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 vitro 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 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 methotrexate elimination.
A comparison of the inactive ingredients of the Applicant’s lyophilized Levoleucovorin Calcium for Injection 50 mg and 175 mg products is presented in Table 3.

<table>
<thead>
<tr>
<th>Calcium Levulinate</th>
<th>Fumarate equivalent to Levoleucovorin (present as Levoleucovorin Calcium)</th>
<th>Mannitol</th>
<th>Sodium Hyaluronate</th>
<th>Hydrochloric Acid</th>
<th>N/A (not applicable)</th>
</tr>
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</table>

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).
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