

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208723Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 208723

SUPPL # N/A

HFD # N/A

Trade Name

Generic Name Levoleucovorin for Injection, Eq. 175 mg base/vial

Applicant Name Actavis, L.L.C.

Approval Date, If Known

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A this application did not require the review of clinical data. A waiver of bioavailability and bioequivalence was requested and will be approved at the same time as the NDA application.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 020140

Fusilev

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical

investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO



Investigation #1

YES   
Explain:

!  
!  
! NO   
! Explain:

Investigation #2

YES   
Explain:

!  
!  
! NO   
! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES  NO

If yes, explain:

=====

Name of person completing form: Rebecca Cohen  
Title: Regulatory Project Manager  
Date: September 14, 2016

Name of Office/ Division Director signing form: Office of Oncology and Hematology Products  
Joseph Gootenberg, M.D.  
Title: Deputy Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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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  
10/17/2016

JOSEPH E GOOTENBERG  
10/17/2016

**PEDIATRIC PAGE**  
**(Complete for all filed original applications and efficacy supplements)**

NDA/BLA#: 208723 Supplement Number: NA NDA Supplement Type (e.g. SE5): NA  
Division Name: DOP2 PDUFA Goal Date: Stamp Date: 12/1/2015  
10/1/2016

Proprietary Name: none  
Established/Generic Name: Levoleucovorin Calcium  
Dosage Form: Eq. 175 mg base/vial  
Applicant/Sponsor: Actavis LLC

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):  
(1) NA  
(2) \_\_\_\_\_  
(3) \_\_\_\_\_  
(4) \_\_\_\_\_

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Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1  
(Attach a completed Pediatric Page for each indication in current application.)

**Indication:** For rescue after high dose-methotrexate therapy in osteosarcoma

**Q1:** Is this application in response to a PREA PMR? Yes  Continue  
No  Please proceed to Question 2.

If Yes, NDA/BLA#: \_\_\_\_\_ Supplement #: \_\_\_\_\_ PMR #: \_\_\_\_\_

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.  
 No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

**Q2:** Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW  active ingredient(s) (includes new combination);  indication(s);  dosage form;  dosing regimen; or  route of administration?\*

(b)  No. PREA does not apply. **Skip to signature block.**

**\* Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

**Q3:** Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**  
 No. Please proceed to the next question.

**Q4:** Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)  
 No: Please check all that apply:  
 Partial Waiver for selected pediatric subpopulations (Complete Sections B)  
 Deferred for some or all pediatric subpopulations (Complete Sections C)  
 Completed for some or all pediatric subpopulations (Complete Sections D)  
 Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)  
 Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section A: Fully Waived Studies (for all pediatric age groups)**

Reason(s) for full waiver: **(check, and attach a brief justification for the reason(s) selected)**

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

*Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).*

			Reason (see below for further detail):				
	minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit*	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver **(check reason corresponding to the category checked above, and attach a brief justification)**:

**#** Not feasible:

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_

## \* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

## † Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

## Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

 Justification attached.

*For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.*

**Section C: Deferred Studies (for selected pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as*

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpmhs@fda.hhs.gov](mailto:cderpmhs@fda.hhs.gov)) OR AT 301-796-0700.

*pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

*If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.*

This page was completed by:

*{See appended electronic signature page}*

\_\_\_\_\_  
Regulatory Project Manager

(Revised: 6/2008)

**NOTE: If you have no other indications for this application, you may delete the attachments from this document.**

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

**Indication #2:** \_\_\_\_**Q1:** Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

**Q2:** Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - Deferred for some or all pediatric subpopulations (Complete Sections C)
  - Completed for some or all pediatric subpopulations (Complete Sections D)
  - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section A: Fully Waived Studies (for all pediatric age groups)**Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

# Not feasible:

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_

\* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)
- Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the

PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

**Section C: Deferred Studies (for some or all pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum					
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

**If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.**

This page was completed by:

*{See appended electronic signature page}*

Regulatory Project Manager

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700**

(Revised: 6/2008)

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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  
02/22/2016

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 208723	NDA Supplement # NA	If NDA, Efficacy Supplement Type: NA <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: NA Established/Proper Name: Levoleucovorin injection, 175 mg base/vial Dosage Form: Powder for Injection Solution'		Applicant: Actavis L.L.C. Agent for Applicant (if applicable):
RPM: Rebecca Cohen		Division: DOP2
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><b>For ALL 505(b)(2) applications, two months prior to EVERY action:</b></p> <ul style="list-style-type: none"> <li>• Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</li> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul> <p><input checked="" type="checkbox"/> No changes 9/19/2016  <input type="checkbox"/> New patent/exclusivity (notify CDER OND IO)            Date of check:</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
<b>❖ Actions</b>		
<ul style="list-style-type: none"> <li>• Proposed action- September 29, 2016</li> <li>• User Fee Goal Date is October 1, 2016</li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>• Previous actions (specify type and date for each action taken)</li> </ul>		<input checked="" type="checkbox"/> None
<b>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?</b> Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received
<b>❖ Application Characteristics<sup>3</sup></b>		

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority:  Standard  Priority  
 Chemical classification (new NDAs only): NA  
 (*confirm chemical classification at time of approval*)

- |   |   |
|---|---|
| <input type="checkbox"/> Fast Track                       | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input type="checkbox"/> Rolling Review                   | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input type="checkbox"/> Breakthrough Therapy designation |   |

**(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: CST SharePoint)**

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
- Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
- Submitted in response to a PMC
- Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
- Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS:  MedGuide  
 Communication Plan  
 ETASU  
 MedGuide w/o REMS  
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

**Action Letters**

❖ Copies of all action letters (including approval letter with final labeling) Action(s) and date(s) 9/29/2016

**Labeling**

❖ Package Insert (write submission/communication date at upper right of first page of PI)

- Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)  Included 9/21/2016
- Original applicant-proposed labeling  Included 12/1/2015

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)

- Medication Guide
- Patient Package Insert
- Instructions for Use
- Device Labeling
- None

- Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)  Included
- Original applicant-proposed labeling  Included

❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)

- Most-recent draft labeling  Included 9/21/2016

❖ Proprietary Name

- Acceptability/non-acceptability letter(s) (indicate date(s))
- Review(s) (indicate date(s))

❖ Labeling reviews (indicate dates of reviews)

RPM:  None  
 1/29/2016 SRPI  
 DMEPA:  None  
 3/10/2016  
 DMPP/PLT (DRISK):  
 None  
 OPDP:  None  
 9/14/2016  
 SEALD:  None  
 CSS:  None  
 Product Quality  None  
 Other:  DPMH 7/29/2016  
 None

**Administrative / Regulatory Documents**

❖ RPM Filing Review<sup>4</sup>/Memo of Filing Meeting (indicate date of each review) 1/29/2016

❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee  Not a (b)(2) 9/19/2016

❖ NDAs only: Exclusivity Summary (signed by Division Director)  Included

❖ Application Integrity Policy (AIP) Status and Related Documents  
<http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm>

- Applicant is on the AIP  Yes  No

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> <li>• This application is on the AIP             <ul style="list-style-type: none"> <li>○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>)             <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>2/24/2016</u> If PeRC review not necessary, explain: <u>PREA not triggered</u></li> </ul> </li> </ul>	PREA not triggered
<ul style="list-style-type: none"> <li>❖ Breakthrough Therapy Designation</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)</li> </ul>	
<ul style="list-style-type: none"> <li>• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul> <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>	
<ul style="list-style-type: none"> <li>❖ <b>Outgoing communications:</b> letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include previous action letters, as these are located elsewhere in package</i>)</li> </ul>	9/19/2016 Proposed label 9/2/2016 Proposed label 7/27/2016 CMC IR 7/22/2016 CMC IR 7/13/2016 CMC IR 5/18/2016 CMC Advice 5/2/2016 CMC IR 3/17/2016 OSE IR 2/19/2016 Micro IR 2/2/2016 Clinical IR 1/29/2016 Filing Issues Not Identified letter 12/17/2015 Ack letter
<ul style="list-style-type: none"> <li>❖ <b>Internal documents:</b> memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)</li> </ul>	8/23/2016 Wrap Up Mtg Mins 4/19/2016 Mid-Cycle Mtg Mins ( <i>DARRTS uploaded 9/12/16</i> ) 3/21/2016 Team Mtg 2 Mins ( <i>DARRTS uploaded 3/22/2016</i> ) 2/19/2016 Team Mtg 1 Mins ( <i>DARRTS uploaded 5/6/2016</i> ) 1/8/2016 Filing Meeting Summary ( <i>DARRTS uploaded 1/20/2016</i> ) 12/17/2015 Planning Meeting Summary ( <i>DARRTS uploaded 1/19/2016</i> )
<ul style="list-style-type: none"> <li>❖ Minutes of Meetings</li> </ul>	
<ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>• EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>• Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A

<ul style="list-style-type: none"> <li>Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) <i>(indicate dates of mtgs)</i></li> </ul>	N/A
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>Date(s) of Meeting(s)</li> </ul>	N/A
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Division Director Summary Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None 9/29/2016
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
PMR/PMC Development Templates <i>(indicate total number)</i>	<input checked="" type="checkbox"/> None
<b>Clinical</b>	
❖ Clinical Reviews	
<ul style="list-style-type: none"> <li>Clinical Team Leader Review(s) <i>(indicate date for each review)</i></li> </ul>	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> <li>Clinical review(s) <i>(indicate date for each review)</i></li> </ul>	7/29/2016 - Final 3/19/2016 – Review of revised labeling in response to No Filing Issues letter 1/6/2016 - Filing
<ul style="list-style-type: none"> <li>Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i></li> </ul>	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input checked="" type="checkbox"/> and include a review/memo explaining why not <i>(indicate date of review/memo)</i>	The financial certification/disclosure statement is not applicable to this application, as no bioequivalence studies were conducted. Actavis requested a BE waiver for this parenteral solution.
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and REMS Supporting Document <i>(indicate date(s) of submission(s))</i></li> <li>REMS Memo(s) and letter(s) <i>(indicate date(s))</i></li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) <i>(indicate date of each review and indicate location/date if incorporated into another review)</i></li> </ul>	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) <i>(include copies of OSI letters to investigators)</i>	<input checked="" type="checkbox"/> None requested
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
<b>Biostatistics</b> <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review
Statistical Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None

<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 9/26/2016
❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	<input checked="" type="checkbox"/> None requested
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None 8/12/2016 – Final 1/15/2016 - Filing
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• Tertiary review (indicate date for each review)	<input type="checkbox"/> None 9/27/2016 (Addendum)
• Secondary review (e.g., Branch Chief) (indicate date for each review)	<input type="checkbox"/> None 9/14/2016
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (indicate date for each review)	<input type="checkbox"/> None 9/5/2016 - Final 2/2/2016 – Filing
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (indicate date of each review)	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	8/16/2016
<input type="checkbox"/> Review & FONSI (indicate date of review)	
<input type="checkbox"/> Review & Environmental Impact Statement (indicate date of each review)	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections (action must be taken prior to the re-evaluation date) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)	<input checked="" type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

**Day of Approval Activities**

❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul>	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
<ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul>	<input checked="" type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> <li>• Notify the CDER BT Program Manager</li> </ul>	<input type="checkbox"/> Done ( <i>Send email to CDER OND IO</i> )
❖ For products that need to be added to the flush list (generally opioids): <u>Flush List</u> <ul style="list-style-type: none"> <li>• Notify the Division of Online Communications, Office of Communications</li> </ul>	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

## Griffin, Norma

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**From:** Griffin, Norma  
**Sent:** Monday, September 19, 2016 9:59 PM  
**To:** 'RegulatoryAffairsUS@actavis.com'; 'joann.stavole@actavis.com'  
**Cc:** Cohen, Rebecca; 'joann.stavole@actavis.com'  
**Subject:** NDA 208723 Actavis - FDA 9.19.2016 Proposed Labeling Edits  
**Attachments:** NDA 208723 Actavis FDA 9.19.16 proposed edits.pdf; NDA 208723 Actavis FDA 9.19.16 proposed edits CLEAN.docx

Good Evening Joann,

Please see the attached levoleucovorin labeling for Actavis NDA 208723. This labeling includes FDA's (final) edits for this application. I have provided you both the PDF tracked changes document as well as the CLEAN WORD document. Our edits were applied to your WORD document received 9.2.2016.

The following is a quick reference of FDA's proposed edits.

- Highlights/Warnings and Precautions-second statement-addition of reference 7
- Table 1/1<sup>st</sup> row/last column – deletion of word (b) (4)
- 2.2/last paragraph – deletion of extra space between “methotrexate elimination”
- 2.3/last paragraph – hyphenation added at (b) (4)
- Edits at 5.2

Please review and provide your [final] edits (if any) or concurrence on the WORD document (in tracked changes). With each comment FDA provided, please respond back with a comment agreeing, disagreeing and/or provide an edit. Again, for reference, our PDF document shows FDA's marked tracked changes and comments.

In addition we have the following edits from our Division of Medication Error Prevention and Analysis (DMEPA) Reviewers for the Carton and Container labels – please see the following 2 comments:

**1. Change the statement, “Single-Dose Vial” to read, “Single-Dose Vial – Discard Unused Portion”.**

**2. Change the statement, (b) (4) to read, “Usual Dosage: See Prescribing Information”.**

Please respond to Rebecca and me via email by Thursday, September 22, 2016, or sooner with your [final] tracked change edits and/or your final agreement/concurrence of this label. Follow this with a formal amendment submission to NDA 208723.

Kindly respond to confirm receipt of this email and the attached labeling. Please let me know if you have any questions or difficulties in opening the documents.

**Norma S. Griffin**  
**Lead Regulatory Health Project Manager**  
**Division of Oncology Products 2**  
**Office of Hematology Oncology Products**  
**Center for Drugs Evaluation and Research**

EMAIL: [Norma.Griffin@fda.hhs.gov](mailto:Norma.Griffin@fda.hhs.gov)  
TELEPHONE: 301.796.4255

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

Mid-Cycle Meeting Summary

Tuesday, April 19, 2016

**NDA 208723- 505(b)(2) Application**

**Product:** Levoleucovorin Calcium for Injection, Eq 175mg/base/vial  
**Submission Date:** December 1, 2015  
**Received Date:** December 1, 2015  
**Sponsor:** Actavis, LLC

**Proposed Indication:**

- Indicated for rescue is indicated after high-dose methotrexate therapy in osteosarcoma.
- Indicated to diminish the toxicity (b) (4) methotrexate elimination (b) (4).
- Limitation of use: Levoleucovorin for injection is not (b) (4) for pernicious anemia and megaloblastic anemias secondary to the lack of vitamin B12. (b) (4) hematologic remission (b) (4)

**Review Team Attendees:**

Rebecca Cohen, Regulatory Health Project Manager  
Joseph Gootenberg, Deputy Director  
Seven Lemery, Associate Deputy Director (Acting)  
Joyce Crich, CMC Team Lead  
Donna Snyder, Pediatric Team Lead  
Sandra Casak, Clinical Team Lead  
Anamitro Banergee, Drug Product Branch Chief  
Steve Kinsley, CMC Regulatory Health Project Manager  
Whitney Helms, Nonclinical Team Lead  
Jennie Chang, SEALD  
Emily Wearne, Nonclinical Reviewer  
Shan Pradhan, Clinical Reviewer  
Tamara Johnson, DPMH Team Lead  
Carol Broadnax, OPDP Reviewer  
Denise Pica-Branco, Maternal Health Reviewer  
Elizabeth Berr, Microbiology Reviewer  
Mike Adams, Product Quality Reviewer  
Rose Xu, Facility Reviewer  
Latonia Ford, OSE Safety RPM  
Jing Li, Biopharmaceutical Reviewer  
Christie Kirk, ORP  
Norma Griffin, Lead Regulatory Health Project Manager

**Agenda Items:**

**1. Regulatory Background:**

Item	Levoluovorin Calcium
Requested review	Standard
Orphan drug	Yes
Bioequivalence waiver	Yes
Pediatric study waiver	Yes
Listed drug	FUSILEV (levoleuovorin) For Injection, 50 mg/vial, by Spectrum Pharms

2. **Reviewed Milestone Dates (per 21<sup>st</sup> Century Review Planner):**

<b>Milestone</b>	<b>NDA 208723 Standard 10 month</b>
<b>Application Received</b>	December 1, 2015
<b>Acknowledgment Letter</b>	December 14, 2015
<b>Filing Action Letter (by Day 60)</b>	Friday, January 29, 2016
<b>Send proposed labeling/PMR/PMC/REMS to applicant (~3 weeks prior to Action - Review Planner Target date)</b>	<b>Friday, September 2, 2016</b> (next milestone deadline) <i>(Actual Sat 9/3/2016)</i>
<b>Labeling/PRM/PMC with Applicant</b>	Friday, September 9, 2016
<b>Review Target Due Dates:</b>  <i>Primary Review Due</i>  <i>Secondary Review Due</i>  <i>CDTL Review Due</i>  <i>Division Director Review Due</i>	Friday, August 26, 2016  <i>(Actual Sat 8/27/2016)</i>  Friday, September 2, 2016 <i>(Actual Sat 9/3/2016)</i>  Friday, September 9, 2016 <i>(Actual Sat 9/10/2016)</i>  Friday, September 30, 2016 <i>(Actual Sat 10/1/2016)</i>
<b>Compile and circulate Action Letter and Action Package</b>	Friday, September 9, 2016
<b>FINAL Action Letter Due</b>	Friday, September 30, 2016 <i>(Actual Sat 10/1/2016)</i>

3. **Consults**

<b>OPDP</b>	Carole Broadnax
<b>OPF</b>	Rose Xu
<b>Pediatric</b>	Donna Snyder
<b>Maternal Health</b>	Carol Kasten
<b>SEALD</b>	Jennie Chang
<b>Pediatric Page/PeRC</b>	Not required (doesn't trigger PREA)

**Upcoming Internal Meetings**

Labeling Meeting #1 June 2, 2016 (next meeting)

Team Meeting #3 June 9, 2016

Labeling Meeting #2 June 17, 2016

Labeling Meeting #3 July 11, 2016

Team Meeting #4 July 19, 2016

Labeling Meeting #4 August 16, 2016

Wrap Up August 23, 2016

**SEE ATTACHED SLIDE PRESENTATION**

**Discussion during meeting:**

- Listed Drug- FUSILEV (levoleucovorin) For Injection, 50 mg/vial, by Spectrum Pharms -Actavis is proposing 175mg/vial with the same formulation and same concentration.
- Biowaiver Request is acceptable
-  (b) (4)
- IRs to be sent by **Friday, April 22, 2016**. IRs to include:

- **Drug Product:** Request acceptance specifications and testing for excipients and packaging components, clarify whether other suppliers of excipient and packaging components will be used, clarify the criterion for the enantiomer identity test, describe the sampling plan for UDU (USP <905>, Weight Variation) testing, clarify and justify the criteria and reporting limits for specified, unspecified and total impurities, request additional information for the method validation and method transfer studies, and provide a safety evaluation of the extractables study results.
- **Product Quality Microbiology:** Request acceptance specifications and testing for excipients and packaging components, clarify whether other suppliers of excipient and packaging components will be used, clarify the criterion for the enantiomer identity test, describe the sampling plan for UDU (USP <905>, Weight Variation) testing, clarify and justify the criteria and reporting limits for specified, unspecified and total impurities, request additional information for the method validation and method transfer studies and provide a safety evaluation of the extractables study results.
- **Facility** is currently reviewing 483 responses. Issues include lack of controls to ensure that electronic data is unaltered and complete, failure to perform periodic inspection of reserve samples, training procedures fail to identify the training required of specific positions, inadequate incoming sampling plan for packaging materials, inadequate performance of QU activities, and failure to document alarm acceptable during production activities.
- Labeling: FDA will encourage Actavis to complete label in PLR format
  - DPMH continues to review
  - Pediatric section needs improvement for safety and will require changes
  - DMEPA- section needs improvement for safety and will require changes. The PI is acceptable from a medication error perspective.
- Patent infringement lawsuit- OCC will further discuss how the lawsuit will effect this NDA



**Mid-Cycle Meeting**  
**April 19, 2016**  
**NDA 208723 Actavis**  
**505(b)(2)**

Levoleucovorin Calcium

Rebecca Cohen, RPM  
Division of Oncology Products 2  
Office of Hematology and Oncology Products



# Listed Drug, Proposed Indication, Vial Dose

## Listed Drug:

- Fusilev

## Proposed Indication:

- For rescue after high-dose methotrexate therapy in osteosarcoma.
- To diminish the toxicity [REDACTED] methotrexate elimination [REDACTED]

(b) (4)

(b) (4)

## Proposed Vial Dose:

- Levoleucovorin Calcium for Injection, Eq. 175 mg base/vial.



# Primary Core Review Team

## Deputy Director

Joseph Gootenberg

## Clinical

Sandra Casak-Team Lead

Shan Pradhan-Reviewer

## Regulatory

Melanie Pierce-CPMS

Rebecca Cohen-RPM

## CMC

Anamitra Banerjee-Acting Branch Chief

Joyce Crich-Product Quality Team Lead and CDTL

Mike Williams-Product Quality Reviewer

Haripada Sarker-Drug Substance Reviewer

Kumar Janoria-Process Reviewer

Rose Xu-Facility Reviewer

Erika Pfeiler-Microbiology Team Lead

Elizabeth Bearr-Microbiology Reviewer



# Review Team

## **Nonclinical**

Whitney Helms-Team Lead

Emily Wearne-Reviewer

## **Clinical Pharmacology**

Jeanne Fourie-Zirkelbach-Team Lead

Safaa Burns-Reviewer

## **Biopharmaceuticals**

Angelica Dorantes-Acting Branch Chief

Okpo Eradiri-Team Lead

Jing Li-Reviewer



## Notable NDA Application Review Milestones (Standard 10-month clock)

- NDA Application Receipt
- Filing Action
- 74-Day Deficiencies
- Labeling -negotiations begin
- Primary Reviews Due
- Secondary Reviews Due
- CDTL Review Due
- **Action and Division Director Sign-Off**
- 12/1/2015
- 1/30/2016
- None noted
- 9/3/2016
- 8/27/2016
- 9/3/2016
- 9/10/2016
- **Saturday 10/1/2016**



# Facility Inspection

Inspected Firm:

Location:

Dates of Inspection:

Inspection Results:



Form 483 issued with 6 items



# Today's Agenda

(b) (4)

- Regulatory - R. Cohen
- CMC

(b) (4)

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**NDA 208723**  
**Levoleucovorin Calcium for**  
**Injection**  
**175 mg base /vial**  
**Actavis LLC**

Reference drug: FUSILEV<sup>®</sup> (levoleucovorin) For Injection,  
50 mg/vial, by Spectrum Pharms

Quality Mid-Cycle Meeting Presentation  
April 19, 2016



# NDA 208723 Quality Review Team

- Branch Chief/ATL – Anamitro Banerjee/Joyce Crich
- Drug Substance – Haripada Sarker
- Drug Product – Mike Adams
- Microbiology – Elizabeth Bearr
- Biopharm – Jing Li <sup>(b) (4)</sup> / Okpo Eradiri <sup>(b) (4)</sup>
- Facilities – Rose Xu
- Drug Process – Kumar Janoria
- RBPM – Steve Kinsley



# Review Timeline

	CMC	OND
Final CMC Review	8/19/16	
GRMP		
Primary/Secondary Reviews		8/26/2016
Wrap-up		8/23/2016
Goal Date		10/01/2016



# Drug Substance Review

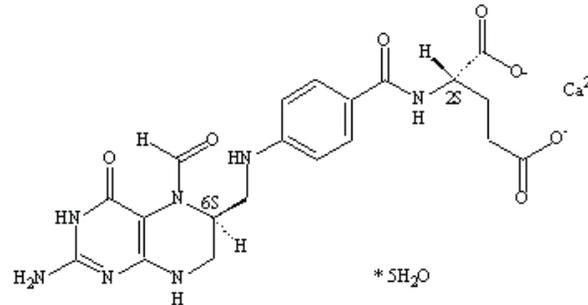
**NDA 208723**

**Mid-Cycle Update**

Haripada Sarker

April 19, 2016

## API - Levoleucovorin Calcium



- ❑ a small molecule, the levo isomeric form of racemic d,l-leucovorin, present as the calcium salt. Levoleucovorin is the pharmacologically active isomer of leucovorin [(6-S)-leucovorin].
- ❑ API Properties:
  - <sup>(b) (4)</sup> Powder,
  - Slightly soluble in water, practically insoluble in acetone and in alcohol
  - Optical Rotation: -15.1 <sup>(b) (4)</sup>
  - Diastereoisomeric property: Natural, biologically active diastereoisomer (S isomer) of Leucovorin Calcium.
- ❑ The API information is cross-referred to DMF <sup>(b) (4)</sup>, which is inadequate at this time for relatively minor issues. <sup>(b) (4)</sup>



**NDA 208723**  
**Levoleucovorin Calcium for**  
**Injection**  
**175 mg base /vial**  
**Actavis LLC**

Reference drug: FUSILEV<sup>®</sup> (levoleucovorin) For Injection,  
50 mg/vial, by Spectrum Pharms

Quality Mid-Cycle Meeting Presentation  
April 19, 2016



# Drug Product Review

**NDA 208273**

**Mid-Cycle Update**

Mike Adams  
April 19, 2016



# Dose and Formulation Composition

Dose: 175 mg/17.5 mL/vial

Formulation: lyophilized powder for Injection

Component	Label Claim	Quantity /vial	After reconstitution with 17.7mL of NaCl 0.9%	Role in formulation	Quality reference
<b>Active ingredient</b>					
Calcium Levofolate Pentahydrate equivalent to Levoleucovorin (present as Levoleucovorin Calcium)	222 mg 175 mg <sup>1</sup>	(b) (4)	N/A 10 mg/mL	Active ingredient	EP <sup>2</sup> and Manufacturer Specification
<b>Inactive ingredients</b>					
Mannitol	175 mg	(b) (4)	10 mg/mL	(b) (4)	USP – current edition
Sodium Hydroxide	To pH 8	(b) (4)	N/A	(b) (4)	USP – current edition
Hydrochloric Acid					

(b) (4)



## Pending Issues

(b) (4)

### **Potential IR Comments:**

- Request acceptance specifications and testing for excipients and packaging components.
- Clarify whether other suppliers of excipient and packaging components will be used.
- Clarify the criterion for the enantiomer identity test.
- Describe the sampling plan for UDU (USP <905>, Weight Variation) testing.
- Clarify and justify the criteria and reporting limits for specified, unspecified and total impurities.
- Request additional information for the method validation and method transfer studies.
- Provide a safety evaluation of the extractables study results.



# Drug Process Review

**NDA 208273**

**Mid-Cycle Update**

Kumar Janoria

April 19, 2016



# Issues to be Communicated

- ❑ Overall the submission document is found acceptable except for few areas which according to reviewer's opinion are resolvable through IRs. (Note: IRs are not yet vetted by secondary).
  
- ❑ Briefly following concerns will be communicate via IRs:
  - Lack of information regarding equipment components and corresponding leachables/extractables.
  - Overfill of additional [REDACTED] (b) (4)
  - Clarification on calculation for weighing the drug substance [REDACTED] (b) (4).
  - Some additional details regarding lyophilization [REDACTED] (b) (4).
  - Details for various rejects and preventative actions [REDACTED] (b) (4)



# Biopharmaceutics Review

## NDA 208273

### Mid-Cycle Update

[Redacted]  
Jing Li [Redacted] / Okpo Eradiri [Redacted]

April 19, 2016  
[Redacted]  
[Redacted]

# Biopharmaceutics: Biowaiver

- No approvability issue from Biopharm perspective
- Biowaiver request adequately supported:
  - Dosage form: lyophilized powder reconstituted to solution for injection
  - Composition: qualitatively the same as the LD (**FUSILEV® 50 mg/vial**)

Component	Proposed Drug Product		Listed Drug	
	mg/Vial	mg/mL after reconstitution	mg/Vial	mg/mL after reconstitution
Ca Folate pentahydrate	222 (eq. 175 Levoleucovorin)	10	(b) (4) (eq. 50 Levoleucovorin)	10
Mannitol	175	10	(b) (4)	10
HCl	q.s.	NA	q.s.	NA
NaOH	q.s.	NA	q.s.	NA
Saline for reconstitution	(b) (4)			

- pH and osmolality: comparable to the LD after reconstitution



# Product Quality

# Microbiology Review

## NDA 208273

## Mid-Cycle Update

Elizabeth Bearr

April 19, 2016



# Resolvable Issues (through IR)

- Results of container closure integrity testing by microbial immersion are acceptable, (b) (4)  
(b) (4) Explanation requested.
- Request for (b) (4)  
(b) (4)
- Request for clarification of (b) (4)  
(b) (4)  
(b) (4)
- Additional validation by media fill simulations.
- Changes required to bacterial endotoxins testing procedure.
- Clarification of how drug product solutions used (b) (4)  
(b) (4)  
(b) (4)



# Facility Review

## NDA 208273

### Mid-Cycle Update

Rose Xu  
April 19, 2016



# Facilities

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment	Recommendation
(b) (4)								
Actavis Italy SPA	3001116953	(b) (4)	Drug product manufacturing, release testing, stability testing as well as DP packaging, labeling	14	15	0	29	AC

The Pre-approval inspection on (b) (4) was conducted on (b) (4) .



## Issues (Resolvable)

- 1) Lack of controls to ensure that electronic data is unaltered and complete;
- 2) Failure to perform periodic inspection of reserve samples;
- 3) Training procedures fail to identify the training required of specific positions;
- 4) Inadequate incoming sampling plan for packaging materials;
- 5) Inadequate performance of QU activities;
- 6) Failure to document alarm acceptable during production activities.

Facility is in process of reviewing response



# Levoleucovorin Calcium Marketed Products

AppI No	TE Cod e	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant	Approval Date
N020140		Yes	LEVOLEUCOVORIN CALCIUM	POWDER;IV	EQ 50MG	FUSILEV	SPECTRUM PHARMS	Mar 7,2008
				(INFUSION);	BASE/VIAL;			Apr20, 2011 sNDA Suppl 11
				SOLUTION;IV	175 mg/17.5 mL,			
				(INFUSION)	250 mg/25 mL			
A203576	AP	No	LEVOLEUCOVORIN CALCIUM	SOLUTION;IV (INFUSION)	EQ 175MG BASE/17.5ML EQ 10MG BASE/ML)	LEVOLEUCOVORIN CALCIUM	MYLAN TEORANTA	Oct 20, 2015
A203576	AP	No	LEVOLEUCOVORIN CALCIUM	SOLUTION;IV (INFUSION)	EQ 250MG BASE/25ML EQ 10MG BASE/ML)	LEVOLEUCOVORIN CALCIUM	MYLAN TEORANTA	Oct 20,2015
A203563	AP	No	LEVOLEUCOVORIN CALCIUM	SOLUTION;IV (INFUSION)	EQ 175MG BASE/17.5ML EQ 10MG BASE/ML)	LEVOLEUCOVORIN CALCIUM	SANDOZ INC	Mar 9, 2015
A203563	AP	No	LEVOLEUCOVORIN CALCIUM	SOLUTION;IV (INFUSION)	EQ 250MG BASE/25ML EQ 10MG BASE/ML)	LEVOLEUCOVORIN CALCIUM	SANDOZ INC	Mar 9, 2015 <sup>26</sup>

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/s/  
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REBECCA L COHEN  
09/12/2016

## Cohen, Rebecca

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**From:** Cohen, Rebecca  
**Sent:** Friday, September 02, 2016 2:01 PM  
**To:** 'Regulatory Affairs US'; 'joann.stavole@actavis.com'  
**Subject:** FW: 208723-FDA Correspondence-Proposed Label  
**Attachments:** NDA 208723 9.2.2016 FDA Proposed Edit CLEAN.docx; NDA 208723 9.2.2016 FDA Proposed Edit tracked changes.pdf

**Importance:** High

Good Morning Joann,

Please see the attached Levoleucovorin proposed label for NDA 208723. This labeling includes FDA's edits. I have provided you both the PDF tracked changes document as well as the CLEAN WORD document. Our edits were applied to your tracked changes WORD document received March 3, 2016, that included Actavis's comments and edits.

Please review and provide your final edits and comments (if any) **in tracked changes** on our CLEAN WORD document. *With each FDA comment, please provide a response back agreeing, disagreeing and/or providing an edit.* Again, for reference, our PDF document shows FDA's marked tracked changes and comments.

Please respond to me via email by **close of business, Friday, September 9, 2016**, or sooner with your final tracked change edits and/or your final agreement/concurrence of this label. Follow this with a formal amendment submission to NDA 208723.

Kindly respond to confirm receipt of this email and the attached labeling. Please let me know if you have any questions or difficulties.

Rebecca Cohen, RN, MPH, OCN  
CDR, U.S. Public Health Service  
Regulatory Health Project Manager  
Division of Oncology Products 2/ Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research/ Food and Drug Administration  
[Rebecca.Cohen@fda.hhs.gov](mailto:Rebecca.Cohen@fda.hhs.gov)

22 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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REBECCA L COHEN  
09/02/2016

## Team Meeting Wrap Up Summary

Tuesday, August 23, 2016

### NDA 208723- 505(b)(2) Application

**Product:** Levoleucovorin for Injection, Eq 175mg/base/vial  
**Submission Date:** December 1, 2015  
**Received Date:** December 1, 2015  
**Sponsor:** Actavis, LLC

#### Proposed Indication:

- Indicated for rescue is indicated after high-dose methotrexate therapy in osteosarcoma.
- Indicated to diminish the toxicity (b) (4) methotrexate elimination (b) (4).
- Limitation of use: Levoleucovorin for injection is not (b) (4) for pernicious anemia and megaloblastic anemias secondary to the lack of vitamin B12. (b) (4) hematologic remission (b) (4)

#### Review Team Attendees:

Rebecca Cohen  
Mimi Biable  
Joe Gootenberg  
Steve Lemery  
Joyce Crich  
Whitney Helms  
Deveonne Hamilton-Stokes  
Steve Kinsley  
Alice Tu  
Carol Kasten  
Emily Wearne  
Mike Adams  
Miriam Dinatale  
Monica Hughes  
Sandra Casak  
Shan Pradhan

## Team Meeting Wrap Up Summary

Tuesday, August 23, 2016

### Agenda Items:

#### 1. Regulatory Background:

Item	Levoleucovorin
Requested Review	Standard
Orphan Drug Designation	Yes, until 2018
Requested waiver from in vivo bioequivalence studies	Yes
Requested full waiver of pediatric studies	Does not trigger PREA This NDA is not a new indication, new active ingredient, new dosage form, new dosing regimen, or new route of administration, therefore did not need to request full waiver
Listed Drug	Fusilev for Injection, Lyophilized Powder, For Solution for Intravenous Use

## Team Meeting Wrap Up Summary

Tuesday, August 23, 2016

### 2. Reviewed Milestone Dates (per 21<sup>st</sup> Century Review Planner):

Milestone	NDA 208723 Standard 10 month
<b>Application Received</b>	December 1, 2015
<b>Acknowledgment Letter</b>	December 14, 2015
<b>Filing Action Letter (by Day 60)</b>	Friday, January 29, 2016
<b>Send proposed labeling/PMR/PMC/REMS to applicant (~3 weeks prior to Action - Review Planner Target date)</b>	<b>Friday, September 2, 2016</b> (next milestone deadline)  (Actual Sat 9/3/2016)
<b>Week after the proposed labeling has been sent, discuss the Labeling/PMR/PMC with Applicant</b>  (Labeling last updated in 2011, will have Actavis improve this NDAs will then go to innovator to improve Fusilev labeling)	Friday, September 9, 2016
<b>Review Target Due Dates:</b>  <i>Primary Review Due</i>  <i>Secondary Review Due</i>  <i>CDTL Review Due</i>  <i>Division Director Review Due</i>	Friday, August 26, 2016 (Actual Sat 8/27/2016)  Friday, September 2, 2016 (Actual Sat 9/3/2016)  Friday, September 9, 2016 (Actual Sat 9/10/2016)  Friday, September 30, 2016 (Actual Sat 10/1/2016)
<b>Compile and circulate Action Letter and Action Package</b>	Friday, September 9, 2016
<b>FINAL Action Letter Due</b>	Friday, September 30, 2016 (Actual Sat 10/1/2016)

## Team Meeting Wrap Up Summary

Tuesday, August 23, 2016

### 3. Discussion

- a. Clinical: Review uploaded
- b. Nonclinical: Review uploaded
- c. Pediatric: Review uploaded
- d. CMC: Review complete, not uploaded
- e. Regulatory:

Date	Information Request
7/27/2016	CMC
7/13/2016	CMC
5/18/2016	CMC
3/17/201	Clinical
2/19/16	Micro
2/5/2016	CMC
2/2/2016	Clinical

- f. Last labeling meeting August 24, 2016. Plan to submit to sponsor by Friday, August 26, 2016.

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/s/  
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REBECCA L COHEN  
08/23/2016

## Cohen, Rebecca

---

**From:** Kinsley, Steven  
**Sent:** Wednesday, July 27, 2016 3:31 PM  
**To:** 'Regulatory Affairs US'  
**Cc:** Cohen, Rebecca  
**Subject:** NDA 208723 CMC Information Request 7-27-16(2)

Dear Joann,

I have received the following information request from our CMC review team. Please respond to the following with a submission to your NDA Wednesday, August 10, 2016

Your proposal to report only the largest unspecified related substance in the drug product release specification for "Any Other Impurity" is not acceptable. Revise this specification to report all unspecified related substance (impurities and degradation products) observed at or above the limit of quantitation for method MA4522XX.

If you have any questions, contact me. Also, please verify receipt of this Information Request via return e-mail.

Best Regards,  
Steve

Steven Kinsley, Ph.D.  
Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
CDER/FDA  
240-402-2773

From: Steven Kinsley  
To: RegulatoryAffairsUS@actavis.com  
Cc: Rebecca Cohen  
Subject: NDA 208723 CMC Information Request 7-22-16  
Date: July 22, 2016

Dear Joann,

I have received the following information request from our CMC review team. Please respond to the following with a submission to your NDA Wednesday, August 10, 2016

The justification for [REDACTED] (b) (4)  
provided in the applicant's submission dated June 10, 2016 is acknowledged.  
Although [REDACTED] (b) (4),  
[REDACTED]  
[REDACTED]  
[REDACTED]

If you have any questions, contact me. Also, please verify receipt of this Information Request via return e-mail.

Best Regards,

Steve

Steven Kinsley, Ph.D.  
Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
CDER/FDA  
240-402-2773

This document is a PDF copy of an e-mail sent to the e-mail address and on the date given above.

Steven Kinsley -A

Digitally signed by Steven Kinsley -A  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People, cn=Steven Kinsley -A,  
0.9.2342.19200300.100.1.1=2001720189  
Date: 2016.07.22 09:54:25 -04'00'



NDA 208723

**INFORMATION REQUEST**

Actavis LLC  
Attention: Joann Stavole, Director, Regulatory Affairs  
400 Interpace Parkway  
Morris Corporate Center III  
Parsippany, NJ 07054

Dear Ms. Stavole,

Please refer to your original New Drug Application received December 1, 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Levoleucovorin Calcium Powder for Injection, 175 mg base/vial.

We also refer to your June 10, 2016 submission, containing responses to the Information Request dated May 2, 2016.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA. Please submit your response prior to COB Wednesday, July 20, 2016.

Regarding your responses to comments 2(a), 3(c), 3(d), 4(c) and 10(a-d):

1. Establish acceptance specifications for mannitol, sodium hydroxide and hydrochloric acid which include a specific test for identity to be performed for acceptance of each lot of each material. Your proposal for Appearance alone [response 2(a)] is not an acceptable test for identity of these materials. 21 CFR 211.84 mandates that an acceptable specification be provided for each excipient; that at least an acceptable identity test be performed for acceptance of each lot of each material; and that reduced testing is permitted once the supplier has been qualified under a protocol acceptable for this purpose. The SOP for supplier qualification is acceptable, however there is no specification for any of the materials listed above and an acceptable identity test is not performed for lot acceptance.
2. Revise the specifications for Related Substance (Any Other Impurity and Total Impurities) to report all impurities and all degradants detected above the reporting limit. Reporting only the largest degradant and unexpected process impurities observed

above the reporting limit [response 3(a)] is not acceptable, as it does not accurately reflect product purity; does not permit trend analysis across batches or within a batch over time; and it does not support mass balance for the reported Total Impurities values which is calculated as the total of all impurities above the reporting limit.

3. Provide a description of the procedure used to obtain an acceptable (representative) sample of finished drug product to be used in the test for Unit Dose Uniformity by (b) (4). Describing the sample as 'representative' [response 3(d)] is not adequate to establish that an appropriate sample is used.
4. Revise the description of method MA4522XX (identity, assay and related substances) to include the system suitability criteria for baseline stability and peak position used in SOP N0815 [response 4(c)]. The inclusion of these criteria in the method description will assure the validity of the obtained test results.
5. Revise the acceptance specifications for vials, stoppers and aluminum overseals to specify that at least dimensions and identity testing be performed for acceptance of each lot of each component. 21 CFR 211.84 permits reduced testing as long as at least an acceptable identity test is performed and the supplier has been validated by a protocol acceptable for this purpose. Accepting lots based on a supplier certificate and periodic monitoring is not adequate [responses 10(a-d)]. We recommend that (b) (4) finished product by the proposed manufacturing process.

If you have any questions, please contact Steven Kinsley, Ph.D. Regulatory Business Process Manager, at (240) 402-2773.

Sincerely,

Joyce Crich  
S

Digitally signed by Joyce Crich -S  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People, cn=Joyce Crich -S,  
0.9.2342.19200300.100.1.1=2000587292  
Date: 2016.07.13 11:12:28 -0400

Joyce Crich  
Application Team Leader (Acting), Branch II  
Office of New Drug Products  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research

## Cohen, Rebecca

---

**Subject:** RE: NDA 208723 Information Request Levoleucovorin Calcium Powder for Injection, 175 mg base/vial

---

**From:** Kinsley, Steven  
**Sent:** Wednesday, May 18, 2016 8:10 AM  
**To:** 'Regina, Beth'  
**Subject:** RE: NDA 208723 Information Request Levoleucovorin Calcium Powder for Injection, 175 mg base/vial

Dear Beth,

Your extension of the submission date for the May 2, 2016 Information Request from May 23, 2016 to June 10, 2016 is acceptable.

Kind Regards,  
Steve

Steven Kinsley, Ph.D.  
Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
CDER/FDA  
240-402-2773

---

**From:** Regina, Beth [<mailto:Beth.Regina@actavis.com>]  
**Sent:** Tuesday, May 17, 2016 9:01 AM  
**To:** Kinsley, Steven; Regulatory Affairs US  
**Cc:** Cohen, Rebecca; Stavole, Joann  
**Subject:** RE: NDA 208723 Information Request Levoleucovorin Calcium Powder for Injection, 175 mg base/vial

Dear Steven,

Actavis LLC is working diligently to provide a complete response to the May 2, 2016 Information Request for our NDA # 208723 – Levoleucovorin Calcium Powder for Injection, 175 mg base/vial. However, we will need additional time to respond to the deficiencies regarding the analytical methods.

Therefore, on behalf of Joann Stavole, Actavis is respectfully requesting from the Agency an extension to June 10, 2016, from the original May 23, 2016 submission due date.

Thank you in advance for your consideration of our request.

Best regards,

**Beth Regina, MA, RAC**  
Manager, Regulatory Affairs

Actavis

Morris Corporate Center III  
400 Interpace Parkway, Building A  
Parsippany, NJ 07054  
United States  
973.658.1804 (office)

(b) (6)



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**From:** Kinsley, Steven [<mailto:Steven.Kinsley@fda.hhs.gov>]  
**Sent:** Monday, May 02, 2016 11:32 AM  
**To:** Regulatory Affairs US  
**Cc:** Cohen, Rebecca  
**Subject:** NDA 208723 Information Request

Dear Joann,

Please find the attached Information Request for NDA 208723. If you have any questions, contact me. Also, please verify receipt of this Request via e-mail. Thank you.

Best Regards,  
Steve

Steven Kinsley, Ph.D.  
Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
CDER/FDA  
240-402-2773

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## Team Meeting #1 Meeting Summary

February 19, 2016

### NDA 208723- 505(b)(2) Application

**Product:** Levoleucovorin Calcium for Injection, Eq 175mg/base/vial  
**Submission Date:** December 1, 2015  
**Received Date:** December 1, 2015  
**Sponsor:** Actavis, LLC

#### Proposed Indication:

- Indicated for rescue is indicated after high-dose methotrexate therapy in osteosarcoma.
- Indicated to diminish the toxicity (b) (4) methotrexate elimination (b) (4)
- Limitation of use: Levoleucovorin for injection is not (b) (4) for pernicious anemia and megaloblastic anemias secondary to the lack of vitamin B12. (b) (4) hematologic remission (b) (4)

#### Review Team Attendees:

Joseph Gootenberg, Deputy Director  
Seven Lemery, Associate Deputy Director (Acting)  
Sandra Casak, Clinical Team Lead  
Shan Pradhan, Clinical Reviewer  
Whitney Helms, Nonclinical Team Lead  
Emily Wearne, Nonclinical Reviewer  
Kumar Janoria, Process Reviewer  
Rose Xu, Facility Reviewer  
Haripada, Drug Substance Reviewer  
Anamitro Banerjee, Drug Product Branch Chief  
Mike Williams, Drug Product Reviewer  
Elizabeth Barret, Micro Reviewer  
Christi Kirk, ORP  
Otto Townsend, Drug Safety Reviewer  
Norma Griffin, Lead Regulatory Health Project Manager  
Rebecca Cohen, Lead Regulatory Health Project Manager

## Team Meeting #1 Meeting Summary

February 19, 2016

\*A standard **reminder** that all team members should notify the RPM and their team leader and other team members as soon as issues arise during the review process, instead of waiting until the next scheduled meeting to discuss.

### Agenda Items:

#### 1. Regulatory Background:

Item	Levolumetin Calcium
Requested Review	Standard
Orphan Drug Granted	No
Requested waiver from in vivo bioequivalence studies	Tbd (preliminary review, appears acceptable)
Requested full waiver of pediatric studies	TBD
Listed Drug	Fusilev <b>Still needs clarification:</b> Is 50mg or 175mg Fusilev the listed drug? The submission has contradicting information.  Labeling will need to be modified to make the distinction.

#### 2. Reviewed Milestone Dates (per 21<sup>st</sup> Century Review Planner):

Milestone	NDA 208723 Standard 10 month
Application Received	December 1, 2015
Acknowledgment Letter	December 14, 2015
Filing Action Letter (by Day 60)	Friday, January 29, 2016
Send proposed labeling/PMR/PMC/REMS to applicant (~3 weeks prior to	Friday, September 2, 2016 <b>(Actual Sat 9/3/2016)</b>

**Team Meeting #1 Meeting Summary**

**February 19, 2016**

<b>Milestone</b>	<b>NDA 208723 Standard 10 month</b>
Action - Review Planner Target date)	
<b>Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant</b>	Friday, September 9, 2016
<b>Review Target Due Dates:</b>  <i>Primary Review Due</i>  <i>Secondary Review Due</i>  <i>CDTL Review Due</i>  <i>Division Director Review Due</i>	Friday, August 26, 2016  (Actual Sat 8/27/2016)  Friday, September 2, 2016 (Actual Sat 9/3/2016)  Friday, September 9, 2016 (Actual Sat 9/10/2016)  Friday, September 30, 2016 (Actual Sat 10/1/2016)
<b>Compile and circulate Action Letter and Action Package</b>	Friday, September 9, 2016
<b>FINAL Action Letter Due</b>	Friday, September 30, 2016 (Actual Sat 10/1/2016)

**3. Consults**

<b>OPDP</b>	Carole Broadnax
<b>OSE</b>	Rose Xu
<b>Pediatric</b>	Donna Snyder

## Team Meeting #1 Meeting Summary

February 19, 2016

<b>Maternal Health</b>	Carol Kasten
<b>SEALD</b>	Jenny Chang
<b>Pediatric Page/PeRC</b>	TBD

### 4. Upcoming Internal Meetings

Team Meeting #2      March 21, 2016

Mid Cycle              April 19, 2016

Team Meeting #3      ~~June 6, 2016 (ASCO)~~ Date to be changed

Team Meeting #4      July 19, 2016 Possible date change. Follow up at March 21<sup>st</sup> meeting

Wrap Up                August 23, 2016

Labeling Meetings to be scheduled

### 5. Discussion

#### *Clinical:*

- A patent certification was submitted February 10, 2016. ORP will assist Clinical in follow up, and indicate if the recent patent infringement law suit will affect the review.
- There was no other clinical discussion.

#### *Nonclinical:*

- No discussion. No nonclinical data submitted. Nonclinical will review labeling.

#### *CMC:*

- The proposed 10.1 mg per solution is not a safety issue.
- Micro will send an IR requesting risk assessment studies.
- Impurity profiles compared to the listed drug have not been reviewed yet. (If the profile is identical, CMC will review. If it is not identical, P/T will review)

## Team Meeting #1 Meeting Summary

February 19, 2016

- The February, 2016, VAI inspection report is not available yet. Further review will occur when report is available.

a. **Regulatory:**

- No issues/deficiencies for Day 74 letter
- IRs submitted to date:

Date	Information Request
2.2.16 (due 2/23)	Maternal Health (PLLR, subsection 8.1)

e. **Other/Miscellaneous**

- CDTL- Anamitro Banerjee (CMC)
- All Product Quality teams will have one combined review uploaded into DARRTS
- During next meeting, Biopharm to provide a review for the biowaiver request

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/s/  
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REBECCA L COHEN  
05/16/2016



NDA 208723

**INFORMATION REQUEST**

Actavis LLC  
Attention: Joann Stavole, MS, RAC  
Director, Regulatory Affairs  
400 Interpace Parkway - Morris Corporate Center III  
Parsippany, NJ 07054

Dear Ms. Stavole,

Please refer to your original New Drug Application received December 1, 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Levoleucovorin Calcium Powder for Injection, 175 mg base/vial.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments. We request a prompt written response in order to continue our evaluation of your NDA. Please submit your response by Monday, May 23, 2016.

**Drug Substance:**

1. The Type II DMF (b) (4) referenced in your submission for the drug substance is currently inadequate. The DMF holder must respond to the deficiency letter in a timely manner, and the DMF must be adequate before we can complete our review of your application.

**Drug Product:**

2. Regarding the proposed excipient specifications:
  - a. Revise the Actavis specifications for (b) (4) sodium hydroxide, hydrochloric acid and mannitol to mandate the testing of each batch for identity and key physicochemical attributes for acceptance. Accepting excipient batches based only on the supplier certificate of analysis does not provide adequate assurance of quality.
  - b. Describe the sampling frequency for (b) (4) provide a copy of the SOP for monitoring the chemical and microbiological quality of this material.
  - c. Describe the acceptance specification and procedure used to qualify a new supplier of each excipient.
3. Regarding the proposed specification for batch release and stability testing:

- a. Revise the test for related substances to include a criterion for (b) (4) as this impurity is typically present at detectable levels in the drug product.
  - b. Revise the criteria for “any other impurity” and “total impurities” to report the test value to two decimal places.
  - c. Revise the criterion for “any other impurity” to report the profile of all impurities and degradation products observed above the method’s limit of quantitation with their relative retention times (RRT). The submitted data indicates that only the largest unspecified impurity is being reported and that this is typically (b) (4). This value should represent degradation products and unexpected process impurities.
  - d. Describe how a representative sample of finished drug product is obtained for the test for unit dose uniformity (b) (4).
  - e. Describe the action taken in the event that the (b) (4) is observed at or above the limit of quantitation for this method.
4. For method MA4522XX:
- a. Verify that the injection volume is 10  $\mu$ L.
  - b. Revise the procedures “preparation of levoleucovorin powder reconstituted solution diluted 5 mg/mL in 0.9% sodium chloride or 0.5% dextrose for related substances” and “preparation of levoleucovorin powder reconstituted solution diluted 0.5 mg/mL in 0.9% sodium chloride or 0.5% dextrose for related substances” to prepare a solution with a concentration of 1 mg/mL. This is the solution concentration used for all other related substances test solutions for this method.
  - c. Revise the system suitability criteria to include parameters which address peak symmetry and peak position for key compounds, column efficiency, and baseline stability.
5. For method MA4465XX:
- a. Verify that the injection volume is 10  $\mu$ L.
  - b. Specify the limit of quantitation for each enantiomer by this method.
6. For method MA0005XX, describe the preparation of the (b) (4) solutions. The mixtures used to obtain the (b) (4) solutions are not specified.
7. For method validation report MA4522XX-1/VR:
- a. Provide information validating the method for the quantitation of (b) (4) and for qualification (b) (4).
  - b. Revise the ruggedness study to report the effects of the method parameter variations on peak symmetry, peak position, column efficiency and baseline stability.
8. Provide the molecular structure for the (b) (4) product with adequate evidence in support of the proposed structure.

9. Provide a justification for the proposed criteria for (b) (4) and for the (b) (4) product in NDA section 3.2.P.5.6 based on safety and product quality.:

10. Regarding the submitted packaging information:

- a. Revise the Actavis acceptance specification for each component to indicate that testing will be performed at your site for batch acceptance. Accepting a batch of packaging component based on supplier certificate of analysis does not provide adequate assurance of quality.
- b. For the proposed glass vial, revise the Actavis specification to include the listed dimensions.
- c. For the proposed (b) (4) stopper, revise the Actavis specification to include material identity and each listed dimension.
- d. For the proposed overseal, revise the Actavis specification to include diameter.
- e. Describe the acceptance specification and procedure used to qualify a new supplier of each excipient.
- f. For (b) (4) provide a toxicological evaluation of the study results. If any significant safety issues are observed, provide data from leachables studies on either or both components.

11. Regarding the submitted stability information:

- a. Provide data to support the proposed storage of reconstituted solution for (b) (4) hours at room temperature in ambient light.
- b. Clarify the reference to “degradation products and functional test(s)” in section 7.2 (acceptance criteria for accelerated studies) of protocol NV/STAB 128ST v.2 addendum 2.

**Process:**

12. We acknowledge you have performed material compatibility studies using various materials such as (b) (4)

(b) (4)

Indicate whether these materials are for single use or product specific multi-use or general multi-use.

13. The target fill volume of (b) (4)/vial. Per the package insert instructions, reconstitution with 17.7 mL will result in a 10 (b) (4) mg/mL solution, resulting in an overage of (b) (4) %. Adjust the target fill volume and ranges accordingly or provide

further justification to support the proposed ranges based on comparison to the RLD and the drug product labeling.

14. Explain how the calculations for assay were derived in the batch records using the actual numbers from CoA.

15. Provide the following additional details on your lyo cycle development:

(b) (4)



16. Provide information on the reported rejects in each of the 3 submission batch records. Discuss any preventive actions taken to reduce such losses in the future. Also mention if any rejects were due to vial breakage.

**Microbiology:**

17. Section 3.2.P.3.5.6 Container Closure Integrity indicates that physical integrity testing of exhibit batches 4LM002, 4LM001, and 4LN002 resulted in rejection of (b) (4) % of container closures tested, respectively. Please provide an explanation for the high rejection rate of the container closures.

18. Section 3.2.P.3.3 Description of Manufacturing Process and Process Controls notes that if filling of the subject drug product is not completed (b) (4),



19. In regard to the environmental monitoring conducted in department (b) (4), address the following:

a. Provide the [REDACTED] (b) (4)

b. It is noted that the [REDACTED] (b) (4)

20.

(b) (4)

21.

(b) (4)

22.

(b) (4)

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

If you have any questions, please contact me at (240) 402-2773.

Sincerely,

**Steven  
Kinsley -A**

Digitally signed by Steven Kinsley -A  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People, cn=Steven Kinsley -  
A,  
0.9.2342.19200300.100.1.1=2001720189  
Date: 2016.05.02 10:59:59 -04'00'

Steven Kinsley, Ph.D.  
Regulatory Business Project Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research

## Team Meeting #2 Summary

Monday, March 21, 2016

### NDA 208723- 505(b)(2) Application

**Product:** Levoleucovorin Calcium for Injection, Eq 175mg/base/vial  
**Submission Date:** December 1, 2015  
**Received Date:** December 1, 2015  
**Sponsor:** Actavis, LLC

#### Proposed Indication:

- Indicated for rescue is indicated after high-dose methotrexate therapy in osteosarcoma.
- Indicated to diminish the toxicity (b) (4) methotrexate elimination (b) (4)
- Limitation of use: Levoleucovorin for injection is not (b) (4) for pernicious anemia and megaloblastic anemias secondary to the lack of vitamin B12. (b) (4) hematologic remission (b) (4)

#### Review Team Attendees:

Rebecca Cohen, RPM  
Joseph Gootenberg, Deputy Director  
Jennie Chang,  
Alice Tu  
Christi Kirk  
Haripada Sarker  
Shan Pradhan  
Sandra Casak  
Emily Wearne  
Whitney Helms  
Anamitra Banerjee  
Joyce Crich  
Elizabeth Berr  
Rose Xu  
Jing Li

## Team Meeting #2 Summary

Monday, March 21, 2016

\*A standard **reminder** that all team members should notify the RPM and their team leader and other team members as soon as issues arise during the review process, instead of waiting until the next scheduled meeting to discuss.

### Agenda Items:

#### 1. Regulatory Background:

Item	Levulucovorin Calcium
Requested Review	Standard
Orphan Drug Granted	No
Requested waiver from in vivo bioequivalence studies	Tbd (preliminary review, appears acceptable)
Requested full waiver of pediatric studies	Does not trigger PREA
Listed Drug	<p><i>Fusilev</i></p> <p>But there is conflicting request in submission.</p> <p>Some sections state that it is self-evident while others, such as bioeq request state that it is for fusilev lyophilized powder, formulation/ concentration/ composition is exactly the same but is just different in mass in the vial</p> <p>Sponsor states info is self-evident, but what exactly does this mean? (Should we just request clarification in IR?)</p> <p><b>Kristie</b> will follow up what are they relying on</p>

**Team Meeting #2 Summary**

**Monday, March 21, 2016**

**2. Reviewed Milestone Dates (per 21<sup>st</sup> Century Review Planner):**

<b>Milestone</b>	<b>NDA 208723 Standard 10 month</b>
<b>Application Received</b>	December 1, 2015
<b>Acknowledgment Letter</b>	December 14, 2015
<b>Filing Action Letter (by Day 60)</b>	Friday, January 29, 2016
<b>Send proposed labeling/PMR/PMC/REMS to applicant (~3 weeks prior to Action - Review Planner Target date)</b>	<b>Friday, September 2, 2016</b> (next milestone deadline)  <i>(Actual Sat 9/3/2016)</i>
<b>Labeling/PRM/PMC with Applicant</b>	Friday, September 9, 2016
<b>Review Target Due Dates:</b>	
<i>Primary Review Due</i>	Friday, August 26, 2016  <i>(Actual Sat 8/27/2016)</i>
<i>Secondary Review Due</i>	Friday, September 2, 2016 <i>(Actual Sat 9/3/2016)</i>
<i>CDTL Review Due</i>	Friday, September 9, 2016 <i>(Actual Sat 9/10/2016)</i>
<i>Division Director Review Due</i>	Friday, September 30, 2016 <i>(Actual Sat 10/1/2016)</i>
<b>Compile and circulate Action Letter and Action Package</b>	Friday, September 9, 2016
<b>FINAL Action Letter Due</b>	Friday, September 30, 2016 <i>(Actual Sat 10/1/2016)</i>

## Team Meeting #2 Summary

Monday, March 21, 2016

### 3. Consults

<b>OPDP</b>	Carole Broadnax
<b>OPF</b>	Rose Xu
<b>Pediatric</b>	Donna Snyder
<b>Maternal Health</b>	Carol Kasten
<b>SEALD</b>	Jennie Chang
<b>Pediatric Page/PeRC</b>	Note required (doesn't trigger PREA)

### Upcoming Internal Meetings

**Mid Cycle**                      **April 19, 2016** (next meeting)

Team Meeting #3              June 9, 2016

Team Meeting #4              July 19, 2016

Wrap Up                         August 23, 2016

### Discussion

#### a. *Labeling*

- 1) Within the submission, the sponsor provided a side by side comparison of product and fusilev. Fusilev last updated in 2011. Actavis will be required to produce, in proper format, their label. (FDA will then request innovator to update Fusilev labeling)
- 2) **Jennie** to give high level look and give to sponsor, and request about a 1 week turn-around. Sponsor return to Jennie in late May.
- 3) **Four labeling meetings** to be scheduled to start in June, therefore accommodating summer AL. Use end of last week of May, then June.

**Team Meeting #2 Summary**

**Monday, March 21, 2016**

Labeling Meeting	Team	Section
Meeting 1	<del>CMC, Clinical, Jennie</del>	<del>3,16,11</del>
Meeting 2	<del>Clin Pharm, Jennie</del>	<del>12, 7</del>
Meeting 3	<del>Nonclinical, Maternal Health, Jennie</del>	<del>2, 8, 5, 13, 17</del>
Meeting 4	Clinical, Jennie Remaining sections	1, 4, 6, 9, 14, 15

**b. CMC**

- 1) Pending IR from Micro. Drug substance, product under review
- 2) Drug Process will provide IR related to fill volume
- 3) Facility was been inspected March 3, 2016-Minor 483 issues were identified. When finalized 483 report completed, will need review

**c. Clinical and Nonclinical:** No information to review

**d. Regulatory:**

- 1) The mid-cycle meeting is April 19, 2016. Please provide me your mid-cycle presentation slides, with FDA logo, by noon, Monday, April 18<sup>th</sup>. (if nothing to review, then may state this)
- 2) No issues/deficiencies for Day 74 letter
- 3) IRs submitted to date:

Date	Information Request	Response Received	Acceptable Response
2.2.16	Maternal Health (provide more information re labeling content of section 8.1)	3/3/2016	Acceptable
2.19.16	Micro (provide risk assessment summary)	pending (due 5/27/2016)	pending

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/s/  
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REBECCA L COHEN  
03/22/2016

**From:** [Regulatory Affairs US](#)  
**To:** [Ford, Latonia M.](#)  
**Cc:** [Cohen, Rebecca](#); [Regulatory Affairs US](#)  
**Subject:** RE: NDA 208723 Levoleucovorin Proprietary Name Request  
**Date:** Thursday, March 17, 2016 10:48:12 AM  
**Attachments:** [image004.png](#)  
[image005.png](#)

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Dear Latonia,

Actavis is not intending to request a proprietary name for this product. We will use the generic name.

Thanks

Joann

**Joann Stavole, MS, RAC**  
Director, Regulatory Affairs

Actavis  
Morris Corporate Center III  
400 Interpace Parkway  
Parsippany, NJ 07054  
United States  
T 862-261-7735

(b) (6)

E [JOANN.STAVOLE@actavis.com](mailto:JOANN.STAVOLE@actavis.com)  
[www.actavis.com](http://www.actavis.com)



---

**From:** Ford, Latonia M. [mailto:Latonia.Ford@fda.hhs.gov]  
**Sent:** Thursday, March 17, 2016 10:19 AM  
**To:** Regulatory Affairs US  
**Cc:** Cohen, Rebecca  
**Subject:** NDA 208723 Levoleucovorin Proprietary Name Request

Dear Mrs. Stavole,

Reference is made to your New Drug Application (NDA) application, 208723 submitted to the FDA on December 1, 2015.

We are inquiring as to when you intend to submit a request for Proprietary Name Review for your product. The PDUFA date is October 1, 2016 and the PNR will require 90 days to review. The content requirements for such a submission can be found in the draft Guidance for Industry, entitled, Contents of a Complete Submission for the Evaluation of Proprietary Names: (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>).

Please do not hesitate to contact me if you have any questions.

*Latonia*

**CDR Latonia M. Ford, RN, BSN, MBA** | Safety Regulatory PM  
FDA/OMPT/CDER/OSE/PMS | 10903 New Hampshire Ave

WO22 RM4423 | Silver Spring, MD 20993 | Office: 301-796-4901

|BB: (b) (4) | Email: [latonia.ford@fda.hhs.gov](mailto:latonia.ford@fda.hhs.gov)

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/s/  
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LATONIA M FORD  
03/17/2016

## Cohen, Rebecca

---

**From:** Cohen, Rebecca  
**Sent:** Friday, February 19, 2016 1:26 PM  
**To:** 'RegulatoryAffairsUS@actavis.com'  
**Subject:** 208723-FDA Correspondence-Information Request

**Importance:** High

Hello Joann,

During our review of NDA 208723 our Micro Reviewer has the Information Request noted below.

Please confirm receipt of this email.

Microbiological studies in support of the post-constitution and post-dilution storage times (as stated in the proposed product labeling) have not been provided. Please provide a risk assessment summarizing studies that demonstrate adventitious microbial contamination does not grow under the specified storage conditions [(i.e., (b) (4) in 0.9% Sodium Chloride Injection, USP and 4 (b) (4) in 5% Dextrose Injection, USP after reconstitution and further dilution with the specified diluents)]. Reference is made to Guidance for Industry: ICH Q8 Pharmaceutical Development, Section II.E and Guidance for Industry: ICH Q1A(R2) Stability Testing of New Drug Substances and Products, Section 2.2.7. Please include a description of the test methods and results of studies that are designed using a minimum countable inoculum (b) (4) to simulate potential microbial contamination that may occur during product constitution or dilution. It is generally accepted that growth is evident when the population increases more than (b) (4) however other evidence of growth may be significant. Please perform the test using the storage conditions (temperature and duration) and diluents specified in product labeling. Please provide justification for the selected test conditions and/or diluents as necessary. Periodic intermediate sample times are recommended, as well as extended sample time points demonstrating that the reconstituted or diluted product does not support microbial growth for at least the maximum storage periods under the specified storage conditions. Challenge organisms may include strains described in USP <51> plus typical skin flora, species associated with nosocomial infection. Please provide a positive control that demonstrates the viability of the organisms over the duration of the test period. The RLD may be tested in parallel to demonstrate equivalence.

If you have any questions, please don't hesitate to ask

Rebecca Cohen, RN, MPH, OCN  
LCDR, U.S. Public Health Service  
Regulatory Health Project Manager  
Division of Oncology Products 2/ Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research/ Food and Drug Administration  
[Rebecca.Cohen@fda.hhs.gov](mailto:Rebecca.Cohen@fda.hhs.gov)

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/s/  
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REBECCA L COHEN  
02/19/2016

## Cohen, Rebecca

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**From:** Cohen, Rebecca  
**Sent:** Tuesday, February 02, 2016 11:56 AM  
**To:** 'RegulatoryAffairsUS@actavis.com'  
**Subject:** NDA 208723- FDA Correspondence-Information Request

**Importance:** High

Good Morning Joann,

We are reviewing the labeling provided in your December 1, 2015 submission for levoleucovorin calcium (NDA 208-723) and have the following comments and information request. We acknowledge that the proposed labeling is in the requested format and structure of the Pregnancy and Lactation Labeling Rule (PLLR) (79 FR 72064); however, during our review of your submitted labeling, we found that you have not provided adequate information to support the labeling content for subsection 8.1. We also acknowledge the comments in Mod 2.5 (Clinical Overview) and your marketing experience with levoleucovorin, however, this document does not provide an integrated review of the published human data on leucovorin exposure during pregnancy. Because the levoleucovorin enantiomer is the pharmacologically active isomer of leucovorin it is reasonable to review the literature on racemic leucovorin use in pregnancy.

Therefore, to further support your proposed labeling, we request that you provide:

1. An integrated review of relevant publications on the effects of leucovorin exposure during pregnancy. Copies of the references cited should accompany the integrated review.
2. Labeling revised to reflect your integrated review of the published literature.

Please address and provide your response to me, via email, by **Tuesday, February 23, 2016**. In addition, formally submit your response through the gateway to NDA 208723.

Please confirm receipt of this email.

Rebecca Cohen, RN, MPH, OCN  
LCDR, U.S. Public Health Service  
Regulatory Health Project Manager  
Division of Oncology Products 2/ Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research/ Food and Drug Administration  
[Rebecca.Cohen@fda.hhs.gov](mailto:Rebecca.Cohen@fda.hhs.gov)

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/s/  
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REBECCA L COHEN  
02/02/2016



NDA 208723

**FILING COMMUNICATION –  
NO FILING REVIEW ISSUES IDENTIFIED**

Actavis LLC  
Attention: Joann Stavole, M.S., R.A.C.  
Director, Regulatory Affairs  
Morris Corporate Center III  
400 Interpace Parkway  
Parsippany, NJ 07054

Dear Ms. Stavole:

Please refer to your New Drug Application (NDA) dated December 1, 2015, received December 1, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Levoleucovorin Calcium, Eq. 175 mg base/vial.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is October 1, 2016.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 3, 2016.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

## **PRESCRIBING INFORMATION**

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

1. "Use in Specific Population"(Section 8) included in the Full Prescribing Information (FPI) and Table of Contents (TOC) was not included in the Highlights. Add this section to the Highlights.
2. Include the “Patient Counseling Statement” information as required in the Highlights.
3. When clinical trial adverse reactions data are included in “Postmarketing Experience” subsection of Adverse Reactions (Section 6), 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. Include Patient Counseling (Section 17) in the Full Prescribing Information.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by February 20, 2016. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

## **PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

## **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

If you have any questions, call Rebecca Cohen, Regulatory Health Project Manager,  
at (240) 402-4996.

Sincerely,

*{See appended electronic signature page}*

Joseph Gootenberg, M.D.  
Deputy Director  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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/s/  
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JOSEPH E GOOTENBERG  
01/29/2016

## Filing Meeting Summary January 8, 2016

Application: NDA 208723- 505(b)(2)  
Sponsor: Actavis, LLC  
Submission Date: December 1, 2015  
Received Date: December 1, 2015

### Proposed Indication:

- Indicated for rescue is indicated after high-dose methotrexate therapy in osteosarcoma.
- Indicated to diminish the toxicity (b) (4) methotrexate elimination (b) (4)
- Limitation of use: Levoleucovorin for injection is not (b) (4) for pernicious anemia and megaloblastic anemias secondary to the lack of vitamin B12. (b) (4) hematologic remission (b) (4)

### Review Team Attendees:

Joe Gootenberg, Deputy Director DOP2  
Steve Lemery, Associate Deputy Director DOP 2  
Melanie Pierce, CPMS, DOP2  
Norma Griffin, Lead Regulatory Health Project Manager  
Rebecca Cohen, Regulatory Health Project Manager  
Sandra Casak, Acting Clinical Team Lead  
Shan Pradhan, Clinical Reviewer  
Emily Wearne, Nonclinical Reviewer  
Anamitro Banerjee, Drug Product Branch Chief  
Mike Adams, Drug Product Reviewer  
Steve Kinsley, OPQ, RPM  
Denise Pica-Branco, DPMH, RPM  
Hari Sarker, Drug Product Reviewer  
Elizabeth Berr, Micro Reviewer  
Derek Smith, Facility Branch Chief  
Kumar Janoria, Process Reviewer  
Jing Li, Biopharmaceuticals Reviewer  
Carole Broadnax, OPDP  
Christy Kirk, ORP  
Carol Kasten, Maternal Health Reviewer

## Discussion Items

### 1. Reviewed Regulatory Status:

- Standard Review, not on the Program
  - 505(b)(2) Listed Drug: Actavis plans to rely on data from Spectrum Pharms, NDA 020140 for the listed drug, Fusilev, and published literature
- The Review Team brought up issues with this application including:*
- *Should this be considered a 505j application?*
  - *The sponsor's proposed drug product has larger dosage, but same composition.*
  - *The listed drug is not the lyophilized product, it is the solution.*
  - *If this is determined that it is a 505j application, then it is reviewed by Generics team.- OND team will let us know Monday, 1/11/16 if this is a 505j application.*
  - *Perhaps the CDER jurisdiction group will help to decide (?Christine Lauritsen?)? If not, then who makes this call?*
  - *If found to be a 505j application, then OND would issue a Refuse to File (RTF).*
  - ***At this point, Filing Determination cannot be decided until the Team/Division has determined if it is a 505(j) application.***
- Labeling: Package insert, carton and container, in addition Actavis provided side-by-side comparison labeling with listed drug, Fusilev
  - Categorical Exclusion/ Environmental Assessment included in submission
  - Request for Waiver from in vivo Bioequivalence Studies included in submission appears fine, biopharm appears fine
  - Request for full waiver of pediatric studies was included in submission

### Additional Discussion by disciplines/representatives: potential RTF issues

- a. Clinical - no filing issues
- b. Nonclinical – no data; no filing issues
- c. ClinPharm/Biopharm - no discussion; from Biopharmaceutics – will likely grant the waiver for bioequivalence studies, but no filing issues.
- d. CMC-no filing issues, there are review issues and comments (IR) will need to be sent out; review to be uploaded.
- e. Pediatrics/Maternal Health-if this is a 505(b)(2), then need to issue an IR requesting for PLLR format; request further literature review (this is not a filing issue, only a review issue); don't need to request PLLR of the Inivator. Denise Pica-Branco asked DPMH questions. Denise indicated that this has Orphan Drug Designation granted and therefore, no PSP is needed.
- f. Facilities: an international facility inspection has been scheduled (b) (4)

g.  (b) (4)

h.  (b) (4)

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/s/  
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REBECCA L COHEN  
01/20/2016

## Initial Planning Meeting Summary December 17, 2015

### NDA 208723- 505(b)(2) Application

**Product:** Levoleucovorin Calcium for Injection, Eq 175mg/base/vial  
**Submission Date:** December 1, 2015  
**Received Date:** December 1, 2015  
**Sponsor:** Actavis, LLC

#### Proposed Indication:

- Indicated for rescue is indicated after high-dose methotrexate therapy in osteosarcoma.
- Indicated to diminish the toxicity (b) (4) methotrexate elimination (b) (4)
- Limitation of use: Levoleucovorin for injection is not (b) (4) for pernicious anemia and megaloblastic anemias secondary to the lack of vitamin B12. (b) (4) hematologic remission (b) (4)

#### Attendees:

Joe Gootenberg, Deputy Director, DOP2  
Steve Lemery, Assistant Deputy Director, DOP 2  
Rebecca Cohen, Regulatory Health Project Manager  
Shan Pradhan, Clinical Reviewer  
Emily Wearne, Nonclinical Reviewer  
Whitney Helms, Nonclinical Team Lead  
Anamitro Banerjee, Drug Product Branch Chief  
Mike Adams, Drug Product Reviewer  
Steve Kinsley, OPQ, RPM  
Hong Zhao, Clinical Pharmacology Team Lead  
Safaa Burns, Clinical Pharmacology Reviewer  
Okpo Eradiri, Biopharmaceuticals Team Lead  
Jing Li, Biopharmaceuticals Reviewer

#### Additional Team Members:

Jessica Derenick Cleck, OPDP Team Lead  
Carole Broadnax, OPDP  
Sandra Casak, Acting Clinical Team Lead  
Kasturi Srinivasachar, Drug Substance Branch Chief  
Hari Sarker, Drug Product Reviewer  
John Arigo, Micro Branch Chief  
Elizabeth Berr, Micro Reviewer  
Derek Smith, Facility Branch Chief  
Rose Xu, Facility Reviewer

Lane Christensen, Process Branch Chief  
 Kumar Janoria, Process Reviewer  
 Christy Kirk, ORP  
 Paul Perdue, ORA (*cc on all meetings*)  
 Debora Livornese, ORA (*cc on all meetings*)  
 Melanie Pierce, CPMS, DOP2 (*cc on all meetings*)

1. **Reviewed Regulatory Status:**

- Review: Standard Review, not on the Program
- 505(b)(2) Listed Drug: Actavis plans to rely on data from Spectrum Pharms, NDA 020140 for the listed drug, Fusilev, and published literature 505(b)(2) or 505(b)(j)?
- Labeling: Package insert, carton and container, in addition Actavis provided side-by-side comparison labeling with listed drug, Fusilev
- Categorical Exclusion requested
- Requested Waiver from in vivo Bioequivalence Studies
- Requested full waiver of pediatric studies

2. **Reviewed Milestone Dates (per 21<sup>st</sup> Century Review Planner):**

Milestone	NDA 208723 Standard 10 month
<b>Application Received</b>	<b>December 1, 2015</b>
<b>Acknowledgment Letter</b>	December 14, 2015
<b>Filing Action Letter (by Day 60)</b>	<b>NEXT DUE DATE: Friday, January 29, 2016</b> (Actual Sat 1/30/2016)
<b>Deficiencies Identified Letter (74 Day Letter)</b>	Friday, February 13, 2016 (Actual Sat 2/14/2016)
<b>Send proposed labeling/PMR/PMC/REMS to applicant (~3 weeks prior to Action - Review Planner Target date)</b>	Friday, September 2, 2016 (Actual Sat 9/3/2016)
<b>Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant</b>	Friday, September 9, 2016
<b>Review Target Due Dates:</b>	
<i>Primary Review Due</i>	Friday, August 26, 2016 (Actual Sat 8/27/2016)
<i>Secondary Review Due</i>	Friday, September 2, 2016 (Actual Sat
<i>CDTL Review Due</i>	9/3/2016)

Milestone	NDA 208723 Standard 10 month
<i>Division Director Review Due</i>	Friday, September 9, 2016 (Actual Sat 9/10/2016)  Friday, September 30, 2016 (Actual Sat 10/1/2016)
<b>Compile and circulate Action Letter and Action Package</b>	Friday, September 9, 2016
<b>FINAL Action Letter Due</b>	Friday, September 30, 2016 (Actual Sat 10/1/2016)

3. **Reviewed list of Consults/Collaborative Reviewers Needed:**

<b>OPDP</b>	yes
<b>OSE</b>	yes
<b>Pediatric/Maternal Health</b>	yes
<b>Patient Labeling Team</b>	no
<b>SEALD</b>	J Chang
<b>Pediatric Page/PeRC</b>	yes
<b>SGE or Patient Representative</b>	no

4. **Reviewed list of scheduled Meetings and target dates:**

- **Filing Meeting-** Filing meeting necessary to consider if 505(b)(2) or 505(j)
- **Team Meetings** – Schedule for every 6 weeks
- **Filing Meeting (by Day 30):** Scheduled for January 8, 2016
- **Mid-Cycle Meeting:** Scheduled for April 19, 2016
- **Wrap- Up Meeting:** target date August 27, 2016-to be determined
- **Labeling Meetings** – Will probably begin in June and possibly need 2-3 meetings, but will decide number of meetings, section groupings, and when to begin labeling meetings after initial label assessment. Will discuss during filing meeting

5. Will be discussed during Filing Meeting: (b) (4)



NDA 208723

**NDA ACKNOWLEDGMENT**

Actavis L.L.C.  
Attention: Joann Stavole, M.S., R.A.C.  
Director, Regulatory Affairs  
Morris Corporate Center III  
400 Interpace Parkway  
Parsippany, NJ 07054

Dear Ms. Stavole:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Date of Application: December 1, 2015

Date of Receipt: December 1, 2015

Our Reference Number: 208723

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 30, 2015, in accordance with 21 CFR 314.101(a).

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Oncology Products 2  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient

information). If you have not already established secure email with the FDA and would like to set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-4255.

Sincerely,

*{See appended electronic signature page}*

Norma Griffin  
Lead Regulatory Health Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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/s/  
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NORMA S GRIFFIN  
12/17/2015