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Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1061, HFA-305
5630 Fishers Lane
Rockville, Maryland 20852

RE: ANDA Suitability Petition
Methotrexate Injection, USP (100 mg/mL)

ANDA Suitability Petition

The undersigned submits this Suitability Petition (the "Petition") under the provisions of the Federal Food, Drug and Cosmetic Act, Section 505(j)(2)(c) and 21 CFR 314.93 to request the Commissioner of Food and Drugs to allow submission of an abbreviated new drug application (ANDA) for Methotrexate Injection, USP in a strength of 1,000 mg/10mL (100 mg/mL) in a 10mL single use vial.

A. Action Requested

The Petitioner requests that the Commissioner of Food and Drugs permits a change in (a) dosage form (lyophilized powder to ready to use liquid) and (b) final drug concentration to allow for submission of an abbreviated new drug application (ANDA) for Methotrexate Injection in a strength of 1,000 mg/10mL (100 mg/mL) in a 10 mL single use vial. The basis of the Petition is the reference listed drug product, Methotrexate Preservative Free for Injection, USP marketed by Bedford Laboratories, which is available in a single-use vial containing 1,000 mg of Methotrexate as Methotrexate Sodium for Injection with instructions to reconstitute with 19.4 mL of 0.9% Sodium Chloride Injection or Dextrose 5% in Water to a concentration of 50 mg/mL. Bedford Laboratories received approval of Methotrexate Preservative Free for Injection, USP under ANDA 40-632 on August 12, 2005.

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B. Statement of Grounds

The subject of the Petition is to request Food and Drug Administration (FDA) permission to implement a change in (a) dosage form (lyophilized powder to ready to use liquid) and (b) final drug concentration for Methotrexate for Injection, USP. The reference listed drug product, Methotrexate Preservative Free for Injection, USP marketed by Bedford Laboratories is available in a single-use vial containing 1,000 mg of Methotrexate as Methotrexate Sodium for Injection with instructions to reconstitute with 19.4 mL of 0.9% Sodium Chloride Injection or Dextrose 5% in Water to a concentration of 50 mg/mL.

PCH's proposed drug product would contain 1,000 mg Methotrexate as Methotrexate Sodium USP at a concentration of 100 mg/mL in a fill volume of 10 mL in a 10 mL single use vial. The proposed concentration is twice that set forth in the package insert for Methotrexate Preservative Free for Injection, USP, the reference listed drug product, after reconstitution with 19.4 mL of a suitable diluent.

Product	Dosage Form	Route of Administration	Strength
Bedford's Methotrexate Preservative Free for Injection USP	Lyophilized Powder	Intravenous	1,000 mg at 50 mg/mL when reconstituted with 19.4 mL of a suitable diluent in a 20 mL single use vial
PCH'S PROPOSED Methotrexate Injection, USP	Liquid	Intravenous	1,000 mg at 100 mg/mL in a 10 mL single use vial

Methotrexate is indicated in the treatment of several neoplastic diseases including gestational choriocarcinoma, chorioadenoma destruens and hydatidiform mole. In acute lymphocytic leukemia, methotrexate is indicated in the prophylaxis of meningeal leukemia and is used in maintenance therapy in combination with other chemotherapeutic agents. Methotrexate is also indicated in the treatment of meningeal leukemia. Methotrexate is used alone or in combination with other anticancer agents in the treatment of breast cancer, epidermoid cancers of the head and neck, advanced mycosis fungoides (cutaneous T cell lymphoma), and lung cancer, particularly squamous cell and small cell types. Methotrexate is also used in combination with other chemotherapeutic agents in the treatment of advanced stage non-Hodgkin's lymphomas.

Methotrexate in high doses followed by leucovorin rescue in combination with other chemotherapeutic agents is effective in prolonging relapse-free survival in patients with non-metastatic osteosarcoma who have undergone surgical resection or amputation for the primary tumor.

Methotrexate is indicated in the symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy.

Methotrexate is indicated in the management of selected adults with severe, active rheumatoid arthritis (ACR criteria), or children with active polyarticular-course juvenile rheumatoid arthritis, who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of first-line therapy including full dose nonsteroidal anti-inflammatory agents (NSAIDs).

The proposed dosage form and concentration contains Methotrexate in an amount recommended in the approved labeling for dilution with 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP.

Methotrexate Preservative Free for Injection, USP is currently approved in one configuration: 1,000 mg in a 20 mL vial for reconstitution with 19.4 mL of a suitable diluent.

The Dosage and Administration section of the approved labeling describes the following IM and IV dosage regimens:

Choriocarcinoa and similar Trophoblastic Diseases
15 mg to 30 mg daily

Leukemia

Induction Regimen	3.3 mg/m^2 daily
Maintenance Regimen 1	30 mg/m^2 total dose per week in two divided doses
Maintenance Regimen 2	2.5 mg/kg every 14 days

Meningeal Leukemia
12 mg/m^2 every 2 to 5 days

Osteosarcoma

High Dose Regimen	12 grams/m^2 up to 15 grams/m^2

Arthritis
10 mg/m^2 every week

Psoriasis
10 mg to 25 mg per week

Based on information included in the approved labeling, it is presumed that the 1,000 mg size is used exclusively for preparing the High Dose Regimen.

When preparing the High Dose Regimen, the calculated dose must be diluted in a suitable

infusion solution. It is recommended that Methotrexate administered via the High Dose Regimen be infused over 4 hours.

Based on Average Body Surface Area of 1.7 m^2, patients receiving the High Dose Regimen would require starting doses of 20.4 grams to 25.5 grams.

In preparing such a dose, the practitioner would be required to reconstitute 20 to 26 vials of Methotrexate Preservative Free for Injection, USP. The total reconstituted volume would be 400 mL to 520 mL.

The proposed configuration, 1,000 mg of Methotrexate as a ready to use preservative free liquid at a concentration of 100 mg/mL would provide practitioners with a convenient alternative to the currently approved form. A copy of the medical rationale is provided in **Attachment 1**.

The proposed strength would allow for more convenient preparation of approved doses for patients with Average Body Surface Area both less than and greater than 1.7 m^2. Because the total volume of drug in liquid form would be half of that compared to the reference listed drug, a practitioner would have greater flexibility in preparing the infusion solution.

The proposed product clearly conforms to the dosage modifications and administration recommendations listed in the approved package insert of the reference listed drug.

Although the number of vials required to prepare a specific dose would not change, the proposed drug product would minimize the potential for contamination resulting from the handling of the product, such as blood borne pathogens from cut fingers and glass particles because it would not require reconstitution.

The proposed presentation would also provide a reduction in hazardous waste disposal and cost for the course of therapy.

The proposed drug is intended for use only as described in the Indications and Dosage and Administration sections of the approved labeling of the RLD. Draft labeling is provided in **Attachment 2**.

Included in **Attachment 3** is the package insert for Methotrexate Preservative Free for Injection USP marketed by Bedford Laboratores. The labeling for the proposed drug is identical to that of Bedford's Methotrexate Preservative Free for Injection USP, but differs only with respect to the product name, dosage preparation, final concentration and volume, the how-supplied statement, and the specific manufacturer's information.

The proposed strength (1,000 mg/10 mL) does not pose a question of safety or efficacy because the uses, the doses, and the route of administration are the same as those of the RLD. The only

difference between the proposed products and the RLD is the dosage form (ready to use liquid versus lyophilized powder) and the final concentration of the drug (100 mg/mL versus 50 mg/mL when reconstituted with 19.4 mL of a suitable diluent). The proposed doses are reflected in the approved labeling of the RLD. For the above reasons, the undersigned requests that the Commissioner approve this petition and find that an application for Methotrexate Injection, USP, 1,000 mg/20mL (100 mg/mL) is suitable for submission as an ANDA.

C. Environmental Impact

In accord with 21 CFR 25.24(c)(1), an Environmental Impact Analysis Statement is not required if there is a determination that Methotrexate Injection is suitable for ANDA status.

D. 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 are unfavorable to the Petition.

We trust you will find the information in the Petition to be satisfactory for your review and approval. If there are any questions concerning this amendment, please do not hesitate in contacting me at (949) 457-2808 or Tania Hoffman, Project Specialist, Regulatory Affairs, at (949) 455-4728. We can also be contacted by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Lowe

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Authorized Agent, Regulatory Affairs