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March 22, 2024

VIA ELECTRONIC SUBMISSION

Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20552

SUITABILITY PETITION

Dear Sir or Madam:

Epic Pharma, LLC is electronically submitting this Citizen Petition pursuant § 505(j)(2)(C) (the "FDC Act") and in accordance with 21 C.F.R. §§ 10.20, 10.30, and 314.93, to request the Commissioner of the Food and Drug Administration (the "Agency" and/or the "FDA") declare that the drug product Leucovorin Calcium Injection (preservative-free, sterile solution) in the new strengths of 200 mg(base)/20 mL and 350 mg(base)/35 mL and new dosage form of a ready-to-use injection is suitable for submission in an Abbreviated New Drug Application ("ANDA").

A. Action Requested

Petitioner seeks to file an ANDA for leucovorin calcium that differs in strength and dosage form from the Reference Listed Drug ("RLD") and Reference Standard ("RS"). To that end, Petitioner requests that the Agency declare that the drug product, Leucovorin Calcium Injection (preservative-free, sterile solution), in the new strengths of 200 mg(base)/20 mL and 350 mg(base)/35 mL, and in a ready-to-use injectable dosage form, is suitable for submission in an ANDA.

B. Statement of Grounds

The FDC Act § 505(j)(2)(C), with 21 C.F.R. §§10.20, 10.30, and 314.93, permits the submission of an ANDA for a drug product that differs in strength and dosage form from the RLD after FDA has approved a petition seeking permission to file such an application. The FDC Act indicates that such a petition must be approved by the Agency unless there is a finding that investigations are needed to demonstrate the safety and effectiveness of the proposed drug product.

Petitioner submits this Petition to request that FDA permit submission of its ANDA for Leucovorin Calcium for Injection in 200 mg(base)/20 mL and 350 mg(base)/35 mL, which represent changes from the RLD. The RLD for all Leucovorin Calcium injection, NDA 008107, was approved in strengths of 3 mg(base)/mL, 50 mg(base)/mL, 100 mg(base)/vial, and 350 mg(base)/vial and was

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supplied as an injectable lyophilized powder. NDA 008107 has been moved to the Discontinued Section of FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book"). Orange Book, 6-288 (44th ed. 2024). FDA determined that the product was not discontinued or withdrawn for safety or efficacy reasons. *See* FDA, Notice, Determination That LEUCOVORIN CALCIUM (Leucovorin Calcium) Injectable and Other Drug Products Were Not Withdrawn from Sale for Reasons of Safety or Effectiveness, 81 Fed. Reg. 26800 (May 4, 2016). A copy of the current Orange Book entry for NDA 008107 is included in ***Attachment 1***.

FDA had designated ANDA 040347, which is held by Hikma Pharmaceuticals USA Inc., as RS. Orange Book, 3-264 (43rd ed. 2023). The products under ANDA 040347 were available in 300 mg (base)/30 mL and 500 mg(base)/50 mL strengths and was supplied as a sterile, preservative-free solution. While products under ANDA 040347 differs in strength and dosage form from the RLD, the difference was approved through suitability petitions under Docket No. 97P-0502/CP2 for 30 mL/vial and 97P-0502/CP1 for 50 mL/vial, on March 31, 1998, according to the Bioequivalence Review for original ANDA 040347. ***Attachment 2***.

Due to the discontinued status of the previous RS ANDA 040347, FDA has designated ANDA 207226 for the strength of 500 mg (base)/50 mL and ANDA 207241 for the strength of 100 mg (base)/10 mL, which are held by Fresenius Kabi USA LLC, as RS. Orange Book, 3-270 (44th ed. 2024). The RS were available in 100 mg (base)/10 mL and 500 mg(base)/50 mL strengths and were also supplied as a sterile, preservative-free solution. While ANDA 207241 and ANDA 207226 differ in strength and dosage form from the RLD, the difference between the RS and RLD was approved through suitability petitions under Docket No. 93P-0427/CP3 for 10 mL/vial and 97P-0502/CP1 for 50 mL/vial. In addition, the suitability petition under Docket No. 93P-0427/CP2 for Leucovorin Calcium Injection, 10 mg/mL (ready-to-use solution), 250 mg single-dose vial has also been approved.

The approval letters of suitability petitions for Leucovorin Calcium Injection (preservative-free, sterile solution), 10 mg(base)/mL under Docket No. 93P-0427/CP3 for 10 mL/vial, 93P-0427/CP2 for 25 mL/vial, 97P-0502/CP2 for 30 mL/vial and 97P-0502/CP1 for 50 mL/vial are enclosed as ***Attachment 3***. A copy of the current electronic edition of the Orange Book for Leucovorin Calcium Injection is provided as ***Attachment 4***.

Petitioner notes that the requested change to the strengths represent only a change in total drug content and not the concentration comparing with the current RS. It will provide the same injection dosage form of intermediate strengths of 200 mg(base)/20 mL and 350 mg(base)/35 mL, and will contain the same active ingredient in the same concentration (10 mg base/1 mL) and labeling as the RS.

Additionally, the change in dosage form from a lyophilized injection to a ready-to-use sterile solution injection would provide an alternative to the currently approved injectable lyophilized powder of the same strengths. The dosage form change has been approved under previous

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suitability petitions, as their approval letters enclosed in ***Attachment 3***. This will offer a more convenient option for healthcare providers and patients.

There are no proposed changes in labeling with the exception of the change in strength and dosage form sought in this petition. The uses, indications, warnings, and dosage and administration will remain the same as that of the RLD and the current RS. Approved labeling for the RLD, NDA 008107, the previous RS, ANDA 040347, and current RS ANDA 207241 and ANDA 207226, are enclosed as ***Attachments 5, 6, 7, and 8***. Draft labeling for the proposed drug product is enclosed as ***Attachment 9***.

Accordingly, based on the information provided above, Epic Pharma, LLC respectfully requests the Commissioner find the proposed strengths of 200 mg(base)/20 mL and 350 mg(base)/35 mL for Leucovorin Calcium Injection (preservative-free, sterile solution) and proposed ready-to-use dosage form should raise no questions of safety or effectiveness and to permit the submission of an ANDA for such strengths.

Applicability of Pediatric Research Equity Act

The Pediatric Research Equity Act ("PREA"), enacted in December 2003, amended the FDC Act by requiring certain applications for a drug submitted under FDC Act § 505 to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is deferred or waived. *See* FDC Act § 505B(a)(1)(A)(i). Specifically, PREA applies to all applications for a new active ingredient, dosage form, indication, route of administration, or dosing regimen. *See id.* ANDAs submitted under an approved suitability petition for a change in strength are not subject to PREA requirements. *See* FDA, Draft Guidance for Industry, How to Comply with the Pediatric Research Equity Act, 4 (Sep. 2005). Petitioner asserts that PREA is not applicable to the proposed change in strength for Leucovorin Calcium Injection.

With respect to the change in dosage form, Petitioner recognizes that PREA requires studies of the safety and effectiveness of the product in pediatric patients; however, Petitioner requests a waiver of PREA requirements. The Act provides for a waiver from PREA requirements if the drug "does not present a meaningful therapeutic benefit over existing therapies for pediatric patients" and "is not likely to be used in a substantial number of pediatric patients." FDC Act § 505B(a)(5)(A). Petitioner contends that the proposed drug product does not provide a meaningful benefit over existing therapies for pediatric patients. The RLD is adequately labeled with a "Precaution" for pediatric patients, and the same active ingredient has been studied in pediatric patients, as reflected in the labeling for another approved leucovorin product, Wellcovorin, approved under NDA 018342 in oral tablets and in several ANDAs in injectable form (ANDA 087439 for example). Further, the RLD has been on the market since 1952 and has a well-known safety and efficacy profile; the proposed product is intended for the exact same use as the RLD and thus there would be no benefit for pediatric patients over the RLD if FDA were to approve the proposed product. Further, because of its route of administration and the availability of an oral dosage form, this product is unlikely to be used by pediatric patients who may need a leucovorin calcium product.

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And, because this product is widely used, there is no reason that pediatric patients would be more likely to switch to this product from existing products. Consequently, Petitioner contends that a waiver of PREA requirements is appropriate.

C. Environmental Impact

The actions requested in this petition are subject to categorical exclusions under 21 C.F.R. § 25.31.

D. Economic Impact

Pursuant to 21 C.F.R. § 10.30(b), economic impact information is submitted only when requested by the Commissioner. This information will be promptly provided if so requested.

E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which is unfavorable to the petition.

If there are any questions concerning this citizen petition, please contact the undersigned by telephone at (347) 238-2729 or via email at RADept@epic-pharma.com.

Sincerely,

Digitally signed by Pei Zhang
DN: cn=Pei Zhang, o=Epic Pharma, LLC, ou=Regulatory Affairs Department, email=p.zhang@epic-pharma.com, c=US
Date: 2024.03.22 15:05:22 -04'00'

Mr. Pei Zhang Ph.D.
Director of Regulatory Affairs
Epic Pharma, LLC

Attachments:

1. **Orange Book Entry for NDA 008107**
2. **Bioequivalence Review for original ANDA 040347**
3. **Suitability Petition Approval Letters for Leucovorin Calcium Injection, 10 mg(base)/mL**
4. **Orange Book Entry for Leucovorin Calcium Injection**
5. **Approved labeling for Reference Listing Drug (NDA 008107)**
6. **Approved labeling for Previous Reference Standard (ANDA 040347)**
7. **Approved labeling for Current Reference Standard (ANDA 207241)**
8. **Approved labeling for Current Reference Standard (ANDA 207226)**
9. **Epic's Proposed Labeling**