

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208723Orig1s000**

**MEDICAL REVIEW(S)**

**FROM:** Shan Pradhan, Medical Officer, DOP2  
**THROUGH:** Sandra Casak, Acting Team Leader, DOP2  
**TO:** File  
**SUBJECT:** NDA 208723 SDN 1  
**SUBMIT DATE:** December 1, 2015  
**PRODUCT:** Levoleucovorin calcium for injection, eq. 175 mg base/vial  
**APPLICANT:** Actavis

Actavis submitted this application for levoleucovorin calcium for injection under the 505(b)(2) regulatory pathway. The reference drug is Fusilev (levoleucovorin) for injection. Actavis did not conduct safety or effectiveness studies to support the application and does not have right of reference to Fusilev's data. Actavis' application relies on FDA's previous findings of efficacy and safety for Fusilev, approved March 7, 2008, for the following clinical indications (b) (4)

- Rescue after high-dose methotrexate therapy in osteosarcoma.
- Diminishing the toxicity (b) (4) methotrexate elimination (b) (4).

The Fusilev label includes a limitation of use as follows: "Fusilev is not approved for pernicious anemia and megaloblastic anemias. Improper use may cause a hematologic remission while neurologic manifestations continue to progress."

Actavis stated that they intend to reference (b) (4) Fusilev® (levoleucovorin) for injection, powder, lyophilized, for solution for intravenous use (Spectrum Pharmaceuticals, NDA 020140), approved March 7, 2008, as the sole support, including for the Pediatric Use section, of the 505(b)(2) application.

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

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

The proposed labeling Actavis submitted was based on, [REDACTED] (b) (4) the Fusilev product labeling (with the colon cancer indication removed). FDA internal labeling meetings are ongoing and FDA will propose updates throughout the label to align with current FDA labeling guidances and practice, [REDACTED] (b) (4)

There are no other clinical issues that would preclude approval of Actavis' application at this time.

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/s/  
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SHAN PRADHAN  
07/29/2016

SANDRA J CASAK  
07/29/2016

<b>NDA</b>	208723
<b>Supporting Document</b>	3
<b>Receipt Date</b>	March 3, 2016
<b>Applicant</b>	Actavis
<b>Product</b>	Levoleucovorin calcium
<b>Reviewer</b>	Shan M. Pradhan

This submission contains revised labeling in response to the No Filing Issues letter that included some comments re labeling and an IR from MHT. Refer to NDA clinical review.

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/s/  
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SHAN PRADHAN  
03/19/2016

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA/BLA Number: 208723**

**Applicant: Actavis**

**Stamp Date: 12/01/15**

**Drug Name: levoleucovorin  
calcium for injection, eq. 175 mg  
base/vial**

**NDA/BLA Type: 505(b)(2)**

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

	Content Parameter	Yes	No	NA	Comment
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			Module 5 consists of references only. Module 2.5 includes a table of contents.
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			Several literature references are provided in abstract form only; for at least one such reference, the original article is not in English.
6.	Is the clinical section legible so that substantive review can begin?	X			
<b>LABELING</b>					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			The overall design of the draft labeling appears on initial review to be in PLR format.
<b>SUMMARIES</b>					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			The application includes a Module 2.5 Clinical Overview; however, Module 2.7 Clinical Summary consists only of a statement that the section is not applicable to the application because no bioequivalence studies were conducted.
9.	Has the applicant submitted the integrated summary of safety (ISS)?			X	See comment for item 3 above.
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	See comment for item 3 above.
11.	Has the applicant submitted a benefit-risk analysis for the	X			Module 2.5 Clinical

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	product?				Overview includes a brief section titled "Benefits and Risk Conclusions"
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	X			505(b)(2)
<b>505(b)(2) Applications</b>					
13.	If appropriate, what is the reference drug?				Reference drug is Fusilev (levoleucovorin) for injection
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	X			Module 1.12.15 contains a request for biowaiver, which states that the conditions of use, active ingredient, and dosage form are related to those of the listed drug, and that a new strength is proposed.
15.	Describe the scientific bridge (e.g., BA/BE studies)				See comment for item 14 above.
<b>DOSE</b>					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product ( <i>i.e.</i> , appropriately designed dose-ranging studies)?			X	See comment for item 3 above.
<b>EFFICACY</b>					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?			X	See comment for item 3 above.
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
<b>SAFETY</b>					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?			X	See comment for item 3 above.
22.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product ( <i>e.g.</i> , QT interval studies, if needed)?			X	
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?			X	
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
26.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?			X	
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	
<b>OTHER STUDIES</b>					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included ( <i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
<b>PEDIATRIC USE</b>					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			The applicant included a request for waiver based on absence of new active ingredient, indication, dosage form, dosing regimen, and route of administration.
<b>ABUSE LIABILITY</b>					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
<b>FOREIGN STUDIES</b>					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	See comment for item 3 above.
<b>DATASETS</b>					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			X	See comment for item 3 above.
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

<sup>2</sup> The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
37.	Are all datasets to support the critical safety analyses available and complete?			X	
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
<b>CASE REPORT FORMS</b>					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	See comment for item 3 above.
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
<b>FINANCIAL DISCLOSURE</b>					
41.	Has the applicant submitted the required Financial Disclosure information?			X	See comment for item 3 above.
<b>GOOD CLINICAL PRACTICE</b>					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			X	See comment for item 3 above.

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? \_\_Yes\_\_**

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

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

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/s/  
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SHAN PRADHAN  
01/06/2016

SANDRA J CASAK  
01/06/2016