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December 8, 2006

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

2005106 DEC 11 AM 10:02

**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/10 mL (100 mg/mL) in a 10 mL single use vial.

**A. Action Requested**

The Petitioner requests that the Commissioner of Food and Drugs permits a change in the strength to allow for submission of an abbreviated new drug application (ANDA) for Methotrexate Injection, USP in a strength of 1,000 mg/10 mL (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 Mayne Pharma USA, which is available in a single-use vial containing 1,000 mg of Methotrexate as Methotrexate Sodium in 40 mL of 0.490% w/v Sodium Chloride. Sodium Hydroxide and, if necessary Hydrochloric Acid are added to adjust the pH to approximately 8.5. Mayne Pharma USA received approval of Methotrexate Injection, USP, Preservative Free under NDA 11-719 on April 13, 2005.

**B. Statement of Grounds**

The subject of the Petition is to request Food and Drug Administration (FDA) permission to implement a change in the strength for Methotrexate Injection, USP. The reference listed drug

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product, Methotrexate Injection, USP, Preservative Free, marketed by Mayne Pharma, USA, is available in a single-use vial containing 1,000 mg of Methotrexate as Methotrexate Sodium in 40 mL (25 mg/mL) of 0.490% w/v Sodium Chloride. Sodium Hydroxide and, if necessary Hydrochloric Acid are added to adjust the pH to approximately 8.5.

Pharmachemie's (PCH) 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 four times that set forth in the package insert for Methotrexate Injection, USP, Preservative Free, the reference listed drug product, which is at 1 g/40 mL or 25 mg/mL. However, the total drug content is identical, i.e. 1,000 mg per vial.

<b>Product</b>	<b>Dosage Form</b>	<b>Route of Administration</b>	<b>Strength</b>
Mayne's Methotrexate Injection, USP Preservative Free	Liquid	Intravenous, intramuscular, intra-arterial, intrathecal	1,000 mg at 25 mg/mL in a 40 mL single-use vial
PCH'S PROPOSED Methotrexate Injection, USP	Liquid	Intravenous, intramuscular, intra-arterial, intrathecal	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 drug product contains Methotrexate in an amount recommended in Mayne's approved labeling for Methotrexate Injection, USP, Preservative Free, for single-use only product.

Methotrexate Injection, USP, Preservative Free, is currently approved in one configuration: 1,000 mg in a 40 mL single use vial.

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

Choriocarcinoma and similar Trophoblastic Diseases  
15 mg to 30 mg daily

Leukemia

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

Meningeal Leukemia

12 mg/m<sup>2</sup> every 2 to 5 days

Lymphosarcomas (Stage 3)

0.625 to 2.5 mg/kg daily

Mycosis fungoides (cutaneous T cell lymphoma)

5 - 50 mg weekly or  
15 to 37.5 mg twice weekly

Osteosarcoma

High Dose Regimen      12 grams/m<sup>2</sup> up to 15 grams/m<sup>2</sup>

Arthritis

10 mg/m<sup>2</sup> 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  $1.7 \text{ m}^2$ , 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 use 20 to 26 vials of Methotrexate Injection, USP (Preservative Free). The total volume used would be 800 mL to 1,040 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  $1.7 \text{ m}^2$ . Because the total volume of drug in liquid form would be one-fourth 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.

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 Injection, USP, Preservative Free marketed by Mayne Pharma USA. The labeling for the proposed drug is identical to that of Mayne's Methotrexate Injection, USP, Preservative Free, but differs only with respect to the product strength (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 concentration of the drug (100 mg/mL versus 25 mg/mL). 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/10mL (100 mg/mL) is suitable for submission as an ANDA.

**C. Environmental Impact**

In accord with 21 CFR 25.31(a), an Environmental Impact Analysis Statement is not required if there is a determination that Methotrexate Injection is suitable for ANDA status.

**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 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  
Director, Regulatory Affairs  
Authorized Agent for Pharmachemie BV