Attachment 2

Medical Rationale for the Proposed Product Included as Statement of Grounds

Medical Rationale

Methotrexate Injection, USP
1,000 mg/10 mL (100 mg/mL) in a 10 mL vial

PHARMACOLOGY:

Methotrexate is an antimetabolite used in the treatment of certain neoplastic diseases, severe psoriasis, and adult rheumatoid arthritis.

Methotrexate inhibits dihydrofolic acid reductase. Dihydrofolates must be reduced to tetrahydrofolates by this enzyme before they can be utilized as carriers of one-carbon groups in the synthesis of purine nucleotides and thymidylate. Therefore, methotrexate interferes with DNA synthesis, repair, and cellular replication. Actively proliferating tissues such as malignant cells, bone marrow, fetal cells, buccal and intestinal mucosa and cells of the urinary bladder are in general more sensitive to this effect of methotrexate. When cellular proliferation in malignant tissues is greater than in most normal tissues, methotrexate may impair malignant growth without irreversible damage to normal tissues.

Methotrexate in high doses, followed by leucovorin rescue, is used as a part of the treatment of patients with non-metastatic osteosarcoma. The original rationale for high dose methotrexate therapy was based on the concept of selective rescue of normal tissues by leucovorin. More recent evidence suggests that high dose methotrexate may also overcome methotrexate resistance caused by impaired active transport, decreased affinity of dihydrofolic acid reductase for methotrexate, increased levels of dihydrofolic acid reductase resulting from gene amplification, or decreased polyglutamation of methotrexate. The actual mechanism of action is unknown.

INDICATIONS FOR USE:

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).

DOSAGE:

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

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.

RATIONALE:

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 High Dose Regimen directs the practitioner to prepare the following doses:
12 grams/m^2 up to 15 grams/m^2.

Example starting doses are calculated in the following table.

	Calculated Dose				
	1.5 m^2	**1.7 m^2**	**1.9 m^2**	**2.1 m^2**	**2.3 m^2**
12g/m^2	18.0g	20.4g	22.8g	25.2g	27.6g
15g/m^2	22.5g	25.5g	28.5g	31.5g	34.5g

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.

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 either 400 mL or 520 mL.

Based on a reasonable range of Average Body Surface Area (1.5 m^2 to 2.3 m^2) practitioners would need 18 to 35 vials of product to prepare an appropriate dose. In preparing such a dose using the RLD, the practitioner would be required to reconstitute each vial before use. The total reconstituted volume could be as high as 700 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.

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 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/10 mL (100 mg/mL) is suitable for submission as an ANDA.

Market research indicates that the proposed 1,000 mg/10 mL (100 mg/mL) vial product would be well received and convenient for practitioners.

SUMMARY:

In summary, the availability of Methotrexate Injection, USP in a 1,000 mg/10 mL (100 mg/mL) size and strength would offer safety, convenience and cost savings advantages over lyophilized Methotrexate Preservative Free for Injection, USP 1,000 mg in 20 mL vials. Specifically, the liquid form and new concentration would provide compounding pharmacists and other trained practitioners with a convenient alternative to reconstituting the RLD and preparing calculated doses. Since the need to reconstitute lyophilized vials would be eliminated, the proposed drug product would reduce the potential for contamination that may result from manipulating the product during the reconstitution and dosage preparation, such as blood borne pathogens from needle sticks. The proposed presentation would also provide a reduction in hazardous waste disposal and cost for the course of therapy.

The proposed drug product size is intended for use only as described in the *Indications and Usage* and *Dosage and Administration* sections of PCH's draft package insert, provided in **Attachment 1**.

We believe that the information presented in this correspondence for Methotrexate Injection supports our claim that the product size is suitable for an abbreviated new drug application.

REFERENCES:

1. Package insert for Methotrexate Preservative Free for Injection, USP, Bedford Laboratories. Revised, April 2005