

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208723Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

NDA/SDN 208723/SDNs 1, 3 and 9

Drug Product: Levoleucovorin Calcium for Injection (Equivalent to 175 mg base/vial)

Submission Dates: 12/1/2015 (SDN 1), 3/3/2016 (SDN 3) and 9/21/2016 (SDN 9)

Applicant: Actavis LLC, Nerviano, Italy

Submission Types: 505 (b) 2 supplement (SDN 1) and labeling supplement (SDN 1, 3, and 9)

This NDA application is submitted for Levoleucovorin Calcium for Injection, Eq. 175 mg/vial in pursuant of Section 505 (b) (2). Accordingly, Actavis submitted revised labeling for the current package insert originally approved on 12/1/2015. The original version was amended on 3/3/2016 and 9/21/2016.

The current submission is primarily based on the safety and efficacy data previously submitted for the approved drug product, Fusilev[®] (levoleucovorin) for injection by Spectrum Pharms (NDA 20-140) as well as published literature, and additional quality data.

In accordance with 21 CFR 320.22(a), Actavis requested a waiver for the requirement to submit *in vivo* BA/BE data for the proposed new drug product, Levoleucovorin Calcium for Injection 175 mg/vial. The proposed new drug product has the same final concentration of active and inactive ingredients when ready for IV administration, same dosage form, same route of administration as (b) (4) as Fusilev[®].

Levoleucovorin Calcium for Injection, Eq. 175 mg/vial has been developed as a lyophilisate for solution for intravenous use after reconstitution with 17.7 mL of sterile 0.9% Sodium Chloride Injection, USP prior to the administration. The proposed indications are as follows:

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



(b) (4)

(b) (4)

(b) (4)

(b) (4)

A comparison of the inactive ingredients of the Applicant's lyophilized Levoleucovorin Calcium for Injection 50 mg and 175 mg products (b) (4) is presented in **Table 3**.

	(b) (4)
Calcium Levovorfolinate Pentahydrate equivalent to Levoleucovorin (present as Levoleucovorin Calcium)	
Mannitol	
Sodium Hydroxide	(b) (4)
Hydrochloric Acid	
N/A = not applicable	

The biowaiver request from BA/BE *in vivo* studies for the proposed Levoleucovorin formulation (175 mg/vial) will be reviewed by the Office of Product Quality (OPQ).

In addition, Actavis revised the currently approved package insert to include information on the new manufacturer/new formulation for Levoleucovorin. The proposed labeling was amended on 3/3/2016 (SDN 3) and 9/21/2016 (SDN 9) to include edits regarding the effect of leucovorin exposure during pregnancy (Section 8: Specific Populations) and to reflect their integrated review of published literature as requested by FDA on 2/2/2016. There were only format based clinical pharmacology edits to the proposed labeling (see attached final revised labeling).

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SAFAA BURNS
09/26/2016

JEANNE FOURIE ZIRKELBACH
09/26/2016