated with improved treatment outcome in some studies but also is associated with increased toxicity. Methotrexate inhibits dihydrofolate reductase which disrupts DNA synthesis and cellular replication resulting in renal failure, hepatotoxicity, leukopenia, anemia, thrombocytopenia, pancytopenia and bone marrow suppression. Treatment with levoleucovorin, along with monitoring of methotrexate serum concentrations, hydration and urine alkalization helps prevent the toxicity. Because of significant variability in methotrexate pharmacokinetics in individual patients, close monitoring of pharmacokinetic parameters is required to prevent toxicity.<sup>3</sup>

### **Regulatory History:**

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. Levoleucovorin Calcium 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. 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 approval.

### **Available Pediatric Information:**

Labeling for the reference product, Fusilev, contains a study on levoleucovorin rescue after of high-dose methotrexate treatment in 16 pediatric patients with osteogenic sarcoma ages 6 to 21 years of age, over 58 courses of chemotherapy, from 5 different pediatric oncology trials. This data was submitted with the original 1990 application. No further studies were required with the re-submission of the application in 2007. Efficacy was based on the demonstration that levoleucovorin prevented the severe toxicity expected to occur in the absence of rescue. At the 1991 meeting of the Oncology Drugs Advisory Committee (ODAC), the committee determined that the submitted data was sufficient to support the safety and efficacy of the product. The 2007 resubmission included literature and safety data from the World Health Organization (WHO) Uppsala Monitoring Center drug monitoring database to further support approval.

The literature submitted the reference product, Fusilev, in 2007, consisted of several

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Emerging Drug Targets. Current Problems in Pediatric Adolescent Health Care 2016;46:213-228

<sup>2</sup> Robert Kliegman. Nelson Textbook of Pediatrics. 20th edition. Philadelphia: Elsevier/Saunders, 2016. pages 2471 -2473

<sup>3</sup> Hegyi, M et al. Clinical reactions of methotrexate pharmacokinetics in the treatment for pediatric osteosarcoma. J Cancer Res Clin Oncol (2012) 138:1697-1702

articles describing the use of levoleucovorin in combination with 5-fluorouracil in the treatment of adults with colon cancer. The sponsor's search extended to back to 1984; two articles were obtained that contributed to the safety and efficacy of the OS indication. These articles reported on the pediatric osteogenic sarcoma patients treated in the original studies used to support the 1991 application and did not provide any additional supporting evidence of efficacy. The FDA conducted a literature search during the review of the Fusilev application in 2007; that search did not reveal any additional clinical evidence of efficacy, however the search did document allergic reactions related to use of levoleucovorin including one case of anaphylaxis.

Data from the WHO Uppsala Monitoring Center drug monitoring database provided additional safety information to support the application. There were 108 reports with 217 events. The majority of these adverse events were reported from Europe, where the product has been marketed since 1991, and South Africa. Most of the reports were from patients treated concomitantly with levoleucovorin and 5-fluorouracil in the treatment of colon cancer. Seven cases were identified in patients treated with methotrexate and levoleucovorin. The reported events were dyspnea, pruritis, rash, temperature changes and rigors.

#### **Discussion: PEDIATRIC USE LABELING**

The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population. For products with pediatric indications, the pediatric information must be placed in the labeling as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population. Since the product will be indicated for use in pediatric patients, the information will be included throughout labeling. DPMH recommendations reflect labeling provided to the Division on July 7, 2016. See the approval letter for the final version of labeling which may differ from what is presented here.

#### **SPONSOR PROPOSED LABELING (December 1, 2015)**

### **8 USE IN SPECIFIC POPULATIONS**

#### **8.4 Pediatric Use**

*[See Clinical Studies (14)]*

### **14 CLINICAL STUDIES**



(b) (4)

## DPMH –RECOMMENDATIONS FOR LABELING

### 8 USE IN SPECIFIC POPULATIONS

#### 8.4 Pediatric Use

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)*]

## 14 CLINICAL STUDIES

### 14.1 High-Dose Methotrexate Therapy

The safety and efficacy of levoleucovorin for injection rescue following high-dose methotrexate were evaluated in 16 patients age 6-21 who received 58 courses of therapy for osteogenic sarcoma. High-dose methotrexate was one component of several different combination chemotherapy regimens evaluated across several trials. Methotrexate 12 g/m<sup>2</sup> IV over 4 hours was administered to 13 patients, who received levoleucovorin for injection 7.5 mg every 6 hours for 60 hours or longer beginning 24 hours after completion of methotrexate. Three patients received methotrexate 12.5 g/m<sup>2</sup> IV over 6 hours, followed by levoleucovorin for injection 7.5 mg every 3 hours for 18 doses beginning 12 hours after completion of methotrexate. The mean number of levoleucovorin for injection doses per course was 18.2 and the mean total dose per course was 350 mg. The efficacy of levoleucovorin for injection rescue following high-dose methotrexate was based on the adverse reaction profile. [See *Adverse Reactions (6)*]

*Reviewer comment: The current labeling proposed by the sponsor contains the statement*

*(b) (4) The language proposed by DPMH for Section 8.4 includes the clinical trial data and supporting data for approval. A more detailed description of the clinical study is included in Section 14. 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.*

**Conclusion:**

DPMH participated in a labeling meeting on July 7, 2016, to discuss the pediatric use subsection of Levoleucovorin Calcium for Injection labeling. DPMH also participated in team meetings during the review of the NDA. This memorandum and labeling review reflect our recommendations provided to the Division.

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/s/  
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DONNA L SNYDER  
07/29/2016

HARI C SACHS  
07/29/2016  
I agree with these recommendations.

LYNNE P YAO  
07/29/2016

September 26, 2016

Please note: Appendix B, section B1 contains an error. It should state, "Since the product could potentially be used as an alternative to the listed drug, Fusilev, we also search Drugs@FDA for approved levoleucovorin products".

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**LABEL AND LABELING REVIEW**

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

**\*\*\* This document contains proprietary information that cannot be released to the public\*\*\***

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**Date of This Review:** March 10, 2016  
**Requesting Office or Division:** Division of Oncology Products 2 (DOP2)  
**Application Type and Number:** NDA 208723  
**Product Name and Strength:** Levoleucovorin for Injection, 175 mg  
**Product Type:** Single Ingredient  
**Rx or OTC:** Rx  
**Applicant/Sponsor Name:** Actavis, Inc.  
**Submission Date:** December 1, 2015 and March 3, 2016  
**OSE RCM #:** 2015-2596  
**DMEPA Primary Reviewer:** Otto L. Townsend, PharmD  
**DMEPA Team Leader:** Chi-Ming (Alice) Tu, PharmD

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## 1 REASON FOR REVIEW

As part of the NDA review process for Levoleucovorin for Injection, DOP2 requested that we review the proposed container labels, carton labeling, and Prescribing Information for areas that may lead to medication errors.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

\*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The Listed Drug (LD) for this 503(b)(2) submission is Fusilev (NDA 020140). The LD is available as a 50 mg vial of lyophilized powder. Fusilev was also approved as injections in vials of 175 mg/17.5 mL and 250 mg/25 mL, but neither is currently marketed under the proprietary name. Generic levoleucovorin 175 mg/17.5 mL and 250 mg/25 mL injections are currently marketed by Sandoz (ANDA 203563) and Mylan (ANDA 203546).

Actavis is proposing a single-dose vial containing 175 mg lyophilized powder. The applicant is only seeking approval for two (b) (4) indications for levoleucovorin (rescue after high-dose methotrexate therapy in osteosarcoma, and to diminish the toxicity (b) (4) methotrexate elimination (b) (4)

The proposed container label and carton labeling contain almost the same information as the LD and utilizes the trade dress used for other Actavis injectable products. In addition, the proposed Prescribing information is very similar to the PI for the LD.

#### **4 CONCLUSION & RECOMMENDATIONS**

The proposed container label and carton labeling could be improved to promote the safe and effective use of the product. We find the PI acceptable from a medication error perspective.

##### **4.1 RECOMMENDATIONS FOR ACTAVIS**

We recommend the following be implemented prior to approval of this NDA:

- A. General Comments (Container label and carton labeling)
  - 1. Change the statement, “Single-Dose Vial” to read, “Single-Dose Vial – Discard Unused Portion”.
  - 2. Change the statement, “Usual Dosage: (b) (4)” to read, “Usual Dosage: See Prescribing Information”.

**APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED**

**APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION**

Table 2 presents relevant product information for Levoleucovorin that Actavis submitted on December 1, 2015, and the listed drug (LD).

<b>Table 2. Relevant Product Information for product name and the Listed Drug</b>		
<b>Product Name</b>	<b>Levoleucovorin for Injection</b>	<b>Fusilev</b>
<b>Initial Approval Date</b>	N/A	March 7, 2008
<b>Active Ingredient</b>	levoleucovorin calcium	levoleucovorin calcium
<b>Indication</b>	<p>Rescue after high-dose methotrexate therapy in osteosarcoma.</p> <p>Diminishing the toxicity (b) (4)                      [REDACTED]                      methotrexate elimination (b) (4)                      [REDACTED]</p>	<p>Rescue after high-dose methotrexate therapy in osteosarcoma.</p> <p>Diminishing the toxicity and counteracting the effects of impaired methotrexate elimination and of inadvertent overdosage of folic acid antagonists.</p> <p>Use in combination chemotherapy with 5-fluorouracil in the palliative treatment of patients with advanced metastatic colorectal cancer.</p>
<b>Route of Administration</b>	Intravenous	Intravenous
<b>Dosage Form</b>	For Injection	For Injection
<b>Strength</b>	175 mg	50 mg
<b>Dose and Frequency</b>	<p><b>Fusilev Rescue After High-Dose (12 gm/m<sup>2</sup> Intravenously over 4 hours) Methotrexate Therapy</b></p> <p>7.5 mg intravenously every 6 hours for 60 hours (10 doses starting at 24 hours after start of methotrexate infusion).</p> <p><b>Inadvertent Methotrexate Overdosage</b></p> <p>7.5 mg (approximately 5 mg/m<sup>2</sup>) by intravenous injection every 6 hours until the serum Methotrexate level is</p>	<p><b>Fusilev Administration in Combination with 5-Fluorouracil (5-FU)</b></p> <p><i>The following regimens have been used historically for the treatment of colorectal cancer:</i></p> <ol style="list-style-type: none"> <li>1. 100 mg/m<sup>2</sup> by slow intravenous injection over a minimum of 3 minutes, followed by 5-FU at 370 mg/m<sup>2</sup> by intravenous injection.</li> <li>2. 10 mg/m<sup>2</sup> by intravenous injection</li> </ol>

Table 2. Relevant Product Information for product name and the Listed Drug		
Product Name	Levoleucovorin for Injection	Fusilev
	less than (b) (4)	<p>followed by 5-FU at 425 mg/m<sup>2</sup> by intravenous injection.</p> <p><b>Fusilev Rescue After High-Dose (12 gm/m<sup>2</sup> Intravenously over 4 hours) Methotrexate Therapy</b></p> <p>7.5 mg intravenously every 6 hours for 60 hours (10 doses starting at 24 hours after start of methotrexate infusion).</p> <p><b>Inadvertent Methotrexate Overdosage</b></p> <p>7.5 mg (approximately 5 mg/m<sup>2</sup>) by intravenous injection every 6 hours until the serum Methotrexate level is less than (b) (4)</p>
<b>How Supplied</b>	175 mg Single Dose Vial	50 mg Single-Use Vial
<b>Storage</b>	<p>Store at 25° C (77 °F) (b) (4)</p> <p>Excursions permitted from 15-30° C (59-86 °F). [See USP Controlled Room Temperature]. Protect from light.</p>	<p>Store at 25°C (77°F) in carton until contents are used. Excursions permitted from 15° to 30° C (59° (b) (4) 86°F). [See USP Controlled Room Temperature]. Protect from light.</p>

## **APPENDIX B. PREVIOUS DMEPA REVIEWS**

### **B.1 Methods**

On January 27, 2016, we searched the L: drive and AIMS using the terms, “levoleucovorin” and “Fusilev” to identify reviews previously performed by DMEPA. Since this product could potentially be used as an alternative to the listed drug, Alimta, we also searched Drugs@FDA for approved pemetrexed products.

### **B.2 Results**

Our search identified four previous reviews<sup>1,2,3,4</sup>. Two were reviews of the labels and labeling for the listed drug, Fusilev, and the other two were responses to suitability or citizen petitions.

We reviewed the recommendations from these previous reviews to determine if they would be applicable to this review.

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<sup>1</sup> Abate, R. Proprietary Name, Labels, and Labeling Review Fusilev (NDA 020140). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2007 OCT 23. RCM No.: 2007-1914.

<sup>2</sup> Abate, R. Label and Labeling Review Fusilev (NDA 020140). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2011 MAR 21. RCM No.: 2011-359.

<sup>3</sup> Schlick, J. Post-marketing Medication Error Review. Levoleucovorin Calcium (Docket No.: FDA-2011-P-0821). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2012 SEP 14. RCM No.: 2012-1530.

<sup>4</sup> Townsend, O. Citizen Petition Response. Levoleucovorin Calcium (FDA Docket No. 2014-P-1649). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 DEC 03. RCM No.: 2014-2301.

## APPENDIX D. ISMP NEWSLETTERS

### D.1 Methods

On January 26, 2016, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care Community Nursing
Search Strategy and Terms	Match Exact Word or Phrase: Levoleucovorin

### D.2 Results

Our search of the ISMP newsletters did not yield any new reports that described medication errors or actions possibly associated with the label and labeling of currently marketed levoleucovorin products.

## APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

### E.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on January 21, 2016 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.<sup>5</sup>

<b>Date Range</b>	<b>No Date Range</b>
<b>Product</b>	<b>LEVOLEUCOVORIN</b> [active ingredient] <b>LEVOLEUCOVORIN CALCIUM</b> [active ingredient] <b>LEVOLEUCOVORIN CALCIUM PENTAHYDRATE</b> [active ingredient] <b>LEVOLEUCOVORIN DISODIUM</b> [active ingredient] <b>FUSILEV</b> [product name]
<b>Event (MedDRA Terms)</b>	<b>DMEPA Official FBIS Search Terms Event List:</b> Contraindicated Drug Administered (PT) Drug Administered to Patient of Inappropriate Age (PT) Inadequate Aseptic Technique in Use of Product (PT) Medication Errors (HLGT) Overdose (PT) Prescribed Overdose (PT) Prescribed Underdose (PT) Product Adhesion Issue (PT) Product Compounding Quality Issue (PT) Product Formulation Issue (PT) Product Label Issues (HLT) Product Packaging Issues (HLT) Product Use Issue (PT) Underdose (PT)

### E.2 Results

Our search did not identify any new cases that described errors related to levoleucovorin products since our last review that were relevant for this review<sup>4</sup>.

<sup>5</sup> The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

### **E.3 List of FAERS Case Numbers**

N/A

### **E.4 Description of FAERS**

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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OTTO L TOWNSEND  
03/10/2016

CHI-MING TU  
03/10/2016

**RPM FILING REVIEW**  
**(Including Memo of Filing Meeting)**

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

<b>Application Information</b>		
NDA #208723 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: NA Established/Proper Name: Levoleucovorin Calcium Dosage Form: Powder for Injection Strengths: 175 mg base/vial		
Applicant: Actavis L.L.C. Agent for Applicant (if applicable): NA		
Date of Application: December 1, 2015 Date of Receipt: December 1, 2015 Date clock started after UN: N/A		
PDUFA/BsUFA Goal Date: October 1, 2016		Action Goal Date (if different):
Filing Date: January 30, 2016		Date of Filing Meeting: January 8, 2016
Chemical Classification (original NDAs only) : <input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): Rescue after high-dose methotrexate therapy in osteosarcoma. • To diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdosage of folic acid antagonists.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<b><i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i></b> <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> .		

Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
<b>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</b>	
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
<b>The application will be a priority review if:</b>	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<ul style="list-style-type: none"> <li>• <b>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</b></li> <li>• <b>The product is a Qualified Infectious Disease Product (QIDP)</b></li> <li>• <b>A Tropical Disease Priority Review Voucher was submitted</b></li> <li>• <b>A Pediatric Rare Disease Priority Review Voucher was submitted</b></li> </ul>	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
<b>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</b>	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product): NA

List referenced IND Number(s): NA

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system?  <b>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in tracking system?  <b>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a>  <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b>If yes, explain in comment column.</b>				NA
<b>If affected by AIP, has OC been notified of the submission?</b> <b>If yes, date notified:</b>	<input type="checkbox"/>	<input type="checkbox"/>		NA
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u>  <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application ( <i>check daily email from <a href="mailto:UserFeeAR@fda.hhs.gov">UserFeeAR@fda.hhs.gov</a></i> ):  <input checked="" type="checkbox"/> Paid <i>Paid 11/25/15</i> <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees:  <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u>  <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf</a>	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i>  <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> NA			
<b>505(b)(2)</b> <b>(NDAs/NDA Efficacy Supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application a 505(b)(2) NDA? ( <i>Check the 356h form, cover letter, and annotated labeling</i> ). <b>If yes, answer the bulleted questions below:</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<ul style="list-style-type: none"> <li>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> </ul>	<input type="checkbox"/>	<input checked="" type="checkbox"/>																		
<ul style="list-style-type: none"> <li>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</li> </ul>	<input type="checkbox"/>	<input checked="" type="checkbox"/>																		
<ul style="list-style-type: none"> <li>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</li> </ul> <p><i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>																		
<ul style="list-style-type: none"> <li>Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</li> </ul> <p><b>Check the Electronic Orange Book at:</b>  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration													<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<b>Exclusivity</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>																
Does another product (same active moiety) have orphan exclusivity for the same indication? <b>Check the Orphan Drug Designations and Approvals list at:</b> <a href="http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</a>	<input type="checkbox"/>	<input checked="" type="checkbox"/>																		
<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>																	
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>																				
<b>NDAs/NDA efficacy supplements only:</b> Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>																	
<b>If yes, # years requested:</b>																				
<i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>																				
<b>NDAs only:</b> Is the proposed product a single enantiomer of a	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>																	

racemic drug previously approved for a different therapeutic use?				
<b>If yes</b> , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?  <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>BLAs only:</b> Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?  <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i>  <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<b>If mixed (paper/electronic) submission</b> , which parts of the application are submitted in electronic format?				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>If electronic submission</b> , does it follow the eCTD guidance? <sup>1</sup> <b>If not</b> , explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Index:</b> Does the submission contain an accurate comprehensive index?	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Document uploaded in gateway, but does not contain a specific comprehensive index page
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21	<input type="checkbox"/>	<input type="checkbox"/>		

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

CFR 601.2 (BLAs/BLA efficacy supplements) including:  <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)  <b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?  <b>If yes, BLA #</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?  <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Patent Certification submitted on Actavis form
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?  <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>  <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Financial Disclosure form submitted on Actavis form. (Actavis stated not applicable to this application, as no bioequivalence studies were conducted)
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?  <i>If yes, ensure that the application is also coded with the</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?  <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i>  <i>Note: Debarment Certification should use wording in FD&amp;C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?  <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i>  <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	This is not a paper submission – however, Field certification in submission in section 1.3.2
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?  <i>If yes, date consult sent to the Controlled Substance Staff:</i>  <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b><u>PREA</u></b>  Does the application trigger PREA?  <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting<sup>2</sup></i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		To be confirmed with submission of Pediatric Page to PeRC.

<i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
<b>If the application triggers PREA</b> , is there an agreed Initial Pediatric Study Plan (iPSP)?  <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Per Pediatric Reviewer during the Filing Meeting, an iPSP is not required.
<b>If required by the agreed iPSP</b> , are the pediatric studies outlined in the agreed iPSP completed and included in the application?  <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b><u>BPCA:</u></b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

2

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

format?				
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? <sup>4</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
<b>For applications submitted on or after June 30, 2015:</b> Is the PI submitted in PLLR format? <sup>5</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.3 is not included on label-
Has a review of the available pregnancy and lactation data been included?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>For applications submitted on or after June 30, 2015:</b> <b>If PI not submitted in PLLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	OSE consulted for the PI
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	OSE/DMEPA consulted Otto Townsend and Chi-Ming Tu
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

5

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b> <i>If yes, distribute minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> <i>If yes, distribute minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input type="checkbox"/>	X		No

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** 1/8/2015

**BACKGROUND:**

Levoleucovorin Calcium (NDA 208723) was submitted and received on December 1, 2015 as a new 505(b)(2) NDA, referencing Spectrum Pharmaceuticals product “Fusilev” and published literature. During the December 17, 2015, Planning Meeting, this submission it was determined that this application be reviewed under a standard 10 month clock, and the application was not in the PDUFA V Program. Actavis requested a categorical exclusion, waiver from in vivo bioequivalence studies, and a waiver of pediatric studies. Per this NDA submission, Actavis plans to administer their drug product as 175 mg/vial levoleucovorin calcium, while the currently FDA approved dose of Fusilev is 50mg/base/vile.

Discussions regarding whether the NDA should be classified as a 505j or 505(b)(2) occurred during both the December 17, 2015, Initial Planning meeting and the January 8, 2016, Filing meeting. It was decided that additional input was needed from the Office of Generic Drugs. On January 12, 2016, it was determined that NDA 208723 application would be classified as a 505(b)(2) application.

During the January 8, 2016, filing meeting, each review discipline determined the application to be fileable and no filing issues were identified. However the disciplines did indicate that there will likely be information requests issued during the review of this application.

**REVIEW TEAM:**

<b>Discipline/Organization</b>	<b>Names</b>		<b>Present at filing meeting? (Y or N)</b>
Regulatory Project Management	RPM:	Rebecca Cohen	Y
	CPMS/TL:	Melanie Pierce/Norma Griffin	Y
Cross-Discipline Team Leader (CDTL)	Sandra Casak		Y
Division Director/Deputy	Joseph Gootenberg		Y
Office Director/Deputy	Richard Pazdur		N
Clinical	Reviewer:	Shan Pradhan	Y
	TL:	Sandra Casak	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:	NA	NA

	TL:	NA	NA
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:	NA	NA
	TL:	NA	NA
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:	NA	NA
	TL:	NA	NA
Clinical Pharmacology	Reviewer:	Safaa Burns	N
	TL:	Hong Zhao	N
• Genomics	Reviewer:	NA	NA
• Pharmacometrics	Reviewer:	NA	NA
Biostatistics	Reviewer:	NA	NA
	TL:	NA	NA
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Emily Wearne	Y
	TL:	Whitney Helms	Y
Statistics (carcinogenicity)	Reviewer:	NA	NA
	TL:	NA	NA
Product Quality (CMC) Review Team:	ATL:	Mike Williams	Y
	RBPM:		NA
• Drug Substance	Reviewer:	Haripada Sarker	Y
• Drug Product	Reviewer:	Mike Adams	Y
• Process	Reviewer:	Kumar Janoria	Y
• Microbiology	Reviewer:	Elizabeth Bearr	Y
• Facility	Reviewer:	Rose Xu	N
• Biopharmaceutics	TL	Okpo Eradiri	Y
• Biopharmaceutics	Reviewer:	Jing Li	Y
• Immunogenicity	Reviewer:	NA	NA
• Labeling (BLAs only)	Reviewer:	NA	NA
• Other (e.g., Branch Chiefs, EA Reviewer)	NA		NA
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	NA	NA
	TL:	NA	NA
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Carole Broadnax	Y

	TL:	Jessica Derenick	N
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Otto Townsend	Y
	TL:	Alice Tu	N
OSE/DRISK (REMS)	Reviewer:	NA	NA
	TL:	NA	NA
OC/OSI/DSC/PMSB (REMS)	Reviewer:	NA	NA
	TL:	NA	NA
Bioresearch Monitoring (OSI)	Reviewer:	NA	NA
	TL:	NA	NA
Controlled Substance Staff (CSS)	Reviewer:	NA	NA
	TL:	NA	NA
Other reviewers/disciplines			
<ul style="list-style-type: none"> <li><b>Discipline</b></li> </ul> <p>*For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"</p>	Reviewer:	NA	NA
	TL:	NA	NA
Other attendees	Lynne Yao, Maternal Health TL, DPMH		Y
	Carol Kasten, Maternal Health Reviewer, DPMH		Y
	Denise Pica-Branco, RPM, DPMH		Y
	*For additional lines, right click here and select "insert rows below"		N

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>505 b)(2) filing issues: <ul style="list-style-type: none"> <li>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</li> </ul> </li> </ul> <p>Describe the scientific bridge (e.g., information to</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>Sponsor requested Waiver of In vivo Bioavailability Testing</p>
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demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments

<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason: This is a 505(b)2 application
<ul style="list-style-type: none"> <li>If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><b>CONTROLLED SUBSTANCE STAFF</b></p> <ul style="list-style-type: none"> <li>Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b> Will likely grant bioequivalence study</p> <ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b> Stats not involved with 505(b)(2) applications</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>New Molecular Entity (NDAs only)</u></b></p> <ul style="list-style-type: none"> <li>Is the product an NME?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>Categorical exclusion for environmental assessment (EA) requested?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

<p><b>If no</b>, was a complete EA submitted?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>Establishment(s) ready for inspection?</li> </ul> <p><b>Comments:</b> Facility inspection scheduled for beginning FEB 2016</p>	<input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>CMC Labeling Review (BLAs only)</u></b></p> <p><b>Comments:</b> NA</p>	<input type="checkbox"/> Review issues for 74-day letter
<p><b>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?</li> <li>If so, were the late submission components all submitted within 30 days?</li> </ul>	<input checked="" type="checkbox"/> N/A  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>What late submission components, if any, arrived after 30 days?</li> </ul>	NA

<ul style="list-style-type: none"> <li>Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<b>REGULATORY PROJECT MANAGEMENT</b>	
<b>Signatory Authority:</b> Joseph Gootenberg	
<b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V): <i>Application is not in ‘the Program’ however the Mic-Cycle meeting is scheduled for April 19, 2016.</i>	
<b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):	
<b>Comments:</b>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter.  <u>Review Classification:</u>  <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
<b>ACTION ITMES</b>	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug). <i>Dates are adjusted after the Day 74 day letter is uploaded</i>
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input type="checkbox"/>	Send review issues/no review issues by day 74 – <i>No filing issues identified; therefore only a No Filing Issues 60-day letter to be issued.</i>
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRA completed: September 2014  
*(attach a copy of your 21<sup>st</sup> Century)*

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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REBECCA L COHEN  
01/29/2016

NORMA S GRIFFIN  
01/29/2016

**REGULATORY PROJECT MANAGER  
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW  
OF THE PRESCRIBING INFORMATION**

**Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements**

**Application:** NDA 208723

**Application Type:** New NDA

**Drug Name(s)/Dosage Form(s):** Levoleucovorin Calcium, Eq. 175 mg base/vial

**Applicant:** Actavis LLC

**Receipt Date:** December 1, 2015

**Goal Date:** October 1, 2016

### **1. Regulatory History and Applicant's Main Proposals**

Actavis submitted a 505(b)(2) NDA application using published literature from Spectrum Pharmaceutical's Fusilev drug product.

### **2. Review of the Prescribing Information**

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

### **3. Conclusions/Recommendations**

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

In addition, the following labeling issues were identified:

1. "Use in Specific Population"(section 8) is in the Full Prescribing Information (FPI) and Table of Contents (TOC), therefore is required, but is not present in HL.
2. "Pt Counseling Statement" or information is required but is not present in HL.
3. When clinical trial adverse reactions data are included in "Post-Marketing Experience Subsection" the following verbatim statement should precede the presentation of adverse reactions: "The following adverse reactions have been identified during post-approval use of levoleucovorin calcium. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."
4. No Patient Counseling section (Section 17) was included.

## **Selected Requirements of Prescribing Information**

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter/an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by DATE [Monday, February 15, 2016](#). The resubmitted PI will be used for further labeling review.

# Selected Requirements of Prescribing Information

## 4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

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### Highlights

See Appendix for a sample tool illustrating Highlights format.

#### HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

**Comment:**

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

**Comment:**

- YES** 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
  - TOC from the Full Prescribing Information (FPI).

**Comment:**

- YES** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

**Comment:**

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

**Comment:**

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

**Comment:**

- NO** 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required
• <b>Product Title</b>	Required

## Selected Requirements of Prescribing Information

• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a BOXED WARNING is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state "None.")
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

***Comment:*** "Use in Specific Population"(section 8) is in FPI and TOC, but is needed in HL. "Pt Counseling Statement" is not present in HL

### HIGHLIGHTS DETAILS

#### Highlights Heading

- YES** 8. At the beginning of HL, the following heading, "**HIGHLIGHTS OF PRESCRIBING INFORMATION**" must be **bolded** and should appear in all UPPER CASE letters.

***Comment:***

#### Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

***Comment:***

#### Product Title in Highlights

- YES** 10. Product title must be **bolded**.

***Comment:***

#### Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

***Comment:***

#### Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

***Comment:***

- N/A** 13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term "**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS**

## Selected Requirements of Prescribing Information

**INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

**Comment:**

- N/A** 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning.***" This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

**Comment:**

- N/A** 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement "***See full prescribing information for complete boxed warning.***")

**Comment:**

### Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

**Comment:**

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

**Comment:**

- N/A** 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

**Comment:**

### Dosage Forms and Strengths in Highlights

- N/A** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

**Comment:**

### Contraindications in Highlights

- YES** 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

**Comment:**

## Selected Requirements of Prescribing Information

### Adverse Reactions in Highlights

- YES** 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**”

*Comment:*

### Patient Counseling Information Statement in Highlights

- NO** 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

*Comment:* *No patient counseling information statement in HL and PI. The following statement should appear: "See 17 for PATIENT COUNSELING INFORMATION"*

### Revision Date in Highlights

- YES** 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015**”).

*Comment:* *Revision date will need to be updated upon approval*

## Selected Requirements of Prescribing Information

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### Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

- YES** 24. The TOC should be in a two-column format.  
*Comment:*
- YES** 25. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS.**” This heading should be in all UPPER CASE letters and **bolded**.  
*Comment:*
- N/A** 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.  
*Comment:*
- YES** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.  
*Comment:*
- YES** 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].  
*Comment:*
- YES** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.  
*Comment:*
- YES** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “**FULL PRESCRIBING INFORMATION: CONTENTS\***” must be followed by an asterisk and the following statement must appear at the end of the TOC: “\*Sections or subsections omitted from the full prescribing information are not listed.”  
*Comment:*

## Selected Requirements of Prescribing Information

### Full Prescribing Information (FPI)

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

<b>BOXED WARNING</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "Labor and Delivery")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "Nursing Mothers")
8.4 Pediatric Use
8.5 Geriatric Use
<b>9 DRUG ABUSE AND DEPENDENCE</b>
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
<b>13 NONCLINICAL TOXICOLOGY</b>
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:** Section 8.3 (Females and Males of Reproductive Potential) is not included

- YES** 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[see *Warnings and Precautions (5.2)*].”

**Comment:**

## Selected Requirements of Prescribing Information

- N/A** 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

*Comment:*

### FULL PRESCRIBING INFORMATION DETAILS

#### FPI Heading

- YES** 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

*Comment:*

#### BOXED WARNING Section in the FPI

- N/A** 35. All text in the BW should be **bolded**.

*Comment:*

- N/A** 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

*Comment:*

#### CONTRAINDICATIONS Section in the FPI

- N/A** 37. If no Contraindications are known, this section must state “None.”

*Comment:* *There is a contraindication listed.*

#### ADVERSE REACTIONS Section in the FPI

- YES** 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

*Comment:* *Statement was added but did not precede the subsection - it was included as part of the subsection "6.1 Clinical Studies in High-Dose Methotrexate Therapy".*

- NO** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

*Comment:* *The statement was not included.*

## Selected Requirements of Prescribing Information

### PATIENT COUNSELING INFORMATION Section in the FPI

- NO** 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:
- Advise the patient to read the FDA-approved patient labeling (Patient Information).
  - Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
  - Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
  - Advise the patient to read the FDA-approved patient labeling (Medication Guide).
  - Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

**Comment:** *No Patient Counseling section included*

- N/A** 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

**Comment:** *No Patient Counseling section included*

# Selected Requirements of Prescribing Information

## Appendix: Highlights and Table of Contents Format

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **PROPRIETARY NAME** safely and effectively. See full prescribing information for **PROPRIETARY NAME**.

**PROPRIETARY NAME** (non-proprietary name) dosage form, route of administration, controlled substance symbol  
Initial U.S. Approval: YYYY

#### WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

#### RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y  
Section Title, Subsection Title (x.x) M/201Y

#### INDICATIONS AND USAGE

**PROPRIETARY NAME** is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

#### DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

#### DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

#### CONTRAINDICATIONS

- Text (4)
- Text (4)

#### WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

#### ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are text (6.x)

To report **SUSPECTED ADVERSE REACTIONS**, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

#### DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

#### USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

See 17 for **PATIENT COUNSELING INFORMATION** and FDA-approved patient labeling **OR** and Medication Guide.

Revised: M/201Y

### FULL PRESCRIBING INFORMATION: CONTENTS\*

#### WARNING: TITLE OF WARNING

#### 1 INDICATIONS AND USAGE

#### 2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

#### 6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

#### 7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

#### 8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

#### 9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

#### 10 OVERDOSAGE

#### 11 DESCRIPTION

#### 12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

#### 13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

#### 14 CLINICAL STUDIES

14.1 Subsection Title

14.2 Subsection Title

#### 15 REFERENCES

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 17 PATIENT COUNSELING INFORMATION

\* Sections or subsections omitted from the full prescribing information are not listed.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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REBECCA L COHEN  
01/29/2016

NORMA S GRIFFIN  
01/29/2016