HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use. RASUVO™ safely and effectively. See full prescribing information for RASUVO.

RASUVO (methotrexate) injection, for subcutaneous use
Initial U.S. Approval: 1953

WARNING: SEVERE TOXIC REACTIONS, INCLUDING EMBRYO- FETAL TOXICITY AND DEATH

See full prescribing information for complete boxed warning.

- **Serious toxic reactions and death have been reported with the use of methotrexate. Patients should be closely monitored for bone marrow, liver, lung, skin, and kidney toxicities (5.1).**
- **Methotrexate has been reported to cause fetal death and/or congenital anomalies and is contraindicated in pregnancy (4, 5.2).**
- **Unexpectedly severe (sometimes fatal) bone marrow suppression, aplastic anemia, and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high dosage) along with some nonsteroidal anti-inflammatory drugs (NSAIDs) (5.1).**
- **Hepatotoxicity, fibrosis, and cirrhosis may occur after prolonged use (5.1).**
- **Methotrexate may cause interstitial pneumonitis at any time during therapy and has been reported at low doses. Pulmonary symptoms (especially a dry, nonproductive cough) may require interruption of treatment and careful investigation (5 1).**
- **Diarrhea, ulcerative stomatitis, hemorrhagic enteritis, and death from intestinal perforation may occur (5.1).**
- **Severe, occasionally fatal, skin reactions have been reported (5.1).**
- **Potentially fatal opportunistic infections may occur (5.1).**

----------INDICATIONS AND USAGE----------

Rasuvo is a folate analog metabolic inhibitor indicated for the:

- Management of patients with severe, active rheumatoid arthritis (RA) and polyarticular juvenile idiopathic arthritis (pJIA), who are intolerant of or had an inadequate response to first-line therapy (1.1)
- Symptomatic control of severe, recalcitrant, disabling psoriasis in adults who are not adequately responsive to other forms of therapy (1.2)

Limitation of Use

Rasuvo is not indicated for the treatment of neoplastic diseases (1.3).

----------DOSAGE AND ADMINISTRATION----------

- Rasuvo is for once weekly subcutaneous use only.
- Administer Rasuvo in the abdomen or thigh. (2.1)
- Use another formulation of methotrexate for patients requiring oral, intramuscular, intravenous, intra-arterial, or intrathecal dosing, doses less than 7 5 mg per week, doses above 30 mg per week, high-dose regimens, or dose adjustments of less than 2.5 mg increments (2.1)
- Starting doses of methotrexate:
  - RA: 7.5 mg once weekly of an oral or subcutaneous formulation (2.2)
  - pJIA: 10 mg/m^2 once weekly (2.2)
  - Psoriasis: 10 to 25 mg once weekly of an oral, intramuscular, subcutaneous, or intravenous formulation (2.3)
- Adjust dose gradually to achieve an optimal response (2.2, 2.3)

----------DOSAGE FORMS AND STRENGTHS----------

Injection: Single-dose manually-triggered auto-injector delivering methotrexate in the following dosage strengths: 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 22.5 mg, 25 mg, 27.5 mg, and 30 mg (3).

----------CONTRAINDICATIONS----------

- Pregnancy (4)
- Nursing mothers (4)
- Alcoholism or liver disease (4)
- Immunodeficiency syndromes (4)
- Preexisting blood dyscrasias (4)
- Hypersensitivity to methotrexate (4)

----------WARNINGS AND PRECAUTIONS----------

- Organ system toxicity: Potential for serious toxicity. Only for use by physicians experienced in antimetabolite therapy (5.1).
- Embryo-fetal toxicity: Exclude pregnancy before treatment. Avoid pregnancy if either partner is receiving Rasuvo. Advise males to avoid pregnancy for a minimum of three months after therapy and females to avoid pregnancy for at least one ovulatory cycle after therapy (5.2).
- Effects on reproduction: May cause impairment of fertility, oligospermia and menstrual dysfunction (5.3)
- Laboratory tests: Monitor complete blood counts, renal function and liver function tests (5.4).
- Risks from improper dosing: Mistaken daily use has led to fatal toxicity (5.5)
- Patients with impaired renal function, ascites, or pleural effusions: Elimination is reduced (5.6).
- Dizziness and fatigue: May impair ability to drive or operate machinery (5.7)

----------ADVERSE REACTIONS----------

Common adverse reactions are: nausea, abdominal pain, dyspepsia, stomatitis/mouth sores, rash, nasopharyngitis, diarrhea, liver function test abnormalities, vomiting, headache, bronchitis, thrombocytopenia, alopecia, leukopenia, pancytopenia, dizziness, photosensitivity, and "burning of skin lesions" (6).

To report SUSPECTED ADVERSE REACTIONS, contact Medac at 1-855-336-3322 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Aspirin, NSAIDs, and steroids: concomitant use may elevate and prolong serum methotrexate levels and cause increased toxicity (7 1)
- Proton pump inhibitors concomitant use may elevate and prolong serum methotrexate levels and cause increased toxicity (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- Pediatric use: Safety and efficacy of methotrexate, including Rasuvo, have not been established in pediatric patients with psoriasis. Safety and efficacy of Rasuvo have not been established in pediatric patients with malignancy (8.4)
- Geriatric use: Use caution in dose selection (8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 07/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: SEVERE TOXIC REACTIONS, INCLUDING EMBRYO-FETAL TOXICITY AND DEATH

Rasuvo should be used only by physicians whose knowledge and experience include the use of antimetabolite therapy. Because of the possibility of serious toxic reactions (which can be fatal), Rasuvo should be used only in patients with psoriasis or rheumatoid arthritis with severe, recalcitrant, disabling disease which is not adequately responsive to other forms of therapy. Deaths have been reported with the use of methotrexate in the treatment of malignancy, psoriasis, and rheumatoid arthritis. Patients should be closely monitored for bone marrow, liver, lung, skin, and kidney toxicities. Patients should be informed by their physician of the risks involved and be under a physician's care throughout therapy *[see Warnings and Precautions (5.1)]*.

1. Methotrexate has been reported to cause fetal death and/or congenital anomalies.

Therefore, Rasuvo is not recommended for females of childbearing potential unless there is clear medical evidence that the benefits can be expected to outweigh the considered risks *[see Warnings and Precautions (5.2)]*. Rasuvo is contraindicated in pregnant women *[see Contraindications (4)]*.

2. Methotrexate elimination is reduced in patients with impaired renal functions, ascites, or pleural effusions. Such patients require especially careful monitoring for toxicity, and require dose reduction or, in some cases, discontinuation of Rasuvo administration *[see Warnings and Precautions (5.6)]*.

3. Unexpectedly severe (sometimes fatal) bone marrow suppression, aplastic anemia, and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high dosage) along with some nonsteroidal anti-inflammatory drugs (NSAIDs) *[see Warnings and Precautions (5.1) and Drug Interactions (7.1)]*.

4. Methotrexate causes hepatotoxicity, fibrosis and cirrhosis, but generally only after prolonged use. Acutely, liver enzyme elevations are frequently seen. These are usually transient and asymptomatic, and also do not appear predictive of subsequent hepatic disease. Liver biopsy after sustained use often shows histologic changes, and fibrosis and cirrhosis have been reported; these latter lesions may not be preceded by symptoms or abnormal liver function tests in the psoriasis population. For this reason, periodic liver biopsies are usually recommended for psoriatic patients who are under long-term treatment. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid arthritis population *[see Warnings and Precautions (5.1)]*.

5. Methotrexate-induced lung disease, including acute or chronic interstitial pneumonitis, is a potentially dangerous lesion, which may occur acutely at any time during therapy and has been reported at low doses. It is not always fully reversible and fatalities have been reported. Pulmonary symptoms (especially a dry, nonproductive cough) may require interruption of treatment and careful investigation *[see Warnings and Precautions (5.1)]*.

6. Diarrhea and ulcerative stomatitis require interruption of therapy: otherwise, hemorrhagic enteritis and death from intestinal perforation may occur *[see Warnings and Precautions (5.1)]*.

7. Malignant lymphomas, which may regress following withdrawal of methotrexate, may occur in patients receiving low-dose methotrexate and, thus, may not require cytotoxic treatment. Discontinue Rasuvo first and, if the lymphoma does not regress, appropriate treatment should be instituted *[see Warnings and Precautions (5.8)]*.

8. Like other cytotoxic drugs, methotrexate may induce "tumor lysis syndrome" in patients with rapidly growing tumors *[see Warnings and Precautions (5.9)]*.

9. Severe, occasionally fatal, skin reactions have been reported following single or multiple doses of methotrexate. Reactions have occurred within days of oral, intramuscular, intravenous, or intrathecal methotrexate administration. Recovery has been reported with discontinuation of therapy *[see Warnings and Precautions (5.1)]*.

10. Potentially fatal opportunistic infections, especially *Pneumocystis jiroveci* pneumonia, may occur with methotrexate therapy *[see Warnings and Precautions (5.1)]*.

11. Methotrexate given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis *[see Warnings and Precautions (5.10)]*.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Rheumatoid Arthritis including Polyarticular Juvenile Idiopathic Arthritis

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

1.2 Psoriasis

Rasuvo is indicated in adults for the symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy, but only when the diagnosis has been established, as by biopsy and/or after dermatologic consultation. It is important to ensure that a psoriasis "flare" is not due to an undiagnosed concomitant disease affecting immune responses.

1.3 Limitation of Use

Rasuvo is not indicated for the treatment of neoplastic diseases.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosing Information

Rasuvo is a single-dose manually-triggered auto-injector for once-weekly subcutaneous use only *[see Warnings and Precautions (5.5)]*. Administer Rasuvo in the abdomen or the thigh. Rasuvo is only available in doses between 7.5 to 30 mg in 2.5 mg increments. Use another formulation of methotrexate for alternative dosing in patients who require oral, intramuscular, intravenous, intra-arterial, or intrathecal dosing, doses less than 7.5 mg per week, doses more than 30 mg per week, high-dose regimens, or dose adjustments of less than 2.5 mg increments.

2.2 Rheumatoid Arthritis including Polyarticular Juvenile Idiopathic Arthritis

Recommended starting dose of methotrexate:

Adult RA: 7.5 mg as a single oral or subcutaneous dose once weekly.

pJIA: 10 mg/m^2 once weekly.

For patients switching from oral methotrexate to Rasuvo, consider any differences in bioavailability between oral and subcutaneously administered methotrexate *[see Clinical Pharmacology (12.3)]*.

Dosages may be adjusted gradually to achieve an optimal response. Limited experience shows a significant increase in the incidence and severity of serious toxic reactions, especially bone marrow suppression, at doses greater than 20 mg/wk in adults. Although there is experience with doses up to 30 mg/m^2/wk in children, there are too few published data to assess how doses over 20 mg/m^2/wk might affect the risk of serious toxicity in children. Experience does suggest, however, that children receiving 20 to 30 mg/m^2/wk (0.65 to 1.0 mg/kg/wk) may have better absorption and fewer gastrointestinal side effects if methotrexate is administered either intramuscularly or subcutaneously.

Therapeutic response usually begins within 3 to 6 weeks and the patient may continue to improve for another 12 weeks or more.

The optimal duration of therapy is unknown. Limited data available from long-term studies in adults indicate that the initial clinical improvement is maintained for at least two years with continued therapy. When methotrexate is discontinued, the arthritis usually worsens within 3 to 6 weeks.

The patient should be fully informed of the risks involved and should be under constant supervision of the physician. Assessment of hematologic, hepatic, renal, and pulmonary function should be made by history, physical examination, and laboratory tests before beginning, periodically during, and before reinstituting Rasuvo therapy *[see Warnings and Precautions (5.4)]*. Females of childbearing potential should not be started on Rasuvo until pregnancy is excluded *[see Contraindications (4) and Warnings and Precautions (5.2)]*.

All schedules should be continually tailored to the individual patient. An initial test dose may be given prior to the regular dosing schedule to detect any extreme sensitivity to adverse effects.

Maximal myelosuppression usually occurs in seven to ten days.

2.3 Psoriasis

Recommended starting dose of methotrexate:

Psoriasis: 10-25 mg as a single oral, intramuscular, subcutaneous, or intravenous dose once weekly.

For patients switching from oral methotrexate to Rasuvo, consider any differences in bioavailability between oral and subcutaneously administered methotrexate *[see Clinical Pharmacology (12.3)]*.

Dosage may be gradually adjusted to achieve optimal clinical response; 30 mg/week should not ordinarily be exceeded. Once optimal clinical response has been achieved, the dosage should be reduced to the lowest possible amount of drug and to the longest possible rest period. The use of Rasuvo may permit the return to conventional topical therapy, which should be encouraged.

2.4 Administration and Handling

Rasuvo is a manually-triggered auto-injector intended for subcutaneous use under the guidance and supervision of a physician.

Patients may self-inject with Rasuvo if a physician determines that it is appropriate, if they have received proper training in how to prepare and administer the correct dose, and if they receive medical follow-up, as necessary.

Rasuvo is injected **once weekly**. The patient must be explicitly informed about the **once weekly** dosing schedule. It is advisable to determine an appropriate fixed day of the week for the injection.

Visually inspect Rasuvo for particulate matter and discoloration prior to administration. Do not use Rasuvo if the seal is broken.

Handle and dispose of Rasuvo consistent with recommendations for handling and disposal of cytotoxic drugs[1].

3 DOSAGE FORMS AND STRENGTHS

Rasuvo is an injection containing methotrexate at a concentration of 50 mg/ml available as a manually-triggered auto-injector that administers a single dose of methotrexate solution in the following dosage strengths:

- 7.5 mg
- 10 mg
- 12.5 mg
- 15 mg
- 17.5 mg
- 20 mg
- 22.5 mg
- 25 mg
- 27.5 mg
- 30 mg

4 CONTRAINDICATIONS

Rasuvo is contraindicated in the following:

- Pregnancy

Rasuvo can cause fetal death or teratogenic effects when administered to a pregnant woman. Rasuvo is contraindicated in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.1)]*.

- Nursing Mothers

Because of the potential for serious adverse reactions from methotrexate in breast fed infants, Rasuvo is contraindicated in nursing mothers *[see Use in Specific Populations (8.3)]*.

- Alcoholism or Liver Disease

Patients with alcoholism, alcoholic liver disease or other chronic liver disease [see *Warnings and Precautions (5.1)*].

- Immunodeficiency Syndromes

Patients who have overt or laboratory evidence of immunodeficiency syndromes [see *Warnings and Precautions (5.1)]*.

- Preexisting Blood Dyscrasias

Patients who have preexisting blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anemia *[see Warnings and Precautions (5.1)]*.

- Hypersensitivity

Patients with a known hypersensitivity to methotrexate. Severe hypersensitivity reactions have been observed with methotrexate use *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1 and 6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Organ System Toxicity

Rasuvo should be used only by physicians whose knowledge and experience include the use of antimetabolite therapy. Because of the possibility of serious toxic reactions (which can be fatal), Rasuvo should be used only in patients with psoriasis or rheumatoid arthritis with severe, recalcitrant, disabling disease which is not adequately responsive to other forms of therapy.

Deaths have been reported with the use of methotrexate in the treatment of malignancy, psoriasis, and rheumatoid arthritis. Patients should be closely monitored for bone marrow, liver, lung and kidney toxicities.

Rasuvo has the potential for serious toxicity. Toxic effects may be related in frequency and severity to dose or frequency of administration but have been seen at all doses. Because they can occur at any time during therapy, it is necessary to follow patients on Rasuvo closely. Most adverse reactions are reversible if detected early. When such reactions do occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken. If necessary, this could include the use of leucovorin calcium and/or acute, intermittent hemodialysis with a high-flux dialyzer [see *Overdosage (10)*]. If Rasuvo therapy is reinstituted, it should be carried out with caution, with adequate consideration of further need for the drug and increased alertness as to possible recurrence of toxicity. The clinical pharmacology of methotrexate has not been well studied in older individuals. Due to diminished hepatic and renal function as well as decreased folate stores in this population, relatively low doses should be considered, and these patients should be closely monitored for early signs of toxicity *[see Use in Specific Populations (8.5)]*.

Gastrointestinal:

Diarrhea and ulcerative stomatitis require interruption of therapy: otherwise, hemorrhagic enteritis and death from intestinal perforation may occur.

If vomiting, diarrhea, or stomatitis occur, which may result in dehydration, Rasuvo should be discontinued until recovery occurs. Rasuvo should be used with extreme caution in the presence of peptic ulcer disease or ulcerative colitis.

Unexpectedly severe (sometimes fatal) gastrointestinal toxicity has been reported with concomitant administration of methotrexate (usually in high dosage) along with some nonsteroidal anti-inflammatory drugs (NSAIDs*) [see Drug Interactions (7.1)]*.

Hematologic:

Rasuvo can suppress hematopoiesis and cause anemia, aplastic anemia, pancytopenia, leukopenia, neutropenia, and/or thrombocytopenia. In patients with preexisting hematopoietic impairment, Rasuvo should be used with caution, if at all. In controlled clinical trials conducted with another formulation of methotrexate in rheumatoid arthritis (n=128), leukopenia (WBC <3000/mm^3) was seen in 2 patients, thrombocytopenia (platelets <100,000/mm^3) in 6 patients, and pancytopenia in 2 patients.

Rasuvo should be stopped immediately if there is a significant drop in blood counts. Patients with profound granulocytopenia and fever should be evaluated immediately and usually require parenteral broad-spectrum antibiotic therapy.

Unexpectedly severe (sometimes fatal) bone marrow suppression and aplastic anemia have been reported with concomitant administration of methotrexate (usually in high dosage) along with some nonsteroidal anti-inflammatory drugs (NSAIDs*) [see Drug Interactions (7.1)]*.

Hepatic:

Rasuvo has the potential for acute (elevated transaminases) and chronic (fibrosis and cirrhosis) hepatotoxicity. Chronic toxicity is potentially fatal; it generally has occurred after prolonged use (generally two years or more) and after a total dose of at least 1.5 grams. In studies in psoriatic patients, hepatotoxicity appeared to be a function of total cumulative dose and appeared to be enhanced by alcoholism, obesity, diabetes and advanced age. An accurate incidence rate has not been determined; the rate of progression and reversibility of lesions is not known. Special caution is indicated in the presence of preexisting liver damage or impaired hepatic function.

In psoriasis, liver function tests, including serum albumin, should be performed periodically prior to dosing but are often normal in the face of developing fibrosis or cirrhosis. These lesions may be detectable only by biopsy. The usual recommendation is to obtain a liver biopsy at 1) pretherapy or shortly after initiation of therapy (2 to 4 months), 2) a total cumulative dose of 1.5 grams, and 3) after each additional 1.0 to 1.5 grams. Moderate fibrosis or any cirrhosis normally leads to discontinuation of the drug; mild fibrosis normally suggests a repeat biopsy in 6 months.

Milder histologic findings such as fatty change and low grade portal inflammation are relatively common pretherapy. Although these mild changes are usually not a reason to avoid or discontinue Rasuvo therapy, the drug should be used with caution.

In rheumatoid arthritis, age at first use of methotrexate and duration of therapy have been reported as risk factors for hepatotoxicity; other risk factors, similar to those observed in psoriasis, may be present in rheumatoid arthritis but have not been confirmed to date. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in this population. There is a combined reported experience in 217 rheumatoid arthritis patients with liver biopsies both before and during treatment (after a cumulative dose of at least 1.5 g) and in 714 patients with a biopsy only during treatment. There are 64 (7%) cases of fibrosis and 1 (0.1%) case of cirrhosis. Of the 64 cases of fibrosis, 60 were deemed mild. The reticulin stain is more sensitive for early fibrosis and its use may increase these figures. It is unknown whether even longer use will increase these risks.

Liver function tests should be performed at baseline and at 4 to 8 week intervals in patients receiving Rasuvo for rheumatoid arthritis. Pretreatment liver biopsy should be performed for patients with a history of excessive alcohol consumption, persistently abnormal baseline liver function test values or chronic hepatitis B or C infection. During therapy, liver biopsy should be performed if there are persistent liver function test abnormalities or there is a decrease in serum albumin below the normal range (in the setting of well controlled rheumatoid arthritis).

If the results of a liver biopsy show mild changes (Roenigk, grades I, II, IIIa), Rasuvo may be continued and the patient monitored as per recommendations listed above. Rasuvo should be discontinued in any patient who displays persistently abnormal liver function tests and refuses liver biopsy or in any patient whose liver biopsy shows moderate to severe changes (Roenigk grade IIIb or IV).

Infection or Immunologic States:

Rasuvo should be used with extreme caution in the presence of active infection, and is contraindicated in patients with overt or laboratory evidence of immunodeficiency syndromes.

Immunization may be ineffective when given during Rasuvo therapy. Immunization with live virus vaccines is generally not recommended. There have been reports of disseminated vaccinia infections after smallpox immunizations in patients receiving methotrexate therapy. Hypogammaglobulinemia has been reported rarely.

Potentially fatal opportunistic infections, especially *Pneumocystis jiroveci* pneumonia, may occur with Rasuvo therapy. When a patient presents with pulmonary symptoms, the possibility of *Pneumocystis jiroveci* pneumonia should be considered.

Neurologic:

There have been reports of leukoencephalopathy following intravenous administration of methotrexate to patients who have had craniospinal irradiation. Serious neurotoxicity, frequently manifested as generalized or focal seizures, has been reported with unexpectedly increased frequency among pediatric patients with acute lymphoblastic leukemia who were treated with intermediate-dose intravenous methotrexate (1 gm/m^2). Symptomatic patients were commonly noted to have leukoencephalopathy and/or microangiopathic calcifications on diagnostic imaging studies. Chronic leukoencephalopathy has also been reported in patients who received repeated doses of high-dose methotrexate with leucovorin rescue even without cranial irradiation.

Discontinuation of methotrexate does not always result in complete recovery. A transient acute neurologic syndrome has been observed in patients treated with high dose regimens. Manifestations of this stroke-like encephalopathy may include confusion, hemiparesis, transient blindness, seizures and coma. The exact cause is unknown. After the intrathecal use of methotrexate, the central nervous system toxicity which may occur can be classified as follows: acute chemical arachnoiditis manifested by such symptoms as headache, back pain, nuchal rigidity, and fever; sub- acute myelopathy characterized by paraparesis/paraplegia associated with involvement with one or more spinal nerve roots; chronic leukoencephalopathy manifested by confusion, irritability, somnolence, ataxia, dementia, seizures and coma. This condition can be progressive and even fatal.

Pulmonary:

Methotrexate-induced lung disease, including acute or chronic interstitial pneumonitis, is a potentially dangerous lesion, which may occur acutely at any time during therapy and has been reported at low doses. It is not always fully reversible and fatalities have been reported.

Pulmonary symptoms (especially a dry nonproductive cough) or a non-specific pneumonitis occurring during Rasuvo therapy may be indicative of a potentially dangerous lesion and require interruption of treatment and careful investigation. Although clinically variable, the typical patient with methotrexate induced lung disease presents with fever, cough, dyspnea, hypoxemia, and an infiltrate on chest X-ray; infection (including pneumonia) needs to be excluded. This lesion can occur at all dosages.

Renal:

Rasuvo may cause renal damage that may lead to acute renal failure. High doses of methotrexate used in the treatment of osteosarcoma may cause renal damage leading to acute renal failure. Nephrotoxicity is due primarily to the precipitation of methotrexate and 7- hydroxymethotrexate in the renal tubules. Close attention to renal function including adequate hydration, urine alkalinization and measurement of serum methotrexate and creatinine levels are essential for safe administration.

Skin:

Severe, occasionally fatal, dermatologic reactions, including toxic epidermal necrolysis, Stevens- Johnson syndrome, exfoliative dermatitis, skin necrosis, and erythema multiforme, have been reported in children and adults, within days of oral, intramuscular, intravenous, or intrathecal methotrexate administration. Reactions were noted after single or multiple low, intermediate, or high doses of methotrexate in patients with neoplastic and non-neoplastic diseases.

Lesions of psoriasis may be aggravated by concomitant exposure to ultraviolet radiation.

Radiation dermatitis and sunburn may be “recalled” by the use of methotrexate.

Other precautions:

Rasuvo should be used with extreme caution in the presence of debility.

Methotrexate exits slowly from third space compartments (e.g., pleural effusions or ascites). This results in a prolonged terminal plasma half-life and unexpected toxicity. In patients with significant third space accumulations, it is advisable to evacuate the fluid before treatment and to monitor plasma methotrexate levels.

5.2 Embryo-Fetal Toxicity

Methotrexate has been reported to cause fetal death and/or congenital anomalies. Therefore, Rasuvo is not recommended for females of childbearing potential unless there is clear medical evidence that the benefits can be expected to outweigh the considered risks. Rasuvo is contraindicated in pregnant women with psoriasis or rheumatoid arthritis.

Females of childbearing potential should not be started on Rasuvo until pregnancy is excluded and should be fully counseled on the serious risk to the fetus should they become pregnant while undergoing treatment. Appropriate steps should be taken to avoid conception during Rasuvo therapy. Pregnancy should be avoided if either partner is receiving Rasuvo; during and for a minimum of three months after therapy for male patients, and during and for at least one ovulatory cycle after therapy for female patients.

5.3 Effects on Reproduction

Methotrexate has been reported to cause impairment of fertility, oligospermia and menstrual dysfunction in humans, during and for a short period after cessation of therapy.

The risk of effects of reproduction should be discussed with both male and female patients taking Rasuvo.

5.4 Laboratory Tests

Patients undergoing Rasuvo therapy should be closely monitored so that toxic effects are detected promptly. Baseline assessment should include a complete blood count with differential and platelet counts, hepatic enzymes, renal function tests and a chest X-ray.

During therapy, monitoring of these parameters is recommended: hematology at least monthly, renal function and liver function every 1 to 2 months [*see Warnings and Precautions (5.1)*].

During initial or changing doses, or during periods of increased risk of elevated methotrexate blood levels (e.g., dehydration), more frequent monitoring may also be indicated.

Liver Function Tests

Transient liver function test abnormalities are observed frequently after methotrexate administration and are usually not cause for modification of methotrexate therapy. Persistent liver function test abnormalities, and/or depression of serum albumin may be indicators of serious liver toxicity and require evaluation [*see Warnings and Precautions (5.1)*].

A relationship between abnormal liver function tests and fibrosis or cirrhosis of the liver has not been established for patients with psoriasis. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid arthritis population.

Pulmonary Function Tests

Pulmonary function tests may be useful if methotrexate-induced lung disease is suspected, especially if baseline measurements are available *[see Warnings and Precautions (5.1)]*.

5.5 Risks from Improper Dosing

Both the physician and pharmacist should emphasize to the patient that Rasuvo is administered once weekly and that mistaken daily use has led to fatal toxicity *[see Dosage and Administration (2)]*.

5.6 Patients with Impaired Renal Function, Ascites, or Pleural Effusions

Methotrexate elimination is reduced in patients with impaired renal function, ascites, or pleural effusions. Such patients require especially careful monitoring for toxicity and require dose reduction or, in some cases, discontinuation of Rasuvo administration.

5.7 Dizziness and Fatigue

Adverse reactions, such as dizziness and fatigue, may affect the ability to drive or operate machinery.

5.8 Malignant Lymphomas

Non-Hodgkin’s lymphoma and other tumors have been reported in patients receiving low-dose oral methotrexate. However, there have been instances of malignant lymphoma arising during treatment with low-dose oral methotrexate, which have regressed completely following withdrawal of methotrexate, without requiring active anti- lymphoma treatment. Discontinue Rasuvo first and, if the lymphoma does not regress, appropriate treatment should be instituted.

5.9 Tumor Lysis Syndrome

Like other cytotoxic drugs, methotrexate may induce “tumor lysis syndrome” in patients with rapidly growing tumors.

5.10 Concomitant Radiation Therapy

Methotrexate given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling.

- Organ System Toxicity *[see Warnings and Precautions (5.1)]*
- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.2)]*
- Effects on Reproduction *[see Warnings and Precautions (5.3)]*
- Malignant Lymphomas *[see Warnings and Precautions (5.8)]*

The most frequently reported adverse reactions include ulcerative stomatitis, leukopenia, nausea, and abdominal distress. Other frequently reported adverse reactions are malaise, undue fatigue, chills and fever, dizziness and decreased resistance to infection.

6.1 Clinical Trials Experience

This section provides a summary of adverse reactions reported in subjects in clinical studies conducted with Rasuvo as well as with methotrexate injection and oral methotrexate.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug, and may not reflect the rates observed in practice.

Rheumatoid Arthritis

The approximate incidences of methotrexate-attributed (i.e. placebo rate subtracted) adverse reactions in 12 to 18 week double-blind studies of patients (n=128) with rheumatoid arthritis treated with low-dose oral (7.5 to 15 mg/week) pulse methotrexate, are listed below. Virtually all of these patients were on concomitant nonsteroidal anti- inflammatory drugs and some were also taking low dosages of corticosteroids. Hepatic histology was not examined in these short-term studies.

Incidence greater than 10%: Elevated liver function tests 15%, nausea/vomiting 10%.

Incidence 3% to 10%: Stomatitis, thrombocytopenia (platelet count less than 100,000/mm^3).

Incidence 1% to 3%: Rash/pruritis/dermatitis, diarrhea, alopecia, leukopenia (WBC less than 3000/mm^3), pancytopenia, dizziness.

Two other controlled trials of patients (n=680) with Rheumatoid Arthritis on 7.5 mg to 15 mg/wk oral doses showed an incidence of interstitial pneumonitis of 1%.

Other less common reactions included decreased hematocrit, headache, upper respiratory infection, anorexia, arthralgias, chest pain, coughing, dysuria, eye discomfort, epistaxis, fever, infection, sweating, tinnitus, and vaginal discharge.

Polyarticular Juvenile Idiopathic Arthritis

The approximate incidences of adverse reactions reported in pediatric patients with pJIA treated with oral, weekly doses of methotrexate (5 to 20 mg/m^2/wk or 0.1 to 0.65 mg/kg/wk) were as follows (virtually all patients were receiving concomitant nonsteroidal anti-inflammatory drugs, and some also were taking low doses of corticosteroids): elevated liver function tests, 14%; gastrointestinal reactions (e.g., nausea, vomiting, diarrhea), 11%; stomatitis, 2%; leukopenia, 2%; headache, 1.2%; alopecia, 0.5%; dizziness, 0.2%; and rash, 0.2%. Although there is experience with dosing up to 30 mg/m^2/wk in pJIA, the published data for doses above 20 mg/m^2/wk are too limited to provide reliable estimates of adverse reaction rates.

Psoriasis

There are two literature reports (Roenigk, 1969, and Nyfors, 1978) describing large series (n=204, 248) of psoriasis patients treated with methotrexate. Dosages ranged up to 25 mg per week and treatment was administered for up to four years. With the exception of alopecia, photosensitivity, and “burning of skin lesions” (each 3% to 10%), the adverse reaction rates in these reports were very similar to those in the rheumatoid arthritis studies. Rarely, painful plaque erosions may appear (Pearce, HP and Wilson, BB: Am Acad Dermatol 35: 835-838, 1996).

6.2 Other Adverse Reactions

Other adverse reactions that have been reported with methotrexate in oncology, RA, pJIA, and psoriasis patients are listed below by organ system.

Alimentary System: gingivitis, pharyngitis, stomatitis, anorexia, nausea, vomiting, diarrhea, hematemesis, melena, gastrointestinal ulceration and bleeding, enteritis, pancreatitis.

Blood and Lymphatic System Disorders: suppressed hematopoiesis, anemia, aplastic anemia, pancytopenia, leukopenia, neutropenia, thrombocytopenia, agranulocytosis, eosinophilia, lymphadenopathy and lymphoproliferative disorders (including reversible). Hypogammaglobulinemia has been reported rarely.

Cardiovascular: pericarditis, pericardial effusion, hypotension, and thromboembolic events (including arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, thrombophlebitis, and pulmonary embolus).

Central Nervous System: headaches, drowsiness, blurred vision, transient blindness, speech impairment including dysarthria and aphasia, hemiparesis, paresis and convulsions have also occurred following administration of methotrexate. Following low doses, there have been occasional reports of transient subtle cognitive dysfunction, mood alteration or unusual cranial sensations, leukoencephalopathy, or encephalopathy.

Hepatobiliary Disorders: hepatotoxicity, acute hepatitis, chronic fibrosis and cirrhosis, hepatic failure, decrease in serum albumin, liver enzyme elevations.

Infection: There have been case reports of sometimes fatal opportunistic infections in patients receiving methotrexate therapy for neoplastic and non-neoplastic diseases. *Pneumocystis jiroveci* pneumonia was the most common opportunistic infection. There have also been reports of infections, pneumonia, Cytomegalovirus infection, including cytomegaloviral pneumonia, sepsis, fatal sepsis, nocardiosis, histoplasmosis, cryptococcosis, *Herpes zoster*, *Herpes simplex* hepatitis, and disseminated *Herpes simplex*.

Musculoskeletal System: stress fracture.

Ophthalmic: conjunctivitis, serious visual changes of unknown etiology.

Pulmonary System: respiratory fibrosis, respiratory failure, alveolitis, interstitial pneumonitis deaths have been reported, and chronic interstitial obstructive pulmonary disease has occasionally occurred.

Skin: erythematous rashes, pruritus, urticaria, photosensitivity, pigmentary changes, alopecia, ecchymosis, telangiectasia, acne, furunculosis, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, skin necrosis, skin ulceration and exfoliative dermatitis.

Urogenital System: severe nephropathy or renal failure, azotemia, cystitis, hematuria, proteinuria; defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, vaginal discharge, and gynecomastia; infertility, abortion, fetal death, fetal defects.

Other rarer reactions related to or attributed to the use of methotrexate such as nodulosis, vasculitis, arthralgia/myalgia, loss of libido/ impotence, diabetes, osteoporosis, sudden death, lymphoma, including reversible lymphomas, tumor lysis syndrome, soft tissue necrosis and osteonecrosis. Anaphylactoid reactions have been reported.

7 DRUG INTERACTIONS

7.1 Aspirin, Nonsteroidal Anti-Inflammatory Drugs, and Steroids

Nonsteroidal anti-inflammatory drugs (NSAIDs) should not be administered prior to or concomitantly with the high doses of methotrexate, such as used in the treatment of osteosarcoma. Concomitant administration of some NSAIDs with high dose methotrexate therapy has been reported to elevate and prolong serum methotrexate levels, resulting in deaths from severe hematologic and gastrointestinal toxicity *[see Warnings and Precautions (5.1)]*.

Caution should be used when NSAIDs and salicylates are administered concomitantly with lower doses of methotrexate, including Rasuvo. These drugs have been reported to reduce the tubular secretion of methotrexate in an animal model and may enhance its toxicity.

Despite the potential interactions, studies of methotrexate in patients with rheumatoid arthritis have usually included concurrent use of constant dosage regimens of NSAIDs, without apparent problems. It should be appreciated, however, that the doses used in rheumatoid arthritis (7.5 to 15 mg/week) are somewhat lower than those used in psoriasis and that larger doses could lead to unexpected toxicity. Aspirin, NSAIDs, and/or low dose steroids may be continued, although the possibility of increased toxicity with concomitant use of NSAIDs including salicylates has not been fully explored. Steroids may be reduced gradually in patients who respond to methotrexate.

7.2 Proton Pump Inhibitors (PPIs) and H_2 Blockers

Use caution if high-dose methotrexate is administered to patients receiving proton pump inhibitor (PPI) therapy. Case reports and published population pharmacokinetic studies suggest that concomitant use of some PPIs, such as omeprazole, esomeprazole, and pantoprazole, with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate, possibly leading to methotrexate toxicities. In two of these cases, delayed methotrexate elimination was observed when high-dose methotrexate was co-administered with PPIs, but was not observed when methotrexate was co-administered with ranitidine. However, no formal drug interaction studies of methotrexate with ranitidine have been conducted.

7.3 Oral Antibiotics

Oral antibiotics such as tetracycline, chloramphenicol, and nonabsorbable broad spectrum antibiotics, may decrease intestinal absorption of methotrexate or interfere with the enterohepatic circulation by inhibiting bowel flora and suppressing metabolism of the drug by bacteria.

Penicillins may reduce the renal clearance of methotrexate; increased serum concentrations of methotrexate with concomitant hematologic and gastrointestinal toxicity have been observed with high and low dose methotrexate. Use of Rasuvo with penicillins should be carefully monitored.

Trimethoprim/sulfamethoxazole has been reported rarely to increase bone marrow suppression in patients receiving methotrexate, probably by decreased tubular secretion and/or an additive antifolate effect.

7.4 Hepatotoxins

The potential for increased hepatotoxicity when methotrexate is administered with other hepatotoxic agents has not been evaluated. However, hepatotoxicity has been reported in such cases. Therefore, patients receiving concomitant therapy with Rasuvo and other potential hepatotoxins (e.g., azathioprine, retinoids, and sulfasalazine) should be closely monitored for possible increased risk of hepatotoxicity.

7.5 Theophylline

Methotrexate may decrease the clearance of theophylline; theophylline levels should be monitored when used concurrently with Rasuvo.

7.6 Folic Acid and Antifolates

Vitamin preparations containing folic acid or its derivatives may decrease responses to systemically administered methotrexate. Preliminary animal and human studies have shown that small quantities of intravenously administered leucovorin enter the CSF primarily as 5-methyltetrahydrofolate and, in humans, remain 1 to 3 orders of magnitude lower than the usual methotrexate concentrations following intrathecal administration. However, high doses of leucovorin may reduce the efficacy of intrathecally administered methotrexate. Folate deficiency states may increase methotrexate toxicity.

Trimethoprim/sulfamethoxazole has been reported rarely to increase bone marrow suppression in patients receiving methotrexate, probably by decreased tubular secretion and/or an additive antifolate effect.

7.7 Mercaptopurine

Methotrexate increases the plasma levels of mercaptopurine. The combination of Rasuvo and mercaptopurine may therefore require dose adjustment.

7.8 Other Drugs

Methotrexate is partially bound to serum albumin, and toxicity may be increased because of displacement by certain drugs, such as salicylates, phenylbutazone, phenytoin, and sulfonamides.

Renal tubular transport is also diminished by probenecid; use of Rasuvo with this drug should be carefully monitored.

Combined use of methotrexate with gold, penicillamine, hydroxychloroquine, sulfasalazine, or cytotoxic agents, has not been studied and may increase the incidence of adverse effects.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X *[see Contraindications (4)]*

Methotrexate has been reported to cause embryotoxicity, fetal death, congenital anomalies, and abortion in humans and is contraindicated in pregnant women.

8.3 Nursing Mothers

Because of the potential for serious adverse reactions from methotrexate in breast fed infants, methotrexate is contraindicated in nursing mothers. Therefore, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Methotrexate has been detected in human breast milk. The highest breast milk to plasma concentration ratio reached was 0.08:1.

8.4 Pediatric Use

The safety and effectiveness of methotrexate, including Rasuvo, have not been established in pediatric patients with psoriasis.

The safety and effectiveness of Rasuvo have not been established in pediatric patients with neoplastic diseases.

The safety and effectiveness of methotrexate have been established in pediatric patients with polyarticular juvenile idiopathic arthritis *[see Clinical Studies (14.2)]*.

Published clinical studies evaluating the use of methotrexate in children and adolescents (i.e., patients 2 to 16 years of age) with pJIA demonstrated safety comparable to that observed in adults with rheumatoid arthritis [*see Adverse Reactions (6.1)*].

Rasuvo does not contain a preservative. However, methotrexate injectable formulations containing the preservative benzyl alcohol are not recommended for use in neonates. There have been reports of fatal ‘gasping syndrome’ in neonates (children less than one month of age) following the administrations of intravenous solutions containing the preservative benzyl alcohol. Symptoms include a striking onset of gasping respiration, hypotension, bradycardia, and cardiovascular collapse.

Serious neurotoxicity, frequently manifested as generalized or focal seizures, has been reported with unexpectedly increased frequency among pediatric patients with acute lymphoblastic leukemia who were treated with intermediate-dose intravenous methotrexate (1 gm/m^2) *[see Warnings and Precautions (5.1)]*.

8.5 Geriatric Use

Clinical studies of methotrexate did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious reflecting the greater frequency of decreased hepatic and renal function, decreased folate stores, concomitant disease or other drug therapy (i.e., that interfere with renal function, methotrexate or folate metabolism) in this population *[see Warnings and Precautions (5.1) Drug Interactions (7.7) and Use in Specific Populations (8.7)*]. Since decline in renal function may be associated with increases in adverse reactions and serum creatinine measurements may over estimate renal function in the elderly, more accurate methods (i.e., creatinine clearance) should be considered. Serum methotrexate levels may also be helpful. Elderly patients should be closely monitored for early signs of hepatic, bone marrow and renal toxicity. In chronic use situations, certain toxicities may be reduced by folate supplementation.

Post-marketing experience suggests that the occurrence of bone marrow suppression, thrombocytopenia, and pneumonitis may increase with age [*see Warnings and Precautions (5.1)]*.

8.6 Females and Males of Reproductive Potential

Rasuvo is not recommended for females of childbearing potential unless there is clear medical evidence that the benefits can be expected to outweigh the considered risks. Females of childbearing potential should not be started on methotrexate until pregnancy is excluded and should be fully counseled on the serious risk to the fetus should they become pregnant while undergoing treatment [see Use in Specific Populations (8.1)].

Appropriate steps should be taken to avoid conception during Rasuvo therapy. Pregnancy should be avoided if either partner is receiving methotrexate; during and for a minimum of three months after therapy for male patients, and during and for at least one ovulatory cycle after therapy for female patients.

Methotrexate has been reported to cause impairment of fertility, oligospermia and menstrual dysfunction in humans, during and for a short period after cessation of therapy.

8.7 Renal Impairment

Methotrexate elimination is reduced in patients with impaired renal function. Such patients require especially careful monitoring for toxicity and require dose reduction or, in some cases, discontinuation of Rasuvo administration.

8.8 Hepatic Impairment

The effect of hepatic impairment on methotrexate pharmacokinetics has not been studied. Rasuvo is contraindicated in patients with alcoholic liver disease or other chronic liver disease. Patients with obesity, diabetes, hepatic fibrosis or steatohepatitis are at increased risk for hepatic injury and fibrosis secondary to methotrexate, and should be monitored closely [*see Warnings and Precautions (5.1)*].

10 OVERDOSAGE

Leucovorin is indicated to diminish the toxicity and counteract the effect of inadvertently administered overdosages of methotrexate. Leucovorin administration should begin as promptly as possible. As the time interval between methotrexate administration and leucovorin initiation increases, the effectiveness of leucovorin in counteracting toxicity decreases. Monitoring of the serum methotrexate concentration is essential in determining the optimal dose and duration of treatment with leucovorin.

In cases of massive overdosage, hydration and urinary alkalinization may be necessary to prevent the precipitation of methotrexate and/or its metabolites in the renal tubules. Generally speaking, neither hemodialysis nor peritoneal dialysis has been shown to improve methotrexate elimination. However, effective clearance of methotrexate has been reported with acute, intermittent hemodialysis using a high-flux dialyzer (Wall, SM et al: *Am J Kidney Dis* 28 (6): 846-854, 1996).

Accidental intrathecal overdosage may require intensive systemic support, high-dose systemic leucovorin, alkaline diuresis and rapid CSF drainage and ventriculolumbar perfusion.

In postmarketing experience, overdose with methotrexate has generally occurred with oral and intrathecal administration, although intravenous and intramuscular overdose have also been reported.

Reports of oral overdose often indicate accidental daily administration instead of weekly (single or divided doses). Symptoms commonly reported following oral overdose include those symptoms and signs reported at pharmacologic doses, particularly hematologic and gastrointestinal reaction. For example, leukopenia, thrombocytopenia, anemia, pancytopenia, bone marrow suppression, mucositis, stomatitis, oral ulceration, nausea, vomiting, gastrointestinal ulceration, gastrointestinal bleeding. In some cases, no symptoms were reported.

There have been reports of death following overdose. In these cases, events such as sepsis or septic shock, renal failure, and aplastic anemia were also reported.

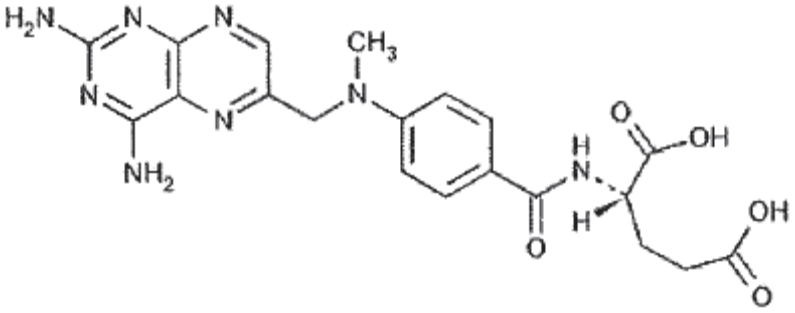
Symptoms of intrathecal overdose are generally central nervous system (CNS) symptoms, including headache, nausea and vomiting, seizure or convulsion, and acute toxic encephalopathy. In some cases, no symptoms were reported. There have been reports of death following intrathecal overdose. In these cases, cerebellar herniation associated with increased intracranial pressure, and acute toxic encephalopathy have also been reported.

There are published case reports of intravenous and intrathecal carboxypeptidase G2 treatment to hasten clearance of methotrexate in cases of overdose.

11 DESCRIPTION

Rasuvo contains methotrexate, a folate analog metabolic inhibitor.

Chemically, methotrexate is [N-[4-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-Lglutamic acid. The structural formula is:



$C_{20}H_{22}N_8O_5$ M.W.= 454.45

Rasuvo contains methotrexate in a sterile, preservative-free, non-pyrogenic solution for a single subcutaneous injection. Rasuvo is an isotonic, clear, yellow to brown solution.

Rasuvo contains the following inactive ingredients: sodium chloride 0.4% w/v; water for injections, sodium hydroxide and, if necessary, hydrochloric acid are added to adjust the pH to approximately 8.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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.

The mechanism of action in rheumatoid arthritis is unknown; it may affect immune function.

12.2 Pharmacodynamics

Two reports describe *in vitro* methotrexate inhibition of DNA precursor uptake by stimulated mononuclear cells, and another describes in animal polyarthritis partial correction by methotrexate of spleen cell hyporesponsiveness and suppressed IL 2 production. Other laboratories, however, have been unable to demonstrate similar effects. Clarification of methotrexate's effect on immune activity and its relation to rheumatoid immunopathogenesis await further studies.

In psoriasis, the rate of production of epithelial cells in the skin is greatly increased over normal skin. This differential in proliferation rates is the basis for the use of methotrexate to control the psoriatic process.

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.

12.3 Pharmacokinetics

Absorption

In adults, oral absorption appears to be dose dependent. Peak serum levels are reached within one to two hours. At doses of 30 mg/m^2 or less, methotrexate is generally well absorbed with a mean bioavailability of about 60%. The absorption of doses greater than 80 mg/m^2 is significantly less, possibly due to a saturation effect.

In a relative bioavailability study in healthy subjects, the systemic exposure of methotrexate (AUC) from Rasuvo at doses of 7.5 mg, 15 mg, 22.5 mg, and 30 mg, was higher than that of oral methotrexate administered at the same doses by 35%, 49%, 51%, and 68%, respectively. In a relative bioavailability study in psoriasis patients, the systemic exposure (AUC) of methotrexate from Rasuvo at a dose of 30 mg, was similar to that of methotrexate administered at the same dose by the intramuscular route.

In leukemic pediatric patients, oral absorption of methotrexate also appears to be dose dependent and has been reported to vary widely (23% to 95%). A twenty fold difference between highest and lowest peak levels (C_{max}: 0.11 to 2.3 micromolar after a 20 mg/m^2 dose) has been reported.

Significant interindividual variability has also been noted in time to peak concentration (T_{max}: 0.67 to 4 hrs after a 15 mg/m^2 dose) and fraction of dose absorbed. The absorption of doses greater than 40 mg/m^2 has been reported to be significantly less than that of lower doses. Food has been shown to delay absorption and reduce peak concentration.

Methotrexate is generally completely absorbed from parenteral routes of injection. After intramuscular injection, peak serum concentrations occur in 30 to 60 minutes.

As in leukemic pediatric patients, a wide interindividual variability in the plasma concentrations of methotrexate has been reported in pediatric patients with JIA. Following oral administration of methotrexate in doses of 6.4 to 11.2 mg/m^2/week in pediatric patients with JIA, mean serum concentrations were 0.59 micromolar (range, 0.03 to 1.40) at 1 hour, 0.44 micromolar (range, 0.01 to 1.00) at 2 hours, and 0.29 micromolar (range, 0.06 to 0.58) at 3 hours.

Distribution

After intravenous administration, the initial volume of distribution is approximately 0.18 L/kg (18% of body weight) and steady-state volume of distribution is approximately 0.4 to 0.8 L/kg (40 to 80% of body weight). Methotrexate competes with reduced folates for active transport across cell membranes by means of a single carrier-mediated active transport process. At serum concentrations greater than 100 micromolar, passive diffusion becomes a major pathway by which effective intracellular concentrations can be achieved. Methotrexate in serum is approximately 50% protein bound. Laboratory studies demonstrate that it may be displaced from plasma albumin by various compounds including sulfonamides, salicylates, tetracyclines, chloramphenicol, and phenytoin.

Methotrexate does not penetrate the blood-cerebrospinal fluid barrier in therapeutic amounts when given orally or parenterally. High CSF concentrations of the drug may be attained by intrathecal administration of other parenteral forms of methotrexate.

In dogs, synovial fluid concentrations after oral dosing were higher in inflamed than uninflamed joints. Although salicylates did not interfere with this penetration, prior prednisone treatment reduced penetration into inflamed joints to the level of normal joints.

Metabolism

After absorption, methotrexate undergoes hepatic and intracellular metabolism to polyglutamated forms which can be converted back to methotrexate by hydrolase enzymes. These polyglutamates act as inhibitors of dihydrofolate reductase and thymidylate synthetase. Small amounts of methotrexate polyglutamates may remain in tissues for extended periods. The retention and prolonged drug action of these active metabolites vary among different cells, tissues and tumors. A small amount of metabolism to 7-hydroxymethotrexate may occur at doses commonly prescribed. Accumulation of this metabolite may become significant at the high doses used in osteogenic sarcoma. The aqueous solubility of 7-hydroxymethotrexate is 3 to 5 fold lower than the parent compound. Methotrexate is partially metabolized by intestinal flora after oral administration.

Half-Life

The terminal half-life reported for methotrexate is approximately three to ten hours for patients receiving treatment for psoriasis, or rheumatoid arthritis or low dose antineoplastic therapy (less than 30 mg/m^2). For patients receiving high doses of methotrexate, the terminal half-life is eight to 15 hours.

In pediatric patients receiving methotrexate for acute lymphocytic leukemia (6.3 to 30 mg/m^2), or for JIA (3.75 to 26.2 mg/m^2), the terminal half-life has been reported to range from 0.7 to 5.8 hours or 0.9 to 2.3 hours, respectively.

Excretion

Renal excretion is the primary route of elimination and is dependent upon dosage and route of administration. With IV administration, 80% to 90% of the administered dose is excreted unchanged in the urine within 24 hours. There is limited biliary excretion amounting to 10% or less of the administered dose. Enterohepatic recirculation of methotrexate has been proposed.

Renal excretion occurs by glomerular filtration and active tubular secretion. Nonlinear elimination due to saturation of renal tubular reabsorption has been observed in psoriatic patients at doses between 7.5 and 30 mg. Impaired renal function, as well as concurrent use of drugs such as weak organic acids that also undergo tubular secretion, can markedly increase methotrexate serum levels.

Excellent correlation has been reported between methotrexate clearance and endogenous creatinine clearance.

Methotrexate clearance rates vary widely and are generally decreased at higher doses. Delayed drug clearance has been identified as one of the major factors responsible for methotrexate toxicity. It has been postulated that the toxicity of methotrexate for normal tissues is more dependent upon the duration of exposure to the drug rather than the peak level achieved. When a patient has delayed drug elimination due to compromised renal function, a third space effusion, or other causes, methotrexate serum concentrations may remain elevated for prolonged periods.

When other forms of parenteral methotrexate are administered during cancer chemotherapy, the potential for toxicity from high dose regimens or delayed excretion is reduced by the administration of leucovorin calcium during the final phase of methotrexate plasma elimination.

Pharmacokinetic monitoring of methotrexate serum concentrations may help identify those patients at high risk for methotrexate toxicity and aid in proper adjustments of leucovorin dosing.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Methotrexate has been evaluated in a number of animal studies for carcinogenic potential with inconclusive results. Although there is evidence that methotrexate causes chromosomal damage to animal somatic cells and human bone marrow cells, the clinical significance remains uncertain.

Data are available regarding the risks for pregnancy and for fertility in humans *[see Use in Specific Populations (8.1 and 8.6)]*.

14 CLINICAL STUDIES

14.1 Rheumatoid Arthritis

Clinical trials in patients with rheumatoid arthritis were performed using other formulations of methotrexate.

In patients with rheumatoid arthritis, effects of methotrexate on articular swelling and tenderness can be seen as early as 3 to 6 weeks.

Most studies of methotrexate in patients with rheumatoid arthritis are relatively short term (3 to 6 months). Limited data from long-term studies indicate that an initial clinical improvement is maintained for at least two years with continued therapy.

14.2 Polyarticular Juvenile Idiopathic Arthritis

Clinical trials in patients with polyarticular juvenile idiopathic arthritis were performed using other formulations of methotrexate.

In a 6-month double-blind, placebo-controlled trial of 127 pediatric patients with pJIA (mean age, 10.1 years; age range, 2.5 to 18 years; mean duration of disease, 5.1 years) on background nonsteroidal anti-inflammatory drugs and/or prednisone, methotrexate given weekly at an oral dose of 10 mg/m^2 provided significant clinical improvement compared to placebo as measured by either the physician's global assessment, or by a patient composite (25% reduction in the articular-severity score plus improvement in parent and physician global assessments of disease activity). Over two-thirds of the patients in this trial had polyarticular-course JIA, and the numerically greatest response was seen in this subgroup treated with 10 mg/m^2/wk methotrexate.

The overwhelming majority of the remaining patients had systemic-course JIA. All patients were unresponsive to NSAIDs; approximately one-third were using low dose corticosteroids.

Weekly methotrexate at a dose of 5 mg/m^2 was not significantly more effective than placebo in this trial.

15 REFERENCES

1. "Hazardous Drugs". *OSHA*. http://www.osha.gov/SLTC/hazardousdrugs/index.html

16 HOW SUPPLIED/STORAGE AND HANDLING

Rasuvo contains methotrexate in a preservative-free sterile solution for a single subcutaneous injection in the following configurations.

Strength	Pack Configuration*	NDC
7.5 mg per 0.15 mL	1	59137-505-01
	4	59137-505-04
10 mg per 0.20 mL	1	59137-510-01
	4	59137-510-04
12.5 mg per 0.25 mL	1	59137-515-01
	4	59137-515-04
15 mg per 0.30 mL	1	59137-520-01
	4	59137-520-04
17.5 mg per 0.35 mL	1	59137-525-01
	4	59137-525-04
20 mg per 0.40 mL	1	59137-530-01
	4	59137-530-04
22.5 mg per 0.45 mL	1	59137-535-01
	4	59137-535-04
25 mg per 0.50 mL	1	59137-540-01
	4	59137-540-04
27.5 mg per 0.55 mL	1	59137-545-01
	4	59137-545-04
30 mg per 0.60 mL	1	59137-550-01
	4	59137-550-04

*Single unit configurations are not for sale. Sample only.

Not all pack sizes may be marketed.

Store at controlled room temperature, 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). PROTECT FROM LIGHT.

Handling and Disposal

Handle and dispose of Rasuvo consistent with recommendations for handling and disposal of cytotoxic drugs.[1]

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information and Instructions for Use)

Risk of Organ Toxicity

Inform patients of the risks of organ toxicity, including gastrointestinal, hematologic, hepatic, infections, neurologic, pulmonary, renal and skin as well as possible signs and symptoms for which they should contact their healthcare provider. Advise patients of the need for close follow-up, including periodic laboratory tests to monitor toxicity [*see Warnings and Precautions (5.1 and 5.4)*].

Importance of Proper Dosing and Administration

Both the physician and pharmacist should emphasize to the patient that the recommended dose is taken once weekly and that mistaken daily use of the recommended dose has led to fatal toxicity [*see Dosing and Administration (2)*].

Rasuvo is intended for use under the guidance and supervision of a physician. Patients should not self- administer until they receive training from a healthcare professional. The patient's or caregiver's ability to administer Rasuvo should be assessed.

Patients should be instructed to use administration sites on the abdomen or the thigh. Administration should not be made within 2 inches of the navel. Instruct patients not to administer Rasuvo to the arms or any other areas of the body, as delineated in the Rasuvo Instructions for Use *[see Instructions for Use]*.

Risks of Pregnancy and Reproduction

Advise patients that Rasuvo can cause fetal harm and is contraindicated in pregnancy. Advise women of childbearing potential that Rasuvo should not be started until pregnancy is excluded. Women should be fully counseled on the serious risk to the fetus should they become pregnant while undergoing treatment. Inform patients to contact their physician if they suspect that they are pregnant.

Advise patients that pregnancy should be avoided if either partner is receiving Rasuvo; during and for a minimum of three months after therapy for male patients, and during and for at least one ovulatory cycle after therapy for female patients *[see Warnings and Precautions (5.2)]*.

Discuss the risk of effects on reproduction with both male and female patients taking Rasuvo.

Inform patients that methotrexate has been reported to cause impairment of fertility, oligospermia and menstrual dysfunction, during and for a short period after cessation of therapy *[see Use in Specific Populations (8.6)]*.

Nursing Mothers

Inform patients that Rasuvo is contraindicated in nursing mothers [*see Use in Specific Populations (8.3)*].

Ability to Drive or Operate Machinery

Inform patients that adverse reactions such as dizziness and fatigue may affect their ability to drive or operate machinery.

Proper Storage and Disposal

Advise patients to store Rasuvo at room temperature (68 to 77°F or 20 to 25°C). Inform patients and caregivers of the need for proper disposal after use, including the use of a sharps disposal container.

Manufactured for:
Medac Pharma Inc.
29 N Wacker Drive, Suite 704
Chicago, IL 60606

Manufactured by:
Oncotec Pharma Produktion GmbH
Am Pharmapark
D-06861 Dessau-Roßlau
Germany

PATIENT INFORMATION

RASUVO™ (ruh-SOO-voh)
(methotrexate)
injection, for subcutaneous use

What is Rasuvo?

Rasuvo is a single-dose manually-triggered auto-injector containing a prescription medicine, methotrexate. Methotrexate is used to:

- treat certain adults with severe, active rheumatoid arthritis (RA), and children with active polyarticular juvenile idiopathic arthritis (pJIA), after treatment with other medicines including non-steroidal anti-inflammatory (NSAIDS) have been used and did not work well.
- control the symptoms of severe, resistant, disabling psoriasis in adults when other types of treatment have been used and did not work well.

Rasuvo is available in doses of 7.5, 10, 12.5, 15, 17.5, 20, 22.5, 25, 27.5 and 30 mg. Your doctor will prescribe a different way to take methotrexate if you need to take methotrexate by mouth or in some other way. Your doctor may also change your prescription if your dose does not match the available Rasuvo doses, such as doses of less than 7.5 mg, more than 30 mg, or doses in between the available Rasuvo doses.

Rasuvo should not be used for the treatment of cancer.

Rasuvo should not be used for the treatment of children with psoriasis.

What is the most important information I should know about Rasuvo?

Rasuvo can cause serious side effects that can lead to death, including:

1. **Organ system toxicity.** People who use methotrexate for the treatment of cancer, psoriasis, or rheumatoid arthritis, have an increased risk of death from organ toxicity. Types of organ toxicity can include:

    - gastrointestinal
    - bone marrow
    - liver
    - immune system
    - nerve
    - lung
    - kidneys
    - skin

    Your doctor will do blood tests and other types of tests before you take and while you are taking Rasuvo to check for signs and symptoms of organ toxicity. Call your doctor right away if you have any of the following symptoms of organ toxicity:

    - vomiting
    - diarrhea
    - mouth sores
    - fever
    - confusion
    - weakness
    - neck stiffness
    - paralysis
    - irritability
    - sleepiness
    - problems with coordination
    - dry cough

- o temporary blindness
- o seizures
- o headache
- o back pain
- o trouble breathing
- o severe skin rash
- o infection

2. **Women who are pregnant are at increased risk for death of the baby and birth defects.** Women who are pregnant or who plan to become pregnant **must not take Rasuvo.** A pregnancy test should be performed before starting Rasuvo.

   Contraception should be used by both females and males while taking Rasuvo. Pregnancy should be avoided if either partner is receiving Rasuvo:

   - for a minimum of 3 months after treatment with Rasuvo for males.
   - during and for at least 1 menstrual cycle after treatment with Rasuvo for females.

Who should not take Rasuvo?

Do not take Rasuvo if you:

- are pregnant or planning to become pregnant. See **"What is the most important information I should know about Rasuvo?"**
- are breastfeeding.
- Rasuvo can pass into your breast milk and may harm your baby. **Do not** breastfeed while taking Rasuvo. Talk to your doctor about the best way to feed your baby if you take Rasuvo.
- have alcohol problems (alcoholism)
- have liver problems
- have problems fighting infection (immunodeficiency syndrome)
- have been told you have (or think you have) a blood disorder such as low levels of white blood cells, red blood cells (anemia), or platelets.
- have had an allergy to methotrexate or any of the ingredients in Rasuvo. See the end of this leaflet for a complete list of ingredients in Rasuvo.

Talk to your doctor before taking this medicine if you have any of these conditions.

What should I tell my doctor before taking Rasuvo?

Before you take Rasuvo, tell your doctor if you have any other medical conditions.

Tell your doctor about all of the medicines you take, including prescription, over-the-counter medicines, vitamins, and herbal supplements.

Rasuvo may affect how other medicines work, and other medicines may affect how Rasuvo works causing side effects.

Ask your doctor or pharmacist for a list of medicines if you are not sure.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take Rasuvo?

- **Read the Instructions for Use that come with Rasuvo.**
- Take Rasuvo exactly as your doctor tells you to take it.
- Inject Rasuvo **only 1 time each week. Do not** take Rasuvo every day.
- Taking Rasuvo every day may cause death from toxicity.
- Your doctor will show you or your caregiver how to inject Rasuvo. You should not inject Rasuvo until you have been trained on the right way to use it.
- Check Rasuvo before you inject it. Rasuvo should be yellow to brown in color and should not have any lumps or particles in it.
- Rasuvo should be injected under the skin of the abdomen or thigh.
- **Do not** inject Rasuvo within 2 inches of the belly button (navel)
- Use a different site each time you inject. This may help to decrease any reactions at the injection site.
- **Do not** inject Rasuvo in the arms or any other areas of the body.
- **Do not** inject Rasuvo in areas where the skin is tender, bruised, red, scaly, hard, or has scars or stretch marks.
- If you are not sure if Rasuvo was injected, or if you have hard time giving the injection, **do not** inject another dose. Call your pharmacist or doctor right away.
- If you inject too much Rasuvo, call your doctor or go to the nearest hospital emergency room right away.

What should I avoid while taking Rasuvo?

- Do not drink alcohol while taking Rasuvo. Drinking alcohol can increase your chances of getting serious side effects.
- Rasuvo can cause dizziness and tiredness. Do not drive a car, operate machinery, or do anything that needs you to be alert until you know how Rasuvo affects you.
- Certain vaccinations should be avoided while taking Rasuvo. Talk to your doctor before you or members of your household receive any vaccines.

What are the possible side effects of Rasuvo?

Rasuvo may cause serious side effects, including:

See **"What is the most important information I should know about Rasuvo?"**

- **fertility problems.** Methotrexate, the active ingredient in Rasuvo, may affect your ability to have a baby. Males may have a decreased sperm count, and females may have changes to their menstrual cycle. This can happen while taking Rasuvo and for a short period of time after you stop.
- **certain cancers.** Some people who have taken methotrexate have had a certain type of cancer called Non-Hodgkin's lymphoma and other tumors. Your doctor may tell you to stop taking Rasuvo if this happens.
- **tissue and bone problems.** Taking methotrexate while having radiation therapy may increase the risk of your tissue or bone not receiving enough blood. This may lead to death of the tissue or bone.

Common side effects of Rasuvo include:

- nausea
- stomach pain
- indigestion (dyspepsia)
- mouth sores
- rash
- stuffy or runny nose and sore throat
- diarrhea
- abnormal liver function tests
- vomiting
- headache
- bronchitis
- low red, white, and platelet blood cell count
- hair loss
- dizziness
- sensitivity to light
- burning skin lesions
- lung problems

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of Rasuvo. For more information, ask your doctor or pharmacist.

Call you doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I dispose of Rasuvo?

- **Do not throw away in the household trash.** Put used Rasuvo in a FDA-cleared sharps disposal container right away after use.
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
  - upright stable during use
  - leak-resistant
  - properly labeled to warn of hazardous waste inside the container
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about the safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.
- Safely dispose of Rasuvo that is out of date or is no longer needed.

How should I store Rasuvo?

Store Rasuvo at room temperature between 68°F to 77°F (20°C to 25°C)

- Do not freeze
- Keep Rasuvo out of the light.

Keep Rasuvo and all medicines out of the reach of children.

General information about the safe and effective use of Rasuvo.

Methotrexate is sometimes prescribed for purposes other than those listed in Patient Information leaflet. Do not use Rasuvo for a condition for which it was not prescribed. Do not give Rasuvo to other people, even if they have the same symptoms that you have. It may harm them.

This Patient Information leaflet summarizes the most important information about Rasuvo. If you would like more information, talk to your doctor. You can ask your doctor or pharmacist for information about Rasuvo that is written for health professionals.

For more information, please contact Medac Pharma, Inc. at our number 1-855-336-3322.

What are the ingredients in Rasuvo?

Active ingredient: methotrexate

Inactive ingredients: sodium chloride, sodium hydroxide and water for injection, USP, and if necessary hydrochloric acid, USP.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Manufactured for:

Medac Pharma, Inc.

29 N Wacker Drive, Suite 704
Chicago, IL 60606

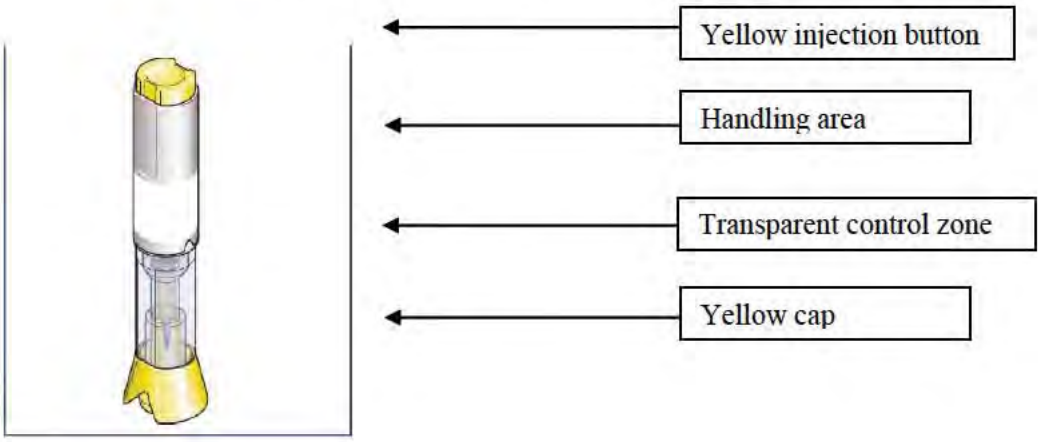
Issued: 07/2014

Read this Instructions for Use before using

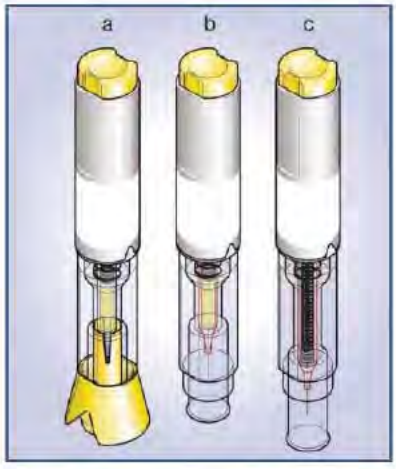
Rasuvo™ (ruh-SOO-voh) (methotrexate) injection, for subcutaneous use

Follow these instructions each time you use Rasuvo™.

Parts of your Rasuvo auto-injector



(Figure A)



(Figure B)

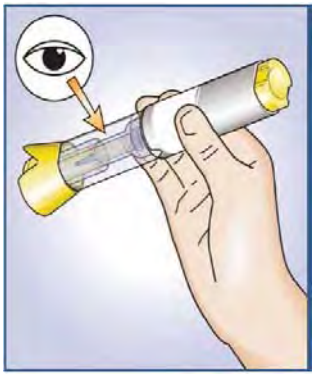
a) Pre-filled auto-injector with cap before injection
b) Pre-filled auto-injector after cap removal before injection
c) Pre-filled auto-injector after injection

Prepare to Use Rasuvo

- Wash your hands well with soap and warm water.

- Select a clean, well-lit, flat work surface, such as a table.
- Place the Rasuvo carton containing the auto-injector on your flat work surface.
- Be sure that the dose, either 7.5, 10, 12.5, 15, 17.5, 20, 22.5, 25, 27.5 or 30 mg, stated on the carton is the same as the dose prescribed by your doctor.
- Check the expiration date on the label. **Do not** use if expired.
- Remove one Rasuvo auto-injector from the packaging.
- If the Rasuvo appears to be damaged **do not** use it. Use another Rasuvo.
- In addition to Rasuvo, you will need the following items: one alcohol swab and one cotton ball or gauze and small adhesive bandage strip, if desired.

Check the Liquid



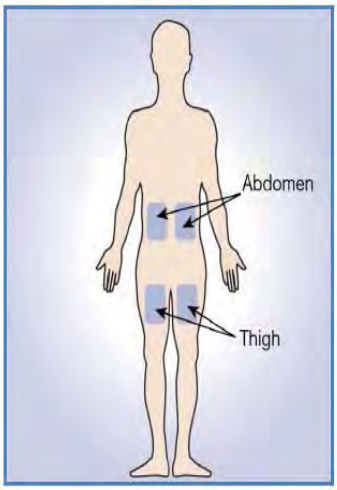
(Figure C)

- Look at the transparent control zone (**see Figure C**). The prefilled syringe is visible within the transparent control zone. Examine the contents of the syringe carefully. If the syringe is cracked or broken, **do not** use it. Use another auto-injector.
- The liquid should be clear and yellow to brown in color and should not have any lumps or particles in it. **Do not** use Rasuvo if the liquid is cloudy, discolored or contains particles.
- You may see an air bubble. This is normal.
- If you are not able to see or to check the Rasuvo auto-injector correctly prior to injection, ask a caretaker for assistance.
- **Do not** remove the yellow cap from the auto-injector until you are ready to use Rasuvo.

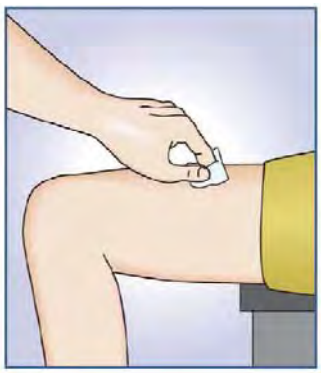
Choose an Injection Site

- Rasuvo should be injected into the stomach (abdomen) or the upper thigh. **Do not** inject Rasuvo within 2 inches of the belly button (navel) (**see Figure D**).
- **Do not** inject Rasuvo in the arms or any other areas of the body.

- **Do not** inject Rasuvo in areas where the skin is tender, bruised, red, scaly, hard, or has scars or stretch marks.
- Use a different site each time you inject. This may help to decrease any reactions at the injection site.
- Wipe the area with an alcohol swab (**see Figure E**).
- Allow the skin to dry and **do not** touch this area again before giving Rasuvo. **Do not** fan or blow on the clean area.



(Figure D)



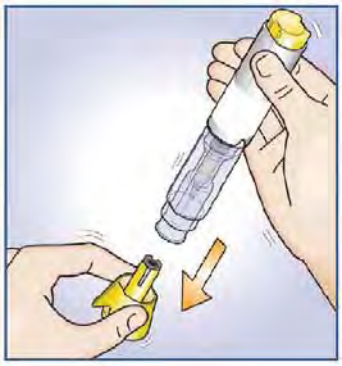
(Figure E)

Give your Injection

STEP 1: Remove the Yellow Cap (see Figure F)

- Hold the Rasuvo auto-injector with one hand in the handling area.

- Use your other hand to pull the yellow cap straight off (**see Figure F**). **Do not** twist the cap. If you are unable to remove the cap, ask a caretaker for assistance.



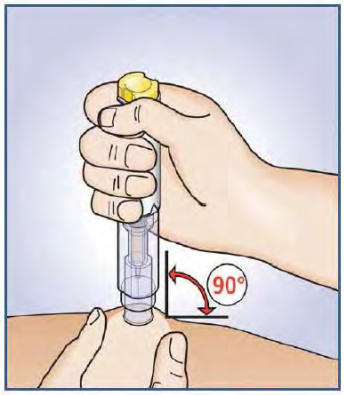
(Figure F)

Caution!

- **Do not** touch the needle end with your hands or fingers.
- This could inject the medicine into your hand.
- To avoid any injury, **never insert your fingers in the opening of the protect tube** covering the needle.
- **Do not** replace the cap after it has been removed.
- After the cap is removed Rasuvo must be used without delay or disposed of safely.
- **Do not** press the yellow injection button until you are ready to inject Rasuvo.

STEP 2: Prepare the Injection

- Pinch a pad of skin surrounding the cleaned injection site with your thumb and forefinger of your free hand by gently squeezing. Patients with rheumatoid arthritis who are unable to pinch the skin can inject directly into the thigh without pinching if needed.
- Hold the skin pinched until Rasuvo is removed from the skin after the injection.
- Position the uncapped transparent end of the Rasuvo auto-injector perpendicular (at a 90 degree angle) to the skin (**see Figure G**).
- Without pressing the button, **push Rasuvo firmly onto your skin until you feel the stop point** in order to unlock the yellow injection button (**see Figure G**).
- If you are unable to push Rasuvo to the stop-point, ask a caretaker for assistance.



(Figure G)

STEP 3: Inject Rasuvo

- While still holding Rasuvo firmly against the skin, **press the yellow injection button** with your thumb (**see Figure H**).
- You will hear a click which indicates the start of the injection. **Hold Rasuvo against the skin until all of the medicine is injected. This can take up to 5 seconds** (slowly count 1, 2, 3, 4, 5). **To avoid an incomplete injection,** do not remove the Rasuvo from the skin before the end of the injection.
- **Look at the transparent control zone while you are injecting to make sure that the entire dose is injected.** When the movement stops, the injection is completed.
- If you have problems with your hearing, slowly count to **5 seconds** from the moment you have pressed the button.
- It is not necessary to keep the button of the Rasuvo pressed down with your thumb after the injection has begun.

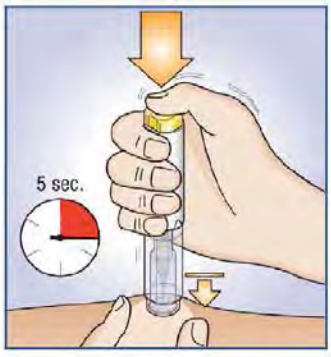


Figure H

- **After completing the injection, remove Rasuvo from the injection site** by pulling straight up (perpendicular to the skin).
- The protective needle shield automatically moves into place and locks over the needle.

- Put a small adhesive bandage strip over the injection site, if desired.

STEP 4: Check the Transparent Control Zone

C**heck visually** to make sure **that there is no liquid left in the** syringe inside **the transparent control zone.**

- If there is liquid left, not all of the medicine has been injected correctly. Consult your doctor or health care professional immediately. **Do not** use another Rasuvo, unless advised by your doctor.

STEP 5: Dispose of Rasuvo

- Each Rasuvo can be used only 1 time.
- **Do not throw away in the household trash.** Put used Rasuvo in a FDA-cleared sharps disposal container right away after use.
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
    - made of a heavy-duty plastic
    - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
    - upright and stable during use
    - leak-resistant
    - properly labeled to warn of hazardous waste inside the container
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about the safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.
- Safely dispose of Rasuvo that is out of date or no longer needed.

How should I store Rasuvo?

- Store Rasuvo at room temperature between 68°F to 77°F (20°C to 25°C). Do not freeze.
- Keep Rasuvo out of the light.
- Always keep your Rasuvo out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured for:
Medac Pharma Inc.

29 N Wacker Drive, Suite 704
Chicago, IL 60606

07/2014

Methotrexate Tablets, USP

672533200409

METHOTREXATE TABLETS, USP

WARNINGS

METHOTREXATE SHOULD BE USED ONLY BY PHYSICIANS WHOSE KNOWLEDGE AND EXPERIENCE INCLUDE THE USE OF ANTIMETABOLITE THERAPY BECAUSE OF THE POSSIBILITY OF SERIOUS TOXIC REACTIONS (WHICH CAN BE FATAL);

METHOTREXATE SHOULD BE USED ONLY IN LIFE THREATENING NEOPLASTIC DISEASES, OR IN PATIENTS WITH PSORIASIS OR RHEUMATOID ARTHRITIS WITH SEVERE, RECALCITRANT, DISABLING DISEASE WHICH IS NOT ADEQUATELY RESPONSIVE TO OTHER FORMS OF THERAPY.

DEATHS HAVE BEEN REPORTED WITH THE USE OF METHOTREXATE IN THE TREATMENT OF MALIGNANCY, PSORIASIS, AND RHEUMATOID ARTHRITIS.

PATIENTS SHOULD BE CLOSELY MONITORED FOR BONE MARROW, LIVER, LUNG AND KIDNEY TOXICITIES. (See **PRECAUTIONS.**)

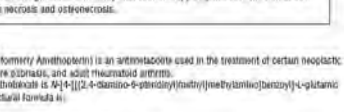
PATIENTS SHOULD BE INFORMED BY THEIR PHYSICIAN OF THE RISKS INVOLVED AND BE UNDER A PHYSICIAN'S CARE THROUGHOUT THERAPY.

1. Methotrexate has been reported to cause fetal death and/or congenital anomalies. Therefore, it is not recommended for women of childbearing potential unless there is clear medical evidence that the benefits can be expected to outweigh the considered risks. Pregnant women with psoriasis or rheumatoid arthritis should not receive methotrexate. (See **CONTRAINDICATIONS.**)
2. Methotrexate elimination is reduced in patients with impaired renal function, ascites, or pleural effusions. Such patients require especially careful monitoring for toxicity, and require dose reduction or, in some cases, discontinuation of methotrexate administration.
3. Unexpectedly severe (sometimes fatal) bone marrow suppression, aplastic anemia, and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high dosage) along with some non-steroidal anti-inflammatory drugs (NSAIDs). (See **PRECAUTIONS, Drug Interactions.**)
4. Methotrexate causes hepatotoxicity, fibrosis and cirrhosis, but generally only after prolonged use. Acutely, liver enzyme elevations are frequently seen. These are usually transient and asymptomatic, and also do not appear predictive of subsequent hepatic disease. Liver biopsy after sustained use often shows histologic changes, and fibrosis and cirrhosis have been reported; these latter lesions may not be preceded by symptoms or abnormal liver function tests in the psoriasis population. For this reason, periodic liver biopsies are usually recommended for psoriatic patients who are under long-term treatment. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid arthritis population. (See **PRECAUTIONS, Organ System Toxicity,** *Hepatic.*)
5. Methotrexate-induced lung disease is a potentially dangerous lesion, which may occur acutely at any time during therapy and which has been reported at doses as low as 7.5 mg/week. It is not always fully reversible. Pulmonary symptoms (especially a dry, nonproductive cough) may require interruption of treatment and careful investigation.
6. Diarrhea and ulcerative stomatitis require interruption of therapy; otherwise, hemorrhagic enteritis and death from intestinal perforation may occur.
7. Malignant lymphomas, which may regress following withdrawal of methotrexate, may occur in patients receiving low-dose methotrexate and, thus, may not require cytotoxic treatment. Discontinue methotrexate first and, if the lymphoma does not regress, appropriate treatment should be instituted.
8. Like other cytotoxic drugs, methotrexate may induce "tumor lysis syndrome" in patients with rapidly growing tumors. Appropriate supportive and pharmacologic measures may prevent or alleviate this complication.
9. Severe, occasionally fatal, skin reactions have been reported following single or multiple doses of methotrexate. Reactions have occurred within days of oral, intramuscular, intravenous, or intrathecal methotrexate administration. Recovery has been reported with discontinuation of therapy. (See **PRECAUTIONS, Organ System Toxicity,** *Skin.*)
10. Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy.
11. Methotrexate given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.

DESCRIPTION

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

Chemically methotrexate is *N*-[4-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-L-glutamic acid. The structural formula is:



Molecular weight: 454.45 $C_{20}H_{22}N_8O_5$

Methotrexate Tablets, USP for oral administration are available in bottles of 100. Methotrexate Tablets, USP contain an amount of methotrexate sodium equivalent to 2.5 mg of methotrexate and the following inactive ingredients: Lactose, Magnesium Stearate and Pregelatinized Starch. May also contain Corn Starch.

CLINICAL PHARMACOLOGY

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.

The mechanism of action in rheumatoid arthritis is unknown; it may affect immune function. Two reports describe in vitro methotrexate inhibition of DNA precursor uptake by stimulated mononuclear cells, and another describes in animal polyarthritis partial correction by methotrexate of spleen cell hyporesponsiveness and suppressed IL 2 production. Other laboratories, however, have been unable to demonstrate similar effects. Clarification of methotrexate's effect on immune activity and its relation to rheumatoid immunopathogenesis await further studies.

In patients with rheumatoid arthritis, effects of methotrexate on articular swelling and tenderness can be seen as early as 3 to 6 weeks. Although methotrexate clearly ameliorates symptoms of inflammation (pain, swelling, stiffness), there is no evidence that it induces remission of rheumatoid arthritis nor has a beneficial effect been demonstrated on bone erosions and other radiologic changes which result in impaired joint use, functional disability, and deformity.

Most studies of methotrexate in patients with rheumatoid arthritis are relatively short term (3 to 6 months). Limited data from long-term studies indicate that an initial clinical improvement is maintained for at least two years with continued therapy.

In psoriasis, the rate of production of epithelial cells in the skin is greatly increased over normal skin. This differential in proliferation ratios is the basis for the use of methotrexate to control the psoriatic process.

In a 6-month, double-blind, placebo-controlled trial of 127 pediatric patients with juvenile rheumatoid arthritis (JRA) (mean age, 10.1 years; age range 2.5 to 16 years, mean duration of disease, 5.1 years) on background non-steroidal anti-inflammatory drugs (NSAIDs) and/or prednisone, methotrexate given weekly at an oral dose of 10 mg/m² provided significant clinical improvement compared to placebo as measured by either the physician's global assessment, or by a patient composite (25% reduction in the articular-severity score plus improvement in parent and physician global assessments of disease activity.) Over two-thirds of the patients in this trial had polyarticular-course JRA, and the numerically greatest response was seen in this subgroup treated with 10 mg/m²/wk methotrexate. The overwhelming majority of the remaining patients had systemic-onset JRA. All patients were unresponsive to NSAIDs; approximately one-third were using low dose corticosteroids. Weekly methotrexate at a dose of 5 mg/m² was not significantly more effective than placebo in this trial.

Pharmacokinetics

Absorption - In adults, oral absorption appears to be dose dependent. Peak serum levels are reached within one to two hours. At doses of 30 mg/m² or less, methotrexate is generally well absorbed with a mean bioavailability of about 60%. The absorption of doses greater than 80 mg/m² is significantly less, possibly due to a saturation effect.

In leukemic pediatric patients, oral absorption of methotrexate also appears to be dose dependent and has been reported to vary widely (23% to 95%). A twenty fold difference between highest and lowest peak levels (C_{max}, 0.11 to 2.3 micromolar after a 20 mg/m² dose) has been reported. Significant interindividual variability has also been noted in time to peak concentration (T_{max} 0.67 to 4 hrs after a 15 mg/m² dose) and fraction of dose absorbed. The absorption of doses greater than 80 mg/m² has been reported to be significantly less than that of lower doses. Food has been shown to delay absorption and reduce peak concentration. Methotrexate is generally completely absorbed from parenteral routes of injection. After intramuscular injection, peak serum concentrations occur in 30 to 60 minutes. As in leukemic pediatric patients, a wide inter-individual variability in the plasma concentrations of methotrexate has been reported in pediatric patients with JRA. Following oral administration of methotrexate in doses of 6.4 to 11.2 mg/m²/week in pediatric patients with JRA, mean serum concentrations were 0.59 micromolar (range, 0.03 to 1.40) at 1 hour, 0.44 micromolar (range, 0.01 to 1.00) at 2 hours, and 0.29 micromolar (range 0.06 to 0.58) at 3 hours. In pediatric patients receiving methotrexate for acute lymphocytic leukemia (6.3 to 30 mg/m²), or for JRA (3.75 to 26.2 mg/m²), the terminal half-life has been reported to range from 0.7 to 5.8 hours or 0.9 to 3.3 hours, respectively.

Distribution - After intravenous administration, the initial volume of distribution is approximately 0.18 L/kg (18% of body weight) and steady-state volume of distribution is approximately 0.4 to 0.8 L/kg (40% to 80% of body weight). Methotrexate competes with reduced folates for active transport across cell membranes by means of a single carrier-mediated active transport process. At serum concentrations greater than 100 micromolar, passive diffusion becomes a major pathway by which effective intracellular concentrations can be achieved. Methotrexate in serum is approximately 50% protein bound. Laboratory studies demonstrate that it may be displaced from plasma albumin by various compounds including sulfonamides, salicylates, tetracyclines, chloramphenicol, and phenytoin.

Methotrexate does not penetrate the blood cerebrospinal fluid barrier in therapeutic amounts when given orally or parenterally. High CSF concentrations of the drug may be obtained by intrathecal administration.

In dogs, synovial fluid concentrations after oral dosing were higher in inflamed than uninflamed joints. Although salicylates did not interfere with this penetration, prior prednisone treatment reduced penetration into inflamed joints to the level of normal joints.

Metabolism - After absorption, methotrexate undergoes hepatic and intracellular metabolism to polyglutamated forms which can be converted back to methotrexate by hydrolase enzymes. These polyglutamates act as inhibitors of dihydrofolate reductase and thymidylate synthetase. Small amounts of methotrexate polyglutamates may remain in tissues for extended periods. The retention and prolonged drug action of these active metabolites vary among different cells, tissues and tumors. A small amount of metabolism to 7-hydroxymethotrexate may occur at doses commonly prescribed. Accumulation of this metabolite may become significant at the high doses used in osteogenic sarcoma. The aqueous solubility of 7-hydroxymethotrexate is 3 to 5 fold lower than the parent compound. Methotrexate is partially metabolized by intestinal flora after oral administration.

Half-Life - The terminal half-life reported for methotrexate is approximately three to ten hours for patients receiving treatment for psoriasis, or rheumatoid arthritis or low dose antineoplastic therapy (less than 30 mg/m²). For patients receiving high doses of methotrexate, the terminal half-life is eight to 15 hours.

Excretion - Renal excretion is the primary route of elimination and is dependent upon dosage and route of administration. With IV administration, 80% to 90% of the administered dose is excreted unchanged in the urine within 24 hours. There is limited biliary excretion amounting to 10% or less of the administered dose. Enterohepatic recirculation of methotrexate has been proposed.

Renal excretion occurs by glomerular filtration and active tubular secretion. Nonlinear elimination due to saturation of renal tubular reabsorption has been observed in psoriatic patients at doses between 7.5 and 30 mg. Impaired renal function, as well as concurrent use of drugs such as weak organic acids that also undergo tubular secretion, can markedly increase methotrexate serum levels. Excellent correlation has been reported between methotrexate clearance and endogenous creatinine clearance.

Methotrexate clearance rates vary widely and are generally decreased at higher doses. Delayed drug clearance has been identified as one of the major factors responsible for methotrexate toxicity. It has been postulated that the toxicity of methotrexate for normal tissues is more dependent upon the duration of exposure to the drug rather than the peak level achieved. When a patient has delayed drug elimination due to compromised renal function, a third space effusion, or other causes, methotrexate serum concentrations may remain elevated for prolonged periods.

The potential for toxicity from high dose regimens or delayed excretion is reduced by the administration of leucovorin calcium during the final phase of methotrexate plasma elimination.

Pharmacokinetic monitoring of methotrexate serum concentrations may help identify those patients at high risk for methotrexate toxicity and aid in proper adjustment of leucovorin dosing. Guidelines for monitoring serum methotrexate levels, and for adjustment of leucovorin dosing to reduce the risk of methotrexate toxicity, are provided below in **DOSAGE AND ADMINISTRATION**.

Methotrexate has been detected in human breast milk. The highest breast milk to plasma concentration ratio reached was 0.08:1.

INDICATIONS AND USAGE

Neoplastic Diseases

Methotrexate is indicated in the treatment of gestational choriocarcinoma, chorio-adenoma destruens and hydatidiform mole.

Methotrexate is used in maintenance therapy in combination with other chemotherapeutic agents. 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.

Psoriasis

Methotrexate is indicated in the symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy, *but only when the diagnosis has been established, as by biopsy and/or after dermatologic consultation.* It is important to ensure that a psoriatic "flare" is not due to an undiagnosed concomitant disease affecting immune responses.

Rheumatoid Arthritis including Polyarticular-Course Juvenile Rheumatoid Arthritis

Methotrexate is indicated in the management of selected adults with severe, active, rheumatoid arthritis (ADR 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 non-steroidal anti-inflammatory agents (NSAIDs).

Aspirin, NSAIDs, and/or low dose steroids may be continued, although the possibility of increased toxicity with concomitant use of NSAIDs including salicylates has not been fully explored. (See **PRECAUTIONS, Drug Interactions.**) Steroids may be reduced gradually in patients who respond to methotrexate. Combined use of methotrexate with gold, penicillamine, hydroxychloroquine, sulfasalazine, or cytotoxic agents, has not been studied and may increase the incidence of adverse effects. Rest and physiotherapy as indicated should be continued.

CONTRAINDICATIONS

Methotrexate can cause fetal death or teratogenic effects when administered to a pregnant woman. Methotrexate is contraindicated in pregnant women with psoriasis or rheumatoid arthritis and should be used in the treatment of neoplastic diseases only when the potential benefit outweighs the risk to the fetus. Women of childbearing potential should not be started on methotrexate until pregnancy is excluded and should be fully counseled on the serious risk to the fetus (See **PRECAUTIONS**) should they become pregnant while undergoing treatment. Pregnancy should be avoided if either partner is receiving methotrexate; during and for a minimum of three months after therapy for male patients, and during and for at least one ovulatory cycle after therapy for female patients. (See Boxed **WARNINGS.**)

Because of the potential for serious adverse reactions from methotrexate in breast fed infants, it is contraindicated in nursing mothers.

Patients with psoriasis or rheumatoid arthritis with alcoholism, alcoholic liver disease or other chronic liver disease should not receive methotrexate.

Patients with psoriasis or rheumatoid arthritis who have overt or laboratory evidence of immunodeficiency syndromes should not receive methotrexate.

Patients with psoriasis or rheumatoid arthritis who have preexisting blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia or significant anemia, should not receive methotrexate.

Patients with a known hypersensitivity to methotrexate should not receive the drug.

WARNINGS - SEE BOXED WARNINGS.

Methotrexate formulations and diluents containing preservatives must not be used for intrathecal or high dose methotrexate therapy.

PRECAUTIONS

General

Methotrexate has the potential for serious toxicity. (See Boxed **WARNINGS.**) Toxic effects may be related to frequency and severity to dose or frequency of administration but have been seen at all doses. Because they can occur at any time during therapy, it is necessary to follow patients on methotrexate closely. Most adverse reactions are reversible if detected early. When such reactions do occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken. If necessary, this could include the use of leucovorin calcium and/or acute, intermittent haemodialysis with a high-flux dialyzer. (See **OVERDOSAGE.**) If methotrexate therapy is reinstituted, it should be carried out with caution, with adequate consideration of further need for the drug and with increased alertness as to possible recurrence of toxicity.

The clinical pharmacology of methotrexate has not been well studied in older individuals. Due to diminished hepatic and renal function as well as decreased total stores in this population, relatively low doses should be considered, and these patients should be closely monitored for early signs of toxicity.

Information for Patients

Patients should be informed of the early signs and symptoms of toxicity, of the need to see their physician promptly if they occur, and the need for close follow-up, including periodic laboratory tests to monitor toxicity.

Both the physician and pharmacist should emphasize to the patient that the recommended dose is taken weekly in rheumatoid arthritis and psoriasis, and that mistaken daily use of the recommended dose has led to fatal toxicity. Patients should be encouraged to read the Patient Instructions sheet within the Dose Pack. Prescriptions should not be written or refilled on a PRN basis.

Patients should be informed of the potential benefit and risk in the use of methotrexate. The risk of effects on reproduction should be discussed with both male and female patients taking methotrexate.

Laboratory Tests

Patients undergoing methotrexate therapy should be closely monitored so that toxic effects are detected promptly. Baseline assessment should include a complete blood count with differential and platelet counts, hepatic enzymes, renal function tests, and a chest X-ray. During therapy of rheumatoid arthritis and psoriasis, monitoring of these parameters is recommended: hematology at least monthly, renal function and liver function every 1 to 2 months. More frequent monitoring is usually indicated during antineoplastic therapy. *During initial or changing doses,* or during periods of increased risk of elevated methotrexate blood levels (eg, dehydration), more frequent monitoring may also be indicated.

Transient liver function test abnormalities are observed frequently after methotrexate administration and are usually not cause for modification of methotrexate therapy. Persistent liver function test abnormalities, and/or depression of serum albumin may be indicators of serious liver toxicity and require evaluation. (See **PRECAUTIONS, Organ System Toxicity,** *Hepatic.*)

A relationship between abnormal liver function tests and fibrosis or cirrhosis of the liver has not been established for patients with psoriasis. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid arthritis population.

Pulmonary function tests may be useful if methotrexate-induced lung disease is suspected, especially if baseline measurements are available.

Drug Interactions

Concomitant administration of some NSAIDs with high dose methotrexate therapy has been reported to elevate and prolong serum methotrexate levels, resulting in deaths from severe hematologic and gastrointestinal toxicity.

Caution should be used when NSAIDs and salicylates are administered concomitantly with lower doses of methotrexate. These drugs have been reported to reduce the tubular secretion of methotrexate in an animal model and may enhance its toxicity.

Despite the potential interactions, studies of methotrexate in patients with rheumatoid arthritis have usually included concurrent use of constant dosage regimens of NSAIDs, without apparent problems. It should be appreciated, however, that the doses used in rheumatoid arthritis (7.5 to 20 mg/week) are somewhat lower than those used in psoriasis and that larger doses could lead to unexpected toxicity.

Methotrexate is partially bound to serum albumin, and toxicity may be increased because of displacement by certain drugs, such as salicylates, phenylbutazone, phenytoin, and sulfonamides. Renal tubular transport is also diminished by probenecid; use of methotrexate with this drug should be carefully monitored.

Oral antibiotics such as tetracycline, chloramphenicol, and nonabsorbable broad spectrum antibiotics, may decrease intestinal absorption of methotrexate or interfere with the enterohepatic circulation by inhibiting bowel flora and suppressing metabolism of the drug by bacteria.

Penicillins may reduce the renal clearance of methotrexate, increased serum concentrations of methotrexate with concomitant hematologic and gastrointestinal toxicity have been observed with methotrexate. Use of methotrexate with penicillins should be carefully monitored.

The potential for increased hepatotoxicity when methotrexate is administered with other hepatotoxic agents has not been evaluated. However, hepatotoxicity has been reported in such cases. Therefore, patients receiving concomitant therapy with methotrexate and other potential hepatotoxins (eg, azathioprine, retinoids, sulfasalazine) should be closely monitored for possible increased risk of hepatotoxicity.

Methotrexate may decrease the clearance of theophylline; theophylline levels should be monitored when used concurrently with methotrexate.

Certain side effects such as mouth sores may be reduced by folate supplementation with methotrexate.

Trimethoprim/sulfamethoxazole has been reported rarely to increase bone marrow suppression in patients receiving methotrexate, probably by an additive antifolate effect.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

No controlled human data exist regarding the risk of neoplasia with methotrexate. Methotrexate has been evaluated in a number of animal studies for carcinogenic potential with inconclusive results. Although there is evidence that methotrexate causes chromosomal damage in animal somatic cells and human bone marrow cells, the clinical significance remains uncertain. Non-Hodgkin's lymphoma and other tumors have been reported in patients receiving low-dose oral methotrexate. However, there have been instances of malignant lymphoma arising during treatment with low-dose oral methotrexate, which have regressed completely following withdrawal of methotrexate, without requiring active anti-lymphoma treatment. Benefits should be weighed against the potential risks before using methotrexate alone or in combination with other drugs, especially in pediatric patients

or young adults. Methotrexate causes embryotoxicity, abortion, and fetal defects in humans. It has also been reported to cause impairment of fertility, oligospermia and menstrual dysfunction in humans, during and for a short period after cessation of therapy.

Pregnancy
Psoriasis and rheumatoid arthritis: Methotrexate is in Pregnancy Category X.
See **CONTRAINDICATIONS**.

Nursing Mothers
See **CONTRAINDICATIONS**.

Pediatric Use
Safety and effectiveness in pediatric patients have been established only in cancer chemotherapy and in polyarticular-course juvenile rheumatoid arthritis.

Published clinical studies evaluating the use of methotrexate in children and adolescents (ie, patients 2 to 16 years of age) with JRA demonstrated safety comparable to that observed in adults with rheumatoid arthritis. (See **CLINICAL PHARMACOLOGY, ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION.**)

Geriatric Use
Clinical studies of methotrexate did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious reflecting the greater frequency of decreased hepatic and renal function, decreased folate stores, concomitant disease or other drug therapy (ie, that interfere with renal function, methotrexate or folate metabolism) in this population (See **PRECAUTIONS, Drug Interactions**). Since decline in renal function may be associated with increases in adverse events and serum creatinine measurements may over estimate renal function in the elderly, more accurate methods (ie, creatine clearance) should be considered. Serum methotrexate levels may also be helpful. Elderly patients should be closely monitored for early signs of hepatic, bone marrow and renal toxicity. In chronic use situations, certain toxicities may be reduced by folate supplementation. Post-marketing experience suggests that the occurence of bone marrow suppression, thrombocytopenia, and pneumonitis may increase with age. See Boxed **WARNINGS** and **ADVERSE REACTIONS**.

Organ System Toxicity
Gastrointestinal: If vomiting, diarrhea, or stomatitis occur, which may result in dehydration, methotrexate should be discontinued until recovery occurs. Methotrexate should be used with extreme caution in the presence of peptic ulcer disease or ulcerative colitis.

Hematologic: Methotrexate can suppress hematopoiesis and cause anemia, aplastic anemia, pancytopenia, leukopenia, neutropenia, and/or thrombocytopenia. In patients with malignancy and preexisting hematopoietic impairment, the drug should be used with caution, if at all. In controlled clinical trials in rheumatoid arthritis (n=128), leukopenia (WBC <3000/mm^3) was seen in 2 patients, thrombocytopenia (platelets <100,000/mm^3) in 6 patients, and pancytopenia in 2 patients.

In psoriasis and rheumatoid arthritis, methotrexate should be stopped immediately if there is a significant drop in blood counts. In the treatment of neoplastic diseases, methotrexate should be continued only if the potential benefit warrants the risk of severe myelosuppression. Patients with profound granulocytopenia and fever should be evaluated immediately and usually require parenteral broad-spectrum antibiotic therapy.

Hepatic: Methotrexate has the potential for acute (elevated transaminases) and chronic (fibrosis and cirrhosis) hepatotoxicity. Chronic toxicity is potentially fatal; it generally has occurred after prolonged use (generally two years or more) and after a total dose of at least 1.5 grams. In studies in psoriatic patients, hepatotoxicity appeared to be a function of total cumulative dose and appeared to be enhanced by alcoholism, obesity, diabetes and advanced age. An accurate incidence rate has not been determined; the rate of progression and reversibility of lesions is not known. Special caution is indicated in the presence of preexisting liver damage or impaired hepatic function.

In psoriasis, liver function tests, including serum albumin, should be performed periodically prior to dosing but are often normal in the face of developing fibrosis or cirrhosis. These lesions may be detectable only by biopsy. The usual recommendation is to obtain a liver biopsy at 1) pretherapy or shortly after initiation of therapy (2 - 4 months), 2) a total cumulative dose of 1.5 grams, and 3) after each additional 1.0 to 1.5 grams. Moderate fibrosis or any cirrhosis normally leads to discontinuation of the drug; mild fibrosis normally suggests a repeat biopsy in 6 months. Milder histologic findings such as fatty change and low grade portal inflammation are relatively common pretherapy. Although these mild changes are usually not a reason to avoid or discontinue methotrexate therapy, the drug should be used with caution.

In rheumatoid arthritis, age at first use of methotrexate and duration of therapy have been reported as risk factors for hepatotoxicity; other risk factors, similar to those observed in psoriasis, may be present in rheumatoid arthritis but have not been confirmed to date. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in this population. There is a combined reported experience in 217 rheumatoid arthritis patients with liver biopsies both before and during treatment (after a cumulative dose of at least 1.5 g) and in 714 patients with a biopsy only during treatment. There are 64 (7%) cases of fibrosis and 1 (0.1%) case of cirrhosis. Of the 64 cases of fibrosis, 60 were deemed mild. The reticulin stain is more sensitive for early fibrosis and its use may increase these figures. It is unknown whether even longer use will increase these risks.

Liver function tests should be performed at baseline and at 4-8 week intervals in patients receiving methotrexate for rheumatoid arthritis. Pretreatment liver biopsy should be performed for patients with a history of excessive alcohol consumption, persistently abnormal baseline liver function test values or chronic hepatitis B or C infection. During therapy, liver biopsy should be performed if there are persistent liver function test abnormalities or there is a decrease in serum albumin below the normal range (in the setting of well controlled rheumatoid arthritis).

If the results of a liver biopsy show mild changes (Roenigk grades I, II, IIIa), methotrexate may be continued and the patient monitored as per recommendations listed above. Methotrexate should be discontinued in any patient who displays persistently abnormal liver function tests and refuses liver biopsy or in any patient whose liver biopsy shows moderate to severe changes (Roenigk grade IIIb or IV).

Infection or Immunologic States: Methotrexate should be used with extreme caution in the presence of active infection, and is usually contraindicated in patients with overt or laboratory evidence of immunodeficiency syndromes. Immunization may be ineffective when given during methotrexate therapy. Immunization with live virus vaccines is generally not recommended. There have been reports of disseminated vaccinia infections after smallpox immunization in patients receiving methotrexate therapy. Hypogammaglobulinemia has been reported rarely.

Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy. When a patient presents with pulmonary symptoms, the possibility of *Pneumocystis carinii* pneumonia should be considered.

Pulmonary: Pulmonary symptoms (especially a dry nonproductive cough) or a nonspecific pneumonitis occurring during methotrexate therapy may be indicative of a potentially dangerous lesion and require interruption of treatment and careful investigation. Although clinically variable, the typical patient with methotrexate induced lung disease presents with fever, cough, dyspnea, hypoxemia, and an infiltrate on chest X-ray; infection (including pneumonia) needs to be excluded. This lesion can occur at all dosages.

Renal: Methotrexate may cause renal damage that may lead to acute renal failure. Nephrotoxicity is due primarily to the precipitation of methotrexate and 7-hydroxymethotrexate in the renal tubules. Close attention to renal function including adequate hydration, urine alkalinization and measurement of serum methotrexate and creatinine levels are essential for safe administration.

Skin: Severe, occasionally fatal, dermatologic reactions, including toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, skin necrosis, and erythema multiforme, have been reported in children and adults, within days of oral, intramuscular, intravenous, or intrathecal methotrexate administration. Reactions were noted after single or multiple, low, intermediate or high doses of methotrexate in patients with neoplastic and non-neoplastic diseases.

Other Precautions: Methotrexate should be used with extreme caution in the presence of debility. Methotrexate exits slowly from third space compartments (eg, pleural effusions or ascites). This results in a prolonged terminal plasma half-life and unexpected toxicity. In patients with significant third space accumulations, it is advisable to evacuate the fluid before treatment and to monitor plasma methotrexate levels.

Lesions of psoriasis may be aggravated by concomitant exposure to ultraviolet radiation. Radiation dermatitis and sunburn may be "recalled" by the use of methotrexate.

ADVERSE REACTIONS
IN GENERAL, THE INCIDENCE AND SEVERITY OF ACUTE SIDE EFFECTS ARE RELATED TO DOSE AND FREQUENCY OF ADMINISTRATION. THE MOST SERIOUS REACTIONS ARE DISCUSSED ABOVE UNDER ORGAN SYSTEM TOXICITY IN THE PRECAUTION SECTION. THAT SECTION SHOULD ALSO BE CONSULTED WHEN LOOKING FOR INFORMATION ABOUT ADVERSE REACTIONS WITH METHOTREXATE.

The most frequently reported adverse reactions include ulcerative stomatitis, leukopenia, nausea, and abdominal distress. Other frequently reported adverse effects are malaise, undue fatigue, chills and fever, dizziness and decreased resistance to infection.

Other adverse reactions that have been reported with methotrexate are listed below by organ system. In the oncology setting, concomitant treatment and the underlying disease make specific attribution of a reaction to methotrexate difficult.

Alimentary System: gingivitis, pharyngitis, stomatitis, anorexia, nausea, vomiting, diarrhea, hematemesis, melena, gastrointestinal ulceration and bleeding, enteritis, pancreatitis.

Blood and Lymphatic System Disorders: suppressed hematopoiesis causing anemia, aplastic anemia, pancytopenia, leukopenia, neutropenia and/or thrombocytopenia, lymphadenopathy and lymphoproliferative disorders (including reversible).Hypogammaglobulinemia has been reported rarely.

Cardiovascular: pericarditis, pericardial effusion, hypotension, and thromboembolic events (including arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, thrombophlebitis, and pulmonary embolus).

Central Nervous System: headaches, drowsiness, blurred vision, transient blindness, speech impairment including dysarthria and aphasia, hemiparesis, paresis and convulsions have also occurred following administration of methotrexate. Following low doses, there have been occasional reports of transient subtle cognitive dysfunction, mood alteration, unusual cranial sensations, leukoencephalopathy, or encephalopathy.

Hepatobiliary: disorders, hepatotoxicity, acute hepatitis, chronic fibrosis and cirrhosis, decrease in serum albumin, liver enzyme elevations.

Infection: There have been case reports of sometimes fatal opportunistic infections in patients receiving methotrexate therapy for neoplastic and non-neoplastic diseases. Pneumocystis carinii pneumonia was the most common opportunistic infection. There have also been reports of infections, pneumonia, sepsis, nocardiosis, histoplasmosis, cryptococcosis, herpes zoster, H. simplex hepatitis, and disseminated H. simplex.

Musculoskeletal System: stress fracture.

Ophthalmic: conjunctivitis, serious visual changes of unknown etiology.

Pulmonary System: respiratory fibrosis, respiratory failure, interstitial pneumonitis; deaths have been reported, and chronic interstitial obstructive pulmonary disease has occasionally occurred.

Skin: erythematous rashes, pruritus, urticaria, photosensitivity, pigmentary changes, alopecia, ecchymosis, telangiectasia, acne, furunculosis, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson Syndrome, skin necrosis, skin ulceration, and exfoliative dermatitis.

Urogenital System: severe nephropathy or renal failure, azotemia, cystitis, hematuria; defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, vaginal discharge, and gynecomastia; infertility, abortion, fetal defects.

Other rarer reactions related to or attributed to the use of methotrexate such as nodulosis, vasculitis, arthralgia/myalgia, loss of libido/impotence, diabetes, osteoporosis, sudden death, reversible lymphomas, tumor lysis syndrome, soft tissue necrosis and osteonecrosis. Anaphylactoid reactions have been reported.

Adverse Reactions in Double-Blind Rheumatoid Arthritis Studies
The approximate incidences of methotrexate attributed (ie, placebo rate subtracted) adverse reactions in 12 to 18 week double-blind studies of patients (n=128) with rheumatoid arthritis treated with low-dose oral (7.5 to 15 mg/week) pulse methotrexate, are listed below. Virtually all of these patients were on concomitant nonsteroidal anti-inflammatory drugs and some were also taking low dosages of corticosteroids. Hepatic histology was not examined in these short-term studies. (See **PRECAUTIONS.**)

Incidence greater than 10%: Elevated liver function tests 15%, nausea/vomiting 10%.

Incidence 3% to 10%: Stomatitis, thrombocytopenia, (platelet count less than 100,000/mm^3).

Incidence 1% to 3%: Rash/pruritus/dermatitis, diarrhea, alopecia, leukopenia (WBC less than 3000/mm^3), pancytopenia, dizziness.

Two other controlled trials of patients (n=680) with Rheumatoid Arthritis on 7.5 mg – 15 mg/wk oral doses showed an incidence of interstitial pneumonitis of 1%. (See **PRECAUTIONS.**)

Other less common reactions included decreased hematocrit, headache, upper respiratory infection, anorexia, arthralgias, chest pain, coughing, dysuria, eye discomfort, epistaxis, fever, infection, sweating, tinnitus, and vaginal discharge.

Adverse Reactions in Psoriasis
There are no recent placebo-controlled trials in patients with psoriasis. There are two literature reports (Roenigk, 1969 and Nyfors, 1978) describing large series (n=204, 248) of psoriasis patients treated with methotrexate. Dosages ranged up to 25 mg per week and treatment was administered for up to four years. With the exception of alopecia, photosensitivity, and "burning of skin lesions" (each 3% to 10%), the adverse reaction rates in these reports were very similar to those in the rheumatoid arthritis studies. Rarely, painful plaque erosions may appear.

Adverse Reactions in JRA Studies
The approximate incidences of adverse reactions reported in pediatric patients with JRA treated with oral, weekly doses of methotrexate (5 to 20 mg/m^2/wk or 0.1 to 0.65 mg/kg/wk) were as follows (virtually all patients were receiving concomitant nonsteroidal anti-inflammatory drugs, and some also were taking low doses of cortico-steroids): elevated liver function tests, 14%; gastrointestinal reactions (eg, nausea, vomiting, diarrhea), 11%; stomatitis, 2%; leukopenia, 2%; headache, 1.2%; alopecia, 0.5%; dizziness, 0.2%; and rash, 0.2%. Although there is experience with dosing up to 30 mg/m2/wk in JRA, the published data for doses above 20 mg/m^2/wk are too limited to provide reliable estimates of adverse reaction rates.

OVERDOSAGE
Leucovorin is indicated to diminish the toxicity and counteract the effect of inadvertently administered overdosages of methotrexate. Leucovorin administration should begin as promptly as possible. As the time interval between methotrexate administration and leucovorin initiation increases, the effectiveness of leucovorin in counteracting toxicity decreases. Monitoring of the serum methotrexate concentration is essential in determining the optimal dose and duration of treatment with leucovorin.

In cases of massive overdosage, hydration and urinary alkalinization may be necessary to prevent the precipitation of methotrexate and/or its metabolites in the renal tubules. Generally speaking, neither hemodialysis nor peritoneal dialysis have been shown to improve methotrexate elimination. However, effective clearance of methotrexate has been reported with acute, intermittent hemodialysis using a high-flux dialyzer (Wall, SM et al: *Am J Kidney Dis* 28(6): 846-854, 1996).

In postmarketing experience, overdose with methotrexate has generally occurred with oral and intrathecal administration, although intravenous and intramuscular overdose have also been reported.

Reports of oral overdose often indicate accidental daily administration instead of weekly (single or divided doses). Symptoms commonly reported following oral overdose include those symptoms and signs reported at pharmacologic doses, particularly hematologic and gastrointestinal reaction. For example, leukopenia, thrombocytopenia, anemia, pancytopenia, bone marrow suppression, mucositis, stomatitis, oral ulceration, nausea, vomiting, gastrointestinal ulceration, gastrointestinal bleeding. In some cases, no symptoms were reported. There have been reports of death following overdose. In these cases, events such as sepsis or septic shock, renal failure, and aplastic anemia were also reported.

DOSAGE AND ADMINISTRATION
Neoplastic Diseases
Oral administration in tablet form is often preferred when low doses are being administered since absorption is rapid and effective serum levels are obtained.

Choriocarcinoma and similar trophoblastic diseases: Methotrexate is administered orally or intramuscularly in doses of 15 to 30 mg daily for a five-day course. Such courses are usually repeated for 3 to 5 times as required, with rest periods of one or more weeks interposed between courses, until any manifesting toxic symptoms subside. The effectiveness of therapy is ordinarily evaluated by 24 hour quantitative analysis of urinary chorionic gonadotropin (hCG), which should return to normal or less than 50 IU/24 hr usually after the third or fourth course and usually be followed by a complete resolution of measurable lesions in 4 to 6 weeks. One to two courses of methotrexate after normalization of hCG is usually recommended. Before each course of the drug careful clinical assessment is essential. Cyclic combination therapy of methotrexate with other antitumor drugs has been reported as being useful.

Since hydatidiform mole may precede choriocarcinoma, prophylactic chemotherapy with methotrexate has been recommended.

Chorioadenoma destruens is considered to be an invasive form of hydatidiform mole. Methotrexate is administered in these disease states in doses similar to those recommended for choriocarcinoma. *Leukemia:* Acute lymphoblastic leukemia in pediatric patients and young adolescents is the most responsive to present day chemotherapy. In young adults and older patients, clinical remission is more difficult to obtain and early relapse is more common.

Methotrexate alone or in combination with steroids was used initially for induction of remission in acute lymphoblastic leukemias. More recently corticosteroid therapy, in combination with other antileukemic drugs or in cyclic combinations with methotrexate included, has appeared to produce rapid and effective remissions. When used for induction, methotrexate in doses of 3.3 mg/m^2 in combination with 60 mg/m^2 of prednisone, given daily, produced remissions in 50% of patients treated, usually within a period of 4 to 6 weeks. Methotrexate in combination with other agents appears to be the drug of choice for securing maintenance of drug-induced remissions. When remission is achieved and supportive care has produced general clinical improvement, maintenance therapy is initiated, as follows: Methotrexate is administered 2 times weekly either by mouth or intramuscularly in total weekly doses of 30 mg/m^2. It has also been given in doses of 2.5 mg/kg intravenously every 14 days. If and when relapse does occur, reinduction of remission can again usually be obtained by repeating the initial induction regimen.

A variety of combination chemotherapy regimens have been used for both induction and maintenance therapy in acute lymphoblastic leukemia. The physician should be familiar with the new advances in antileukemic therapy.

Lymphomas: In Burkitt's tumor, Stages I-II, methotrexate has produced prolonged remissions in some cases. Recommended dosage is 10 to 25 mg/day orally for 4 to 8 days. In Stage III, methotrexate is commonly given concomitantly with other anti-tumor agents. Treatment in all stages usually consists of several courses of the drug interposed with 7 to 10 day rest periods. Lymphosarcomas in Stage III may respond to combined drug therapy with methotrexate given in doses of 0.625 to 2.5 mg/kg daily.

Mycosis Fungoides (cutaneous T cell lymphoma): Therapy with methotrexate as a single agent appears to produce clinical responses in up to 50% of patients treated. Dosage in early stages is usuallly 5 to 50 mg once weekly. Dose reduction or cessation is guided by patient response and hematologic monitoring. Methotrexate has also been administered twice weekly in doses ranging from 15 to 37.5 mg in patients who have responded poorly to weekly therapy.

Psoriasis, Rheumatoid Arthritis, and Juvenile Rheumatoid Arthritis
Adult Rheumatoid Arthritis: Recommended Starting Dosage Schedules

1. Single oral doses of 7.5 mg once weekly.

2. Divided oral dosages of 2.5 mg at 12 hour intervals for 3 doses given as a course once weekly
Polyarticular-Course Juvenile Rheumatoid Arthritis: The recommended starting dose is 10 mg/m^2 given once weekly.

For either adult RA or polyarticular-course JRA dosages may be adjusted gradually to achieve an optimal response. Limited experience shows a significant increase in the incidence and severity of serious toxic reactions, especially bone marrow suppression, at doses greater than 20 mg/wk in adults. Although there is experience with doses up to 30 mg/m^2/wk in children, there are too few published data to assess how doses over 20 mg/m^2/wk might affect the risk of serious toxicity in children. Experience does suggest, however, that children receiving 20 to 30 mg/m^2/wk (0.65 to 1.0 mg/kg/wk) may have better absorption and fewer gastrointestinal side effects if methotrexate is administered either intramuscularly or subcutaneously.

Therapeutic response usually begins within 3 to 6 weeks and the patient may continue to improve for another 12 weeks or more.

The optimal duration of therapy is unknown. Limited data available from long-term studies in adults indicate that the initial clinical improvement is maintained for at least two years with continued therapy. When methotrexate is discontinued, the arthritis usually worsens within 3 to 6 weeks.

The patient should be fully informed of the risks involved and should be under constant supervision of the physician. (See **Information for Patients** under **PRECAUTIONS**.) Assessment of hematologic, hepatic, renal, and pulmonary function should be made by history, physical examination, and laboratory tests before beginning, periodically during, and before reinstituting methotrexate therapy. (See **PRECAUTIONS**.) Appropriate steps should be taken to avoid conception during methotrexate therapy. (See **PRECAUTIONS** and **CONTRAINDICATIONS**.)

All schedules should be continually tailored to the individual patient. An initial test dose may be given prior to the regular dosing schedule to detect any extreme sensitivity to adverse effects. (See **ADVERSE REACTIONS**.) Maximal myelosuppression usually occurs in seven to ten days.

Psoriasis: Recommended Starting Dose Schedules
1. Weekly single oral, IM or IV dose schedule: 10 to 25 mg per week until adequate response is achieved.

2. Divided oral dose schedule: 2.5 mg at 12-hour intervals for three doses.

Dosages in each schedule may be gradually adjusted to achieve optimal clinical response; 30 mg/week should not ordinarily be exceeded.

Once optimal clinical response has been achieved, each dosage schedule should be reduced to the lowest possible amount of drug and to the longest possible rest period. The use of methotrexate may permit the return to conventional topical therapy, which should be encouraged.

HANDLING AND DISPOSAL
Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-5] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED
Oral:
Description
Methotrexate Tablets, USP contain an amount of methotrexate sodium equivalent to 2.5 mg of methotrexate and are round, convex, yellow tablets, scored in half on one side, engraved with M above the score, and 1 below.
NDC 67253-320-10 - bottle of 100 count
NDC 67253-320-36 - bottle of 36 count

Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]

REFERENCES

1. Controlling occupational exposure to hazardous drugs (OSHA Work-Practice Guidelines). *Am J Health Syst Pharm* 1996: 53: 1669-1685.
2. National Study Commission on Cytotoxic Exposure - Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, Sc D, Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
3. Clinical Oncological Society of Australia: Guidelines and recommendations for safe handling of antineoplastic agents. *Med J Australia* 1983; 1:426-428.
4. Jones RB, et al. Safe handling of chemotherapeutic agents: A report from the Mount Sinai Medical Center. CA - *A Cancer Journal for Clinicians* Sept/Oct 1983; 258-263.
5. American Society of Hospital Pharmacists technical assistance bulletin on handling cytotoxic and hazardous drugs. *Am J Hosp Pharm* 1990; 47:1033-1049.

Manufactured For:
DAVA Pharmaceuticals, Inc.
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By:
EXCELLA GmbH
Feucht, Germany

Rev. 04/09

METHOTREXATE SODIUM FOR INJECTION

Rx only

WARNINGS

METHOTREXATE SHOULD BE USED ONLY BY PHYSICIANS WHOSE KNOWLEDGE AND EXPERIENCE INCLUDE THE USE OF ANTIMETABOLITE THERAPY.

BECAUSE OF THE POSSIBILITY OF SERIOUS TOXIC REACTIONS (WHICH CAN BE FATAL):

METHOTREXATE SHOULD BE USED ONLY IN LIFE THREATENING NEOPLASTIC DISEASES, OR IN PATIENTS WITH PSORIASIS OR RHEUMATOID ARTHRITIS WITH SEVERE, RECALCITRANT, DISABLING DISEASE WHICH IS NOT ADEQUATELY RESPONSIVE TO OTHER FORMS OF THERAPY.

DEATHS HAVE BEEN REPORTED WITH THE USE OF METHOTREXATE IN THE TREATMENT OF MALIGNANCY, PSORIASIS, AND RHEUMATOID ARTHRITIS.

PATIENTS SHOULD BE CLOSELY MONITORED FOR BONE MARROW, LIVER, LUNG AND KIDNEY TOXICITIES. (See **PRECAUTIONS**.)

PATIENTS SHOULD BE INFORMED BY THEIR PHYSICIAN OF THE RISKS INVOLVED AND BE UNDER A PHYSICIAN'S CARE THROUGHOUT THERAPY.

THE USE OF METHOTREXATE HIGH DOSE REGIMENS RECOMMENDED FOR OSTEOSARCOMA REQUIRES METICULOUS CARE. (See **DOSAGE AND ADMINISTRATION**.) HIGH DOSE REGIMENS FOR OTHER NEOPLASTIC DISEASES ARE INVESTIGATIONAL AND A THERAPEUTIC ADVANTAGE HAS NOT BEEN ESTABLISHED.

METHOTREXATE FORMULATIONS AND DILUENTS CONTAINING PRESERVATIVES MUST NOT BE USED FOR INTRATHECAL OR HIGH DOSE METHOTREXATE THERAPY.

1. Methotrexate has been reported to cause fetal death and/or congenital anomalies. Therefore, it is not recommended for women of childbearing potential unless there is clear medical evidence that the benefits can be expected to outweigh the considered risks. Pregnant women with psoriasis or rheumatoid arthritis should not receive methotrexate. (See **CONTRAINDICATIONS**.)

2. Methotrexate elimination is reduced in patients with impaired renal function, ascites, or pleural effusions. Such patients require especially careful monitoring for toxicity, and require dose reduction or, in some cases, discontinuation of methotrexate administration.

3. Unexpectedly severe (sometimes fatal) bone marrow suppression, aplastic anemia, and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high dosage) along with some nonsteroidal anti-inflammatory drugs (NSAIDs). (See **PRECAUTIONS, Drug Interactions**.)

4. Methotrexate causes hepatotoxicity, fibrosis and cirrhosis, but generally only after prolonged use. Acutely, liver enzyme elevations are frequently seen. These are usually transient and asymptomatic, and also do not appear predictive of subsequent hepatic disease. Liver biopsy after sustained use often shows histologic changes, and fibrosis and cirrhosis have been reported; these latter lesions may not be preceded by symptoms or abnormal liver function tests in the psoriasis population. For this reason, periodic liver biopsies are usually recommended for psoriatic patients who are under long-term treatment. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid arthritis population. (See **PRECAUTIONS, Organ System Toxicity,** *Hepatic*.)

5. Methotrexate-induced lung disease, including acute or chronic interstitial pneumonitis, is a potentially dangerous lesion, which may occur acutely at any time during therapy and has been reported at low doses. It is not always fully reversible and fatalities have been reported. Pulmonary symptoms (especially a dry, nonproductive cough) may require interruption of treatment and careful investigation.

6. Diarrhea and ulcerative stomatitis require interruption of therapy; otherwise, hemorrhagic enteritis and death from intestinal perforation may occur.

7. Malignant lymphomas, which may regress following withdrawal of methotrexate, may occur in patients receiving low-dose methotrexate and, thus, may not require cytotoxic treatment. Discontinue methotrexate first and, if the lymphoma does not regress, appropriate treatment should be instituted.

8. Like other cytotoxic drugs, methotrexate may induce “tumor lysis syndrome” in patients with rapidly growing tumors. Appropriate supportive and pharmacologic measures may prevent or alleviate this complication.

9. Severe, occasionally fatal, skin reactions have been reported following single or multiple doses of methotrexate. Reactions have occurred within days of oral, intramuscular, intravenous, or intrathecal methotrexate administration. Recovery has been reported with discontinuation of therapy. (See **PRECAUTIONS, Organ System Toxicity,** *Skin*.)

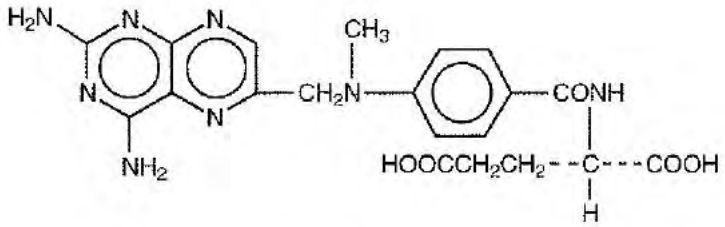
10. Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy.

11. Methotrexate given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.

DESCRIPTION

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

Chemically methotrexate is *N*-[4-[[(2,4-diamino-6-pteridinyl)methyl]-methylamino]benzoyl]-L-glutamic acid. The structural formula is:



Molecular weight: 454.45 $C_{20}H_{22}N_8O_5$

Methotrexate Sodium for Injection products are sterile and non-pyrogenic and may be given by the intramuscular, intravenous, intra-arterial or intrathecal route. (See **DOSAGE AND ADMINISTRATION**.)

Methotrexate Sodium for Injection, Lyophilized, Preservative Free, for single use only, is available in 20 mg and 1 gram vials.

Each 20 mg and 1 g vial of lyophilized powder contains methotrexate sodium equivalent to 20 mg and 1 g methotrexate respectively. Contains no preservative. Sodium Hydroxide and, if necessary, Hydrochloric Acid are added during manufacture to adjust the pH. The 20 mg vial contains approximately 0.14 mEq of Sodium and the 1 g vial contains approximately 7 mEq Sodium.

CLINICAL PHARMACOLOGY

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.

The mechanism of action in rheumatoid arthritis is unknown; it may affect immune function. Two reports describe *in vitro* methotrexate inhibition of DNA precursor uptake by stimulated mononuclear cells, and another describes in animal polyarthritis partial correction by methotrexate of spleen cell hyporesponsiveness and suppressed IL 2 production. Other laboratories, however, have been unable to demonstrate similar effects. Clarification of methotrexate's effect on immune activity and its relation to rheumatoid immunopathogenesis await further studies.

In patients with rheumatoid arthritis, effects of methotrexate on articular swelling and tenderness can be seen as early as 3 to 6 weeks. Although methotrexate clearly ameliorates symptoms of inflammation (pain, swelling, stiffness), there is no evidence that it induces remission of rheumatoid arthritis nor has a beneficial effect been demonstrated on bone erosions and other radiologic changes which result in impaired joint use, functional disability, and deformity.

Most studies of methotrexate in patients with rheumatoid arthritis are relatively short term (3 to 6 months). Limited data from long-term studies indicate that an initial clinical improvement is maintained for at least two years with continued therapy.

In psoriasis, the rate of production of epithelial cells in the skin is greatly increased over normal skin. This differential in proliferation rates is the basis for the use of methotrexate to control the psoriatic process.

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.

In a 6-month double-blind, placebo-controlled trial of 127 pediatric patients with juvenile rheumatoid arthritis (JRA) (mean age, 10.1 years; age range, 2.5 to 18 years; mean duration of disease, 5.1 years) on background nonsteroidal anti-inflammatory drugs (NSAIDs) and/or prednisone, methotrexate given weekly at an oral dose of 10 mg/m^2 provided significant clinical improvement compared to placebo as measured by either the physician's global assessment, or by a patient composite (25% reduction in the articular-severity score plus improvement in parent and physician global assessments of disease activity). Over two-thirds of the patients in this trial had polyarticular-course JRA, and the numerically greatest response was seen in this subgroup treated with 10 mg/m^2/wk methotrexate. The overwhelming majority of the remaining patients had systemic-course JRA. All patients were unresponsive to NSAIDs; approximately one-third were using low dose corticosteroids. Weekly methotrexate at a dose of 5 mg/m^2 was not significantly more effective than placebo in this trial.

Two Pediatric Oncology Group studies (one randomized and one non-randomized) demonstrated a significant improvement in relapse-free survival in patients with non-metastatic osteosarcoma, when high dose methotrexate with leucovorin rescue was used in combination with other chemotherapeutic agents following surgical resection of the primary tumor. These studies were not designed to demonstrate the specific contribution of high dose methotrexate/leucovorin rescue therapy to the efficacy of the combination. However, a contribution can be inferred from the reports of objective responses to this therapy in patients with metastatic osteosarcoma, and from reports of extensive tumor necrosis following preoperative administration of this therapy to patients with non-metastatic osteosarcoma.

Pharmacokinetics

Absorption – In adults, oral absorption appears to be dose dependent. Peak serum levels are reached within one to two hours. At doses of 30 mg/m^2 or less, methotrexate is generally well absorbed with a mean bioavailability of about 60%. The absorption of doses greater than 80 mg/m^2 is significantly less, possibly due to a saturation effect.

In leukemic pediatric patients, oral absorption of methotrexate also appears to be dose dependent and has been reported to vary widely (23% to 95%). A twenty fold difference between highest and lowest peak levels (C_{max}: 0.11 to 2.3 micromolar after a 20 mg/m^2 dose) has been reported. Significant interindividual variability has also been noted in time to peak concentration (T_{max}: 0.67 to 4 hrs after a 15 mg/m^2 dose) and fraction of dose absorbed. The absorption of doses greater than 40 mg/m^2 has been reported to be significantly less than that of lower doses. Food has been shown to delay absorption and reduce peak concentration. Methotrexate is generally completely absorbed from parenteral routes of injection. After intramuscular injection, peak serum concentrations occur in 30 to 60 minutes. As in leukemic pediatric patients, a wide interindividual variability in the plasma concentrations of methotrexate has been reported in pediatric patients with JRA. Following oral administration of methotrexate in doses of 6.4 to 11.2 mg/m^2/week in pediatric patients with JRA, mean serum concentrations were 0.59 micromolar (range, 0.03 to 1.40) at 1 hour, 0.44 micromolar (range, 0.01 to 1.00) at 2 hours, and 0.29 micromolar (range, 0.06 to 0.58) at 3 hours. In pediatric patients receiving methotrexate for acute lymphocytic leukemia (6.3 to 30 mg/m^2), or for JRA (3.75 to 26.2 mg/m^2), the terminal half-life has been reported to range from 0.7 to 5.8 hours or 0.9 to 2.3 hours, respectively.

Distribution – After intravenous administration, the initial volume of distribution is approximately 0.18 L/kg (18% of body weight) and steady-state volume of distribution is approximately 0.4 to 0.8 L/kg (40% to 80% of body weight). Methotrexate competes with reduced folates for active transport across cell membranes by means of a single carrier-mediated active transport process. At serum concentrations greater than 100 micromolar, passive diffusion becomes a major pathway by which effective intracellular concentrations can be achieved. Methotrexate in serum is approximately 50% protein bound. Laboratory studies demonstrate that it may be displaced from plasma albumin by various compounds including sulfonamides, salicylates, tetracyclines, chloramphenicol, and phenytoin.

Methotrexate does not penetrate the blood-cerebrospinal fluid barrier in therapeutic amounts when given orally or parenterally. High CSF concentrations of the drug may be attained by intrathecal administration.

In dogs, synovial fluid concentrations after oral dosing were higher in inflamed than uninflamed joints. Although salicylates did not interfere with this penetration, prior prednisone treatment reduced penetration into inflamed joints to the level of normal joints.

Metabolism – After absorption, methotrexate undergoes hepatic and intracellular metabolism to polyglutamated forms which can be converted back to methotrexate by hydrolase enzymes. These polyglutamates act as inhibitors of dihydrofolate reductase and thymidylate synthetase. Small amounts of methotrexate polyglutamates may remain in tissues for extended periods. The retention and prolonged drug action of these active metabolites vary among different cells, tissues and tumors. A small amount of metabolism to 7-hydroxymethotrexate may occur at doses commonly prescribed. Accumulation of this metabolite may become significant at the high doses used in osteogenic sarcoma. The aqueous solubility of 7-hydroxymethotrexate is 3 to 5 fold lower than the parent compound. Methotrexate is partially metabolized by intestinal flora after oral administration.

Half-Life – The terminal half-life reported for methotrexate is approximately three to ten hours for patients receiving treatment for psoriasis, or rheumatoid arthritis or low dose antineoplastic therapy (less than 30 mg/m^2). For patients receiving high doses of methotrexate, the terminal half-life is eight to 15 hours.

Excretion – Renal excretion is the primary route of elimination and is dependent upon dosage and route of administration. With IV administration, 80% to 90% of the administered dose is excreted unchanged in the urine within 24 hours. There is limited biliary excretion amounting to 10% or less of the administered dose. Enterohepatic recirculation of methotrexate has been proposed.

Renal excretion occurs by glomerular filtration and active tubular secretion. Nonlinear elimination due to saturation of renal tubular reabsorption has been observed in psoriatic patients at doses between 7.5 and 30 mg. Impaired renal function, as well as concurrent use of drugs such as weak organic acids that also undergo tubular secretion, can markedly increase methotrexate serum levels. Excellent correlation has been reported between methotrexate clearance and endogenous creatinine clearance.

Methotrexate clearance rates vary widely and are generally decreased at higher doses. Delayed drug clearance has been identified as one of the major factors responsible for methotrexate toxicity. It has been postulated that the toxicity of methotrexate for normal tissues is more dependent upon the duration of exposure to the drug rather than the peak level achieved. When a patient has delayed drug elimination due to compromised renal function, a third space effusion, or other causes, methotrexate serum concentrations may remain elevated for prolonged periods.

The potential for toxicity from high dose regimens or delayed excretion is reduced by the administration of leucovorin calcium during the final phase of methotrexate plasma elimination. Pharmacokinetic monitoring of methotrexate serum concentrations may help identify those patients at high risk for methotrexate toxicity and aid in proper adjustment of leucovorin dosing. Guidelines for monitoring serum methotrexate levels, and for adjustment of leucovorin dosing to reduce the risk of methotrexate toxicity, are provided below in **DOSAGE AND ADMINISTRATION**.

Methotrexate has been detected in human breast milk. The highest breast milk to plasma concentration ratio reached was 0.08:1.

INDICATIONS AND USAGE

Neoplastic Diseases

Methotrexate is indicated in the treatment of 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.

Psoriasis

Methotrexate is indicated in the symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy, *but only when the diagnosis has been established, as by biopsy and/or after dermatologic consultation.* It is important to ensure that a psoriasis "flare" is not due to an undiagnosed concomitant disease affecting immune responses.

Rheumatoid Arthritis including Polyarticular-Course Juvenile Rheumatoid Arthritis

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 non-steroidal anti-inflammatory agents (NSAIDs).

Aspirin, (NSAIDs), and/or low dose steroids may be continued, although the possibility of increased toxicity with concomitant use of NSAIDs including salicylates has not been fully explored. (See **PRECAUTIONS, Drug Interactions**.) Steroids may be reduced gradually in patients who respond to methotrexate. Combined use of methotrexate with gold, penicillamine, hydroxychloroquine, sulfasalazine, or cytotoxic agents, has not been studied and may increase the incidence of adverse effects. Rest and physiotherapy as indicated should be continued.

CONTRAINDICATIONS

Methotrexate can cause fetal death or teratogenic effects when administered to a pregnant woman. Methotrexate is contraindicated in pregnant women with psoriasis or rheumatoid arthritis and should be used in the treatment of neoplastic diseases only when the potential benefit outweighs the risk to the fetus. Women of childbearing potential should not be started on methotrexate until pregnancy is excluded and should be fully counseled on the serious risk to the fetus (See **PRECAUTIONS**) should they become pregnant while undergoing treatment. Pregnancy should be avoided if either partner is receiving methotrexate; during and for a minimum of three months after therapy for male patients, and during and for at least one ovulatory cycle after therapy for female patients. (See Boxed **WARNINGS**.)

Because of the potential for serious adverse reactions from methotrexate in breast fed infants, it is contraindicated in nursing mothers.

Patients with psoriasis or rheumatoid arthritis with alcoholism, alcoholic liver disease or other chronic liver disease should not receive methotrexate.

Patients with psoriasis or rheumatoid arthritis who have overt or laboratory evidence of immunodeficiency syndromes should not receive methotrexate.

Patients with psoriasis or rheumatoid arthritis who have preexisting blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia or significant anemia, should not receive methotrexate.

Patients with a known hypersensitivity to methotrexate should not receive the drug.

WARNINGS – SEE BOXED WARNINGS.

Methotrexate formulations and diluents containing preservatives must not be used for intrathecal or high dose methotrexate therapy.

PRECAUTIONS

General

Methotrexate has the potential for serious toxicity. (See Boxed **WARNINGS**.) Toxic effects may be related in frequency and severity to dose or frequency of administration but have been seen at all doses. Because they can occur at any time during therapy, it is necessary to follow patients on methotrexate closely. Most adverse reactions are reversible if detected early. When such reactions do occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken. If necessary, this could include the use of leucovorin calcium and/or acute, intermittent hemodialysis with a high-flux dialyzer. (See **OVERDOSAGE**.) If methotrexate therapy is reinstituted, it should be carried out with caution, with adequate consideration of further need for the drug and with increased alertness as to possible recurrence of toxicity.

The clinical pharmacology of methotrexate has not been well studied in older individuals. Due to diminished hepatic and renal function as well as decreased folate stores in this population, relatively low doses should be considered, and these patients should be closely monitored for early signs of toxicity.

Some of the effects mentioned under **ADVERSE REACTIONS**, such as dizziness and fatigue, may affect the ability to drive or operate machinery.

Information for Patients

Patients should be informed of the early signs and symptoms of toxicity, of the need to see their physician promptly if they occur, and the need for close follow-up, including periodic laboratory tests to monitor toxicity.

Both the physician and pharmacist should emphasize to the patient that the recommended dose is taken weekly in rheumatoid arthritis and psoriasis, and that mistaken daily use of the recommended dose has led to fatal toxicity. Prescriptions should not be written or refilled on a PRN basis.

Patients should be informed of the potential benefit and risk in the use of methotrexate. The risk of effects on reproduction should be discussed with both male and female patients taking methotrexate.

Laboratory Tests

Patients undergoing methotrexate therapy should be closely monitored so that toxic effects are detected promptly. Baseline assessment should include a complete blood count with differential and platelet counts, hepatic enzymes, renal function tests, and a chest X-ray. During therapy of rheumatoid arthritis and psoriasis, monitoring of these parameters is recommended: hematology at least monthly, renal function and liver function every 1 to 2 months. More frequent monitoring is usually indicated during antineoplastic therapy. *During initial or changing doses,* or during periods of increased risk of elevated methotrexate blood levels (eg, dehydration), more frequent monitoring may also be indicated.

Transient liver function test abnormalities are observed frequently after methotrexate administration and are usually not cause for modification of methotrexate therapy. Persistent liver function test abnormalities, and/or depression of serum albumin may be indicators of serious liver toxicity and require evaluation. (See **PRECAUTIONS, Organ System Toxicity,** *Hepatic*.)

A relationship between abnormal liver function tests and fibrosis or cirrhosis of the liver has not been established for patients with psoriasis. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid arthritis population.

Pulmonary function tests may be useful if methotrexate-induced lung disease is suspected, especially if baseline measurements are available.

Drug Interactions

Nonsteroidal anti-inflammatory drugs should not be administered prior to or concomitantly with the high doses of methotrexate, such as used in the treatment of osteosarcoma. Concomitant administration of some NSAIDs with high dose methotrexate therapy has been reported to elevate and prolong serum methotrexate levels, resulting in deaths from severe hematologic and gastrointestinal toxicity.

Caution should be used when NSAIDs and salicylates are administered concomitantly with lower doses of methotrexate. These drugs have been reported to reduce the tubular secretion of methotrexate in an animal model and may enhance its toxicity.

Despite the potential interactions, studies of methotrexate in patients with rheumatoid arthritis have usually included concurrent use of constant dosage regimens of NSAIDs, without apparent problems. It should be appreciated, however, that the doses used in rheumatoid arthritis (7.5 to 15 mg/week) are somewhat lower than those used in psoriasis and that larger doses could lead to unexpected toxicity.

Methotrexate is partially bound to serum albumin, and toxicity may be increased because of displacement by certain drugs, such as salicylates, phenylbutazone, phenytoin, and sulfonamides. Renal tubular transport is also diminished by probenecid; use of methotrexate with this drug should be carefully monitored.

In the treatment of patients with osteosarcoma, caution must be exercised if high-dose methotrexate is administered in combination with a potentially nephrotoxic chemotherapeutic agent (eg, cisplatin).

Methotrexate increases the plasma levels of mercaptopurine. The combination of methotrexate and mercaptopurine may therefore require dose adjustment.

Oral antibiotics such as tetracycline, chloramphenicol, and nonabsorbable broad spectrum antibiotics, may decrease intestinal absorption of methotrexate or interfere with the enterohepatic circulation by inhibiting bowel flora and suppressing metabolism of the drug by bacteria.

Penicillins may reduce the renal clearance of methotrexate; increased serum concentrations of methotrexate with concomitant hematologic and gastrointestinal toxicity have been observed with high and low dose methotrexate. Use of methotrexate with penicillins should be carefully monitored.

The potential for increased hepatotoxicity when methotrexate is administered with other hepatotoxic agents has not been evaluated. However, hepatotoxicity has been reported in such cases. Therefore, patients receiving concomitant therapy with methotrexate and other potential hepatotoxins (eg, azathioprine, retinoids, sulfasalazine) should be closely monitored for possible increased risk of hepatotoxicity.

Methotrexate may decrease the clearance of theophylline; theophylline levels should be monitored when used concurrently with methotrexate.

Vitamin preparations containing folic acid or its derivatives may decrease responses to systemically administered methotrexate. Preliminary animal and human studies have shown that small quantities of intravenously administered leucovorin enter the CSF primarily as 5-methyltetrahydrofolate and, in humans, remain 1 - 3 orders of magnitude lower than the usual methotrexate concentrations following intrathecal administration. However, high doses of leucovorin may reduce the efficacy of intrathecally administered methotrexate.

Folate deficiency states may increase methotrexate toxicity. Trimethoprim/sulfamethoxazole has been reported rarely to increase bone marrow suppression in patients receiving methotrexate, probably by decreased tubular secretion and/or additive antifolate effect.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

No controlled human data exist regarding the risk of neoplasia with methotrexate. Methotrexate has been evaluated in a number of animal studies for carcinogenic potential with inconclusive results. Although there is evidence that methotrexate causes chromosomal damage to animal somatic cells and human bone marrow cells, the clinical significance remains uncertain. Non-Hodgkin's lymphoma and other tumors have been reported in patients receiving low-dose oral methotrexate. However, there have been instances of malignant lymphoma arising during treatment with low-dose oral methotrexate, which have regressed completely following withdrawal of methotrexate, without requiring active anti-lymphoma treatment. Benefits should be weighed against the potential risks before using methotrexate alone or in combination with other drugs, especially in pediatric patients or young adults. Methotrexate causes embryotoxicity, abortion, and fetal defects in humans. It has also been reported to cause impairment of fertility, oligospermia and menstrual dysfunction in humans, during and for a short period after cessation of therapy.

Pregnancy

Psoriasis and rheumatoid arthritis: Methotrexate is in Pregnancy Category X. See **CONTRAINDICATIONS**.

Nursing Mothers

See **CONTRAINDICATIONS**.

Pediatric Use

Safety and effectiveness in pediatric patients have been established only in cancer chemotherapy and in polyarticular-course juvenile rheumatoid arthritis.

Published clinical studies evaluating the use of methotrexate in children and adolescents (i.e., patients 2 to 16 years of age) with JRA demonstrated safety comparable to that observed in adults with rheumatoid arthritis. (see **CLINICAL PHARMACOLOGY, ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**.)

Methotrexate injectable formulations containing the preservative benzyl alcohol are not recommended for use in neonates. There have been reports of fatal 'gasping syndrome' in neonates (children less than one month of age) following the administrations of intravenous solutions containing the preservative benzyl alcohol. Symptoms include a striking onset of gasping respiration, hypotension, bradycardia, and cardiovascular collapse.

Serious neurotoxicity, frequently manifested as generalized or focal seizures, has been reported with unexpectedly increased frequency among pediatric patients with acute lymphoblastic leukemia who were treated with intermediate-dose intravenous methotrexate (1 gm/m^2). (See **PRECAUTIONS, Organ System Toxicity,** *Neurologic*.)

Geriatric Use

Clinical studies of methotrexate did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious reflecting the greater frequency of decreased hepatic and renal function, decreased folate stores, concomitant disease or other drug therapy (ie, that interfere with renal function, methotrexate or folate metabolism) in this population (See **PRECAUTIONS, Drug Interactions**). Since decline in renal function may be associated with increases in adverse events and serum creatinine measurements may over estimate renal function in the elderly, more accurate methods (ie, creatinine clearance) should be considered. Serum methotrexate levels may also be helpful. Elderly patients should be closely monitored for early signs of hepatic, bone marrow and renal toxicity. In chronic use situations, certain toxicities may be reduced by folate supplementation. Post-marketing experience suggests that the occurrence of bone marrow suppression, thrombocytopenia, and pneumonitis may increase with age. See Boxed **WARNINGS** and **ADVERSE REACTIONS**.

Organ System Toxicity

Gastrointestinal: If vomiting, diarrhea, or stomatitis occur, which may result in dehydration, methotrexate should be discontinued until recovery occurs. Methotrexate should be used with extreme caution in the presence of peptic ulcer disease or ulcerative colitis.

Hematologic: Methotrexate can suppress hematopoiesis and cause anemia, aplastic anemia, pancytopenia, leukopenia, neutropenia, and/or thrombocytopenia. In patients with malignancy and preexisting hematopoietic impairment, the drug should be used with caution, if at all. In controlled clinical trials in rheumatoid arthritis (n=128), leukopenia (WBC $<3000/mm^3$) was seen in 2 patients, thrombocytopenia (platelets $<100,000/mm^3$) in 6 patients, and pancytopenia in 2 patients.

In psoriasis and rheumatoid arthritis, methotrexate should be stopped immediately if there is a significant drop in blood counts. In the treatment of neoplastic diseases, methotrexate should be continued only if the potential benefit warrants the risk of severe myelosuppression. Patients with profound granulocytopenia and fever should be evaluated immediately and usually require parenteral broad-spectrum antibiotic therapy.

Hepatic: Methotrexate has the potential for acute (elevated transaminases) and chronic (fibrosis and cirrhosis) hepatotoxicity. Chronic toxicity is potentially fatal; it generally has occurred after prolonged use (generally two years or more) and after a total dose of at least 1.5 grams. In studies in psoriatic patients, hepatotoxicity appeared to be a function of total cumulative dose and appeared to be enhanced by alcoholism, obesity, diabetes and advanced age. An accurate incidence rate has not been determined; the rate of progression and reversibility of lesions is not known. Special caution is indicated in the presence of preexisting liver damage or impaired hepatic function.

In psoriasis, liver function tests, including serum albumin, should be performed periodically prior to dosing but are often normal in the face of developing fibrosis or cirrhosis. These lesions may be detectable only by biopsy. The usual recommendation is to obtain a liver biopsy at 1) pretherapy or shortly after initiation of therapy (2 - 4 months), 2) a total cumulative dose of 1.5 grams, and 3) after each additional 1.0 to 1.5 grams. Moderate fibrosis or any cirrhosis normally leads to discontinuation of the drug; mild fibrosis normally suggests a repeat biopsy in 6 months. Milder histologic findings such as fatty change and low grade portal inflammation are relatively common pretherapy. Although these mild changes are usually not a reason to avoid or discontinue methotrexate therapy, the drug should be used with caution.

In rheumatoid arthritis, age at first use of methotrexate and duration of therapy have been reported as risk factors for hepatotoxicity; other risk factors, similar to those observed in psoriasis, may be present in rheumatoid arthritis but have not been confirmed to date. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in this population. There is a combined reported experience in 217 rheumatoid arthritis patients with liver biopsies both before and during treatment (after a cumulative dose of at least 1.5 g) and in 714 patients with a biopsy only during treatment. There are 64 (7%) cases of fibrosis and 1 (0.1%) case of cirrhosis. Of the 64 cases of fibrosis, 60 were deemed mild. The reticulin stain is more sensitive for early fibrosis and its use may increase these figures. It is unknown whether even longer use will increase these risks.

Liver function tests should be performed at baseline and at 4-8 week intervals in patients receiving methotrexate for rheumatoid arthritis. Pretreatment liver biopsy should be performed for patients with a history of excessive alcohol consumption, persistently abnormal baseline liver function test values or chronic hepatitis B or C infection. During therapy, liver biopsy should be performed if there are persistent liver function test abnormalities or there is a decrease in serum albumin below the normal range (in the setting of well controlled rheumatoid arthritis).

If the results of a liver biopsy show mild changes (Roenigk grades I, II, IIIa), methotrexate may be continued and the patient monitored as per recommendations listed above. Methotrexate should be discontinued in any patient who displays persistently abnormal liver function tests and refuses liver biopsy or in any patient whose liver biopsy shows moderate to severe changes (Roenigk grade IIIb or IV).

Infection or Immunologic States: Methotrexate should be used with extreme caution in the presence of active infection, and is usually contraindicated in patients with overt or laboratory evidence of immunodeficiency syndromes. Immunization may be ineffective when given during methotrexate therapy. Immunization with live virus vaccines is generally not recommended. There have been reports of disseminated vaccinia infections after smallpox immunization in patients receiving methotrexate therapy. Hypogammaglobulinemia has been reported rarely.

Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy. When a patient presents with pulmonary symptoms, the possibility of *Pneumocystis carinii* pneumonia should be considered.

Neurologic: There have been reports of leukoencephalopathy following intravenous administration of methotrexate to patients who have had craniospinal irradiation. Serious neurotoxicity, frequently manifested as generalized or focal seizures, has been reported with unexpectedly increased frequency among pediatric patients with acute lymphoblastic leukemia who were treated with intermediate-dose intravenous methotrexate (1 gm/m^2). Symptomatic patients were commonly noted to have leukoencephalopathy and/or microangiopathic calcifications on diagnostic imaging studies. Chronic leukoencephalopathy has also been reported in patients who received repeated doses of high-dose methotrexate with leucovorin rescue even without cranial irradiation. Discontinuation of methotrexate does not always result in complete recovery.

A transient acute neurologic syndrome has been observed in patients treated with high dosage regimens. Manifestations of this stroke-like encephalopathy may include confusion, hemiparesis, transient blindness, seizures and coma. The exact cause is unknown.

After the intrathecal use of methotrexate, the central nervous system toxicity which may occur can be classified as follows: acute chemical arachnoiditis manifested by such symptoms as headache, back pain, nuchal rigidity, and fever; sub-acute myelopathy characterized by paraparesis/paraplegia associated with involvement with one or more spinal nerve roots; chronic leukoencephalopathy manifested by confusion, irritability, somnolence, ataxia, dementia, seizures and coma. This condition can be progressive and even fatal.

Pulmonary: Pulmonary symptoms (especially a dry nonproductive cough) or a nonspecific pneumonitis occurring during methotrexate therapy may be indicative of a potentially dangerous lesion and require interruption of treatment and careful investigation. Although clinically variable, the typical patient with methotrexate induced lung disease presents with fever, cough, dyspnea, hypoxemia, and an infiltrate on chest X-ray; infection (including pneumonia) needs to be excluded. This lesion can occur at all dosages.

Renal: Methotrexate may cause renal damage that may lead to acute renal failure. High doses of methotrexate used in the treatment of osteosarcoma may cause renal damage leading to acute renal failure. Nephrotoxicity is due primarily to the precipitation of methotrexate and 7-hydroxymethotrexate in the renal tubules. Close attention to renal function including adequate hydration, urine alkalinization and measurement of serum methotrexate and creatinine levels are essential for safe administration.

Skin: Severe, occasionally fatal, dermatologic reactions, including toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, skin necrosis, and erythema multiforme, have been reported in children and adults, within days of oral, intramuscular, intravenous, or intrathecal methotrexate administration. Reactions were noted after single or multiple, low, intermediate or high doses of methotrexate in patients with neoplastic and non-neoplastic diseases.

Other Precautions: Methotrexate should be used with extreme caution in the presence of debility.

Methotrexate exits slowly from third space compartments (eg, pleural effusions or ascites). This results in a prolonged terminal plasma half-life and unexpected toxicity. In patients with significant third space accumulations, it is advisable to evacuate the fluid before treatment and to monitor plasma methotrexate levels.

Lesions of psoriasis may be aggravated by concomitant exposure to ultraviolet radiation. Radiation dermatitis and sunburn may be "recalled" by the use of methotrexate.

ADVERSE REACTIONS

IN GENERAL, THE INCIDENCE AND SEVERITY OF ACUTE SIDE EFFECTS ARE RELATED TO DOSE AND FREQUENCY OF ADMINISTRATION. THE MOST SERIOUS REACTIONS ARE DISCUSSED ABOVE UNDER ORGAN SYSTEM TOXICITY IN THE PRECAUTION SECTION. THAT SECTION SHOULD ALSO BE CONSULTED WHEN LOOKING FOR INFORMATION ABOUT ADVERSE REACTIONS WITH METHOTREXATE.

The most frequently reported adverse reactions include ulcerative stomatitis, leukopenia, nausea, and abdominal distress. Other frequently reported adverse effects are malaise, undue fatigue, chills and fever, dizziness and decreased resistance to infection.

Other adverse reactions that have been reported with methotrexate are listed below by organ system. In the oncology setting, concomitant treatment and the underlying disease make specific attribution of a reaction to methotrexate difficult.

Alimentary System: gingivitis, pharyngitis, stomatitis, anorexia, nausea, vomiting, diarrhea, hematemesis, melena, gastrointestinal ulceration and bleeding, enteritis, pancreatitis.

Blood and Lymphatic System Disorders: suppressed hematopoiesis, anemia, aplastic anemia, pancytopenia, leukopenia, neutropenia, thrombocytopenia, agranulocytosis, eosinophilia, lymphadenopathy and lymphoproliferative disorders (including reversible). Hypogammaglobulinemia has been reported rarely.

Cardiovascular: pericarditis, pericardial effusion, hypotension, and thromboembolic events (including arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, thrombophlebitis, and pulmonary embolus).

Central Nervous System: headaches, drowsiness, blurred vision, transient blindness, speech impairment including dysarthria and aphasia, hemiparesis, paresis and convulsions have also occurred following administration of methotrexate. Following low doses, there have been occasional reports of transient subtle cognitive dysfunction, mood alteration, unusual cranial sensations, leukoencephalopathy, or encephalopathy.

Hepatobiliary Disorders: hepatotoxicity, acute hepatitis, chronic fibrosis and cirrhosis, hepatic failure, decrease in serum albumin, liver enzyme elevations.

Infection: There have been case reports of sometimes fatal opportunistic infections in patients receiving methotrexate therapy for neoplastic and non-neoplastic diseases. *Pneumocystis carinii* pneumonia was the most common opportunistic infection. There have also been reports of infections, pneumonia, Cytomegalovirus infection, including cytomegaloviral pneumonia, sepsis, fatal sepsis, nocardiosis; histoplasmosis, cryptococcosis, *Herpes zoster, H. simplex* hepatitis, and disseminated *H. simplex.*

Musculoskeletal System: stress fracture.

Ophthalmic: conjunctivitis, serious visual changes of unknown etiology.

Pulmonary System: respiratory fibrosis, respiratory failure, alveolitis, interstitial pneumonitis deaths have been reported, and chronic interstitial obstructive pulmonary disease has occasionally occurred.

Skin: erythematous rashes, pruritus, urticaria, photosensitivity, pigmentary changes, alopecia, ecchymosis, telangiectasia, acne, furunculosis, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, skin necrosis, skin ulceration, and exfoliative dermatitis.

Urogenital System: severe nephropathy or renal failure, azotemia, cystitis, hematuria, proteinuria; defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, vaginal discharge, and gynecomastia; infertility, abortion, fetal death, fetal defects.

Other rarer reactions related to or attributed to the use of methotrexate such as nodulosis, vasculitis, arthralgia/myalgia, loss of libido/impotence, diabetes, osteoporosis, sudden death, lymphoma, including reversible lymphomas, tumor lysis syndrome, soft tissue necrosis and osteonecrosis. Anaphylactoid reactions have been reported.

Adverse Reactions in Double-Blind Rheumatoid Arthritis Studies

The approximate incidences of methotrexate-attributed (ie, placebo rate subtracted) adverse reactions in 12 to 18 week double-blind studies of patients (n=128) with rheumatoid arthritis treated with low-dose oral (7.5 to 15 mg/week) pulse methotrexate, are listed below. Virtually all of these patients were on concomitant nonsteroidal anti-inflammatory drugs and some were also taking low dosages of corticosteroids. Hepatic histology was not examined in these short-term studies. (See **PRECAUTIONS**.)

Incidence greater than 10%: Elevated liver function tests 15%, nausea/vomiting 10%.

Incidence 3% to 10%: Stomatitis, thrombocytopenia (platelet count less than 100,000/mm^3).

Incidence 1% to 3%: Rash/pruritus/dermatitis, diarrhea, alopecia, leukopenia (WBC less than 3000/mm^3), pancytopenia, dizziness.

Two other controlled trials of patients (n=680) with Rheumatoid Arthritis on 7.5 mg – 15 mg/wk oral doses showed an incidence of interstitial pneumonitis of 1%. (See **PRECAUTIONS**.)

Other less common reactions included decreased hematocrit, headache, upper respiratory infection, anorexia, arthralgias, chest pain, coughing, dysuria, eye discomfort, epistaxis, fever, infection, sweating, tinnitus, and vaginal discharge.

Adverse Reactions in Psoriasis

There are no recent placebo-controlled trials in patients with psoriasis. There are two literature reports (Roenigk, 1969 and Nyfors, 1978) describing large series (n=204, 248) of psoriasis patients treated with methotrexate. Dosages ranged up to 25 mg per week and treatment was administered for up to four years. With the exception of alopecia, photosensitivity, and "burning of skin lesions" (each 3% to 10%), the adverse reaction rates in these reports were very similar to those in the rheumatoid arthritis studies. Rarely, painful plaque erosions may appear (Pearce, HP and Wilson, BB: *Am Acad Dermatol 35:* 835-838, 1996).

Adverse Reactions in JRA Studies

The approximate incidences of adverse reactions reported in pediatric patients with JRA treated with oral, weekly doses of methotrexate (5 to 20 mg/m^2/wk or 0.1 to 0.65 mg/kg/wk) were as follows (virtually all patients were receiving concomitant nonsteroidal anti-inflammatory drugs, and some also were taking low doses of corticosteroids): elevated liver function tests, 14%; gastrointestinal reactions (eg, nausea, vomiting, diarrhea), 11%; stomatitis, 2%; leukopenia, 2%; headache, 1.2%; alopecia, 0.5%; dizziness, 0.2%; and rash, 0.2%. Although there is experience with dosing up to 30 mg/m^2/wk in JRA, the published data for doses above 20 mg/m^2/wk are too limited to provide reliable estimates of adverse reaction rates.

OVERDOSAGE

Leucovorin is indicated to diminish the toxicity and counteract the effect of inadvertently administered overdosages of methotrexate. Leucovorin administration should begin as promptly as possible. As the time interval between methotrexate administration and leucovorin initiation increases, the effectiveness of leucovorin in counteracting toxicity decreases. Monitoring of the serum methotrexate concentration is essential in determining the optimal dose and duration of treatment with leucovorin.

In cases of massive overdosage, hydration and urinary alkalinization may be necessary to prevent the precipitation of methotrexate and/or its metabolites in the renal tubules. Generally speaking, neither hemodialysis nor peritoneal dialysis have been shown to improve methotrexate elimination. However, effective clearance of methotrexate has been reported with acute, intermittent hemodialysis using a high-flux dialyzer (Wall, SM et al: *Am J Kidney Dis* 28(6):846-854, 1996).

Accidental intrathecal overdosage may require intensive systemic support, high-dose systemic leucovorin, alkaline diuresis and rapid CSF drainage and ventriculolumbar perfusion.

In postmarketing experience, overdose with methotrexate has generally occurred with oral and intrathecal administration, although intravenous and intramuscular overdose have also been reported.

Reports of oral overdose often indicate accidental daily administration instead of weekly (single or divided doses). Symptoms commonly reported following oral overdose include those symptoms and signs reported at pharmacologic doses, particularly hematologic and gastrointestinal reaction. For example, leukopenia, thrombocytopenia, anemia, pancytopenia, bone marrow suppression, mucositis, stomatitis, oral ulceration, nausea, vomiting, gastrointestinal ulceration, gastrointestinal bleeding. In some cases, no symptoms were reported. There have been reports of death following overdose. In these cases, events such as sepsis or septic shock, renal failure, and aplastic anemia were also reported.

Symptoms of intrathecal overdose are generally central nervous system (CNS) symptoms, including headache, nausea and vomiting, seizure or convulsion, and acute toxic encephalopathy. In some cases, no symptoms were reported. There have been reports of death following intrathecal overdose. In these cases, cerebellar herniation associated with increased intracranial pressure, and acute toxic encephalopathy have also been reported.

There are published case reports of intravenous and intrathecal carboxypeptidase G2 treatment to hasten clearance of methotrexate in cases of overdose.

DOSAGE AND ADMINISTRATION

Neoplastic Diseases

Oral administration in tablet form is often preferred when low doses are being administered since absorption is rapid and effective serum levels are obtained. Methotrexate sodium for injection may be given by the intramuscular, intravenous, intra-arterial or intrathecal route. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Choriocarcinoma and similar trophoblastic diseases: Methotrexate is administered orally or intramuscularly in doses of 15 to 30 mg daily for a five-day course. Such courses are usually repeated for 3 to 5 times as required, with rest periods of one or more weeks interposed between courses, until any manifesting toxic symptoms subside. The effectiveness of therapy is ordinarily evaluated by 24 hour quantitative analysis of urinary chorionic gonadotropin (hCG), which should return to normal or less than 50 IU/24 hr usually after the third or fourth course and usually be followed by a complete resolution of measurable lesions in 4 to 6 weeks. One to two courses of methotrexate after normalization of hCG is usually recommended. Before each course of the drug careful clinical assessment is essential. Cyclic combination therapy of methotrexate with other antitumor drugs has been reported as being useful.

Since hydatidiform mole may precede choriocarcinoma, prophylactic chemotherapy with methotrexate has been recommended.

Chorioadenoma destruens is considered to be an invasive form of hydatidiform mole. Methotrexate is administered in these disease states in doses similar to those recommended for choriocarcinoma.

Leukemia: Acute lymphoblastic leukemia in pediatric patients and young adolescents is the most responsive to present day chemotherapy. In young adults and older patients, clinical remission is more difficult to obtain and early relapse is more common.

Methotrexate alone or in combination with steroids was used initially for induction of remission in acute lymphoblastic leukemias. More recently corticosteroid therapy, in combination with other antileukemic drugs or in cyclic combinations with methotrexate included, has appeared to produce rapid and effective remissions. When used for induction, methotrexate in doses of 3.3 mg/m^2 in combination with 60 mg/m^2 of prednisone, given daily, produced remissions in 50% of patients treated, usually within a period of 4 to 6 weeks. Methotrexate in combination with other agents appears to be the drug of choice for securing maintenance of drug-induced remissions. When remission is achieved and supportive care has produced general clinical improvement, maintenance therapy is initiated, as follows: Methotrexate is administered 2 times weekly either by mouth or intramuscularly in total weekly doses of 30 mg/m^2. It has also been given in doses of 2.5 mg/kg intravenously every 14 days. If and when relapse does occur, reinduction of remission can again usually be obtained by repeating the initial induction regimen.

A variety of combination chemotherapy regimens have been used for both induction and maintenance therapy in acute lymphoblastic leukemia. The physician should be familiar with the new advances in antileukemic therapy.

Meningeal Leukemia: In the treatment or prophylaxis of meningeal leukemia, methotrexate must be administered intrathecally. Preservative free methotrexate is diluted to a concentration of 1 mg/mL in an appropriate sterile, preservative free medium such as 0.9% Sodium Chloride Injection, USP.

The cerebrospinal fluid volume is dependent on age and not on body surface area. The CSF is at 40% of the adult volume at birth and reaches the adult volume in several years.

Intrathecal methotrexate administration at a dose of 12 mg/m^2 (maximum 15 mg) has been reported to result in low CSF methotrexate concentrations and reduced efficacy in pediatric patients and high concentrations and neurotoxicity in adults. The following dosage regimen is based on age instead of body surface area:

Age (years)	Dose (mg)
< 1	6
1	8
2	10
3 or older	12

In one study in patients under the age of 40, this dosage regimen appeared to result in more consistent CSF methotrexate concentrations and less neurotoxicity. Another study in pediatric patients with acute lymphocytic leukemia compared this regimen to a dose of 12 mg/m^2 (maximum 15 mg), a significant reduction in the rate of CNS relapse was observed in the group whose dose was based on age.

Because the CSF volume and turnover may decrease with age, a dose reduction may be indicated in elderly patients.

For the treatment of meningeal leukemia, intrathecal methotrexate may be given at intervals of 2 to 5 days. However, administration at intervals of less than 1 week may result in increased subacute toxicity. Methotrexate is administered until the cell count of the cerebrospinal fluid returns to normal. At this point one additional dose is advisable. For prophylaxis against meningeal leukemia, the dosage is the same as for treatment except for the intervals of administration. On this subject, it is advisable for the physician to consult the medical literature.

Untoward side effects may occur with any given intrathecal injection and are commonly neurological in character. Large doses may cause convulsions. Methotrexate given by the intrathecal route appears significantly in the systemic circulation and may cause systemic methotrexate toxicity. Therefore, systemic antileukemic therapy with the drug should be appropriately adjusted, reduced, or discontinued. Focal leukemic involvement of the central nervous system may not respond to intrathecal chemotherapy and is best treated with radiotherapy.

Lymphomas: In Burkitt's tumor, Stages I-II, methotrexate has produced prolonged remissions in some cases. Recommended dosage is 10 to 25 mg/day orally for 4 to 8 days. In Stage III, methotrexate is commonly given concomitantly with other antitumor agents. Treatment in all stages usually consists of several courses of the drug interposed with 7 to 10 day rest periods. Lymphosarcomas in Stage III may respond to combined drug therapy with methotrexate given in doses of 0.625 to 2.5 mg/kg daily.

Mycosis Fungoides (cutaneous T cell lymphoma): Therapy with methotrexate as a single agent appears to produce clinical responses in up to 50% of patients treated. Dosage in early stages is usually 5 to 50 mg once weekly. Dose reduction or cessation is guided by patient response and hematologic monitoring. Methotrexate has also been administered twice weekly in doses ranging from 15 to 37.5 mg in patients who have responded poorly to weekly therapy. Combination chemotherapy regimens that include intravenous methotrexate administered at higher doses with leucovorin rescue have been utilized in advanced stages of the disease.

Osteosarcoma: An effective adjuvant chemotherapy regimen requires the administration of several cytotoxic chemotherapeutic agents. In addition to high-dose methotrexate with leucovorin rescue, these agents may include doxorubicin, cisplatin, and the combination of bleomycin, cyclophosphamide and dactinomycin (BCD) in the doses and schedule shown in the table below. The starting dose for high dose methotrexate treatment is 12 grams/m^2. If this dose is not sufficient to produce a peak serum methotrexate concentration of 1,000 micromolar (10^{-3} mol/L) at the end of the methotrexate infusion, the dose may be escalated to 15 grams/m^2 in subsequent treatments. If the patient is vomiting or is unable to tolerate oral medication, leucovorin is given IV or IM at the same dose and schedule.

Drug*	Dose*	Treatment Week After Surgery
Methotrexate	12 g/m^2 IV as 4 hour infusion (starting dose)	4,5,6,7,11,12,15, 16,29,30,44,45
Leucovorin	15 mg orally every six hours for 10 doses starting at 24 hours after start of methotrexate infusion.	
Doxorubicin† as a single drug	30 mg/m^2/day IV x 3 days	8,17
Doxorubicin†	50 mg/m^2 IV	20,23,33,36
Cisplatin†	100 mg/m^2 IV	20,23,33,36
Bleomycin†	15 units/m^2 IV x 2 days	2,13,26,39,42
Cyclophosphamide†	600 mg/m^2 IV x 2 days	2,13,26,39,42
Dactinomycin†	0.6 mg/m^2 IV x 2 days	2,13,26,39,42

*Link MP, Goorin AM, Miser AW, et al: The effect of adjuvant chemotherapy on relapse-free survival in patients with osteosarcoma of the extremity. *N Engl J of Med* 1986; 314(No.25):1600-1606.

†See each respective package insert for full prescribing information. Dosage modifications may be necessary because of drug-induced toxicity.

When these higher doses of methotrexate are to be administered, the following safety guidelines should be closely observed.

GUIDELINES FOR METHOTREXATE THERAPY WITH LEUCOVORIN RESCUE

1. Administration of methotrexate should be delayed until recovery if:

   - the WBC count is less than 1500/microliter
   - the neutrophil count is less than 200/microliter
   - the platelet count is less than 75,000/microliter
   - the serum bilirubin level is greater than 1.2 mg/dL

- the SGPT level is greater than 450 U
- mucositis is present, until there is evidence of healing
- persistent pleural effusion is present; this should be drained dry prior to infusion.

2. Adequate renal function must be documented.

    a. Serum creatinine must be normal, and creatinine clearance must be greater than 60 mL/min, before initiation of therapy.

    b. Serum creatinine must be measured prior to each subsequent course of therapy. If serum creatinine has increased by 50% or more compared to a prior value, the creatinine clearance must be measured and documented to be greater than 60 mL/min (even if the serum creatinine is still within the normal range).

3. Patients must be well hydrated, and must be treated with sodium bicarbonate for urinary alkalinization.

    a. Administer 1,000 mL/m^2 of intravenous fluid over 6 hours prior to initiation of the methotrexate infusion. Continue hydration at 125 mL/m^2/hr (3 liters/m^2/day) during the methotrexate infusion, and for 2 days after the infusion has been completed.

    b. Alkalinize urine to maintain pH above 7.0 during methotrexate infusion and leucovorin calcium therapy. This can be accomplished by the administration of sodium bicarbonate orally or by incorporation into a separate intravenous solution.

4. Repeat serum creatinine and serum methotrexate 24 hours after starting methotrexate and at least once daily until the methotrexate level is below $5x10^{-8}$ mol/L (0.05 micromolar).

5. The table below provides guidelines for leucovorin calcium dosage based upon serum methotrexate levels. (See table below. ‡)

Patients who experience delayed early methotrexate elimination are likely to develop nonreversible oliguric renal failure. In addition to appropriate leucovorin therapy, these patients require continuing hydration and urinary alkalinization, and close monitoring of fluid and electrolyte status, until the serum methotrexate level has fallen to below 0.05 micromolar and the renal failure has resolved. If necessary, acute, intermittent hemodialysis with a high-flux dialyzer may also be beneficial in these patients.

6. Some patients will have abnormalities in methotrexate elimination, or abnormalities in renal function following methotrexate administration, which are significant but less severe than the abnormalities described in the table below. These abnormalities may or may not be associated with significant clinical toxicity. If significant clinical toxicity is observed, leucovorin rescue should be extended for an additional 24 hours (total 14 doses over 84 hours) in subsequent courses of therapy. The possibility that the patient is taking other medications which interact with methotrexate (eg, medications which may interfere with methotrexate binding to serum albumin, or elimination) should always be reconsidered when laboratory abnormalities or clinical toxicities are observed.

CAUTION: DO NOT ADMINISTER LEUCOVORIN INTRATHECALLY.

Psoriasis, Rheumatoid Arthritis, and Juvenile Rheumatoid Arthritis

Adult Rheumatoid Arthritis: Recommended Starting Dosage Schedules

1. Single oral doses of 7.5 mg once weekly. †

2. Divided oral dosages of 2.5 mg at 12 hour intervals for 3 doses given as a course once weekly. †

†Methotrexate Sodium Tablets for oral administration are available.

Polyarticular-Course Juvenile Rheumatoid Arthritis: The recommended starting dose is 10 mg/m^2 given once weekly.

For either adult RA or polyarticular-course JRA dosages may be adjusted gradually to achieve an optimal response. Limited experience shows a significant increase in the incidence and severity of serious toxic reactions, especially bone marrow suppression, at doses greater than 20 mg/wk in adults. Although there is experience with doses up to 30 mg/m^2/wk in children, there are too few published data to assess how doses over 20 mg/m^2/wk might affect the risk of serious toxicity in children. Experience does suggest, however, that children receiving 20 to 30 mg/m^2/wk (0.65 to 1.0 mg/kg/wk) may have better absorption and fewer gastrointestinal side effects if methotrexate is administered either intramuscularly or subcutaneously.

Therapeutic response usually begins within 3 to 6 weeks and the patient may continue to improve for another 12 weeks or more.

The optimal duration of therapy is unknown. Limited data available from long-term studies in adults indicate that the initial clinical improvement is maintained for at least two years with continued therapy. When methotrexate is discontinued, the arthritis usually worsens within 3 to 6 weeks.

The patient should be fully informed of the risks involved and should be under constant supervision of the physician. (See **Information for Patients** under **PRECAUTIONS**.) Assessment of hematologic, hepatic, renal, and pulmonary function should be made by history, physical examination, and laboratory tests before beginning, periodically during, and before reinstituting methotrexate therapy. (See **PRECAUTIONS**.) Appropriate steps should be taken to avoid conception during methotrexate therapy. (See **PRECAUTIONS** and **CONTRAINDICATIONS**.)

All schedules should be continually tailored to the individual patient. An initial test dose may be given prior to the regular dosing schedule to detect any extreme sensitivity to adverse effects. (See **ADVERSE REACTIONS**.) Maximal myelosuppression usually occurs in seven to ten days.

Psoriasis: Recommended Starting Dose Schedules

1. Weekly single oral, IM or IV dose schedule: 10 to 25 mg per week until adequate response is achieved. †

2. Divided oral dose schedule: 2.5 mg at 12-hour intervals for three doses. †

†Methotrexate Sodium Tablets for oral administration are available.

Dosages in each schedule may be gradually adjusted to achieve optimal clinical response; 30 mg/week should not ordinarily be exceeded.

Once optimal clinical response has been achieved, each dosage schedule should be reduced to the lowest possible amount of drug and to the longest possible rest period. The use of methotrexate may permit the return to conventional topical therapy, which should be encouraged.

HANDLING AND DISPOSAL

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

RECONSTITUTION OF LYOPHILIZED POWDERS

Reconstitute immediately prior to use.

Methotrexate Sodium for Injection should be reconstituted with an appropriate sterile, preservative free medium such as 5% Dextrose Solution, USP, or Sodium Chloride Injection, USP. Reconstitute the 20 mg vial to a concentration no greater than 25 mg/mL. **The 1 gram vial should be reconstituted with 19.4 mL to a concentration of 50 mg/mL.** When high doses of methotrexate are administered by IV infusion, the total dose is diluted in 5% Dextrose Solution.

For intrathecal injection, reconstitute to a concentration of 1 mg/mL with an appropriate sterile, preservative free medium such as Sodium Chloride Injection, USP.

HOW SUPPLIED

Parenteral:

Methotrexate Sodium for Injection, Lyophilized, Preservative Free, for Single Use Only. Each 20 mg and 1 g vial of lyophilized powder contains methotrexate sodium equivalent to 20 mg and 1 g methotrexate respectively.

20 mg Vial – NDC 66479-137-21
1 g Vial – NDC 66479-139-29

Store at controlled room temperature, 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F). PROTECT FROM LIGHT.

XANODYNE

Manufactured for
Xanodyne Pharmacal, Inc.
Florence, KY 41042
by
LEDERLE PARENTERALS, INC.
Carolina, Puerto Rico 00987

W10456C002
ET02
Rev 10/03

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‡LEUCOVORIN RESCUE SCHEDULES FOLLOWING TREATMENT WITH HIGHER DOSES OF METHOTREXATE

Clinical Situation	Laboratory Findings	Leucovorin Dosage and Duration
Normal Methotrexate Elimination	Serum methotrexate level approximately 10 micromolar at 24 hours after administration, 1 micromolar at 48 hours, and less than 0.2 micromolar at 72 hours.	15 mg PO, IM or IV q 6 hours for 60 hours (10 doses starting at 24 hours after start of methotrexate infusion).
Delayed Late Methotrexate Elimination	Serum methotrexate level remaining above 0.2 micromolar at 72 hours, and more than 0.05 micromolar at 96 hours after administration.	Continue 15 mg PO, IM or IV q six hours, until methotrexate level is less than 0.05 micromolar.
Delayed Early Methotrexate Elimination and/or Evidence of Acute Renal Injury	Serum methotrexate level of 50 micromolar or more at 24 hours, or 5 micromolar or more at 48 hours after administration, OR; a 100% or greater increase in serum creatinine level at 24 hours after methotrexate administration (eg, an increase from 0.5 mg/dL to a level of 1 mg/dL or more).	150 mg IV q three hours, until methotrexate level is less than 1 micromolar; then 15 mg IV q three hours, until methotrexate level is less than 0.05 micromolar.

WARNINGS

METHOTREXATE SHOULD BE USED ONLY BY PHYSICIANS WHOSE KNOWLEDGE AND EXPERIENCE INCLUDE THE USE OF ANTIMETABOLITE THERAPY.
BECAUSE OF THE POSSIBILITY OF SERIOUS TOXIC REACTIONS (WHICH CAN BE FATAL):

METHOTREXATE SHOULD BE USED ONLY IN LIFE THREATENING NEOPLASTIC DISEASES, OR IN PATIENTS WITH PSORIASIS OR RHEUMATOID ARTHRITIS WITH SEVERE, RECALCITRANT, DISABLING DISEASE WHICH IS NOT ADEQUATELY RESPONSIVE TO OTHER FORMS OF THERAPY.

DEATHS HAVE BEEN REPORTED WITH THE USE OF METHOTREXATE IN THE TREATMENT OF MALIGNANCY, PSORIASIS, AND RHEUMATOID ARTHRITIS.

PATIENTS SHOULD BE CLOSELY MONITORED FOR BONE MARROW, LIVER, LUNG AND KIDNEY TOXICITIES. (See **PRECAUTIONS**).

PATIENTS SHOULD BE INFORMED BY THEIR PHYSICIAN OF THE RISKS INVOLVED AND BE UNDER A PHYSICIAN'S CARE THROUGHOUT THERAPY.

THE USE OF METHOTREXATE HIGH DOSE REGIMENS RECOMMENDED FOR OSTEOSARCOMA REQUIRES METICULOUS CARE. (See **DOSAGE AND ADMINISTRATION**.) HIGH DOSE REGIMENS FOR OTHER NEOPLASTIC DISEASES ARE INVESTIGATIONAL AND A THERAPEUTIC ADVANTAGE HAS NOT BEEN ESTABLISHED. METHOTREXATE FORMULATIONS AND DILUENTS CONTAINING PRESERVATIVES MUST NOT BE USED FOR INTRATHECAL OR HIGH DOSE METHOTREXATE THERAPY.

1. Methotrexate has been reported to cause fetal death and/or congenital anomalies.Therefore, it is not recommended for women of childbearing potential unless there is clear medical evidence that the benefits can be expected to outweigh the considered risks. Pregnant women with psoriasis or rheumatoid arthritis should not receive methotrexate. (See **CONTRAINDICATIONS**).
2. Methotrexate elimination is reduced in patients with impaired renal functions, ascites, or pleural effusions. Such patients require especially careful monitoring for toxicity, and require dose reduction or, in some cases, discontinuation of methotrexate administration.
3. Unexpectedly severe (sometimes fatal) bone marrow suppression, aplastic anemia, and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high dosage) along with some nonsteroidal anti-inflammatory drugs (NSAIDs). (See **PRECAUTIONS**, **Drug Interactions**).
4. Methotrexate causes hepatotoxicity, fibrosis and cirrhosis, but generally only after prolonged use. Acutely, liver enzyme elevations are frequently seen. These are usually transient and asymptomatic, and also do not appear predictive of subsequent hepatic disease. Liver biopsy after sustained use often shows histologic changes, and fibrosis and cirrhosis have been reported; these latter lesions may not be preceded by symptoms or abnormal liver function tests in the psoriasis population. For this reason, periodic liver

biopsies are usually recommended for psoriatic patients who are under long-term treatment. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid arthritis population. (See **PRECAUTIONS**, **Organ System Toxicity**, *Hepatic*).

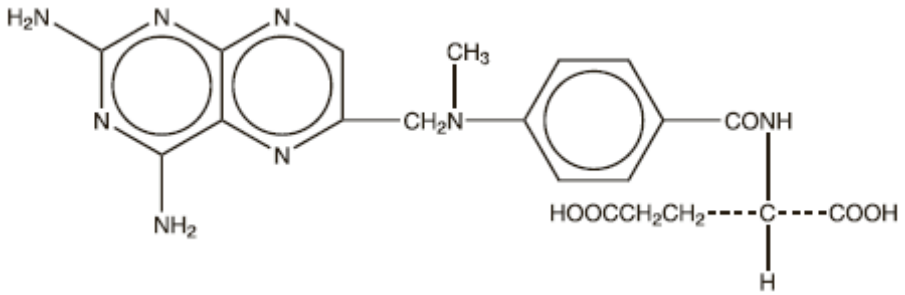
5. Methotrexate-induced lung disease, including acute or chronic interstitial pneumonitis, is a potentially dangerous lesion, which may occur acutely at any time during therapy and has been reported at low doses. It is not always fully reversible and fatalities have been reported. Pulmonary symptoms (especially a dry, nonproductive cough) may require interruption of treatment and careful investigation.
6. Diarrhea and ulcerative stomatitis require interruption of therapy: otherwise, hemorrhagic enteritis and death from intestinal perforation may occur.
7. Malignant lymphomas, which may regress following withdrawal of methotrexate, may occur in patients receiving low-dose methotrexate and, thus, may not require cytotoxic treatment. Discontinue methotrexate first and, if the lymphoma does not regress, appropriate treatment should be instituted.
8. Like other cytotoxic drugs, methotrexate may induce "tumor lysis syndrome" in patients with rapidly growing tumors. Appropriate supportive and pharmacologic measures may prevent or alleviate this complication.
9. Severe, occasionally fatal, skin reactions have been reported following single or multiple doses of methotrexate. Reactions have occurred within days of oral, intramuscular, intravenous, or intrathecal methotrexate administration. Recovery has been reported with discontinuation of therapy. (See **PRECAUTIONS, Organ System Toxicity,** *Skin*.)
10. Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy.
11. Methotrexate given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.

DESCRIPTION

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

Chemically methotrexate is *N*-[4-[[(2,4-diamino-6-pteridinyl) methyl]methylamino]benzoyl]-L-glutamic acid.

The structural formula is:



Molecular weight: 454.45 $C_{20}H_{22}N_8O_5$

Methotrexate Injection, USP is sterile and non-pyrogenic and may be given by the intramuscular, intravenous or intra-arterial route. (See **DOSAGE AND ADMINISTRATION.**) ***However, the***

preserved formulation contains Benzyl Alcohol and must not be used for intrathecal or high dose therapy.

Methotrexate Injection, USP Isotonic Liquid, Contains Preservative is available in 25 mg/mL, 2 mL (50 mg) vials.

Each 25 mg/mL, 2 mL vial contains methotrexate sodium equivalent to 50 mg methotrexate, 0.9% w/v of Benzyl Alcohol as a preservative, and the following inactive ingredients: Sodium Chloride 0.260% w/v and Water for Injection qs ad 100% v. Sodium Hydroxide and, if necessary, Hydrochloric Acid are added to adjust the pH to approximately 8.5.

Methotrexate Injection, USP, Isotonic Liquid, Preservative Free, for single use only, is available in 10 mg/mL, 2 mL (20 mg) vials and 25 mg/mL, 20 mL (500 mg), 40 mL (1 g) and 100 mL (2.5 g) vials.

Each 10 mg/mL, 2 mL vial contains methotrexate sodium equivalent to 20 mg methotrexate, and the following inactive ingredients: Sodium Chloride 0.70% w/v. Sodium Hydroxide and, if necessary, Hydrochloric Acid are added to adjust the pH to approximately 8.5.

Each 25 mg/mL, 20 mL, 40 mL and 100 mL vial contains methotrexate sodium equivalent to 500 mg, 1 g and 2.5 g methotrexate, respectively, and the following inactive ingredients: Sodium Chloride 0.490% w/v. Sodium Hydroxide and, if necessary, Hydrochloric Acid are added to adjust the pH to approximately 8.5.

CLINICAL PHARMACOLOGY

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.

The mechanism of action in rheumatoid arthritis is unknown; it may affect immune function. Two reports describe *in vitro* methotrexate inhibition of DNA precursor uptake by stimulated mononuclear cells, and another describes in animal polyarthritis partial correction by methotrexate of spleen cell hyporesponsiveness and suppressed IL 2 production. Other laboratories, however, have been unable to demonstrate similar effects. Clarification of methotrexate's effect on immune activity and its relation to rheumatoid immunopathogenesis await further studies.

In patients with rheumatoid arthritis, effects of methotrexate on articular swelling and tenderness can be seen as early as 3 to 6 weeks. Although methotrexate clearly ameliorates symptoms of inflammation (pain, swelling, stiffness), there is no evidence that it induces remission of rheumatoid arthritis nor has a beneficial effect been demonstrated on bone erosions and other radiologic changes which result in impaired joint use, functional disability, and deformity.

Most studies of methotrexate in patients with rheumatoid arthritis are relatively short term (3 to 6 months). Limited data from long-term studies indicate that an initial clinical improvement is maintained for at least two years with continued therapy.

In psoriasis, the rate of production of epithelial cells in the skin is greatly increased over normal skin. This differential in proliferation rates is the basis for the use of methotrexate to control the psoriatic process.

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.

In a 6-month double-blind, placebo-controlled trial of 127 pediatric patients with juvenile rheumatoid arthritis (JRA) (mean age, 10.1 years; age range, 2.5 to 18 years; mean duration of disease, 5.1 years) on background nonsteroidal anti-inflammatory drugs (NSAIDs) and/or prednisone, methotrexate given weekly at an oral dose of 10 mg/m^2 provided significant clinical improvement compared to placebo as measured by either the physician's global assessment, or by a patient composite (25% reduction in the articular-severity score plus improvement in parent and physician global assessments of disease activity). Over two-thirds of the patients in this trial had polyarticular-course JRA, and the numerically greatest response was seen in this subgroup treated with 10 mg/m^2/wk methotrexate. The overwhelming majority of the remaining patients had systemic-course JRA. All patients were unresponsive to NSAIDs; approximately one-third were using low dose corticosteroids. Weekly methotrexate at a dose of 5 mg/m^2 was not significantly more effective than placebo in this trial.

Two Pediatric Oncology Group studies (one randomized and one non-randomized) demonstrated a significant improvement in relapse-free survival in patients with nonmetastatic osteosarcoma, when high dose methotrexate with leucovorin rescue was used in combination with other chemotherapeutic agents following surgical resection of the primary tumor. These studies were not designed to demonstrate the specific contribution of high dose methotrexate/leucovorin rescue therapy to the efficacy of the combination. However, a contribution can be inferred from the reports of objective responses to this therapy in patients with metastatic osteosarcoma, and from reports of extensive tumor necrosis following preoperative administration of this therapy to patients with non-metastatic osteosarcoma.

Pharmacokinetics

Absorption- In adults, oral absorption appears to be dose dependent. Peak serum levels are reached within one to two hours. At doses of 30 mg/m^2 or less, methotrexate is generally well absorbed with a mean bioavailability of about 60%. The absorption of doses greater than 80 mg/m^2 is significantly less, possibly due to a saturation effect.

In leukemic pediatric patients, oral absorption of methotrexate also appears to be dose dependent and has been reported to vary widely (23% to 95%). A twenty fold difference between highest and lowest peak levels (C_{max}: 0.11 to 2.3 micromolar after a 20 mg/m^2 dose) has been reported. Significant interindividual variability has also been noted in time to peak concentration (T_{max}: 0.67 to 4 hrs after a 15 mg/m^2 dose) and fraction of dose absorbed. The absorption of doses greater than 40 mg/m^2 has been reported to be significantly less than that of lower doses. Food has been shown to delay absorption and reduce peak concentration. Methotrexate is generally completely absorbed from parenteral routes of injection. After intramuscular injection, peak

serum concentrations occur in 30 to 60 minutes. As in leukemic pediatric patients, a wide interindividual variability in the plasma concentrations of methotrexate has been reported in pediatric patients with JRA. Following oral administration of methotrexate in doses of 6.4 to 11.2 mg/m^2/week in pediatric patients with JRA, mean serum concentrations were 0.59 micromolar (range, 0.03 to 1.40) at 1 hour, 0.44 micromolar (range, 0.01 to 1.00) at 2 hours, and 0.29 micromolar (range, 0.06 to 0.58) at 3 hours. In pediatric patients receiving methotrexate for acute lymphocytic leukemia (6.3 to 30 mg/m^2), or for JRA (3.75 to 26.2 mg/m^2), the terminal half-life has been reported to range from 0.7 to 5.8 hours or 0.9 to 2.3 hours, respectively.

Distribution- After intravenous administration, the initial volume of distribution is approximately 0.18 L/kg (18% of body weight) and steady-state volume of distribution is approximately 0.4 to 0.8 L/kg (40 to 80% of body weight). Methotrexate competes with reduced folates for active transport across cell membranes by means of a single carrier-mediated active transport process. At serum concentrations greater than 100 micromolar, passive diffusion becomes a major pathway by which effective intracellular concentrations can be achieved. Methotrexate in serum is approximately 50% protein bound. Laboratory studies demonstrate that it may be displaced from plasma albumin by various compounds including sulfonamides, salicylates, tetracyclines, chloramphenicol, and phenytoin.

Methotrexate does not penetrate the blood-cerebrospinal fluid barrier in therapeutic amounts when given orally or parenterally. High CSF concentrations of the drug may be attained by intrathecal administration.

In dogs, synovial fluid concentrations after oral dosing were higher in inflamed than uninflamed joints. Although salicylates did not interfere with this penetration, prior prednisone treatment reduced penetration into inflamed joints to the level of normal joints.

Metabolism- After absorption, methotrexate undergoes hepatic and intracellular metabolism to polyglutamated forms which can be converted back to methotrexate by hydrolase enzymes. These polyglutamates act as inhibitors of dihydrofolate reductase and thymidylate synthetase. Small amounts of methotrexate polyglutamates may remain in tissues for extended periods. The retention and prolonged drug action of these active metabolites vary among different cells, tissues and tumors. A small amount of metabolism to 7-hydroxymethotrexate may occur at doses commonly prescribed. Accumulation of this metabolite may become significant at the high doses used in osteogenic sarcoma. The aqueous solubility of 7-hydroxymethotrexate is 3 to 5 fold lower than the parent compound. Methotrexate is partially metabolized by intestinal flora after oral administration.

Half-Life - The terminal half-life reported for methotrexate is approximately three to ten hours for patients receiving treatment for psoriasis, or rheumatoid arthritis or low dose antineoplastic therapy (less than 30 mg/m^2). For patients receiving high doses of methotrexate, the terminal half-life is eight to 15 hours.

Excretion - Renal excretion is the primary route of elimination and is dependent upon dosage and route of administration. With IV administration, 80% to 90% of the administered dose is excreted unchanged in the urine within 24 hours. There is limited biliary excretion amounting to 10% or less of the administered dose. Enterohepatic recirculation of methotrexate has been proposed.

Renal excretion occurs by glomerular filtration and active tubular secretion. Nonlinear elimination due to saturation of renal tubular reabsorption has been observed in psoriatic patients at doses between 7.5 and 30 mg. Impaired renal function, as well as concurrent use of drugs such as weak organic acids that also undergo tubular secretion, can markedly increase methotrexate serum levels. Excellent correlation has been reported between methotrexate clearance and endogenous creatinine clearance.

Methotrexate clearance rates vary widely and are generally at higher doses. Delayed drug clearance has been identified as one of the major factors responsible for methotrexate toxicity. It has been postulated that the toxicity of methotrexate for normal tissues is more dependent upon the duration of exposure to the drug rather than the peak level achieved. When a patient has delayed drug elimination due to compromised renal function, a third space effusion, or other causes, methotrexate serum concentrations may remain elevated for prolonged periods.

The potential for toxicity from high dose regimens or delayed excretion is reduced by the administration of leucovorin calcium during the final phase of methotrexate plasma elimination.

Pharmacokinetic monitoring of methotrexate serum concentrations may help identify those patients at high risk for methotrexate toxicity and aid in proper adjustments of leucovorin dosing. Guidelines for monitoring serum methotrexate levels, and for adjustment of leucovorin dosing to reduce the risk of methotrexate toxicity, are provided below in **DOSAGE AND ADMINISTRATION**.

Methotrexate has been detected in human breast milk. The highest breast milk to plasma concentration ratio reached was 0.08:1.

INDICATIONS AND USAGE

Neoplastic Diseases

Methotrexate is indicated in the treatment of 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.

Psoriasis

Methotrexate is indicated in the symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy, *but only when the diagnosis has been established, as by biopsy and/or after dermatologic consultation.* It is important to ensure that a psoriasis “flare” is not due to an undiagnosed concomitant disease affecting immune responses.

Rheumatoid Arthritis including Polyarticular-Course Juvenile Rheumatoid Arthritis
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 non-steroidal anti-inflammatory agents (NSAIDs).

Aspirin, (NSAIDs), and/or low dose steroids may be continued, although the possibility of increased toxicity with concomitant use of NSAIDs including salicylates has not been fully explored. (See **PRECAUTIONS, Drug Interactions**.) Steroids may be reduced gradually in patients who respond to methotrexate. Combined use of methotrexate with gold, penicillamine, hydroxychloroquine, sulfasalazine, or cytotoxic agents, has not been studied and may increase the incidence of adverse effects. Rest and physiotherapy as indicated should be continued.

CONTRAINDICATIONS

Methotrexate can cause fetal death or teratogenic effects when administered to a pregnant woman. Methotrexate is contraindicated in pregnant women with psoriasis or rheumatoid arthritis and should be used in the treatment of neoplastic diseases only when the potential benefit outweighs the risk to the fetus. Women of childbearing potential should not be started on methotrexate until pregnancy is excluded and should be fully counseled on the serious risk to the fetus (see **PRECAUTIONS**) should they become pregnant while undergoing treatment. Pregnancy should be avoided if either partner is receiving methotrexate; during and for a minimum of three months after therapy for male patients, and during and for at least one ovulatory cycle after therapy for female patients. (See Boxed **WARNINGS**).

Because of the potential for serious adverse reactions from methotrexate in breast fed infants, it is contraindicated in nursing mothers.

Patients with psoriasis or rheumatoid arthritis with alcoholism, alcoholic liver disease or other chronic liver disease should not receive methotrexate.

Patients with psoriasis or rheumatoid arthritis who have overt or laboratory evidence of immunodeficiency syndromes should not receive methotrexate.

Patients with psoriasis or rheumatoid arthritis who have preexisting blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anemia, should not receive methotrexate.

Patients with a known hypersensitivity to methotrexate should not receive the drug.

WARNINGS - SEE BOXED WARNINGS.

Use caution when administering high-dose methotrexate to patients receiving proton pump inhibitor (PPI) therapy. Case reports and published population pharmacokinetic studies suggest that concomitant use of some PPIs, such as omeprazole, esomeprazole, and pantoprazole, with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate, possibly leading to methotrexate toxicities. In two of these cases, delayed methotrexate elimination was observed when high-dose methotrexate was co-administered with PPIs, but was not observed when methotrexate was co-administered with ranitidine. However, no formal drug interaction studies of methotrexate with ranitidine have been conducted.

Methotrexate formulations and diluents containing preservatives must not be used for intrathecal or high dose methotrexate therapy.

PRECAUTIONS

General

Methotrexate has the potential for serious toxicity (See Boxed **WARNINGS**). Toxic effects may be related in frequency and severity to dose or frequency of administration but have been seen at all doses. Because they can occur at any time during therapy, it is necessary to follow patients on methotrexate closely. Most adverse reactions are reversible if detected early. When such reactions do occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken. If necessary, this could include the use of leucovorin calcium and/or acute, intermittent hemodialysis with a high-flux dialyzer. (See **OVERDOSAGE**). If methotrexate therapy is reinstituted, it should be carried out with caution, with adequate consideration of further need for the drug and increased alertness as to possible recurrence of toxicity.

The clinical pharmacology of methotrexate has not been well studied in older individuals. Due to diminished hepatic and renal function as well as decreased folate stores in this population, relatively low doses should be considered, and these patients should be closely monitored for early signs of toxicity.

Some of the effects mentioned under **ADVERSE REACTIONS**, such as dizziness and fatigue, may affect the ability to drive or operate machinery.

Information for Patients

Patients should be informed of the early signs and symptoms of toxicity, of the need to see their physician promptly if they occur, and the need for close follow-up, including periodic laboratory tests to monitor toxicity.

Both the physician and pharmacist should emphasize to the patient that the recommended dose is taken weekly in rheumatoid arthritis and psoriasis, and that mistaken daily use of the recommended dose has led to fatal toxicity. Prescriptions should not be written or refilled on a PRN basis.

Patients should be informed of the potential benefit and risk in the use of methotrexate. The risk of effects on reproduction should be discussed with both male and female patients taking methotrexate.

Laboratory Tests

Patients undergoing methotrexate therapy should be closely monitored so that toxic effects are detected promptly. Baseline assessment should include a complete blood count with differential and platelet counts, hepatic enzymes, renal function tests and a chest X-ray. During therapy of rheumatoid arthritis and psoriasis, monitoring of these parameters is recommended: hematology at least monthly, renal function and liver function every 1 to 2 months. More frequent monitoring is usually indicated during antineoplastic therapy. *During initial or changing doses*, or during periods of increased risk of elevated methotrexate blood levels (e.g., dehydration), more frequent monitoring may also be indicated.

Transient liver function test abnormalities are observed frequently after methotrexate administration and are usually not cause for modification of methotrexate therapy. Persistent

liver function test abnormalities, and/or depression of serum albumin may be indicators of serious liver toxicity and require evaluation. (See **PRECAUTIONS, Organ System Toxicity,** *Hepatic*).

A relationship between abnormal liver function tests and fibrosis or cirrhosis of the liver has not been established for patients with psoriasis. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid arthritis population.

Pulmonary function tests may be useful if methotrexate-induced lung disease is suspected, especially if baseline measurements are available.

Drug Interactions

Nonsteroidal anti-inflammatory drugs should not be administered prior to or concomitantly with the high doses of methotrexate, such as used in the treatment of osteosarcoma. Concomitant administration of some NSAIDs with high dose methotrexate therapy has been reported to elevate and prolong serum methotrexate levels, resulting in deaths from severe hematologic and gastrointestinal toxicity.

Caution should be used when NSAIDs and salicylates are administered concomitantly with lower doses of methotrexate. These drugs have been reported to reduce the tubular secretion of methotrexate in an animal model and may enhance its toxicity.

Despite the potential interactions, studies of methotrexate in patients with rheumatoid arthritis have usually included concurrent use of constant dosage regimens of NSAIDs, without apparent problems. It should be appreciated, however, that the doses used in rheumatoid arthritis (7.5 to 15 mg/week) are somewhat lower than those used in psoriasis and that larger doses could lead to unexpected toxicity.

Methotrexate is partially bound to serum albumin, and toxicity may be increased because of displacement by certain drugs, such as salicylates, phenylbutazone, phenytoin, and sulfonamides. Renal tubular transport is also diminished by probenecid; use of methotrexate with this drug should be carefully monitored.

In the treatment of patients with osteosarcoma, caution must be exercised if high-dose methotrexate is administered in combination with a potentially nephrotoxic chemotherapeutic agent (e.g., cisplatin).

Methotrexate increases the plasma levels of mercaptopurine. The combination of methotrexate and mercaptopurine may therefore require dose adjustment.

Oral antibiotics such as tetracycline, chloramphenicol, and nonabsorbable broad spectrum antibiotics, may decrease intestinal absorption of methotrexate or interfere with the enterohepatic circulation by inhibiting bowel flora and suppressing metabolism of the drug by bacteria.

Penicillins may reduce the renal clearance of methotrexate; increased serum concentrations of methotrexate with concomitant hematologic and gastrointestinal toxicity have been observed with high and low dose methotrexate. Use of methotrexate with penicillins should be carefully monitored.

The potential for increased hepatotoxicity when methotrexate is administered with other hepatotoxic agents has not been evaluated. However, hepatotoxicity has been reported in such cases. Therefore, patients receiving concomitant therapy with methotrexate and other potential

hepatotoxins (e.g., azathioprine, retinoids, sulfasalazine) should be closely monitored for possible increased risk of hepatotoxicity.

Methotrexate may decrease the clearance of theophylline; theophylline levels should be monitored when used concurrently with methotrexate.

Vitamin preparations containing folic acid or its derivatives may decrease responses to systemically administered methotrexate. Preliminary animal and human studies have shown that small quantities of intravenously administered leucovorin enter the CSF primarily as 5-methyltetrahydrofolate and, in humans, remain 1 to 3 orders of magnitude lower than the usual methotrexate concentrations following intrathecal administration. However, high doses of leucovorin may reduce the efficacy of intrathecally administered methotrexate.

Folate deficiency states may increase methotrexate toxicity. Trimethoprim/sulfamethoxazole has been reported rarely to increase bone marrow suppression in patients receiving methotrexate, probably by decreased tubular secretion and/or an additive antifolate effect.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No controlled human data exist regarding the risk of neoplasia with methotrexate. Methotrexate has been evaluated in a number of animal studies for carcinogenic potential with inconclusive results. Although there is evidence that methotrexate causes chromosomal damage to animal somatic cells and human bone marrow cells, the clinical significance remains uncertain. Non-Hodgkin's lymphoma and other tumors have been reported in patients receiving low-dose oral methotrexate. However, there have been instances of malignant lymphoma arising during treatment with low-dose oral methotrexate, which have regressed completely following withdrawal of methotrexate, without requiring active anti-lymphoma treatment. Benefits should be weighed against the potential risk before using methotrexate alone or in combination with other drugs, especially in pediatric patients or young adults. Methotrexate causes embryotoxicity, abortion, and fetal defects in humans. It has also been reported to cause impairment of fertility, oligospermia and menstrual dysfunction in humans, during and for a short period after cessation of therapy.

Pregnancy
Psoriasis and rheumatoid arthritis: Methotrexate is in Pregnancy Category X. See **CONTRAINDICATIONS**.

Nursing Mothers
See **CONTRAINDICATIONS**.

Pediatric Use
Safety and effectiveness in pediatric patients have been established only in cancer chemotherapy and in polyarticular-course juvenile rheumatoid arthritis.

Published clinical studies evaluating the use of methotrexate in children and adolescents (i.e., patients 2 to 16 years of age) with JRA demonstrated safety comparable to that observed in adults with rheumatoid arthritis (see **CLINICAL PHARMACOLOGY, ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**.)

Methotrexate injectable formulations containing the preservative benzyl alcohol are not recommended for use in neonates. There have been reports of fatal 'gasping syndrome' in neonates (children less than one month of age) following the administrations of intravenous

solutions containing the preservative benzyl alcohol. Symptoms include a striking onset of gasping respiration, hypotension, bradycardia, and cardiovascular collapse.

Serious neurotoxicity, frequently manifested as generalized or focal seizures, has been reported with unexpectedly increased frequency among pediatric patients with acute lymphoblastic leukemia who were treated with intermediate-dose intravenous methotrexate (1 gm/m^2). (See **PRECAUTIONS, Organ System Toxicity**, *Neurologic*).

Geriatric Use
Clinical studies of methotrexate did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious reflecting the greater frequency of decreased hepatic and renal function, decreased folate stores, concomitant disease or other drug therapy (i.e., that interfere with renal function, methotrexate or folate metabolism) in this population (See **PRECAUTIONS, Drug Interactions**). Since decline in renal function may be associated with increases in adverse events and serum creatinine measurements may over estimate renal function in the elderly, more accurate methods (i.e., creatinine clearance) should be considered. Serum methotrexate levels may also be helpful. Elderly patients should be closely monitored for early signs of hepatic, bone marrow and renal toxicity. In chronic use situations, certain toxicities may be reduced by folate supplementation. Post-marketing experience suggests that the occurrence of bone marrow suppression, thrombocytopenia, and pneumonitis may increase with age. See Boxed **WARNINGS** and **ADVERSE REACTIONS**.

Organ System Toxicity
Gastrointestinal: If vomiting, diarrhea, or stomatitis occur, which may result in dehydration, methotrexate should be discontinued until recovery occurs. Methotrexate should be used with extreme caution in the presence of peptic ulcer disease or ulcerative colitis.

Hematologic: Methotrexate can suppress hematopoiesis and cause anemia, aplastic anemia, pancytopenia, leukopenia, neutropenia, and/or thrombocytopenia. In patients with malignancy and preexisting hematopoietic impairment, the drug should be used with caution, if at all. In controlled clinical trials in rheumatoid arthritis (n=128), leukopenia (WBC <3000/mm^3) was seen in 2 patients, thrombocytopenia (platelets <100,000/mm^3) in 6 patients, and pancytopenia in 2 patients.

In psoriasis and rheumatoid arthritis, methotrexate should be stopped immediately if there is a significant drop in blood counts. In the treatment of neoplastic diseases, methotrexate should be continued only if the potential benefit warrants the risk of severe myelosuppression. Patients with profound granulocytopenia and fever should be evaluated immediately and usually require parenteral broad-spectrum antibiotic therapy.

Hepatic: Methotrexate has the potential for acute (elevated transaminases) and chronic (fibrosis and cirrhosis) hepatotoxicity. Chronic toxicity is potentially fatal; it generally has occurred after prolonged use (generally two years or more) and after a total dose of at least 1.5 grams. In studies in psoriatic patients, hepatotoxicity appeared to be a function of total cumulative dose and appeared to be enhanced by alcoholism, obesity, diabetes and advanced age. An accurate incidence rate has not been determined; the rate of progression and reversibility of lesions is not known. Special caution is indicated in the presence of preexisting liver damage or impaired hepatic function.

In psoriasis, liver function tests, including serum albumin, should be performed periodically prior to dosing but are often normal in the face of developing fibrosis or cirrhosis. These lesions may be detectable only by biopsy. The usual recommendation is to obtain a liver biopsy at 1) pretherapy or shortly after initiation of therapy (2 to 4 months), 2) a total cumulative dose of 1.5 grams, and 3) after each additional 1.0 to 1.5 grams. Moderate fibrosis or any cirrhosis normally leads to discontinuation of the drug; mild fibrosis normally suggests a repeat biopsy in 6 months. Milder histologic findings such as fatty change and low grade portal inflammation, are relatively common pretherapy. Although these mild changes are usually not a reason to avoid or discontinue methotrexate therapy, the drug should be used with caution.

In rheumatoid arthritis, age at first use of methotrexate and duration of therapy have been reported as risk factors for hepatotoxicity; other risk factors, similar to those observed in psoriasis, may be present in rheumatoid arthritis but have not been confirmed to date. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in this population. There is a combined reported experience in 217 rheumatoid arthritis patients with liver biopsies both before and during treatment (after a cumulative dose of at least 1.5 g) and in 714 patients with a biopsy only during treatment. There are 64 (7%) cases of fibrosis and 1 (0.1%) case of cirrhosis. Of the 64 cases of fibrosis, 60 were deemed mild. The reticulin stain is more sensitive for early fibrosis and its use may increase these figures. It is unknown whether even longer use will increase these risks.

Liver function tests should be performed at baseline at 4 to 8 week intervals in patients receiving methotrexate for rheumatoid arthritis. Pretreatment liver biopsy should be performed for patients with a history of excessive alcohol consumption, persistently abnormal baseline liver function test values or chronic hepatitis B or C infection. During therapy, liver biopsy should be performed if there are persistent liver function test abnormalities or there is a decrease in serum albumin below the normal range (in the setting of well controlled rheumatoid arthritis).

If the results of a liver biopsy show mild changes (Roenigk, grades I, II, IIIa), methotrexate may be continued and the patient monitored as per recommendations listed above. Methotrexate should be discontinued in any patient who displays persistently abnormal liver function tests and refuses liver biopsy or in any patient whose liver biopsy shows moderate to severe changes (Roenigk grade IIIb or IV).

Infection or Immunologic States: Methotrexate should be used with extreme caution in the presence of active infection, and is usually contraindicated in patients with overt or laboratory evidence of immunodeficiency syndromes. Immunization may be ineffective when given during methotrexate therapy. Immunization with live virus vaccines is generally not recommended. There have been reports of disseminated vaccinia infections after smallpox immunizations in patients receiving methotrexate therapy. Hypogammaglobulinemia has been reported rarely.

Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy. When a patient presents with pulmonary symptoms, the possibility of *Pneumocystis carinii* pneumonia should be considered.

Neurologic: There have been reports of leukoencephalopathy following intravenous administration of methotrexate to patients who have had craniospinal irradiation. Serious neurotoxicity, frequently manifested as generalized or focal seizures, has been reported with unexpectedly increased frequency among pediatric patients with acute lymphoblastic leukemia who were treated with intermediate-dose intravenous methotrexate (1 gm/m^2). Symptomatic

patients were commonly noted to have leukoencephalopathy and/or microangiopathic calcifications on diagnostic imaging studies. Chronic leukoencephalopathy has also been reported in patients who received repeated doses of high-dose methotrexate with leucovorin rescue even without cranial irradiation. Discontinuation of methotrexate does not always result in complete recovery.

A transient acute neurologic syndrome has been observed in patients treated with high dose regimens. Manifestations of this stroke-like encephalopathy may include confusion, hemiparesis, transient blindness, seizures and coma. The exact cause is unknown.

After the intrathecal use of methotrexate, the central nervous system toxicity which may occur can be classified as follows: acute chemical arachnoiditis manifested by such symptoms as headache, back pain, nuchal rigidity, and fever; sub-acute myelopathy characterized by paraparesis/paraplegia associated with involvement with one or more spinal nerve roots; chronic leukoencephalopathy manifested by confusion, irritability, somnolence, ataxia, dementia, seizures and coma. This condition can be progressive and even fatal.

Pulmonary: Pulmonary symptoms (especially a dry nonproductive cough) or a non-specific pneumonitis occurring during methotrexate therapy may be indicative of a potentially dangerous lesion and require interruption of treatment and careful investigation. Although clinically variable, the typical patient with methotrexate induced lung disease presents with fever, cough, dyspnea, hypoxemia, and an infiltrate on chest X-ray; infection (including pneumonia) needs to be excluded. This lesion can occur at all dosages.

Renal: Methotrexate may cause renal damage that may lead to acute renal failure. High doses of methotrexate used in the treatment of osteosarcoma may cause renal damage leading to acute renal failure. Nephrotoxicity is due primarily to the precipitation of methotrexate and 7-hydroxymethotrexate in the renal tubules. Close attention to renal function including adequate hydration, urine alkalinization and measurement of serum methotrexate and creatinine levels are essential for safe administration.

Skin: Severe, occasionally fatal, dermatologic reactions, including toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, skin necrosis, and erythema multiforme, have been reported in children and adults, within days of oral, intramuscular, intravenous, or intrathecal methotrexate administration. Reactions were noted after single or multiple low, intermediate, or high doses of methotrexate in patients with neoplastic and non-neoplastic diseases.

Other precautions: Methotrexate should be used with extreme caution in the presence of debility.

Methotrexate exits slowly from third space compartments (e.g., pleural effusions or ascites). This results in a prolonged terminal plasma half-life and unexpected toxicity. In patients with significant third space accumulations, it is advisable to evacuate the fluid before treatment and to monitor plasma methotrexate levels.

Lesions of psoriasis may be aggravated by concomitant exposure to ultraviolet radiation. Radiation dermatitis and sunburn may be “recalled” by the use of methotrexate.

ADVERSE REACTIONS
IN GENERAL, THE INCIDENCE AND SEVERITY OF ACUTE SIDE EFFECTS ARE RELATED TO DOSE AND FREQUENCY OF ADMINISTRATION. THE MOST

SERIOUS REACTIONS ARE DISCUSSED ABOVE UNDER ORGAN SYSTEM TOXICITY IN THE PRECAUTION SECTION. THAT SECTION SHOULD ALSO BE CONSULTED WHEN LOOKING FOR INFORMATION ABOUT ADVERSE REACTIONS WITH METHOTREXATE.

The most frequently reported adverse reactions include ulcerative stomatitis, leukopenia, nausea, and abdominal distress. Other frequently reported adverse effects are malaise, undue fatigue, chills and fever, dizziness and decreased resistance to infection.

Other adverse reactions that have been reported with methotrexate are listed below by organ system. In the oncology setting, concomitant treatment and the underlying disease make specific attribution of a reaction to methotrexate difficult.

Alimentary System: gingivitis, pharyngitis, stomatitis, anorexia, nausea, vomiting, diarrhea, hematemesis, melena, gastrointestinal ulceration and bleeding, enteritis, pancreatitis.

Blood and Lymphatic System Disorders: suppressed hematopoiesis, anemia, aplastic anemia, pancytopenia, leukopenia, neutropenia, thrombocytopenia, agranulocytosis, eosinophilia, lymphadenopathy and lymphoproliferative disorders (including reversible). Hypogammaglobulinemia has been reported rarely.

Cardiovascular: pericarditis, pericardial effusion, hypotension, and thromboembolic events (including arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, thrombophlebitis, and pulmonary embolus).

Central Nervous System: headaches, drowsiness, blurred vision, transient blindness, speech impairment including dysarthria and aphasia, hemiparesis, paresis and convulsions have also occurred following administration of methotrexate. Following low doses, there have been occasional reports of transient subtle cognitive dysfunction, mood alteration or unusual cranial sensations, leukoencephalopathy, or encephalopathy.

Hepatobiliary Disorders: hepatotoxicity, acute hepatitis, chronic fibrosis and cirrhosis, hepatic failure, decrease in serum albumin, liver enzyme elevations.

Infection: There have been case reports of sometimes fatal opportunistic infections in patients receiving methotrexate therapy for neoplastic and non-neoplastic diseases. *Pneumocystis carinii* pneumonia was the most common opportunistic infection. There have also been reports of infections, pneumonia, Cytomegalovirus infection, including cytomegaloviral pneumonia, sepsis, fatal sepsis, nocardiosis; histoplasmosis, cryptococcosis, *Herpes zoster, H. simplex* hepatitis, and disseminated *H. simplex.*

Musculoskeletal System: stress fracture.

Ophthalmic: conjunctivitis, serious visual changes of unknown etiology.

Pulmonary System: respiratory fibrosis, respiratory failure, alveolitis, interstitial pneumonitis deaths have been reported, and chronic interstitial obstructive pulmonary disease has occasionally occurred.

Skin: erythematous rashes, pruritus, urticaria, photosensitivity, pigmentary changes, alopecia, ecchymosis, telangiectasia, acne, furunculosis, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, skin necrosis, skin ulceration and exfoliative dermatitis.

Urogenital System: severe nephropathy or renal failure, azotemia, cystitis, hematuria, proteinuria; defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, vaginal discharge, and gynecomastia; infertility, abortion, fetal death, fetal defects.

Other rarer reactions related to or attributed to the use of methotrexate such as nodulosis, vasculitis, arthralgia/myalgia, loss of libido/impotence, diabetes, osteoporosis, sudden death, lymphoma, including reversible lymphomas, tumor lysis syndrome, soft tissue necrosis and osteonecrosis. Anaphylactoid reactions have been reported.

Adverse Reactions in Double-Blind Rheumatoid Arthritis Studies
The approximate incidences of methotrexate-attributed (i.e. placebo rate subtracted) adverse reactions in 12 to 18 week double-blind studies of patients (n=128) with rheumatoid arthritis treated with low-dose oral (7.5 to 15 mg/week) pulse methotrexate, are listed below. Virtually all of these patients were on concomitant nonsteroidal anti-inflammatory drugs and some were also taking low dosages of corticosteroids. Hepatic histology was not examined in these short-term studies. (See **PRECAUTIONS**).

Incidence greater than 10%: Elevated liver function tests 15%, nausea/vomiting 10%.

Incidence 3% to 10%: Stomatitis, thrombocytopenia (platelet count less than 100,000/mm^3).

Incidence 1% to 3%: Rash/pruritis/dermatitis, diarrhea, alopecia, leukopenia (WBC less than 3000/mm^3), pancytopenia, dizziness.

Two other controlled trials of patients (n=680) with Rheumatoid Arthritis on 7.5 mg to 15 mg/wk oral doses showed an incidence of interstitial pneumonitis of 1%. (See **PRECAUTIONS**.)

Other less common reactions included decreased hematocrit, headache, upper respiratory infection, anorexia, arthralgias, chest pain, coughing, dysuria, eye discomfort, epistatix, fever, infection, sweating, tinnitus, and vaginal discharge.

Adverse Reactions in Psoriasis:
There are no recent placebo-controlled trials in patients with psoriasis. There are two literature reports (Roenigk, 1969, and Nyfors, 1978) describing large series (n=204, 248) of psoriasis patients treated with methotrexate. Dosages ranged up to 25 mg per week and treatment was administered for up to four years. With the exception of alopecia, photosensitivity, and “burning of skin lesions” (each 3% to 10%), the adverse reaction rates in these reports were very similar to those in the rheumatoid arthritis studies. Rarely, painful plaque erosions may appear (Pearce, HP and Wilson, BB: *Am Acad Dermatol* 35: 835-838, 1996).

Adverse Reactions in JRA Studies
The approximate incidences of adverse reactions reported in pediatric patients with JRA treated with oral, weekly doses of methotrexate (5 to 20 mg/m^2/wk or 0.1 to 0.65 mg/kg/wk) were as follows (virtually all patients were receiving concomitant nosteroidal anti-inflammatory drugs, and some also were taking low doses of corticosteroids): elevated liver function tests, 14%; gastrointestinal reactions (e.g., nausea, vomiting, diarrhea), 11%; stomatitis, 2%; leukopenia, 2%; headache, 1.2%; alopecia, 0.5%; dizziness, 0.2%; and rash, 0.2%. Although there is experience with dosing up to 30 mg/m^2/wk in JRA, the published data for doses above 20 mg/m^2/wk are too limited to provide reliable estimates of adverse reaction rates.

OVERDOSAGE

Leucovorin is indicated to diminish the toxicity and counteract the effect of inadvertently administered overdosages of methotrexate. Leucovorin administration should begin as promptly as possible. As the time interval between methotrexate administration and leucovorin initiation increases, the effectiveness of leucovorin in counteracting toxicity decreases. Monitoring of the serum methotrexate concentration is essential in determining the optimal dose and duration of treatment with leucovorin.

In cases of massive overdosage, hydration and urinary alkalinization may be necessary to prevent the precipitation of methotrexate and/or its metabolites in the renal tubules. Generally speaking, neither hemodialysis nor peritoneal dialysis has been shown to improve methotrexate elimination. However, effective clearance of methotrexate has been reported with acute, intermittent hemodialysis using a high-flux dialyzer (Wall, SM et al: *Am J Kidney Dis* 28 (6): 846-854, 1996).

Accidental intrathecal overdosage may require intensive systemic support, high-dose systemic leucovorin, alkaline diuresis and rapid CSF drainage and ventriculolumbar perfusion.

In postmarketing experience, overdose with methotrexate has generally occurred with oral and intrathecal administration, although intravenous and intramuscular overdose have also been reported.

Reports of oral overdose often indicate accidental daily administration instead of weekly (single or divided doses). Symptoms commonly reported following oral overdose include those symptoms and signs reported at pharmacologic doses, particularly hematologic and gastrointestinal reaction. For example, leukopenia, thrombocytopenia, anemia, pancytopenia, bone marrow suppression, mucositis, stomatitis, oral ulceration, nausea, vomiting, gastrointestinal ulceration, gastrointestinal bleeding. In some cases, no symptoms were reported. There have been reports of death following overdose. In these cases, events such as sepsis or septic shock, renal failure, and aplastic anemia were also reported.

Symptoms of intrathecal overdose are generally central nervous system (CNS) symptoms, including headache, nausea and vomiting, seizure or convulsion, and acute toxic encephalopathy. In some cases, no symptoms were reported. There have been reports of death following intrathecal overdose. In these cases, cerebellar herniation associated with increased intracranial pressure, and acute toxic encephalopathy have also been reported.

There are published case reports of intravenous and intrathecal carboxypeptidase G2 treatment to hasten clearance of methotrexate in cases of overdose.

DOSAGE AND ADMINISTRATION

Neoplastic Diseases

Oral administration in tablet form is often preferred when low doses are being administered since absorption is rapid and effective serum levels are obtained. Methotrexate injection may be given by the intramuscular, intravenous or intra-arterial route. ***However, the preserved formulation contains Benzyl Alcohol and must not be used for intrathecal or high dose therapy.*** Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Choriocarcinoma and similar trophoblastic diseases: Methotrexate is administered orally or intramuscularly in doses of 15 to 30 mg daily for a five-day course. Such courses are usually repeated for 3 to 5 times as required, with rest periods of one or more weeks interposed between courses, until any manifesting toxic symptoms subside. The effectiveness of therapy is ordinarily evaluated by 24 hour quantitative analysis of urinary chorionic gonadotropin (hCG), which should return to normal or less than 50 IU/24 hr usually after the third or fourth course and usually be followed by a complete resolution of measurable lesions in 4 to 6 weeks. One to two courses of methotrexate after normalization of hCG is usually recommended. Before each course of the drug careful clinical assessment is essential. Cyclic combination therapy of methotrexate with other antitumor drugs has been reported as being useful.

Since hydatidiform mole may precede choriocarcinoma, prophylactic chemotherapy with methotrexate has been recommended.

Chorioadenoma destruens is considered to be an invasive form of hydatidiform mole.

Methotrexate is administered in these disease states in doses similar to those recommended for choriocarcinoma.

Leukemia: Acute lymphoblastic leukemia in pediatric patients and young adolescents is the most responsive to present day chemotherapy. In young adults and older patients, clinical remission is more difficult to obtain and early relapse is more common.

Methotrexate alone or in combination with steroids was used initially for induction of remission in acute lymphoblastic leukemias. More recently corticosteroid therapy, in combination with other antileukemic drugs or in cyclic combinations with methotrexate included, has appeared to produce rapid and effective remissions. When used for induction, methotrexate in doses of 3.3 mg/m^2 in combination with 60 mg/m^2 of prednisone, given daily, produced remissions in 50% of patients treated, usually within a period of 4 to 6 weeks. Methotrexate in combination with other agents appears to be the drug of choice for securing maintenance of drug-induced remissions. When remission is achieved and supportive care has produced general clinical improvement, maintenance therapy is initiated, as follows: Methotrexate is administered 2 times weekly either by mouth or intramuscularly in total weekly doses of 30 mg/m^2. It has also been given in doses of 2.5 mg/kg intravenously every 14 days. If and when relapse does occur, reinduction of remission can again usually be obtained by repeating the initial induction regimen.

A variety of combination chemotherapy regimens have been used for both induction and maintenance therapy in acute lymphoblastic leukemia. The physician should be familiar with the new advances in antileukemic therapy.

Meningeal Leukemia: In the treatment of prophylaxis of meningeal leukemia, methotrexate must be administered intrathecally. Preservative free methotrexate is diluted to a concentration of 1 mg/mL in an appropriate sterile, preservative free medium such as 0.9% Sodium Chloride Injection, USP.

The cerebrospinal fluid volume is dependent on age and not on body surface area. The CSF is at 40% of the adult volume at birth and reaches the adult volume in several years.

Intrathecal methotrexate administration at a dose of 12 mg/m^2 (maximum 15 mg) has been reported to result in low CSF methotrexate concentrations and reduced efficacy in pediatric patients and high concentrations and neurotoxicity in adults. The following dosage regimen is based on age instead of body surface area:

AGE (years)	DOSE (mg)
<1	6
1	8
2	10
3 or older	12

In one study in patients under the age of 40, this dosage regimen appeared to result in more consistent CSF methotrexate concentrations and less neurotoxicity. Another study in pediatric patients with acute lymphocytic leukemia compared this regimen to a dose of 12 mg/m^2 (maximum 15 mg), a significant reduction in the rate of CNS relapse was observed in the group whose dose was based on age.

Because the CSF volume and turnover may decrease with age, a dose reduction may be indicated in elderly patients.

For treatment of meningeal leukemia, intrathecal methotrexate may be given at intervals of 2 to 5 days. However, administration at intervals of less than 1 week may result in increased subacute toxicity. Methotrexate is administered until the cell count of the cerebrospinal fluid returns to normal. At this point one additional dose is advisable. For prophylaxis against meningeal leukemia, the dosage is the same as for treatment except for the intervals of administration. On this subject, it is advisable for the physician to consult the medical literature.

Untoward side effects may occur with any given intrathecal injection and are commonly neurological in character. Large doses may cause convulsions. Methotrexate given by the intrathecal route appears significantly in the systemic circulation and may cause systemic methotrexate toxicity. Therefore, systemic antileukemic therapy with the drug should be appropriately adjusted, reduced or discontinued. Focal leukemic involvement of the central nervous system may not respond to intrathecal chemotherapy and is best treated with radiotherapy.

Lymphomas: In Burkitt's tumor, Stages I-II, methotrexate has produced prolonged remissions in some cases. Recommended dosage is 10 to 25 mg/day orally for 4 to 8 days. In Stage III, methotrexate is commonly given concomitantly with other antitumor agents. Treatment in all stages usually consists of several courses of the drug interposed with 7 to 10 day rest periods. Lymphosarcomas in Stage III may respond to combined drug therapy with methotrexate given in doses of 0.625 to 2.5 mg/kg daily.

Mycosis fungoides (cutaneous T cell lymphoma): Therapy with methotrexate as a single agent appears to produce clinical responses in up to 50% of patients treated. Dosage in early stages is usually 5 to 50 mg once weekly. Dose reduction or cessation is guided by patient response and hematologic monitoring. Methotrexate has also been administered twice weekly in doses ranging from 15 to 37.5 mg in patients who have responded poorly to weekly therapy. Combination chemotherapy regimens that include intravenous methotrexate administered at higher doses with leucovorin rescue have been utilized in advanced stages of the disease.

Osteosarcoma: An effective adjuvant chemotherapy regimen requires the administration of several cytotoxic chemotherapeutic agents. In addition to high-dose methotrexate with leucovorin rescue, these agents may include doxorubicin, cisplatin, and the combination of bleomycin, cyclophosphamide and dactinomycin (BCD) in the doses and schedule shown in the

table below. The starting dose for high-dose methotrexate treatment is 12 grams/m^2. If this dose is not sufficient to produce a peak serum methotrexate concentration of 1,000 micromolar (10^{-3} mol/L) at the end of the methotrexate infusion, the dose may be escalated to 15 grams/m^2 in subsequent treatments. If the patient is vomiting or is unable to tolerate oral medication, leucovorin is given IV or IM at the same dose and schedule.

Drug*	Dose*	Treatment Week After Surgery
Methotrexate	12 g/m^2 IV as 4 hour infusion (starting dose)	4,5,6,7,11,12,15,16,29,30,44,45
Leucovorin	15 mg orally every six hours for 10 doses starting at 24 hours after start of methotrexate infusion	- - -
Doxorubicin† as a single drug	30 mg/m^2 day IV x 3 days	8,17
Doxorubicin†	50 mg/m^2 IV	20,23,33,36
Cisplatin†	100 mg/m^2 IV	20,23,33,36
Bleomycin†	15 units/m^2 IV x 2 days	2,13,26,39,42
Cyclophosphamide†	600 mg/m^2 IV x 2 days	2,13,26,39,42
Dactinomycin†	0.6 mg/m^2 IV x 2 days	2,13,26,39,42

* Link MP, Goorin AM, Miser AW, et al: The effect of adjuvant chemotherapy on relapse-free survival in patients with osteosarcoma of the extremity. *N Engl J of Med* 1986; 314 (No.25): 1600-1606.

† See each respective package insert for full prescribing information. Dosage modifications may be necessary because of drug-induced toxicity.

When these higher doses of methotrexate are to be administered, the following safety guidelines should be closely observed.

GUIDELINES FOR METHOTREXATE THERAPY WITH LEUCOVORIN RESCUE

1. Administration of methotrexate should be delayed until recovery if:
   - the WBC count is less than 1500/microliter
   - the neutrophil count is less than 200/microliter
   - the platelet count is less than 75,000/microliter
   - the serum bilirubin level is greater than 1.2 mg/dL
   - the SGPT level is greater than 450 U
   - mucositis is present, until there is evidence of healing
   - persistent pleural effusion is present; this should be drained dry prior to infusion.
2. Adequate renal function must be documented.
   a. Serum creatinine must be normal, and creatinine clearance must be greater than 60 mL/min, before initiation of therapy.
   b. Serum creatinine must be measured prior to each subsequent course of therapy. If serum creatinine has increased by 50% or more compared to a prior value, the creatinine clearance must be measured and documented to be greater than 60 mL/min (even if the serum creatinine is still within the normal range).
3. Patients must be well hydrated, and must be treated with sodium bicarbonate for urinary alkalinization.

a. Administer 1,000 mL/m^2 of intravenous fluid over 6 hours prior to initiation of the methotrexate infusion. Continue hydration at 125 mL/m^2/hr (3 liters/m^2/day) during the methotrexate infusion, and for 2 days after the infusion has been completed.
b. Alkalinize urine to maintain pH above 7.0 during methotrexate infusion and leucovorin calcium therapy. This can be accomplished by the administration of sodium bicarbonate orally or by incorporation into a separate intravenous solution.

4. Repeat serum creatinine and serum methotrexate 24 hours after starting methotrexate and at least once daily until the methotrexate level is below 5 x 10^{-8} mol/L (0.05 micromolar).
5. The table below provides guidelines for leucovorin calcium dosage based upon serum methotrexate levels. (See table below.[‡])

Patients who experience delayed early methotrexate elimination are likely to develop nonreversible oliguric renal failure. In addition to appropriate leucovorin therapy, these patients require continuing hydration and urinary alkalinization, and close monitoring of fluid and electrolyte status, until the serum methotrexate level has fallen to below 0.05 micromolar and the renal failure has resolved. If necessary, acute, intermittent hemodialysis with a high-flux dialyzer may also be beneficial in these patients.

6. Some patients will have abnormalities in methotrexate elimination, or abnormalities in renal function following methotrexate administration, which are significant but less severe than the abnormalities described in the table below. These abnormalities may or may not be associated with significant clinical toxicity. If significant toxicity is observed, leucovorin rescue should be extended for an additional 24 hours (total 14 doses over 84 hours) in subsequent courses of therapy. The possibility that the patient is taking other medications which interact with methotrexate (e.g., medications which may interfere with methotrexate binding to serum albumin, or elimination) should always be reconsidered when laboratory abnormalities or clinical toxicities are observed.

CAUTION: DO NOT ADMINISTER LEUCOVORIN INTRATHECALLY.

Psoriasis, Rheumatoid Arthritis, and Juvenile Rheumatoid Arthritis

Adult Rheumatoid Arthritis: Recommended Starting Dosage Schedules

1. Single oral doses of 7.5 mg once weekly.[†]
2. Divided oral dosages of 2.5 mg at 12 hour intervals for 3 doses given as a course once weekly.[†]

[†] Methotrexate Sodium Tablets for oral administration are available.

Polyarticular-Course Juvenile Rheumatoid Arthritis: The recommended starting dose is 10 mg/m^2 given once weekly.

For either adult RA or polyarticular-course JRA, dosages may be adjusted gradually to achieve an optimal response. Limited experience shows a significant increase in the incidence and severity of serious toxic reactions, especially bone marrow suppression, at doses greater than 20 mg/wk in adults. Although there is experience with doses up to 30 mg/m^2/wk in children, there are too few published data to assess how doses over 20 mg/m^2/wk might affect the risk of serious toxicity in children. Experience does suggest, however, that children receiving 20 to 30 mg/m^2/wk (0.65 to 1.0 mg/kg/wk) may have better absorption and fewer gastrointestinal side effects if methotrexate is administered either intramuscularly or subcutaneously.

Therapeutic response usually begins within 3 to 6 weeks and the patient may continue to improve for another 12 weeks or more.

The optimal duration of therapy is unknown. Limited data available from long-term studies in adults indicate that the initial clinical improvement is maintained for at least two years with continued therapy. When methotrexate is discontinued, the arthritis usually worsens within 3 to 6 weeks.

The patient should be fully informed of the risks involved and should be under constant supervision of the physician. (See **Information for Patients** under **PRECAUTIONS**). Assessment of hematologic, hepatic, renal, and pulmonary function should be made by history, physical examination, and laboratory tests before beginning, periodically during, and before reinstituting methotrexate therapy. (See **PRECAUTIONS**). Appropriate steps should be taken to avoid conception during methotrexate therapy. (See **PRECAUTIONS** and **CONTRAINDICATIONS**).

All schedules should be continually tailored to the individual patient. An initial test dose may be given prior to the regular dosing schedule to detect any extreme sensitivity to adverse effects (See **ADVERSE REACTIONS**). Maximal myelosuppression usually occurs in seven to ten days.

Psoriasis: Recommended Starting Dose Schedule:

1. Weekly single oral, IM or IV dosage schedule: 10 to 25 mg per week until adequate response is achieved.†
2. Divided oral dose schedule 2.5 mg at 12 hour intervals for three doses.†

†Methotrexate Sodium Tablets for oral administration are available.

Dosages in each schedule may be gradually adjusted to achieve optimal clinical response; 30 mg/week should not ordinarily be exceeded.

Once optimal clinical response has been achieved, each dosage schedule should be reduced to the lowest possible amount of drug and to the longest possible rest period. The use of methotrexate may permit the return to conventional topical therapy, which should be encouraged.

HANDLING AND DISPOSAL

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

DILUTION INSTRUCTIONS FOR LIQUID METHOTREXATE INJECTION PRODUCT

Methotrexate Injection, USP, Isotonic Liquid, Contains Preservative

If desired, the solution may be further diluted with a compatible medium such as Sodium Chloride Injection, USP. Storage for 24 hours at a temperature of 21°C to 25°C results in a product which is within 90% of label potency.

Methotrexate Injection, USP, Isotonic Liquid, Preservative Free, for Single Use Only

If desired, the solution may be further diluted immediately prior to use with an appropriate sterile, preservative free medium such as 5% Dextrose Solution, USP or Sodium Chloride Injection, USP.

HOW SUPPLIED
Parenteral:
Methotrexate Injection, USP, Isotonic Liquid, Contains Preservative. Each 25 mg/mL, 2 mL vial contains methotrexate sodium equivalent to 50 mg methotrexate.

50 mg, 2 mL Vial NDC 61703-350-38

Methotrexate Injection, USP, Isotonic Liquid, Preservative Free, for Single Use Only. Each 10 mg/mL, 2 mL vial contains methotrexate sodium equivalent to 20 mg methotrexate.

20 mg, 2 mL Vial NDC 61703-352-07

Methotrexate Injection, USP, Isotonic Liquid, Preservative Free, for Single Use Only. Each 25 mg/mL, 20 mL, 40 mL and 100 mL vial contains methotrexate sodium equivalent to 500 mg, 1 g and 2.5 g methotrexate respectively.

500 mg, 20 mL Vial NDC 61703-408-22
1 g, 40 mL Vial NDC 61703-408-41
2.5 g, 100 mL Vial NDC 61703-351-59

Store at controlled room temperature, 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). PROTECT FROM LIGHT.

Hospira, Inc.
Lake Forest, IL 60045

Hospira

Product of Australia

Revised: October, 2011

‡LEUCOVORIN RESCUE SCHEDULES FOLLOWING TREATMENT WITH HIGHER DOSES OF METHOTREXATE

Clinical Situation	Laboratory Findings	Leucovorin Dosage and Duration
Normal Methotrexate Elimination	Serum methotrexate level approximately 10 micromolar at 24 hours after administration, 1 micromolar at 48 hours, and less than 0.2 micromolar at 72 hours.	15 mg PO, IM, or IV q 6 hours for 60 hours (10 doses starting at 24 hours after start of methotrexate infusion).
Delayed Late Methotrexate Elimination	Serum methotrexate level remaining above 0.2 micromolar at 72 hours, and more than 0.05 micromolar at 96 hours after administration.	Continue 15 mg PO, IM, or IV q six hours, until methotrexate level is less than 0.05 micromolar.
Delayed Early Methotrexate Elimination and/or Evidence of Acute Renal Injury	Serum methotrexate level of 50 micromolar or more at 24 hours, or 5 micromolar or more at 48 hours after administration, OR; a 100% or greater increase in serum creatinine level at 24 hours after methotrexate administration, (e.g., an increase from 0.5 mg/dL to a level of 1 mg/dL or more).	150 mg IV q three hours, until methotrexate level is less than 1 micromolar; then 15 mg IV q three hours until methotrexate level is less than 0.05 micromolar.

REFERENCES

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4. National Study Commission on Cytotoxic Exposure-Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD, Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
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NDA 011719/S-117
Methotrexate Injection, USP
“Contains preservative”

(*Methotrexate Injection, USP Isotonic Liquid, Contains Preservative*)

Methotrexate Injection, USP

(Contains Preservative)

Rx only

Hospira

WARNINGS

METHOTREXATE SHOULD BE USED ONLY BY PHYSICIANS WHOSE KNOWLEDGE AND EXPERIENCE INCLUDE THE USE OF ANTIMETABOLITE THERAPY.

BECAUSE OF THE POSSIBILITY OF SERIOUS TOXIC REACTIONS (WHICH CAN BE FATAL):

METHOTREXATE SHOULD BE USED ONLY IN LIFE THREATENING NEOPLASTIC DISEASES, OR IN PATIENTS WITH PSORIASIS OR RHEUMATOID ARTHRITIS WITH SEVERE, RECALCITRANT, DISABLING DISEASE WHICH IS NOT ADEQUATELY RESPONSIVE TO OTHER FORMS OF THERAPY.

DEATHS HAVE BEEN REPORTED WITH THE USE OF METHOTREXATE IN THE TREATMENT OF MALIGNANCY, PSORIASIS, AND RHEUMATOID ARTHRITIS.

PATIENTS SHOULD BE CLOSELY MONITORED FOR BONE MARROW, LIVER, LUNG AND KIDNEY TOXICITIES. (See **PRECAUTIONS**.)

PATIENTS SHOULD BE INFORMED BY THEIR PHYSICIAN OF THE RISKS INVOLVED AND BE UNDER A PHYSICIAN'S CARE THROUGHOUT THERAPY.

THE USE OF METHOTREXATE HIGH DOSE REGIMENS RECOMMENDED FOR OSTEOSARCOMA REQUIRES METICULOUS CARE. (See **DOSAGE AND ADMINISTRATION**.) HIGH DOSE REGIMENS FOR OTHER NEOPLASTIC DISEASES ARE INVESTIGATIONAL AND A THERAPEUTIC ADVANTAGE HAS NOT BEEN ESTABLISHED.

METHOTREXATE FORMULATIONS AND DILUENTS CONTAINING PRESERVATIVES MUST NOT BE USED FOR INTRATHECAL OR HIGH DOSE METHOTREXATE THERAPY.

1. Methotrexate has been reported to cause fetal death and/or congenital anomalies. Therefore, it is not recommended for women of childbearing potential unless there is clear medical evidence that the benefits can be expected to outweigh the considered risks. Pregnant women with psoriasis or rheumatoid arthritis should not receive methotrexate. (See **CONTRAINDICATIONS**.)
2. Methotrexate elimination is reduced in patients with impaired renal functions, ascites, or pleural effusions. Such patients require especially careful monitoring for toxicity, and require dose reduction or, in some cases, discontinuation of methotrexate administration.
3. Unexpectedly severe (sometimes fatal) bone marrow suppression, aplastic anemia, and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high dosage) along with some nonsteroidal anti-inflammatory drugs (NSAIDs). (See **PRECAUTIONS**, **Drug Interactions**.)

4. Methotrexate causes hepatotoxicity, fibrosis and cirrhosis, but generally only after prolonged use. Acutely, liver enzyme elevations are frequently seen. These are usually transient and asymptomatic, and also do not appear predictive of subsequent hepatic disease. Liver biopsy after sustained use often shows histologic changes, and fibrosis and cirrhosis have been reported; these latter lesions may not be preceded by symptoms or abnormal liver function tests in the psoriasis population. For this reason, periodic liver biopsies are usually recommended for psoriatic patients who are under long-term treatment. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid arthritis population. (See **PRECAUTIONS**, **Organ System Toxicity**, **Hepatic**.)

5. Methotrexate-induced lung disease, including acute or chronic interstitial pneumonitis, is a potentially dangerous lesion, which may occur acutely at any time during therapy and has been reported at low doses. It is not always fully reversible and fatalities have been reported. Pulmonary symptoms (especially a dry, nonproductive cough) may require interruption of treatment and careful investigation.

6. Diarrhea and ulcerative stomatitis require interruption of therapy: otherwise, hemorrhagic enteritis and death from intestinal perforation may occur.

7. Malignant lymphomas, which may regress following withdrawal of methotrexate, may occur in patients receiving low-dose methotrexate and, thus, may not require cytotoxic treatment. Discontinue methotrexate first and, if the lymphoma does not regress, appropriate treatment should be instituted.

8. Like other cytotoxic drugs, methotrexate may induce “tumor lysis syndrome” in patients with rapidly growing tumors. Appropriate supportive and pharmacologic measures may prevent or alleviate this complication.

9. Severe, occasionally fatal, skin reactions have been reported following single or multiple doses of methotrexate. Reactions have occurred within days of oral, intramuscular, intravenous, or intrathecal methotrexate administration. Recovery has been reported with discontinuation of therapy. (See **PRECAUTIONS**, **Organ System Toxicity**, **Skin**.)

10. Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy.

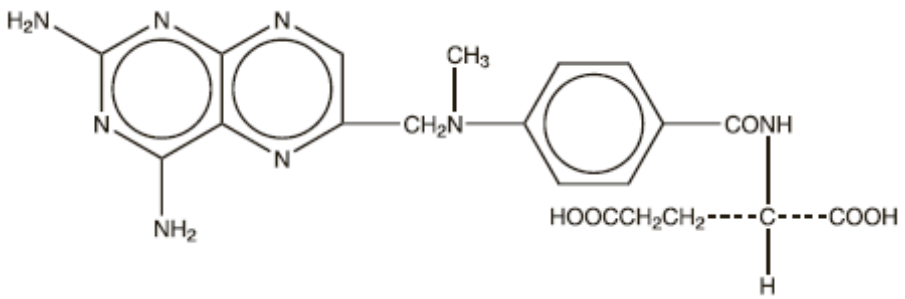
11. Methotrexate given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.

DESCRIPTION

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

Chemically methotrexate is *N*-[4-[[(2,4-diamino-6-pteridinyl) methyl]methylamino]benzoyl]-L-glutamic acid.

The structural formula is:



Molecular weight: 454.45 $C_{20}H_{22}N_8O_5$

Methotrexate Injection, USP is sterile and non-pyrogenic and may be given by the intramuscular, intravenous or intra-arterial route. (See **DOSAGE AND ADMINISTRATION**.) ***However, the preserved formulation contains Benzyl Alcohol and must not be used for intrathecal or high dose therapy.***

Methotrexate Injection, USP Isotonic Liquid, Contains Preservative is available in 25 mg/mL, 2 mL (50 mg) vials.

Each 25 mg/mL, 2 mL vial contains methotrexate sodium equivalent to 50 mg methotrexate, 0.9% w/v of Benzyl Alcohol as a preservative, and the following inactive ingredients: Sodium Chloride 0.260% w/v and Water for Injection qs ad 100% v. Sodium Hydroxide and, if necessary, Hydrochloric Acid are added to adjust the pH to approximately 8.5.

CLINICAL PHARMACOLOGY

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.

The mechanism of action in rheumatoid arthritis is unknown; it may affect immune function. Two reports describe *in vitro* methotrexate inhibition of DNA precursor uptake by stimulated mononuclear cells, and another describes in animal polyarthritis partial correction by methotrexate of spleen cell hyporesponsiveness and suppressed IL 2 production. Other laboratories, however, have been unable to demonstrate similar effects. Clarification of methotrexate's effect on immune activity and its relation to rheumatoid immunopathogenesis await further studies.

In patients with rheumatoid arthritis, effects of methotrexate on articular swelling and tenderness can be seen as early as 3 to 6 weeks. Although methotrexate clearly ameliorates symptoms of inflammation (pain, swelling, stiffness), there is no evidence that it induces remission of rheumatoid arthritis nor has a beneficial effect been demonstrated on bone erosions and other radiologic changes which result in impaired joint use, functional disability, and deformity.

Most studies of methotrexate in patients with rheumatoid arthritis are relatively short term (3 to 6 months). Limited data from long-term studies indicate that an initial clinical improvement is maintained for at least two years with continued therapy.

In psoriasis, the rate of production of epithelial cells in the skin is greatly increased over normal skin. This differential in proliferation rates is the basis for the use of methotrexate to control the psoriatic process.

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.

In a 6-month double-blind, placebo-controlled trial of 127 pediatric patients with juvenile rheumatoid arthritis (JRA) (mean age, 10.1 years; age range, 2.5 to 18 years; mean duration of disease, 5.1 years) on background nonsteroidal anti-inflammatory drugs (NSAIDs) and/or prednisone, methotrexate given weekly at an oral dose of 10 mg/m^2 provided significant clinical improvement compared to placebo as measured by either the physician's global assessment, or by a patient composite (25% reduction in the articular-severity score plus improvement in parent and physician global assessments of disease activity). Over two-thirds of the patients in this trial had polyarticular-course JRA, and the numerically greatest response was seen in this subgroup treated with 10 mg/m^2/wk methotrexate. The overwhelming majority of the remaining patients had systemic-course JRA. All patients were unresponsive to NSAIDs; approximately one-third were using low dose corticosteroids. Weekly methotrexate at a dose of 5 mg/m^2 was not significantly more effective than placebo in this trial.

Two Pediatric Oncology Group studies (one randomized and one non-randomized) demonstrated a significant improvement in relapse-free survival in patients with nonmetastatic osteosarcoma, when high dose methotrexate with leucovorin rescue was used in combination with other chemotherapeutic agents following surgical resection of the primary tumor. These studies were not designed to demonstrate the specific contribution of high dose methotrexate/leucovorin rescue therapy to the efficacy of the combination. However, a contribution can be inferred from the reports of objective responses to this therapy in patients with metastatic osteosarcoma, and from reports of extensive tumor necrosis following preoperative administration of this therapy to patients with non-metastatic osteosarcoma.

Pharmacokinetics

Absorption - In adults, oral absorption appears to be dose dependent. Peak serum levels are reached within one to two hours. At doses of 30 mg/m^2 or less, methotrexate is generally well absorbed with a mean bioavailability of about 60%. The absorption of doses greater than 80 mg/m^2 is significantly less, possibly due to a saturation effect.

In leukemic pediatric patients, oral absorption of methotrexate also appears to be dose dependent and has been reported to vary widely (23% to 95%). A twenty fold difference between highest and lowest peak levels (C_{max}: 0.11 to 2.3 micromolar after a 20 mg/m^2 dose) has been reported. Significant interindividual variability has also been noted in time to peak concentration (T_{max}: 0.67 to 4 hrs after a 15 mg/m^2 dose) and fraction of dose absorbed. The absorption of doses

greater than 40 mg/m^2 has been reported to be significantly less than that of lower doses. Food has been shown to delay absorption and reduce peak concentration. Methotrexate is generally completely absorbed from parenteral routes of injection. After intramuscular injection, peak serum concentrations occur in 30 to 60 minutes. As in leukemic pediatric patients, a wide interindividual variability in the plasma concentrations of methotrexate has been reported in pediatric patients with JRA. Following oral administration of methotrexate in doses of 6.4 to 11.2 mg/m^2/week in pediatric patients with JRA, mean serum concentrations were 0.59 micromolar (range, 0.03 to 1.40) at 1 hour, 0.44 micromolar (range, 0.01 to 1.00) at 2 hours, and 0.29 micromolar (range, 0.06 to 0.58) at 3 hours. In pediatric patients receiving methotrexate for acute lymphocytic leukemia (6.3 to 30 mg/m^2), or for JRA (3.75 to 26.2 mg/m^2), the terminal half-life has been reported to range from 0.7 to 5.8 hours or 0.9 to 2.3 hours, respectively.

Distribution - After intravenous administration, the initial volume of distribution is approximately 0.18 L/kg (18% of body weight) and steady-state volume of distribution is approximately 0.4 to 0.8 L/kg (40 to 80% of body weight). Methotrexate competes with reduced folates for active transport across cell membranes by means of a single carrier-mediated active transport process. At serum concentrations greater than 100 micromolar, passive diffusion becomes a major pathway by which effective intracellular concentrations can be achieved. Methotrexate in serum is approximately 50% protein bound. Laboratory studies demonstrate that it may be displaced from plasma albumin by various compounds including sulfonamides, salicylates, tetracyclines, chloramphenicol, and phenytoin.

Methotrexate does not penetrate the blood-cerebrospinal fluid barrier in therapeutic amounts when given orally or parenterally. High CSF concentrations of the drug may be attained by intrathecal administration.

In dogs, synovial fluid concentrations after oral dosing were higher in inflamed than uninflamed joints. Although salicylates did not interfere with this penetration, prior prednisone treatment reduced penetration into inflamed joints to the level of normal joints.

Metabolism - After absorption, methotrexate undergoes hepatic and intracellular metabolism to polyglutamated forms which can be converted back to methotrexate by hydrolase enzymes. These polyglutamates act as inhibitors of dihydrofolate reductase and thymidylate synthetase. Small amounts of methotrexate polyglutamates may remain in tissues for extended periods. The retention and prolonged drug action of these active metabolites vary among different cells, tissues and tumors. A small amount of metabolism to 7-hydroxymethotrexate may occur at doses commonly prescribed. Accumulation of this metabolite may become significant at the high doses used in osteogenic sarcoma. The aqueous solubility of 7-hydroxymethotrexate is 3 to 5 fold lower than the parent compound. Methotrexate is partially metabolized by intestinal flora after oral administration.

Half-Life - The terminal half-life reported for methotrexate is approximately three to ten hours for patients receiving treatment for psoriasis, or rheumatoid arthritis or low dose antineoplastic therapy (less than 30 mg/m^2). For patients receiving high doses of methotrexate, the terminal half-life is eight to 15 hours.

Excretion - Renal excretion is the primary route of elimination and is dependent upon dosage and route of administration. With IV administration, 80% to 90% of the administered dose is excreted unchanged in the urine within 24 hours. There is limited biliary excretion amounting to

10% or less of the administered dose. Enterohepatic recirculation of methotrexate has been proposed.

Renal excretion occurs by glomerular filtration and active tubular secretion. Nonlinear elimination due to saturation of renal tubular reabsorption has been observed in psoriatic patients at doses between 7.5 and 30 mg. Impaired renal function, as well as concurrent use of drugs such as weak organic acids that also undergo tubular secretion, can markedly increase methotrexate serum levels. Excellent correlation has been reported between methotrexate clearance and endogenous creatinine clearance.

Methotrexate clearance rates vary widely and are generally at higher doses. Delayed drug clearance has been identified as one of the major factors responsible for methotrexate toxicity. It has been postulated that the toxicity of methotrexate for normal tissues is more dependent upon the duration of exposure to the drug rather than the peak level achieved. When a patient has delayed drug elimination due to compromised renal function, a third space effusion, or other causes, methotrexate serum concentrations may remain elevated for prolonged periods.

The potential for toxicity from high dose regimens or delayed excretion is reduced by the administration of leucovorin calcium during the final phase of methotrexate plasma elimination. Pharmacokinetic monitoring of methotrexate serum concentrations may help identify those patients at high risk for methotrexate toxicity and aid in proper adjustments of leucovorin dosing. Guidelines for monitoring serum methotrexate levels, and for adjustment of leucovorin dosing to reduce the risk of methotrexate toxicity, are provided below in **DOSAGE AND ADMINISTRATION**.

Methotrexate has been detected in human breast milk. The highest breast milk to plasma concentration ratio reached was 0.08:1.

INDICATIONS AND USAGE

Neoplastic Diseases

Methotrexate is indicated in the treatment of 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.

Psoriasis

Methotrexate is indicated in the symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy, *but only when the diagnosis has been*

established, as by biopsy and/or after dermatologic consultation. It is important to ensure that a psoriasis "flare" is not due to an undiagnosed concomitant disease affecting immune responses.

Rheumatoid Arthritis including Polyarticular-Course Juvenile Rheumatoid Arthritis
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 non-steroidal anti-inflammatory agents (NSAIDs).

Aspirin, (NSAIDs), and/or low dose steroids may be continued, although the possibility of increased toxicity with concomitant use of NSAIDs including salicylates has not been fully explored. (See **PRECAUTIONS**, **Drug Interactions**.) Steroids may be reduced gradually in patients who respond to methotrexate. Combined use of methotrexate with gold, penicillamine, hydroxychloroquine, sulfasalazine, or cytotoxic agents, has not been studied and may increase the incidence of adverse effects. Rest and physiotherapy as indicated should be continued.

CONTRAINDICATIONS
Methotrexate can cause fetal death or teratogenic effects when administered to a pregnant woman. Methotrexate is contraindicated in pregnant women with psoriasis or rheumatoid arthritis and should be used in the treatment of neoplastic diseases only when the potential benefit outweighs the risk to the fetus. Women of childbearing potential should not be started on methotrexate until pregnancy is excluded and should be fully counseled on the serious risk to the fetus (see **PRECAUTIONS**) should they become pregnant while undergoing treatment. Pregnancy should be avoided if either partner is receiving methotrexate; during and for a minimum of three months after therapy for male patients, and during and for at least one ovulatory cycle after therapy for female patients. (See Boxed **WARNINGS**.)

Because of the potential for serious adverse reactions from methotrexate in breast fed infants, it is contraindicated in nursing mothers.

Patients with psoriasis or rheumatoid arthritis with alcoholism, alcoholic liver disease or other chronic liver disease should not receive methotrexate.

Patients with psoriasis or rheumatoid arthritis who have overt or laboratory evidence of immunodeficiency syndromes should not receive methotrexate.

Patients with psoriasis or rheumatoid arthritis who have preexisting blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anemia, should not receive methotrexate.

Patients with a known hypersensitivity to methotrexate should not receive the drug.

WARNINGS - SEE BOXED WARNINGS.

Use caution when administering high-dose methotrexate to patients receiving proton pump inhibitor (PPI) therapy. Case reports and published population pharmacokinetic studies suggest that concomitant use of some PPIs, such as omeprazole, esomeprazole, and pantoprazole, with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate, possibly leading to methotrexate toxicities. In two of these cases, delayed methotrexate elimination was observed when high-dose methotrexate was co-administered with PPIs, but was not observed when methotrexate was co-administered with

ranitidine. However, no formal drug interaction studies of methotrexate with ranitidine have been conducted.

Methotrexate formulations and diluents containing preservatives must not be used for intrathecal or high dose methotrexate therapy.

PRECAUTIONS

General

Methotrexate has the potential for serious toxicity. (See Boxed **WARNINGS**.) Toxic effects may be related in frequency and severity to dose or frequency of administration but have been seen at all doses. Because they can occur at any time during therapy, it is necessary to follow patients on methotrexate closely. Most adverse reactions are reversible if detected early. When such reactions do occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken. If necessary, this could include the use of leucovorin calcium and/or acute, intermittent hemodialysis with a high-flux dialyzer. (See **OVERDOSAGE**.) If methotrexate therapy is reinstituted, it should be carried out with caution, with adequate consideration of further need for the drug and increased alertness as to possible recurrence of toxicity.

The clinical pharmacology of methotrexate has not been well studied in older individuals. Due to diminished hepatic and renal function as well as decreased folate stores in this population, relatively low doses should be considered, and these patients should be closely monitored for early signs of toxicity.

Some of the effects mentioned under **ADVERSE REACTIONS**, such as dizziness and fatigue, may affect the ability to drive or operate machinery.

Information for Patients

Patients should be informed of the early signs and symptoms of toxicity, of the need to see their physician promptly if they occur, and the need for close follow-up, including periodic laboratory tests to monitor toxicity.

Both the physician and pharmacist should emphasize to the patient that the recommended dose is taken weekly in rheumatoid arthritis and psoriasis, and that mistaken daily use of the recommended dose has led to fatal toxicity. Prescriptions should not be written or refilled on a PRN basis.

Patients should be informed of the potential benefit and risk in the use of methotrexate. The risk of effects on reproduction should be discussed with both male and female patients taking methotrexate.

Laboratory Tests

Patients undergoing methotrexate therapy should be closely monitored so that toxic effects are detected promptly. Baseline assessment should include a complete blood count with differential and platelet counts, hepatic enzymes, renal function tests and a chest X-ray. During therapy of rheumatoid arthritis and psoriasis, monitoring of these parameters is recommended: hematology at least monthly, renal function and liver function every 1 to 2 months. More frequent monitoring is usually indicated during antineoplastic therapy. *During initial or changing doses,* or during periods of increased risk of elevated methotrexate blood levels (e.g., dehydration), more frequent monitoring may also be indicated.

Transient liver function test abnormalities are observed frequently after methotrexate administration and are usually not cause for modification of methotrexate therapy. Persistent liver function test abnormalities, and/or depression of serum albumin may be indicators of serious liver toxicity and require evaluation. (See **PRECAUTIONS**, **Organ System Toxicity**, *Hepatic*.)

A relationship between abnormal liver function tests and fibrosis or cirrhosis of the liver has not been established for patients with psoriasis. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid arthritis population.

Pulmonary function tests may be useful if methotrexate-induced lung disease is suspected, especially if baseline measurements are available.

Drug Interactions
Nonsteroidal anti-inflammatory drugs should not be administered prior to or concomitantly with the high doses of methotrexate, such as used in the treatment of osteosarcoma. Concomitant administration of some NSAIDs with high dose methotrexate therapy has been reported to elevate and prolong serum methotrexate levels, resulting in deaths from severe hematologic and gastrointestinal toxicity.

Caution should be used when NSAIDs and salicylates are administered concomitantly with lower doses of methotrexate. These drugs have been reported to reduce the tubular secretion of methotrexate in an animal model and may enhance its toxicity.

Despite the potential interactions, studies of methotrexate in patients with rheumatoid arthritis have usually included concurrent use of constant dosage regimens of NSAIDs, without apparent problems. It should be appreciated, however, that the doses used in rheumatoid arthritis (7.5 to 15 mg/week) are somewhat lower than those used in psoriasis and that larger doses could lead to unexpected toxicity.

Methotrexate is partially bound to serum albumin, and toxicity may be increased because of displacement by certain drugs, such as salicylates, phenylbutazone, phenytoin, and sulfonamides. Renal tubular transport is also diminished by probenecid; use of methotrexate with this drug should be carefully monitored.

In the treatment of patients with osteosarcoma, caution must be exercised if high-dose methotrexate is administered in combination with a potentially nephrotoxic chemotherapeutic agent (e.g., cisplatin).

Methotrexate increases the plasma levels of mercaptopurine. The combination of methotrexate and mercaptopurine may therefore require dose adjustment.

Oral antibiotics such as tetracycline, chloramphenicol, and nonabsorbable broad spectrum antibiotics, may decrease intestinal absorption of methotrexate or interfere with the enterohepatic circulation by inhibiting bowel flora and suppressing metabolism of the drug by bacteria.

Penicillins may reduce the renal clearance of methotrexate; increased serum concentrations of methotrexate with concomitant hematologic and gastrointestinal toxicity have been observed with high and low dose methotrexate. Use of methotrexate with penicillins should be carefully monitored.

The potential for increased hepatotoxicity when methotrexate is administered with other hepatotoxic agents has not been evaluated. However, hepatotoxicity has been reported in such

cases. Therefore, patients receiving concomitant therapy with methotrexate and other potential hepatotoxins (e.g., azathioprine, retinoids, sulfasalazine) should be closely monitored for possible increased risk of hepatotoxicity.

Methotrexate may decrease the clearance of theophylline; theophylline levels should be monitored when used concurrently with methotrexate.

Vitamin preparations containing folic acid or its derivatives may decrease responses to systemically administered methotrexate. Preliminary animal and human studies have shown that small quantities of intravenously administered leucovorin enter the CSF primarily as 5-methyltetrahydrofolate and, in humans, remain 1 to 3 orders of magnitude lower than the usual methotrexate concentrations following intrathecal administration. However, high doses of leucovorin may reduce the efficacy of intrathecally administered methotrexate.

Folate deficiency states may increase methotrexate toxicity. Trimethoprim/sulfamethoxazole has been reported rarely to increase bone marrow suppression in patients receiving methotrexate, probably by decreased tubular secretion and/or an additive antifolate effect.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No controlled human data exist regarding the risk of neoplasia with methotrexate. Methotrexate has been evaluated in a number of animal studies for carcinogenic potential with inconclusive results. Although there is evidence that methotrexate causes chromosomal damage to animal somatic cells and human bone marrow cells, the clinical significance remains uncertain. Non-Hodgkin's lymphoma and other tumors have been reported in patients receiving low-dose oral methotrexate. However, there have been instances of malignant lymphoma arising during treatment with low-dose oral methotrexate, which have regressed completely following withdrawal of methotrexate, without requiring active anti-lymphoma treatment. Benefits should be weighed against the potential risk before using methotrexate alone or in combination with other drugs, especially in pediatric patients or young adults. Methotrexate causes embryotoxicity, abortion, and fetal defects in humans. It has also been reported to cause impairment of fertility, oligospermia and menstrual dysfunction in humans, during and for a short period after cessation of therapy.

Pregnancy
Psoriasis and rheumatoid arthritis: Methotrexate is in Pregnancy Category X. See **CONTRAINDICATIONS**.

Nursing Mothers
See **CONTRAINDICATIONS**.

Pediatric Use
Safety and effectiveness in pediatric patients have been established only in cancer chemotherapy and in polyarticular-course juvenile rheumatoid arthritis.

Published clinical studies evaluating the use of methotrexate in children and adolescents (i.e., patients 2 to 16 years of age) with JRA demonstrated safety comparable to that observed in adults with rheumatoid arthritis. (See **CLINICAL PHARMACOLOGY**, **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**.)

Methotrexate injectable formulations containing the preservative benzyl alcohol are not recommended for use in neonates. There have been reports of fatal 'gasping syndrome' in neonates (children less than one month of age) following the administrations of intravenous

solutions containing the preservative benzyl alcohol. Symptoms include a striking onset of gasping respiration, hypotension, bradycardia, and cardiovascular collapse.

Serious neurotoxicity, frequently manifested as generalized or focal seizures, has been reported with unexpectedly increased frequency among pediatric patients with acute lymphoblastic leukemia who were treated with intermediate-dose intravenous methotrexate (1 gm/m^2). (See **PRECAUTIONS**, **Organ System Toxicity**, *Neurologic*.)

Geriatric Use

Clinical studies of methotrexate did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious reflecting the greater frequency of decreased hepatic and renal function, decreased folate stores, concomitant disease or other drug therapy (i.e., that interfere with renal function, methotrexate or folate metabolism) in this population. (See **PRECAUTIONS**, **Drug Interactions**.) Since decline in renal function may be associated with increases in adverse events and serum creatinine measurements may over estimate renal function in the elderly, more accurate methods (i.e., creatinine clearance) should be considered. Serum methotrexate levels may also be helpful. Elderly patients should be closely monitored for early signs of hepatic, bone marrow and renal toxicity. In chronic use situations, certain toxicities may be reduced by folate supplementation. Post-marketing experience suggests that the occurrence of bone marrow suppression, thrombocytopenia, and pneumonitis may increase with age. See Boxed **WARNINGS** and **ADVERSE REACTIONS**.

Organ System Toxicity

Gastrointestinal: If vomiting, diarrhea, or stomatitis occur, which may result in dehydration, methotrexate should be discontinued until recovery occurs. Methotrexate should be used with extreme caution in the presence of peptic ulcer disease or ulcerative colitis.

Hematologic: Methotrexate can suppress hematopoiesis and cause anemia, aplastic anemia, pancytopenia, leukopenia, neutropenia, and/or thrombocytopenia. In patients with malignancy and preexisting hematopoietic impairment, the drug should be used with caution, if at all. In controlled clinical trials in rheumatoid arthritis (n=128), leukopenia (WBC <3000/mm^3) was seen in 2 patients, thrombocytopenia (platelets <100,000/mm^3) in 6 patients, and pancytopenia in 2 patients.

In psoriasis and rheumatoid arthritis, methotrexate should be stopped immediately if there is a significant drop in blood counts. In the treatment of neoplastic diseases, methotrexate should be continued only if the potential benefit warrants the risk of severe myelosuppression. Patients with profound granulocytopenia and fever should be evaluated immediately and usually require parenteral broad-spectrum antibiotic therapy.

Hepatic: Methotrexate has the potential for acute (elevated transaminases) and chronic (fibrosis and cirrhosis) hepatotoxicity. Chronic toxicity is potentially fatal; it generally has occurred after prolonged use (generally two years or more) and after a total dose of at least 1.5 grams. In studies in psoriatic patients, hepatotoxicity appeared to be a function of total cumulative dose and appeared to be enhanced by alcoholism, obesity, diabetes and advanced age. An accurate incidence rate has not been determined; the rate of progression and reversibility of lesions is not known. Special caution is indicated in the presence of preexisting liver damage or impaired hepatic function.

In psoriasis, liver function tests, including serum albumin, should be performed periodically prior to dosing but are often normal in the face of developing fibrosis or cirrhosis. These lesions may be detectable only by biopsy. The usual recommendation is to obtain a liver biopsy at 1) pretherapy or shortly after initiation of therapy (2 to 4 months), 2) a total cumulative dose of 1.5 grams, and 3) after each additional 1.0 to 1.5 grams. Moderate fibrosis or any cirrhosis normally leads to discontinuation of the drug; mild fibrosis normally suggests a repeat biopsy in 6 months. Milder histologic findings such as fatty change and low grade portal inflammation, are relatively common pretherapy. Although these mild changes are usually not a reason to avoid or discontinue methotrexate therapy, the drug should be used with caution.

In rheumatoid arthritis, age at first use of methotrexate and duration of therapy have been reported as risk factors for hepatotoxicity; other risk factors, similar to those observed in psoriasis, may be present in rheumatoid arthritis but have not been confirmed to date. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in this population. There is a combined reported experience in 217 rheumatoid arthritis patients with liver biopsies both before and during treatment (after a cumulative dose of at least 1.5 g) and in 714 patients with a biopsy only during treatment. There are 64 (7%) cases of fibrosis and 1 (0.1%) case of cirrhosis. Of the 64 cases of fibrosis, 60 were deemed mild. The reticulin stain is more sensitive for early fibrosis and its use may increase these figures. It is unknown whether even longer use will increase these risks.

Liver function tests should be performed at baseline at 4 to 8 week intervals in patients receiving methotrexate for rheumatoid arthritis. Pretreatment liver biopsy should be performed for patients with a history of excessive alcohol consumption, persistently abnormal baseline liver function test values or chronic hepatitis B or C infection. During therapy, liver biopsy should be performed if there are persistent liver function test abnormalities or there is a decrease in serum albumin below the normal range (in the setting of well controlled rheumatoid arthritis).

If the results of a liver biopsy show mild changes (Roenigk, grades I, II, IIIa), methotrexate may be continued and the patient monitored as per recommendations listed above. Methotrexate should be discontinued in any patient who displays persistently abnormal liver function tests and refuses liver biopsy or in any patient whose liver biopsy shows moderate to severe changes (Roenigk grade IIIb or IV).

Infection or Immunologic States: Methotrexate should be used with extreme caution in the presence of active infection, and is usually contraindicated in patients with overt or laboratory evidence of immunodeficiency syndromes. Immunization may be ineffective when given during methotrexate therapy. Immunization with live virus vaccines is generally not recommended. There have been reports of disseminated vaccinia infections after smallpox immunizations in patients receiving methotrexate therapy. Hypogammaglobulinemia has been reported rarely.

Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy. When a patient presents with pulmonary symptoms, the possibility of *Pneumocystis carinii* pneumonia should be considered.

Neurologic: There have been reports of leukoencephalopathy following intravenous administration of methotrexate to patients who have had craniospinal irradiation. Serious neurotoxicity, frequently manifested as generalized or focal seizures, has been reported with unexpectedly increased frequency among pediatric patients with acute lymphoblastic leukemia who were treated with intermediate-dose intravenous methotrexate (1 gm/m^2). Symptomatic

patients were commonly noted to have leukoencephalopathy and/or microangiopathic calcifications on diagnostic imaging studies. Chronic leukoencephalopathy has also been reported in patients who received repeated doses of high-dose methotrexate with leucovorin rescue even without cranial irradiation. Discontinuation of methotrexate does not always result in complete recovery.

A transient acute neurologic syndrome has been observed in patients treated with high dose regimens. Manifestations of this stroke-like encephalopathy may include confusion, hemiparesis, transient blindness, seizures and coma. The exact cause is unknown.

After the intrathecal use of methotrexate, the central nervous system toxicity which may occur can be classified as follows: acute chemical arachnoiditis manifested by such symptoms as headache, back pain, nuchal rigidity, and fever; sub-acute myelopathy characterized by paraparesis/paraplegia associated with involvement with one or more spinal nerve roots; chronic leukoencephalopathy manifested by confusion, irritability, somnolence, ataxia, dementia, seizures and coma. This condition can be progressive and even fatal.

Pulmonary: Pulmonary symptoms (especially a dry nonproductive cough) or a non-specific pneumonitis occurring during methotrexate therapy may be indicative of a potentially dangerous lesion and require interruption of treatment and careful investigation. Although clinically variable, the typical patient with methotrexate induced lung disease presents with fever, cough, dyspnea, hypoxemia, and an infiltrate on chest X-ray; infection (including pneumonia) needs to be excluded. This lesion can occur at all dosages.

Renal: Methotrexate may cause renal damage that may lead to acute renal failure. High doses of methotrexate used in the treatment of osteosarcoma may cause renal damage leading to acute renal failure. Nephrotoxicity is due primarily to the precipitation of methotrexate and 7-hydroxymethotrexate in the renal tubules. Close attention to renal function including adequate hydration, urine alkalinization and measurement of serum methotrexate and creatinine levels are essential for safe administration.

Skin: Severe, occasionally fatal, dermatologic reactions, including toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, skin necrosis, and erythema multiforme, have been reported in children and adults, within days of oral, intramuscular, intravenous, or intrathecal methotrexate administration. Reactions were noted after single or multiple low, intermediate, or high doses of methotrexate in patients with neoplastic and non-neoplastic diseases.

Other precautions: Methotrexate should be used with extreme caution in the presence of debility.

Methotrexate exits slowly from third space compartments (e.g., pleural effusions or ascites). This results in a prolonged terminal plasma half-life and unexpected toxicity. In patients with significant third space accumulations, it is advisable to evacuate the fluid before treatment and to monitor plasma methotrexate levels.

Lesions of psoriasis may be aggravated by concomitant exposure to ultraviolet radiation. Radiation dermatitis and sunburn may be “recalled” by the use of methotrexate.

ADVERSE REACTIONS

IN GENERAL, THE INCIDENCE AND SEVERITY OF ACUTE SIDE EFFECTS ARE RELATED TO DOSE AND FREQUENCY OF ADMINISTRATION. THE MOST

SERIOUS REACTIONS ARE DISCUSSED ABOVE UNDER ORGAN SYSTEM TOXICITY IN THE PRECAUTION SECTION. THAT SECTION SHOULD ALSO BE CONSULTED WHEN LOOKING FOR INFORMATION ABOUT ADVERSE REACTIONS WITH METHOTREXATE.

The most frequently reported adverse reactions include ulcerative stomatitis, leukopenia, nausea, and abdominal distress. Other frequently reported adverse effects are malaise, undue fatigue, chills and fever, dizziness and decreased resistance to infection.

Other adverse reactions that have been reported with methotrexate are listed below by organ system. In the oncology setting, concomitant treatment and the underlying disease make specific attribution of a reaction to methotrexate difficult.

Alimentary System: gingivitis, pharyngitis, stomatitis, anorexia, nausea, vomiting, diarrhea, hematemesis, melena, gastrointestinal ulceration and bleeding, enteritis, pancreatitis.

Blood and Lymphatic System Disorders: suppressed hematopoiesis, anemia, aplastic anemia, pancytopenia, leukopenia, neutropenia, thrombocytopenia, agranulocytosis, eosinophilia, lymphadenopathy and lymphoproliferative disorders (including reversible). Hypogammaglobulinemia has been reported rarely.

Cardiovascular: pericarditis, pericardial effusion, hypotension, and thromboembolic events (including arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, thrombophlebitis, and pulmonary embolus).

Central Nervous System: headaches, drowsiness, blurred vision, transient blindness, speech impairment including dysarthria and aphasia, hemiparesis, paresis and convulsions have also occurred following administration of methotrexate. Following low doses, there have been occasional reports of transient subtle cognitive dysfunction, mood alteration or unusual cranial sensations, leukoencephalopathy, or encephalopathy.

Hepatobiliary Disorders: hepatotoxicity, acute hepatitis, chronic fibrosis and cirrhosis, hepatic failure, decrease in serum albumin, liver enzyme elevations.

Infection: There have been case reports of sometimes fatal opportunistic infections in patients receiving methotrexate therapy for neoplastic and non-neoplastic diseases. *Pneumocystis carinii* pneumonia was the most common opportunistic infection. There have also been reports of infections, pneumonia, Cytomegalovirus infection, including cytomegaloviral pneumonia, sepsis, fatal sepsis, nocardiosis; histoplasmosis, cryptococcosis, *Herpes zoster*, *H. simplex* hepatitis, and disseminated *H. simplex.*

Musculoskeletal System: stress fracture.

Ophthalmic: conjunctivitis, serious visual changes of unknown etiology.

Pulmonary System: respiratory fibrosis, respiratory failure, alveolitis, interstitial pneumonitis deaths have been reported, and chronic interstitial obstructive pulmonary disease has occasionally occurred.

Skin: erythematous rashes, pruritus, urticaria, photosensitivity, pigmentary changes, alopecia, ecchymosis, telangiectasia, acne, furunculosis, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, skin necrosis, skin ulceration and exfoliative dermatitis.

Urogenital System: severe nephropathy or renal failure, azotemia, cystitis, hematuria, proteinuria; defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, vaginal discharge, and gynecomastia; infertility, abortion, fetal death, fetal defects.

Other rarer reactions related to or attributed to the use of methotrexate such as nodulosis, vasculitis, arthralgia/myalgia, loss of libido/impotence, diabetes, osteoporosis, sudden death, lymphoma, including reversible lymphomas, tumor lysis syndrome, soft tissue necrosis and osteonecrosis. Anaphylactoid reactions have been reported.

Adverse Reactions in Double-Blind Rheumatoid Arthritis Studies
The approximate incidences of methotrexate-attributed (i.e. placebo rate subtracted) adverse reactions in 12 to 18 week double-blind studies of patients (n=128) with rheumatoid arthritis treated with low-dose oral (7.5 to 15 mg/week) pulse methotrexate, are listed below. Virtually all of these patients were on concomitant nonsteroidal anti-inflammatory drugs and some were also taking low dosages of corticosteroids. Hepatic histology was not examined in these short-term studies. (See **PRECAUTIONS**.)

Incidence greater than 10%: Elevated liver function tests 15%, nausea/vomiting 10%.

Incidence 3% to 10%: Stomatitis, thrombocytopenia (platelet count less than 100,000/mm^3).

Incidence 1% to 3%: Rash/pruritis/dermatitis, diarrhea, alopecia, leukopenia (WBC less than 3000/mm^3), pancytopenia, dizziness.

Two other controlled trials of patients (n=680) with Rheumatoid Arthritis on 7.5 mg to 15 mg/wk oral doses showed an incidence of interstitial pneumonitis of 1%. (See **PRECAUTIONS**.)

Other less common reactions included decreased hematocrit, headache, upper respiratory infection, anorexia, arthralgias, chest pain, coughing, dysuria, eye discomfort, epistatix, fever, infection, sweating, tinnitus, and vaginal discharge.

Adverse Reactions in Psoriasis
There are no recent placebo-controlled trials in patients with psoriasis. There are two literature reports (Roenigk, 1969, and Nyfors, 1978) describing large series (n=204, 248) of psoriasis patients treated with methotrexate. Dosages ranged up to 25 mg per week and treatment was administered for up to four years. With the exception of alopecia, photosensitivity, and “burning of skin lesions” (each 3% to 10%), the adverse reaction rates in these reports were very similar to those in the rheumatoid arthritis studies. Rarely, painful plaque erosions may appear (Pearce, HP and Wilson, BB: *Am Acad Dermatol* 35: 835-838, 1996).
Adverse Reactions in JRA Studies
The approximate incidences of adverse reactions reported in pediatric patients with JRA treated with oral, weekly doses of methotrexate (5 to 20 mg/m^2/wk or 0.1 to 0.65 mg/kg/wk) were as follows (virtually all patients were receiving concomitant nonsteroidal anti-inflammatory drugs, and some also were taking low doses of corticosteroids): elevated liver function tests, 14%; gastrointestinal reactions (e.g., nausea, vomiting, diarrhea), 11%; stomatitis, 2%; leukopenia, 2%; headache, 1.2%; alopecia, 0.5%; dizziness, 0.2%; and rash, 0.2%. Although there is experience with dosing up to 30 mg/m^2/wk in JRA, the published data for doses above 20 mg/m^2/wk are too limited to provide reliable estimates of adverse reaction rates.

OVERDOSAGE

Leucovorin is indicated to diminish the toxicity and counteract the effect of inadvertently administered overdosages of methotrexate. Leucovorin administration should begin as promptly as possible. As the time interval between methotrexate administration and leucovorin initiation increases, the effectiveness of leucovorin in counteracting toxicity decreases. Monitoring of the serum methotrexate concentration is essential in determining the optimal dose and duration of treatment with leucovorin.

In cases of massive overdosage, hydration and urinary alkalinization may be necessary to prevent the precipitation of methotrexate and/or its metabolites in the renal tubules. Generally speaking, neither hemodialysis nor peritoneal dialysis has been shown to improve methotrexate elimination. However, effective clearance of methotrexate has been reported with acute, intermittent hemodialysis using a high-flux dialyzer (Wall, SM et al: *Am J Kidney Dis* 28 (6): 846-854, 1996).

Accidental intrathecal overdosage may require intensive systemic support, high-dose systemic leucovorin, alkaline diuresis and rapid CSF drainage and ventriculolumbar perfusion.

In postmarketing experience, overdose with methotrexate has generally occurred with oral and intrathecal administration, although intravenous and intramuscular overdose have also been reported.

Reports of oral overdose often indicate accidental daily administration instead of weekly (single or divided doses). Symptoms commonly reported following oral overdose include those symptoms and signs reported at pharmacologic doses, particularly hematologic and gastrointestinal reaction. For example, leukopenia, thrombocytopenia, anemia, pancytopenia, bone marrow suppression, mucositis, stomatitis, oral ulceration, nausea, vomiting, gastrointestinal ulceration, gastrointestinal bleeding. In some cases, no symptoms were reported. There have been reports of death following overdose. In these cases, events such as sepsis or septic shock, renal failure, and aplastic anemia were also reported.

Symptoms of intrathecal overdose are generally central nervous system (CNS) symptoms, including headache, nausea and vomiting, seizure or convulsion, and acute toxic encephalopathy. In some cases, no symptoms were reported. There have been reports of death following intrathecal overdose. In these cases, cerebellar herniation associated with increased intracranial pressure, and acute toxic encephalopathy have also been reported.

There are published case reports of intravenous and intrathecal carboxypeptidase G2 treatment to hasten clearance of methotrexate in cases of overdose.

DOSAGE AND ADMINISTRATION

Neoplastic Diseases

Oral administration in tablet form is often preferred when low doses are being administered since absorption is rapid and effective serum levels are obtained. Methotrexate injection may be given by the intramuscular, intravenous or intra-arterial route. ***The preserved formulation contains Benzyl Alcohol and must not be used for intrathecal or high dose therapy.*** Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Choriocarcinoma and similar trophoblastic diseases: Methotrexate is administered orally or intramuscularly in doses of 15 to 30 mg daily for a five-day course. Such courses are usually repeated for 3 to 5 times as required, with rest periods of one or more weeks interposed between courses, until any manifesting toxic symptoms subside. The effectiveness of therapy is ordinarily evaluated by 24 hour quantitative analysis of urinary chorionic gonadotropin (hCG), which should return to normal or less than 50 IU/24 hr usually after the third or fourth course and usually be followed by a complete resolution of measurable lesions in 4 to 6 weeks. One to two courses of methotrexate after normalization of hCG is usually recommended. Before each course of the drug careful clinical assessment is essential. Cyclic combination therapy of methotrexate with other antitumor drugs has been reported as being useful.

Since hydatidiform mole may precede choriocarcinoma, prophylactic chemotherapy with methotrexate has been recommended.

Chorioadenoma destruens is considered to be an invasive form of hydatidiform mole. Methotrexate is administered in these disease states in doses similar to those recommended for choriocarcinoma.

Leukemia: Acute lymphoblastic leukemia in pediatric patients and young adolescents is the most responsive to present day chemotherapy. In young adults and older patients, clinical remission is more difficult to obtain and early relapse is more common.

Methotrexate alone or in combination with steroids was used initially for induction of remission in acute lymphoblastic leukemias. More recently corticosteroid therapy, in combination with other antileukemic drugs or in cyclic combinations with methotrexate included, has appeared to produce rapid and effective remissions. When used for induction, methotrexate in doses of 3.3 mg/m^2 in combination with 60 mg/m^2 of prednisone, given daily, produced remissions in 50% of patients treated, usually within a period of 4 to 6 weeks. Methotrexate in combination with other agents appears to be the drug of choice for securing maintenance of drug-induced remissions. When remission is achieved and supportive care has produced general clinical improvement, maintenance therapy is initiated, as follows: Methotrexate is administered 2 times weekly either by mouth or intramuscularly in total weekly doses of 30 mg/m^2. It has also been given in doses of 2.5 mg/kg intravenously every 14 days. If and when relapse does occur, reinduction of remission can again usually be obtained by repeating the initial induction regimen.

A variety of combination chemotherapy regimens have been used for both induction and maintenance therapy in acute lymphoblastic leukemia. The physician should be familiar with the new advances in antileukemic therapy.

Meningeal Leukemia: In the treatment of prophylaxis of meningeal leukemia, methotrexate must be administered intrathecally. Preservative free methotrexate is diluted to a concentration of 1 mg/mL in an appropriate sterile, preservative free medium such as 0.9% Sodium Chloride Injection, USP.

The cerebrospinal fluid volume is dependent on age and not on body surface area. The CSF is at 40% of the adult volume at birth and reaches the adult volume in several years.

Intrathecal methotrexate administration at a dose of 12 mg/m^2 (maximum 15 mg) has been reported to result in low CSF methotrexate concentrations and reduced efficacy in pediatric patients and high concentrations and neurotoxicity in adults. The following dosage regimen is based on age instead of body surface area:

AGE (years)	DOSE (mg)
<1	6
1	8
2	10
3 or older	12

In one study in patients under the age of 40, this dosage regimen appeared to result in more consistent CSF methotrexate concentrations and less neurotoxicity. Another study in pediatric patients with acute lymphocytic leukemia compared this regimen to a dose of 12 mg/m^2 (maximum 15 mg), a significant reduction in the rate of CNS relapse was observed in the group whose dose was based on age.

Because the CSF volume and turnover may decrease with age, a dose reduction may be indicated in elderly patients.

For treatment of meningeal leukemia, intrathecal methotrexate may be given at intervals of 2 to 5 days. However, administration at intervals of less than 1 week may result in increased subacute toxicity. Methotrexate is administered until the cell count of the cerebrospinal fluid returns to normal. At this point one additional dose is advisable. For prophylaxis against meningeal leukemia, the dosage is the same as for treatment except for the intervals of administration. On this subject, it is advisable for the physician to consult the medical literature.

Untoward side effects may occur with any given intrathecal injection and are commonly neurological in character. Large doses may cause convulsions. Methotrexate given by the intrathecal route appears significantly in the systemic circulation and may cause systemic methotrexate toxicity. Therefore, systemic antileukemic therapy with the drug should be appropriately adjusted, reduced or discontinued. Focal leukemic involvement of the central nervous system may not respond to intrathecal chemotherapy and is best treated with radiotherapy.

Lymphomas: In Burkitt's tumor, Stages I-II, methotrexate has produced prolonged remissions in some cases. Recommended dosage is 10 to 25 mg/day orally for 4 to 8 days. In Stage III, methotrexate is commonly given concomitantly with other antitumor agents. Treatment in all stages usually consists of several courses of the drug interposed with 7 to 10 day rest periods. Lymphosarcomas in Stage III may respond to combined drug therapy with methotrexate given in doses of 0.625 to 2.5 mg/kg daily.

Mycosis fungoides (cutaneous T cell lymphoma): Therapy with methotrexate as a single agent appears to produce clinical responses in up to 50% of patients treated. Dosage in early stages is usually 5 to 50 mg once weekly. Dose reduction or cessation is guided by patient response and hematologic monitoring. Methotrexate has also been administered twice weekly in doses ranging from 15 to 37.5 mg in patients who have responded poorly to weekly therapy. Combination chemotherapy regimens that include intravenous methotrexate administered at higher doses with leucovorin rescue have been utilized in advanced stages of the disease.

Osteosarcoma: An effective adjuvant chemotherapy regimen requires the administration of several cytotoxic chemotherapeutic agents. In addition to high-dose methotrexate with leucovorin rescue, these agents may include doxorubicin, cisplatin, and the combination of bleomycin, cyclophosphamide and dactinomycin (BCD) in the doses and schedule shown in the

table below. The starting dose for high-dose methotrexate treatment is 12 grams/m^2. If this dose is not sufficient to produce a peak serum methotrexate concentration of 1,000 micromolar (10^{-3} mol/L) at the end of the methotrexate infusion, the dose may be escalated to 15 grams/m^2 in subsequent treatments. If the patient is vomiting or is unable to tolerate oral medication, leucovorin is given IV or IM at the same dose and schedule.

Drug*	**Dose***	**Treatment Week After Surgery**
Methotrexate	12 g/m^2 IV as 4 hour infusion (starting dose)	4,5,6,7,11,12,15,16,29,30,44,45
Leucovorin	15 mg orally every six hours for 10 doses starting at 24 hours after start of methotrexate infusion	- - -
Doxorubicin† as a single drug	30 mg/m^2 day IV x 3 days	8,17
Doxorubicin†	50 mg/m^2 IV	20,23,33,36
Cisplatin†	100 mg/m^2 IV	20,23,33,36
Bleomycin†	15 units/m^2 IV x 2 days	2,13,26,39,42
Cyclophosphamide†	600 mg/m^2 IV x 2 days	2,13,26,39,42
Dactinomycin†	0.6 mg/m^2 IV x 2 days	2,13,26,39,42

*Link MP, Goorin AM, Miser AW, et al: The effect of adjuvant chemotherapy on relapse-free survival in patients with osteosarcoma of the extremity. *N Engl J of Med* 1986; 314 (No.25): 1600-1606.
†See each respective package insert for full prescribing information. Dosage modifications may be necessary because of drug-induced toxicity.

When these higher doses of methotrexate are to be administered, the following safety guidelines should be closely observed.

GUIDELINES FOR METHOTREXATE THERAPY WITH LEUCOVORIN RESCUE

1. Administration of methotrexate should be delayed until recovery if:
    - the WBC count is less than 1500/microliter
    - the neutrophil count is less than 200/microliter
    - the platelet count is less than 75,000/microliter
    - the serum bilirubin level is greater than 1.2 mg/dL
    - the SGPT level is greater than 450 U
    - mucositis is present, until there is evidence of healing
    - persistent pleural effusion is present; this should be drained dry prior to infusion.
2. Adequate renal function must be documented.
    a. Serum creatinine must be normal, and creatinine clearance must be greater than 60 mL/min, before initiation of therapy.
    b. Serum creatinine must be measured prior to each subsequent course of therapy. If serum creatinine has increased by 50% or more compared to a prior value, the

creatinine clearance must be measured and documented to be greater than 60 mL/min (even if the serum creatinine is still within the normal range).

3. Patients must be well hydrated, and must be treated with sodium bicarbonate for urinary alkalinization.
    a. Administer 1,000 mL/m^2 of intravenous fluid over 6 hours prior to initiation of the methotrexate infusion. Continue hydration at 125 mL/m^2/hr (3 liters/m^2/day) during the methotrexate infusion, and for 2 days after the infusion has been completed.
    b. Alkalinize urine to maintain pH above 7.0 during methotrexate infusion and leucovorin calcium therapy. This can be accomplished by the administration of sodium bicarbonate orally or by incorporation into a separate intravenous solution.
4. Repeat serum creatinine and serum methotrexate 24 hours after starting methotrexate and at least once daily until the methotrexate level is below 5 x 10^{-8} mol/L (0.05 micromolar).
5. The table below provides guidelines for leucovorin calcium dosage based upon serum methotrexate levels. (See table below.[‡])

Patients who experience delayed early methotrexate elimination are likely to develop nonreversible oliguric renal failure. In addition to appropriate leucovorin therapy, these patients require continuing hydration and urinary alkalinization, and close monitoring of fluid and electrolyte status, until the serum methotrexate level has fallen to below 0.05 micromolar and the renal failure has resolved. If necessary, acute, intermittent hemodialysis with a high-flux dialyzer may also be beneficial in these patients.

6. Some patients will have abnormalities in methotrexate elimination, or abnormalities in renal function following methotrexate administration, which are significant but less severe than the abnormalities described in the table below. These abnormalities may or may not be associated with significant clinical toxicity. If significant toxicity is observed, leucovorin rescue should be extended for an additional 24 hours (total 14 doses over 84 hours) in subsequent courses of therapy. The possibility that the patient is taking other medications which interact with methotrexate (e.g., medications which may interfere with methotrexate binding to serum albumin, or elimination) should always be reconsidered when laboratory abnormalities or clinical toxicities are observed.

CAUTION: DO NOT ADMINISTER LEUCOVORIN INTRATHECALLY.

Psoriasis, Rheumatoid Arthritis, and Juvenile Rheumatoid Arthritis
Adult Rheumatoid Arthritis: Recommended Starting Dosage Schedules

1. Single oral doses of 7.5 mg once weekly.[†]
2. Divided oral dosages of 2.5 mg at 12 hour intervals for 3 doses given as a course once weekly.[†]

[†] Methotrexate Sodium Tablets for oral administration are available.

Polyarticular-Course Juvenile Rheumatoid Arthritis: The recommended starting dose is 10 mg/m^2 given once weekly.

For either adult RA or polyarticular-course JRA, dosages may be adjusted gradually to achieve an optimal response. Limited experience shows a significant increase in the incidence and severity of serious toxic reactions, especially bone marrow suppression, at doses greater than 20

mg/wk in adults. Although there is experience with doses up to 30 mg/m^2/wk in children, there are too few published data to assess how doses over 20 mg/m^2/wk might affect the risk of serious toxicity in children. Experience does suggest, however, that children receiving 20 to 30 mg/m^2/wk (0.65 to 1.0 mg/kg/wk) may have better absorption and fewer gastrointestinal side effects if methotrexate is administered either intramuscularly or subcutaneously.

Therapeutic response usually begins within 3 to 6 weeks and the patient may continue to improve for another 12 weeks or more.

The optimal duration of therapy is unknown. Limited data available from long-term studies in adults indicate that the initial clinical improvement is maintained for at least two years with continued therapy. When methotrexate is discontinued, the arthritis usually worsens within 3 to 6 weeks.

The patient should be fully informed of the risks involved and should be under constant supervision of the physician. (See **Information for Patients** under **PRECAUTIONS**.)

Assessment of hematologic, hepatic, renal, and pulmonary function should be made by history, physical examination, and laboratory tests before beginning, periodically during, and before reinstituting methotrexate therapy. (See **PRECAUTIONS**.) Appropriate steps should be taken to avoid conception during methotrexate therapy. (See **PRECAUTIONS** and **CONTRAINDICATIONS**.)

All schedules should be continually tailored to the individual patient. An initial test dose may be given prior to the regular dosing schedule to detect any extreme sensitivity to adverse effects (See **ADVERSE REACTIONS**.) Maximal myelosuppression usually occurs in seven to ten days.

Psoriasis: Recommended Starting Dose Schedule:

1. Weekly single oral, IM or IV dosage schedule: 10 to 25 mg per week until adequate response is achieved.†
2. Divided oral dose schedule 2.5 mg at 12 hour intervals for three doses.†

†Methotrexate Sodium Tablets for oral administration are available.

Dosages in each schedule may be gradually adjusted to achieve optimal clinical response; 30 mg/week should not ordinarily be exceeded.

Once optimal clinical response has been achieved, each dosage schedule should be reduced to the lowest possible amount of drug and to the longest possible rest period. The use of methotrexate may permit the return to conventional topical therapy, which should be encouraged.

HANDLING AND DISPOSAL

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

DILUTION INSTRUCTIONS FOR LIQUID METHOTREXATE INJECTION PRODUCT

Methotrexate Injection USP, Isotonic Liquid, Contains Preservative

If desired, the solution may be further diluted with a compatible medium such as Sodium Chloride Injection, USP. Storage for 24 hours at a temperature of 21° to 25°C results in a product which is within 90% of label potency.

HOW SUPPLIED
Parenteral:
Methotrexate Injection USP, Isotonic Liquid, Contains Preservative. Each 25 mg/mL, 2 mL vial contains methotrexate sodium equivalent to 50 mg methotrexate.

50 mg, 2 mL Vial NDC 61703-350-38

Store at controlled room temperature, 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F). PROTECT FROM LIGHT.

‡LEUCOVORIN RESCUE SCHEDULES FOLLOWING TREATMENT WITH HIGHER DOSES OF METHOTREXATE

Clinical Situation	Laboratory Findings	Leucovorin Dosage and Duration
Normal Methotrexate Elimination	Serum methotrexate level approximately 10 micromolar at 24 hours after administration, 1 micromolar at 48 hours, and less than 0.2 micromolar at 72 hours.	15 mg PO, IM, or IV q 6 hours for 60 hours (10 doses starting at 24 hours after start of methotrexate infusion).
Delayed Late Methotrexate Elimination	Serum methotrexate level remaining above 0.2 micromolar at 72 hours, and more than 0.05 micromolar at 96 hours after administration.	Continue 15 mg PO, IM, or IV q six hours, until methotrexate level is less than 0.05 micromolar.
Delayed Early Methotrexate Elimination and/or Evidence of Acute Renal Injury	Serum methotrexate level of 50 micromolar or more at 24 hours, or 5 micromolar or more at 48 hours after administration, OR; a 100% or greater increase in serum creatinine level at 24 hours after methotrexate administration, (e.g., an increase from 0.5 mg/dL to a level of 1 mg/dL or more).	150 mg IV q three hours, until methotrexate level is less than 1 micromolar; then 15 mg IV q three hours until methotrexate level is less than 0.05 micromolar.

REFERENCES

1. Controlling Occupation Exposure to Hazardous Drugs (OSHA Work-Practice Guidelines). *Am J Health Syst Pharma* 1996: 53:1669-1685.
2. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402.
3. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. *JAMA*, 1985; 253(11):1590-1592.
4. National Study Commission on Cytotoxic Exposure - Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD, Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
5. Clinical Oncological Society of Australia: Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. *Med J Australia* 1983; 1:426-428.

6. Jones RB, et al. Safe Handling of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center. Ca- *A Cancer Journal for Clinicians* Sept/Oct 1983; 258-263.
7. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. *Am J Hosp Pharm* 1990; 47:1033-1049.

Hospira, Inc.
Lake Forest, IL 60045

Product of Australia

Revised: October, 2011

432926

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 40-233

Approval Letter

ANDA 40-233

JUN 17 1999

Duramed Pharmaceuticals, Inc.
Attention: John R. Rapoza
5040 Lester Road
Cincinnati, OH 45213

Dear Sir:

This is in reference to your abbreviated new drug application dated December 20, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Methotrexate Tablets USP, 2.5 mg.

Reference is also made to your amendments dated October 13, and May 20, 1999.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Methotrexate Tablets USP, 2.5 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Methotrexate Tablets, 2.5 mg, of Lederle Laboratories). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy, which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

6/17/99

cc: ANDA 40-233

/S/

Endorsements:

6/7/99

6/7/99

/S/

8/99

6/11/99

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 40-233

FINAL PRINTED LABELING

METHOTREXATE Tablets, USP

℞ only

WARNINGS

METHOTREXATE SHOULD BE USED ONLY BY PHYSICIANS WHOSE KNOWLEDGE AND EXPERIENCE INCLUDE THE USE OF ANTIMETABOLITE THERAPY

BECAUSE OF THE POSSIBILITY OF SERIOUS TOXIC REACTIONS (WHICH CAN BE FATAL)

METHOTREXATE SHOULD BE USED ONLY IN LIFE THREATENING NEOPLASTIC DISEASES OR IN PATIENTS WITH PSORIASIS OR RHEUMATOID ARTHRITIS WITH SEVERE RECALCITRANT DISABLING DISEASE WHICH IS NOT ADEQUATELY RESPONSIVE TO OTHER FORMS OF THERAPY

DEATHS HAVE BEEN REPORTED WITH THE USE OF METHOTREXATE IN THE TREATMENT OF MALIGNANCY, PSORIASIS, AND RHEUMATOID ARTHRITIS

PATIENTS SHOULD BE CLOSELY MONITORED FOR BONE MARROW, LIVER, LUNG, AND KIDNEY TOXICITIES. (See PRECAUTIONS.)

PATIENTS SHOULD BE INFORMED BY THEIR PHYSICIAN OF THE RISKS INVOLVED AND BE UNDER A PHYSICIAN'S CARE THROUGHOUT THERAPY

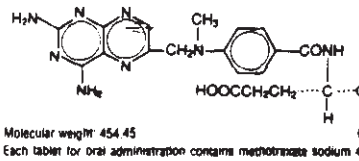
1. Methotrexate has been reported to cause fetal death and/or congenital anomalies. Therefore, it is not recommended for women of childbearing potential unless there is clear medical evidence that the benefits can be expected to outweigh the considered risks. Pregnant women with psoriasis or rheumatoid arthritis should not receive methotrexate. (See CONTRAINDICATIONS.)
2. Methotrexate elimination is reduced in patients with impaired renal function, ascites, or pleural effusions. Such patients require especially careful monitoring for toxicity, and require dose reduction or, in some cases, discontinuation of methotrexate administration.
3. Unexpectedly severe (sometimes fatal) bone marrow suppression and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high dosage) along with some nonsteroidal anti-inflammatory drugs (NSAIDs). (See PRECAUTIONS, Drug Interactions.)
4. Methotrexate causes hepatotoxicity, fibrosis and cirrhosis, but generally only after prolonged use. Acutely, liver enzyme elevations are frequently seen. These are usually transient and asymptomatic, and also do not appear predictive of subsequent hepatic disease. Liver biopsy after sustained use often shows histologic changes, and fibrosis and cirrhosis have been reported; these latter lesions may not be preceded by symptoms or abnormal liver function tests in the psoriasis population. For this reason, periodic liver biopsies are usually recommended for psoriatic patients who are under long-term treatment. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid arthritis population. (See PRECAUTIONS, Organ System Toxicity, *Hepatic*.)
5. Methotrexate-induced lung disease is a potentially dangerous lesion, which may occur acutely at any time during therapy and which has been reported at doses as low as 7.5 mg/week. It is not always fully reversible. Pulmonary symptoms (especially a dry, nonproductive cough) may require interruption of treatment and careful investigation.
6. Diarrhea and ulcerative stomatitis require interruption of therapy; otherwise, hemorrhagic enteritis and death from intestinal perforation may occur.
7. Malignant lymphomas, which may regress following withdrawal of methotrexate, may occur in patients receiving low-dose methotrexate and thus, may not require cytotoxic treatment. Discontinue methotrexate first and, if the lymphoma does not regress, appropriate treatment should be instituted.
8. Like other cytotoxic drugs, methotrexate may induce "tumor lysis syndrome" in patients with rapidly growing tumors. Appropriate supportive and pharmacologic measures may prevent or alleviate this complication.
9. Severe, occasionally fatal, skin reactions have been reported following single or multiple doses of methotrexate. Reaction have occurred within days of oral, intramuscular, intravenous, or intrathecal methotrexate administration. Recovery has been reported with discontinuation of therapy. (See **PRECAUTIONS, Organ System Toxicity,** *Skin*.)
10. Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy.

DESCRIPTION

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

Chemically methotrexate is *N*-[4-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-L-glutamic acid.

The structural formula is:



Molecular weight: 454.45 $C_{20}H_{22}N_8O_5$

Each tablet for oral administration contains methotrexate sodium equivalent to 2.5 mg of methotrexate. In addition, each tablet contains the following inactive ingredients: lactose monohydrate, magnesium stearate and pregelatinized starch.

CLINICAL PHARMACOLOGY

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.

The mechanism of action in rheumatoid arthritis is unknown; it may affect immune function. Two reports describe *in vitro* methotrexate inhibition of DNA precursor uptake by stimulated mononuclear cells, and another describes in animal polyarthritis partial correction by methotrexate of spleen cell hyporesponsiveness and suppressed IL 2 production. Other laboratories, however, have been unable to demonstrate similar effects. Clarification of methotrexate's effect on immune activity and its relation to rheumatoid immunopathogenesis await further studies.

In patients with rheumatoid arthritis, effects of methotrexate on articular [illegible] weeks. Although methotrexate clearly ameliorates symptoms of inflammation (pain, swelling, stiffness), there is no evidence that it induces remission of rheumatoid arthritis nor has a beneficial effect been demonstrated on bone erosions and other radiologic changes which result in impaired joint use, functional disability and deformity.

Most studies of methotrexate in patients with rheumatoid arthritis are relatively short term (3 to 6 months). Limited data from long-term studies indicate that an initial clinical improvement is maintained for at least two years with continued therapy.

In psoriasis, the rate of production of epithelial cells in the skin is greatly increased over normal skin. This difference in proliferation rates is the basis for the use of methotrexate to control the psoriatic process.

Pharmacokinetics

Absorption- In adults, oral absorption appears to be dose dependent. Peak serum levels are reached within one to two hours. At doses of 30 mg/m² or less, methotrexate is generally well absorbed with a mean bioavailability of about 60%. The absorption of doses greater than 80 mg/m² is significantly less, possibly due to a saturation effect.

In leukemic pediatric patients, oral absorption has been reported to vary widely (23% to 95%). A twenty fold difference between highest and lowest peak levels (C_{max} 0.11 to 2.3 micromolar after a 20 mg/m² dose) has been reported. Significant interindividual variability has also been noted in time to peak concentration (T_{max} 0.67 to 4 hrs after a 15 mg/m² dose) and fraction of dose absorbed. Food has been shown to delay absorption and reduce peak concentration.

Distribution- After intravenous administration, the initial volume of distribution is approximately 0.18 L/kg (18% of body weight) and steady-state volume of distribution is approximately 0.4 to 0.8 L/kg (40% to 80% of body weight). Methotrexate competes with reduced folates for active transport across cell membranes by means of a single carrier-mediated active transport process. At serum concentrations greater than 100 micromolar, passive diffusion becomes a major pathway by which effective intracellular concentrations can be achieved. Methotrexate in serum is approximately 50% protein bound. Laboratory studies demonstrate that it may be displaced from plasma albumin by various compounds including sulfonamides, salicylates, tetracyclines, chloramphenicol, and phenytoin.

Methotrexate does not penetrate the blood-cerebrospinal fluid barrier in therapeutic amounts when given orally or parenterally. High CSF concentrations of the drug may be attained by intrathecal administration.

In dogs, synovial fluid concentrations after oral dosing were higher in inflamed than uninflamed joints. Although salicylates did not interfere with this penetration, prior prednisone treatment reduced penetration into inflamed joints to the level of normal joints.

Metabolism- After absorption, methotrexate undergoes hepatic and intracellular metabolism to polyglutamated forms which can be converted back to methotrexate by hydrolase enzymes. These polyglutamates act as inhibitors of dihydrofolate reductase and thymidylate synthetase. Small amounts of methotrexate polyglutamates may remain in tissues for extended periods. The retention and prolonged drug action of these active metabolites vary among different cells, tissues and tumors. A small amount of metabolism to 7-hydroxymethotrexate may occur at doses commonly prescribed. Accumulation of this metabolite may become significant at the high doses used in osteogenic sarcoma. Methotrexate is partially metabolized by intestinal flora after oral administration.

Half-Life- The terminal half-life reported for methotrexate is approximately three to ten hours for patients receiving treatment for psoriasis, or rheumatoid arthritis or low dose antineoplastic therapy (less than 30 mg/m²). For patients receiving high doses of methotrexate, the terminal half-life is 8 to 15 hours.

Excretion- Renal excretion is the primary route of elimination and is dependent upon dosage and route of administration. With IV administration, 80% to 90% of the administered dose is excreted unchanged in the urine within 24 hours. There is limited biliary excretion amounting to 10% or less of the administered dose. Enterohepatic recirculation of methotrexate has been proposed.

Renal excretion occurs by glomerular filtration and active tubular secretion. Nonlinear elimination due to saturation of renal tubular reabsorption has been observed in psoriatic patients at doses between 7.5 and 30 mg. Impaired renal function, as well as concurrent use of drugs such as weak organic acids that also undergo tubular secretion, can markedly increase methotrexate serum levels. Excellent correlation has been reported between methotrexate clearance and endogenous creatinine clearance.

Methotrexate clearance rates vary widely and are generally decreased at higher doses. Delayed drug clearance has been identified as one of the major factors responsible for methotrexate toxicity. It has been postulated that the toxicity of methotrexate for normal tissues is more dependent upon the duration of exposure to the drug rather than the peak level achieved. When a patient has delayed drug elimination due to compromised renal function, a third space effusion, or other causes, methotrexate serum concentrations may remain elevated for prolonged periods.

Methotrexate has been detected in human breast milk. The highest breast milk to plasma concentration ratio reached was 0.08:1.

INDICATIONS AND USAGE

Neoplastic Diseases

Methotrexate is indicated in the treatment of gestational choriocarcinoma, chorioadenoma destruens and hydatidiform mole.

In acute lymphocytic leukemia, methotrexate is indicated 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 anti-cancer agents in the treatment of breast cancer, epidermoid cancers of the head and neck, advanced mycosis fungoides, 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.

Psoriasis

Methotrexate is indicated in the symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy, *but only when the diagnosis has been established, as by biopsy and/or after dermatologic consultation*. It is important to ensure that a psoriasis "flare" is not due to an undiagnosed concomitant disease affecting immune responses.

Rheumatoid Arthritis

Methotrexate is indicated in the management of selected adults with severe, active, classical or definite rheumatoid arthritis (ARA criteria) who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of first-line therapy including full dose NSAIDs and usually a trial of at least one or more disease-modifying antirheumatic drugs.

Aspirin, nonsteroidal anti-inflammatory agents, and/or low dose steroids may be continued, although the possibility of increased toxicity with concomitant use of NSAIDs including salicylates has not been fully explored. (See PRECAUTIONS, Drug Interactions.) Steroids may be reduced gradually in patients who respond to methotrexate. Combined use of methotrexate with gold, penicillamine, hydroxychloroquine, sulfasalazine, or cytotoxic agents, has not been studied and may increase the incidence of adverse effects. Rest and physiotherapy as indicated should be continued.

CONTRAINDICATIONS

Methotrexate can cause fetal death or teratogenic effects when administered to a pregnant woman. Methotrexate is contraindicated in pregnant women with psoriasis or rheumatoid arthritis and should be used in the treatment of neoplastic diseases only when the potential benefit outweighs the risk to the fetus. Women of childbearing potential should not be started on methotrexate until pregnancy is excluded and should be fully counseled on the serious risk to the fetus (see PRECAUTIONS) should they become pregnant while undergoing treatment. Pregnancy should be avoided if either partner is receiving methotrexate; during and for a minimum of three months after therapy for male patients, and during and for at least one ovulatory cycle after therapy for female patients. See Boxed WARNINGS.

Because of the potential for serious adverse reactions from methotrexate in breastfed infants, it is contraindicated in nursing mothers.

Patients with psoriasis or rheumatoid arthritis with alcoholism, hepatic liver disease or other chronic liver disease should not receive methotrexate.

Patients with psoriasis or rheumatoid arthritis who have overt or laboratory evidence of immunodeficiency syndromes should not receive methotrexate.

Patients with psoriasis or rheumatoid arthritis who have preexisting blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia or significant anemia, should not receive methotrexate.

Patients with a known hypersensitivity to methotrexate should not receive the drug.

WARNINGS — SEE BOXED WARNINGS.

PRECAUTIONS

General

Methotrexate has the potential for serious toxicity. (See Boxed WARNINGS.) Toxic effects may be related in frequency and severity to dose or frequency of administration but have been seen at all doses. Because they can occur at any time during therapy, it is necessary to follow patients on methotrexate closely. Most adverse reactions are reversible if detected early. When such reactions do occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken if necessary; this could include the use of leucovorin calcium. (See OVERDOSAGE.) If methotrexate therapy is reinstituted, it should be carried out with caution with adequate consideration of further need for the drug and with increased alertness as to possible recurrence of toxicity.

The clinical pharmacology of methotrexate has not been well studied in older individuals. Due to diminished hepatic and renal function as well as decreased folate stores in this population, relatively low doses should be considered, and these patients should be closely monitored for earlier signs of toxicity.

Information for Patients

Patients should be informed of the early signs and symptoms of toxicity, of the need to see their physician promptly if they occur, and the need for close follow-up, including periodic laboratory tests to monitor toxicity.

Both the physician and pharmacist should emphasize to the patient that the recommended dose is taken weekly in rheumatoid arthritis and psoriasis, and that mistaken daily use of the recommended dose has led to fatal toxicity. Prescriptions should not be written or refilled on a PRN basis.

Patients should be informed of the potential benefit and risk in the use of methotrexate. The risk of effects on reproduction should be discussed with both male and female patients taking methotrexate.

Laboratory Tests

Patients undergoing methotrexate therapy should be closely monitored so that toxic effects are detected promptly. Baseline assessment should include a complete blood count with differential and platelet counts, hepatic enzymes, renal function tests, and a chest X-ray. During therapy of rheumatoid arthritis and psoriasis, monitoring of these parameters is recommended: hematology at least monthly, renal function and liver function every 1 to 2 months. More frequent monitoring is usually indicated during antineoplastic therapy. *During initial or changing doses*, or during periods of increased risk of elevated methotrexate blood levels (eg, dehydration), more frequent monitoring may also be indicated.

Transient liver function test abnormalities are observed frequently after methotrexate administration and are usually not cause for modification of methotrexate therapy. Persistent liver function test abnormalities, and/or depression of serum albumin may be indicators of serious liver toxicity and require evaluation. (See PRECAUTIONS, Organ System Toxicity, *Hepatic*.)

A relationship between abnormal liver function tests and the development of cirrhosis of the liver has not been established for patients with psoriasis. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid arthritis population.

Pulmonary function tests may be useful if methotrexate-induced lung disease is suspected, especially if baseline measurements are available.

Drug Interactions

Concomitant administration of some NSAIDs with high dose methotrexate therapy has been reported to elevate and prolong serum methotrexate levels, resulting in deaths from severe hematologic and gastrointestinal toxicity.

Caution should be used when NSAIDs and salicylates are administered concomitantly with lower doses of methotrexate. These drugs have been reported to reduce the tubular secretion of methotrexate in an animal model and may enhance its toxicity.

Despite the potential interactions, studies of methotrexate in patients with rheumatoid arthritis have usually included concurrent use of constant dosage regimens of NSAIDs, without apparent problems. It should be appreciated, however, that the doses used in rheumatoid arthritis (7.5 to 15 mg/week) are somewhat lower than those used in psoriasis and that larger doses could lead to unexpected toxicity.

Methotrexate is partially bound to serum albumin, and toxicity may be increased because of displacement by certain drugs, such as salicylates, phenylbutazone, phenytoin, and sulfonamides. Renal tubular transport is also diminished by probenecid; use of methotrexate with this drug should be carefully monitored.

Oral antibiotics such as tetracycline, chloramphenicol, and nonabsorbable broad spectrum antibiotics, may decrease intestinal absorption of methotrexate or interfere with the enterohepatic circulation by inhibiting bowel flora and suppressing metabolism of the drug by bacteria.

Penicillins may reduce the renal clearance of methotrexate, increasing serum concentrations of methotrexate with concomitant hematologic and gastrointestinal toxicity have been observed with high and low dose methotrexate. Use of methotrexate with penicillins should be carefully monitored.

Patients receiving concomitant therapy with methotrexate and etretinate or other retinoids should be monitored closely for possible increased risk of hepatotoxicity.

Methotrexate may decrease the clearance of theophylline; theophylline levels should be monitored when used concurrently with methotrexate.

Vitamin preparations containing folic acid or its derivatives may decrease responses to systemically administered methotrexate. Preliminary animal and human studies have shown that small quantities of intravenously administered leucovorin enter the CSF primarily as 5-methyltetrahydrofolate and, in humans, remain 1-3 orders of magnitude lower than the usual methotrexate concentrations following intrathecal administration. However, high doses of leucovorin may reduce the efficacy of intrathecally administered methotrexate.

Folate deficiency states may increase methotrexate toxicity. Trimethoprim/sulfamethoxazole has been reported rarely to increase bone marrow suppression in patients receiving methotrexate probably by an additive antifolate effect.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No controlled human data exist regarding the risk of neoplasia with methotrexate. Methotrexate has been evaluated in a number of animal studies for carcinogenic potential with inconclusive results. Although there is evidence that methotrexate causes chromosomal damage to animal somatic cells and human bone marrow cells, the clinical significance remains uncertain. Lymphomas [illegible] and other tumors have been reported in patients receiving low-dose oral methotrexate.

METHOTREXATE TABLETS, USP

3248

METHOTREXATE TABLETS, USP

during treatment with low-dose oral methotrexate, which have regressed completely following withdrawal of methotrexate without requiring active anti-lymphoma treatment. Benefits should be weighed against the potential risks before using methotrexate alone or in combination with other drugs, especially in pediatric patients or young adults. Methotrexate causes embryotoxicity, abortion, and fetal defects in humans. It has also been reported to cause impairment of fertility, oligospermia and menstrual dysfunction in humans, during and for a short period after cessation of therapy.

Pregnancy

Psoriasis and rheumatoid arthritis: Methotrexate is in Pregnancy Category X. See CONTRAINDICATIONS.

Nursing Mothers

See CONTRAINDICATIONS.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established other than in cancer chemotherapy.

Organ System Toxicity

Gastrointestinal: If vomiting, diarrhea, or stomatitis occur, which may result in dehydration, methotrexate should be discontinued until recovery occurs. Methotrexate should be used with extreme caution in the presence of peptic ulcer disease or ulcerative colitis.

Hematologic: Methotrexate can suppress hematopoiesis and cause anemia, leukopenia, and/or thrombocytopenia. In patients with malignancy and preexisting hematopoietic impairment, the drug should be used with caution, if at all. In controlled clinical trials in rheumatoid arthritis (n = 128), leukopenia (WBC <3000/mm³) was seen in 2 patients, thrombocytopenia (platelets <100,000/mm³) in 6 patients, and pancytopenia in 2 patients.

In psoriasis and rheumatoid arthritis, methotrexate should be stopped immediately if there is a significant drop in blood counts. In the treatment of neoplastic diseases, methotrexate should be continued only if the potential benefit warrants the risk of severe myelosuppression. Patients with profound granulocytopenia and fever should be evaluated immediately and usually require parenteral broad-spectrum antibiotic therapy.

Hepatic: Methotrexate has the potential for acute (elevated transaminases) and chronic (fibrosis and cirrhosis) hepatotoxicity. Chronic toxicity is potentially fatal; it generally has occurred after prolonged use (generally two years or more) and after a total dose of at least 1.5 grams. In studies in psoriatic patients, hepatotoxicity appeared to be a function of total cumulative dose and appeared to be enhanced by alcoholism, obesity, diabetes, and advanced age. An accurate incidence rate has not been determined; the rate of progression and reversibility of lesions is not known. Special caution is indicated in the presence of preexisting liver damage or impaired hepatic function.

In psoriasis, liver function tests, including serum albumin, should be performed periodically prior to dosing but are often normal in the face of developing fibrosis or cirrhosis. These lesions may be detectable only by biopsy. The usual recommendation is to obtain a liver biopsy at 1) pretherapy or shortly after initiation of therapy (2 - 4 months), 2) a total cumulative dose of 1.5 grams, and 3) after each additional 1.0 to 1.5 grams.[1] Moderate fibrosis or any cirrhosis normally leads to discontinuation of the drug; mild fibrosis normally suggests a repeat biopsy in 6 months. Milder histologic findings, such as fatty change and low grade portal inflammation are relatively common pretherapy. Although these mild changes are usually not a reason to avoid or discontinue methotrexate therapy, the drug should be used with caution.

In rheumatoid arthritis, age at first use of methotrexate and duration of therapy have been reported as risk factors for hepatotoxicity; other risk factors, similar to those observed in psoriasis, may be present in rheumatoid arthritis but have not been confirmed to date. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in this population. There is a combined reported experience in 217 rheumatoid arthritis patients with liver biopsies both before and during treatment (after a cumulative dose of at least 1.5 g) and in 714 patients with a biopsy only during treatment. There are 64 (7%) cases of fibrosis and 1 (0.1%) case of cirrhosis. Of the 64 cases of fibrosis, 60 were deemed mild. The reticulin stain is more sensitive for early fibrosis and its use may increase these figures. It is unknown whether even longer use will increase these risks.

Liver function tests should be performed at baseline and at 4 - 8 week intervals in patients receiving methotrexate for rheumatoid arthritis. Pretreatment liver biopsy should be performed for patients with a history of excessive alcohol consumption, persistently abnormal baseline liver function test values or chronic hepatitis B or C infection. During therapy, liver biopsy should be performed if there are persistent liver function test abnormalities or there is a decrease in serum albumin below the normal range (in the setting of well controlled rheumatoid arthritis).

If the results of liver biopsy show mild changes (Roenigk grades I, II, IIIa), methotrexate may be continued and the patient monitored as per recommendations listed above. Methotrexate should be discontinued in any patient who displays persistently abnormal liver function tests and refuses liver biopsy or in any patient whose liver biopsy shows moderate to severe changes (Roenigk grade IIIb or IV).[2]

Infection or Immunologic States: Methotrexate should be used with extreme caution in the presence of active infection, and is usually contraindicated in patients with overt or laboratory evidence of immunodeficiency syndromes. Immunization may be ineffective when given during methotrexate therapy. Immunization with live virus vaccines is generally not recommended. There have been reports of disseminated vaccinia infections after smallpox immunization in patients receiving methotrexate therapy. Hypogammaglobulinemia has been reported rarely.

Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy. When a patient presents with pulmonary symptoms, the possibility of *Pneumocystis carinii* pneumonia should be considered.

Neurologic: There have been reports of leukoencephalopathy following intravenous administration of methotrexate to patients who have had craniospinal irradiation.

Pulmonary: Pulmonary symptoms (especially a dry, nonproductive cough) or a nonspecific pneumonitis occurring during methotrexate therapy may be indicative of a potentially dangerous lesion and require interruption of treatment and careful investigation. Although clinically variable, the typical patient with methotrexate induced lung disease presents with fever, cough, dyspnea, hypoxemia, and an infiltrate on chest X-ray; infection needs to be excluded. This lesion can occur at all dosages.

Renal: High doses of methotrexate used in the treatment of osteosarcoma may cause renal damage leading to acute renal failure. Nephrotoxicity is due primarily to the precipitation of methotrexate and 7-hydroxymethotrexate in the renal tubules. Close attention to renal function including adequate hydration, urine alkalinization and measurement of serum methotrexate and creatinine levels are essential for safe administration.

Skin: Severe, occasionally fatal, dermatologic reactions, including toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, skin necrosis and erythema multiforme, have been reported in children and adults, within days of oral, intramuscular, intravenous, or intrathecal methotrexate administration. Reactions were noted after single or multiple, low, intermediate or high doses of methotrexate in patients with neoplastic and non-neoplastic diseases.

Other Precautions: Methotrexate should be used with extreme caution in the presence of debility.

Methotrexate exits slowly from third-space compartments (eg, pleural effusions or ascites). This results in a prolonged terminal plasma half-life and unexpected toxicity in patients with significant third space accumulations. It is advisable to evacuate the fluid before treatment and to monitor plasma methotrexate levels.

Lesions of psoriasis may be aggravated by concomitant exposure to ultraviolet radiation. Radiation dermatitis and sunburn may be "recalled" by the use of methotrexate.

ADVERSE REACTIONS

IN GENERAL, THE INCIDENCE AND SEVERITY OF ACUTE SIDE EFFECTS ARE RELATED TO DOSE AND FREQUENCY OF ADMINISTRATION. THE MOST SERIOUS REACTIONS ARE DISCUSSED ABOVE UNDER ORGAN SYSTEM TOXICITY IN THE PRECAUTIONS SECTION. THAT SECTION SHOULD ALSO BE CONSULTED WHEN LOOKING FOR INFORMATION ABOUT ADVERSE REACTIONS WITH METHOTREXATE.

The most frequently reported adverse reactions include ulcerative stomatitis, leukopenia, nausea, and abdominal distress. Other frequently reported adverse effects are malaise, undue fatigue, chills and fever, dizziness and decreased resistance to infection.

Other adverse reactions that have been reported with methotrexate are listed below by organ system. In the oncology setting, concomitant treatment and the underlying disease make specific attribution of a reaction to methotrexate difficult.

Alimentary System: gingivitis, pharyngitis, stomatitis, anorexia, nausea, vomiting, diarrhea, hematemesis, melena, gastrointestinal ulceration and bleeding, enteritis, pancreatitis.

Cardiovascular: pericarditis, pericardial effusion, hypotension, and thromboembolic events (including arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, thrombophlebitis, and pulmonary embolus).

Central Nervous System: headaches, drowsiness, blurred vision. Aphasia, hemiparesis, paresis, and convulsions have also occurred following administration of methotrexate. Following low doses, there have been occasional reports of transient subtle cognitive dysfunction, mood alteration, unusual cranial sensations, leukoencephalopathy, or encephalopathy.

Infection: There have been case reports of sometimes fatal opportunistic infections in patients receiving methotrexate therapy for neoplastic and non-neoplastic diseases. *Pneumocystis carinii* pneumonia was the most common infection. Other reported infections included nocardiosis; histoplasmosis, cryptococcosis, Herpes zoster, H. simplex hepatitis, and disseminated H. simplex.

Ophthalmic: conjunctivitis, serious visual changes of unknown etiology.

Pulmonary System: interstitial pneumonitis deaths have been reported, and chronic interstitial obstructive pulmonary disease has occasionally occurred.

Skin: erythematous rashes, pruritus, urticaria, photosensitivity, pigmentary changes, alopecia, ecchymosis, telangiectasia, acne, furunculosis, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson Syndrome, skin necrosis, and exfoliative dermatitis.

Urogenital System: severe nephropathy or renal failure, azotemia, cystitis, hematuria; defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, vaginal discharge, and gynecomastia; infertility, abortion, fetal defects.

Other rarer reactions related to or attributed to the use of methotrexate such as nodulosis, vasculitis, arthralgia/myalgia, loss of libido/impotence, diabetes, osteoporosis, sudden death, and reversible lymphomas. Anaphylactoid reactions have been reported.

Adverse Reactions in Double-Blind Rheumatoid Arthritis Studies

The approximate incidences of methotrexate attributed (ie, placebo rate subtracted) adverse reactions in 12 to 18 week double-blind studies of patients (n = 128) with rheumatoid arthritis treated with low-dose oral (7.5 to 15 mg/week) pulse methotrexate, are listed below. Virtually all of these patients were on concomitant nonsteroidal anti-inflammatory drugs and some were also taking low dosages of corticosteroids.

Incidence greater than 10%: Elevated liver function tests 15%, nausea/vomiting 10%.

Incidence 3% to 10%: Stomatitis, thrombocytopenia, (platelet count less than 100,000/mm³).

Incidence 1% to 3%: Rash/pruritus/dermatitis, diarrhea, alopecia, leukopenia (WBC less than 3000/mm³), pancytopenia, dizziness.

No pulmonary toxicity was seen in these two trials. Thus, the incidence is probably less than 2.5% (95% C.L.). Hepatic histology was not examined in these short-term studies. (See PRECAUTIONS.)

Other less common reactions included decreased hematocrit, headache, upper respiratory infection, anorexia, arthralgias, chest pain, coughing, dysuria, eye discomfort, epistaxis, fever, infection, sweating, tinnitus, and vaginal discharge.

Adverse Reactions in Psoriasis

There are no recent placebo-controlled trials in patients with psoriasis. There are two literature reports (Roenigk, 1969 and Nyfors, 1978) describing large series (n = 204, 248) of psoriasis patients treated with methotrexate. Dosages ranged up to 25 mg per week and treatment was administered for up to four years. With the exception of alopecia, photosensitivity, and "burning of skin lesions" (each 3% to 10%), the adverse reaction rates in these reports were very similar to those in the rheumatoid arthritis studies.

OVERDOSAGE

Leucovorin is indicated to diminish the toxicity and counteract the effect of inadvertently administered overdosages of methotrexate. Leucovorin administration should begin as promptly as possible. As the time interval between methotrexate administration and leucovorin initiation increases, the effectiveness of leucovorin in counteracting toxicity decreases. Monitoring of the serum methotrexate concentration is essential in determining the optimal dose and duration of treatment with leucovorin.

In cases of massive overdosage, hydration and urinary alkalinization may be necessary to prevent the precipitation of methotrexate and/or its metabolites in the renal tubules. Neither hemodialysis nor peritoneal dialysis have been shown to improve methotrexate elimination.

DOSAGE AND ADMINISTRATION

Neoplastic Diseases

Oral administration in tablet form is often preferred when low doses are being administered since absorption is rapid and effective serum levels are obtained. Methotrexate sodium injection and for injection may be given by the intramuscular, intravenous, intra-arterial or intrathecal route. However, the preserved formulation contains Benzyl Alcohol and must not be used for intrathecal or high dose therapy.

Choriocarcinoma and similar trophoblastic diseases: Methotrexate is administered orally or intramuscularly in doses of 15 to 30 mg daily for a five-day course. Such courses are usually repeated for 3 to 5 times as required, with rest periods of one or more weeks interposed between courses, until any manifesting toxic symptoms subside. The effectiveness of therapy is ordinarily evaluated by 24 hour quantitative analysis of urinary chorionic gonadotropin (hCG), which should return to normal or less than 50 IU/24 hr usually after the third or fourth course and usually be followed by a complete resolution of measurable lesions in 4 to 6 weeks. One to two courses of methotrexate after normalization of hCG is usually recommended. Before each course of the drug careful clinical assessment is essential. Cyclic combination therapy of methotrexate with other antitumor drugs has been reported as being useful.

Since hydatidiform mole may precede choriocarcinoma, prophylactic chemotherapy with methotrexate has been recommended.

Chorioadenoma destruens is considered to be an invasive form of hydatidiform mole. Methotrexate is administered in these disease states in doses similar to those recommended for choriocarcinoma.

Leukemia: Acute lymphoblastic leukemia in pediatric patients and young adolescents is the most responsive to present day chemotherapy. In young adults and older patients, clinical remission is more difficult to obtain and early relapse is more common.

Methotrexate alone or in combination with steroids was used initially for induction of remission in acute lymphoblastic leukemias. More recently corticosteroid therapy, in combination with other antileukemic drugs or in cyclic combinations with methotrexate included, has appeared to produce rapid and effective remissions. When used for induction, methotrexate in doses of 3.3 mg/m² in combination with 60 mg/m² of prednisone, given daily, produced remissions in 50% of patients treated, usually within a period of 4 to 6 weeks. Methotrexate in combination with other agents appears to be the drug of choice for securing maintenance of drug-induced remissions. When remission is achieved and supportive care has produced general clinical improvement, maintenance therapy is initiated, as follows: Methotrexate is administered 2 times weekly either by mouth or intramuscularly in total weekly doses of 30 mg/m². It has also been given in doses of 2.5 mg/kg intravenously every 14 days. If and when relapse does occur, reinduction of remission can again usually be obtained by repeating the initial induction regimen.

A variety of combination chemotherapy regimens have been used for both induction and maintenance therapy in acute lymphoblastic leukemia. The physician should be familiar with the new advances in antileukemic therapy.

Lymphomas: In Burkitt's tumor, Stages I-II, methotrexate has produced prolonged remissions in some cases. Recommended dosage is 10 to 25 mg/day orally for 4 to 8 days. In Stage III, methotrexate is commonly given concomitantly with other anti-tumor agents. Treatment in all stages usually consists of several courses of the drug interposed with 7 to 10 day rest periods. Lymphosarcomas in Stage III may respond to combined drug therapy with methotrexate given in doses of 0.625 to 2.5 mg/kg daily.

Mycosis Fungoides: Therapy with methotrexate appears to produce clinical remissions in one half of the cases treated. Dosage is usually 2.5 to 10 mg daily by mouth for weeks or months. Dose levels of drug and adjustment of dose regimen by reduction or cessation of drug are guided by patient response and hematologic monitoring. Methotrexate has also been given intramuscularly in doses of 50 mg once weekly or 25 mg 2 times weekly.

Psoriasis and Rheumatoid Arthritis

The patient should be fully informed of the risks involved and should be under constant supervision of the physician. (See Information for Patients under PRECAUTIONS.) Assessment of hematologic, hepatic, renal and pulmonary function should be made by history, physical examination, and laboratory tests before beginning, periodically during, and before reinstituting methotrexate therapy. (See PRECAUTIONS.) Appropriate steps should be taken to avoid conception during methotrexate therapy. (See PRECAUTIONS AND CONTRAINDICATIONS.)

All schedules should be continually tailored to the individual patient. An initial test dose may be given prior to the regular dosing schedule to detect any extreme sensitivity to adverse effects. (See ADVERSE REACTIONS.) Maximal myelosuppression usually occurs in seven to ten days.

Psoriasis: Recommended Starting Dose Schedules

1. Weekly single oral, IM or IV dose schedule: 10 to 25 mg per week until adequate response is achieved.
2. Divided oral dose schedule: 2.5 mg at 12-hour intervals for three doses.

Dosages in each schedule may be gradually adjusted to achieve optimal clinical response; 30 mg/week should not ordinarily be exceeded.

Once optimal clinical response has been achieved, each dosage schedule should be reduced to the lowest possible amount of drug and to the longest possible rest period. The use of methotrexate may permit the return to conventional topical therapy, which should be encouraged.

Rheumatoid Arthritis: Recommended Starting Dosage Schedules

1. Single oral doses of 7.5 mg once weekly.
2. Divided oral dosages of 2.5 mg at 12 hour intervals for 3 doses given as a course once weekly.

Dosages in each schedule may be adjusted gradually to achieve an optimal response, but not ordinarily to exceed a total weekly dose of 20 mg. Limited experience shows a significant increase in the incidence and severity of serious toxic reactions, especially bone marrow suppression, at doses greater than 20 mg/wk.

Once response has been achieved, each schedule should be reduced, if possible, to the lowest possible effective dose.

Therapeutic response usually begins within 3 to 6 weeks and the patient may continue to improve for another 12 weeks or more.

The optimal duration of therapy is unknown. Limited data available from long-term studies indicate that the initial clinical improvement is maintained for at least two years with continued therapy. When methotrexate is discontinued, the arthritis usually worsens within 3 to 6 weeks.

HANDLING AND DISPOSAL

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[3-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Methotrexate tablets, USP, 2.5 mg, are yellow, oval and debossed on the scored side with "[illegible]" and "509" in bottles of 36 (NDC 51285-509-36) and 100 (NDC 51285-509-02).

Store at 25°C (77°F), excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]

Protect From Light.

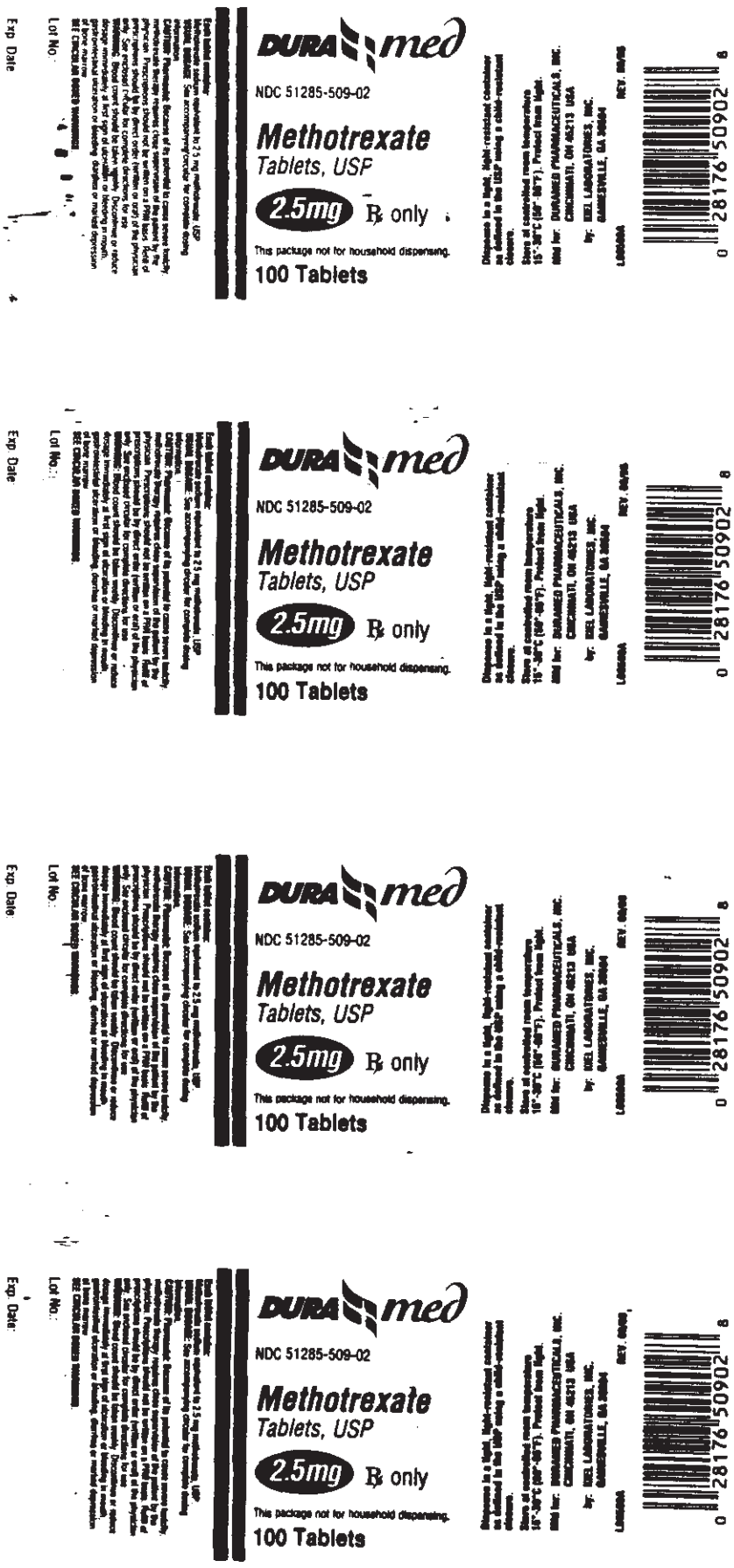
Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Mfd. for: DURAMED PHARMACEUTICALS, INC.
Cincinnati, OH 45213 USA
by: KIEL LABORATORIES, INC.
Gainesville, GA 30504 USA

[illegible]3240 REV. 04/99

REFERENCES

1. Roenigk HH, Auerbach R, Maibach HI, et al. Methotrexate in Psoriasis: Revised Guidelines. *J Am Acad Dermatol* 1988; 19:145-156.
2. Kremer JM, et al. Methotrexate for Rheumatoid Arthritis: Suggested Guidelines for Monitoring Liver Toxicity. *Arth Rheum* 1994; 37:316-328.
3. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402.
4. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. *JAMA*, March 15, 1985.
5. National Study Commission on Cytotoxic Exposure—Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
6. Clinical Oncological Society of Australia: Guidelines And Recommendations For Safe Handling Of Antineoplastic Agents. *Med J Australia* 1983; 1:426-428.
7. Jones RB, et al. Safe handling of chemotherapeutic agents: A report from the Mount Sinai Medical Center. *Ca - A Cancer Journal for Clinicians*, 1983; (Sept/Oct) 258-263.
8. American Society of Hospital Pharmacists. Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. *Am J Hosp Pharm* 1990; 47:1033-1049.


DURA med
NDC 51285-509-02
Methotrexate
Tablets, USP
2.5mg
℞ only
This package not for household dispensing.
100 Tablets
Exp Date
Lot No.
0 28176 50902 8

Exp. Date:

Lot No.:

DURAmed

NDC 51285-509-36

Methotrexate

Tablets, USP

2.5mg ℞ only

This package not for household dispensing

36 Tablets

0 28176 50936 5

Exp. Date:

Lot No.:

DURAmed

NDC 51285-509-36

Methotrexate

Tablets, USP

2.5mg ℞ only

This package not for household dispensing

36 Tablets

0 28176 50936 5

Exp. Date:

Lot No.:

DURAmed

NDC 51285-509-36

Methotrexate

Tablets, USP

2.5mg ℞ only

This package not for household dispensing

36 Tablets

0 28176 50936 5

Exp. Date:

Lot No.:

DURAmed

NDC 51285-509-36

Methotrexate

Tablets, USP

2.5mg ℞ only

This package not for household dispensing

36 Tablets

0 28176 50936 5

DURA med

NDC 51285-509-02

Methotrexate

Tablets, USP

2.5mg Rx only

This package not for household dispensing.

100 Tablets

Exp. Date

Lot No.

DURA med

NDC 51285-509-02

Methotrexate

Tablets, USP

2.5mg Rx only

This package not for household dispensing.

100 Tablets

Exp. Date

Lot No.

DURA med

NDC 51285-509-02

Methotrexate

Tablets, USP

2.5mg Rx only

This package not for household dispensing.

100 Tablets

Exp. Date

Lot No.

DURA med

NDC 51285-509-02

Methotrexate

Tablets, USP

2.5mg Rx only

This package not for household dispensing.

100 Tablets

Exp. Date

Lot No.

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 40-233

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 40-233

3. NAME AND ADDRESS OF APPLICANT
Duramed Pharmaceuticals, Inc.
5040 Lester Road
Cincinnati, OH 45213

4. LEGAL BASIS FOR SUBMISSION
Expired patent.
Listed Drug Product: Methotrexate Sodium Tablets (Lederle Laboratories)

The indications the proposed drug product is going to be used for, active ingredient, route of administration, dosage form, strength and labeling is same as listed drug product.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None used.

7. NONPROPRIETARY NAME
Methotrexate Tablets USP, 2.5 mg

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
FIRM:
Original submission: 12-20-96
Amendment: 3-13-97
Amendment: 4-16-97
Major Amendment: 10-9-98 (Response to 7-18-98 NA letter)
* Fax Amendment: 5-20-99 (Response to 4-17-99 letter)

FDA:
Refuse to file Letter: 2-28-97
Date acceptable for filing: 3-14-97
[Acknowledgement Letter issued on: 4-7-97]
NA letter: 7-18-98
NA letter: 4-27-99

10. PHARMACOLOGICAL CATEGORY
Antineoplastic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
ANDA 81-099..Barr... Approved on 10-15-90
ANDA 81-235..Mylan.. Approved on 5-15-92
ANDA 40-054..Roxane..Approved on 8-1-94

13. DOSAGE FORM
Tablets

14. POTENCY
2.5 mg

15. CHEMICAL NAME AND STRUCTURE
SEE CR # 1.

16. RECORDS AND REPORTS
N/A

17. COMMENTS
1. DMF for manufacturer active substance is adequate per M. Shaikh's review dated 6-24-97. No new information is submitted.
2. Labeling is acceptable as of 5-24-99.
3. Bio Review is acceptable.
4. EER status for all the facilities is withhold.
5. Approved ANDA 40-054 is consulted to conduct review of this ANDA with respect to release and stability specifications.

18. CONCLUSIONS AND RECOMMENDATIONS
Approved pending acceptable EER status.

19. REVIEWER:
Mujahid L. Shaikh

DATE COMPLETED:
5-27-99

Endorsements:

Page(s) 10

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

Chemist Review #3

APR 27 1999

38. Chemistry Comments to be Provided to the Applicant

ANDA: 40-233 APPLICANT: Duramed Pharmaceuticals, Inc.

DRUG PRODUCT: Methotrexate Tablets USP, 2.5 mg

The deficiencies presented below represent Facsimile deficiencies.

A. Deficiencies:

iire.

2. Your proposed blend uniformity specification as a routine in-process control is acceptable but you failed to include relative standard deviation (RSD) of Please be advised that test sample should be size of 1-3 tablets.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. A satisfactory cGMP compliance of all facilities listed in your application is required prior to the approval of this application.

2. Your bioequivalence data is pending review.

6. You must also address the labeling deficiencies in your response.

Sincerely yours,

/S/

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

TABLE OF CONTENTS

Duramed Pharmaceuticals, Inc.

ANDA # 40-233 Methotrexate Tablets, USP, 2.5 mg

October 9, 1998 Amendment

JUL 18 1997

38. Chemistry Comments to be Provided to the Applicant

ANDA: 40-233 APPLICANT: Duramed Pharmaceuticals, Inc.

DRUG PRODUCT: Methotrexate Tablets USP, 2.5 mg

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

Page(s) 1

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Christy Noon

#78

7/18/97

4.

5. Your bioequivalence data is pending review.

6. You must also address the labeling deficiencies in your response.

Sincerely yours,

/S/

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 40-233

BIOEQUIVALENCE REVIEW(S)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA/AADA: 40-233 APPLICANT: Duramed

DRUG PRODUCT: Methotrexate, USP, 2.5 mg tablets

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in U.S.P. 23.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

Methotrexate Tablets	Duramed
2.5 mg Tablets	Cincinnati, OH
ANDA #40-233	Submission Date: 12/20/96
Reviewer: Moo Park	

REF PRODUCT	Methotrexate Sodium Tablets, 2.5 mg, manufactured by Lederle Laboratories
BE STUDY DESIGN	Open-label, balanced, randomized, two period, single dose, crossover study
STUDY SITE	A
STUDY SUMMARY	1. **Pharmacokinetic and statistical evaluation:** Twenty-six healthy male subjects enrolled and all 26 completed the crossover study. Peak mean plasma levels for the test and reference products were 128.9 ng/mL at 0.67 hour and 131.6 ng/mL at 0.83 hour, respectively. The LSMEANS are comparable for the test and reference products. The Test/Reference ratios range 0.97-1.02. The 90% confidence intervals for the log-transformed AUCT, AUCI and CMAX are within the acceptable range of 80-125%. 2. **Drug products:** The assay and content uniformity data for the test and reference products are acceptable. The batch size of the test product was tablets. 3. **Medical events:** No serious medical events were reported during the study.
BIOASSAY VALIDATION	Pre-study and within-study validation data are acceptable.
DISSOLUTION	The test product, lot #GA194, met the USP dissolution specifications.
WAIVER	n/a

/S/

INITIAL: _____ DATE: 7/8/97
REVIEWER: Moo Park, Ph.D.
BRANCH: III

INITIAL: /S/ DATE: 7/9/97
TEAM LEADER: Ramakant M. Mhatre, Ph.D.
BRANCH: III

INITIAL: /S/ DATE: 1/16/98
DIRECTOR: ~~Nicholas Fleischer, Ph.D.~~
DIVISION OF BIOEQUIVALENCE

INITIAL: _____ DATE: _____
DIRECTOR
OFFICE OF GENERIC DRUGS

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

Methotrexate Tablets	Duramed
2.5 mg Tablets	Cincinnati, OH
ANDA #40-233	Submission Date: 12/20/96
Reviewer: Moo Park	

REF PRODUCT	Methotrexate Sodium Tablets, 2.5 mg, manufactured by Lederle Laboratories
BE STUDY DESIGN	Open-label, balanced, randomized, two period, single dose, crossover study
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BIOASSAY VALIDATION	Pre-study and within-study validation data are acceptable.
DISSOLUTION	The test product, lot #GA194, met the USP dissolution specifications.
WAIVER	n/a

INITIAL: _____ DATE: 7/f/97
REVIEWER: Moo Park, Ph.D.
BRANCH: III

INITIAL: _____ DATE: 7/9/97
TEAM LEADER: Ramakant M. Mhatre, Ph.D.
BRANCH: III

INITIAL: _____ DATE: 1/16/98
DIRECTOR: ~~Nicholas Fleischer, Ph.D.~~
DIVISION OF BIOEQUIVALENCE

INITIAL: _____ DATE: _____
DIRECTOR
OFFICE OF GENERIC DRUGS

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA/AADA: 40-233 APPLICANT: Duramed

DRUG PRODUCT: Methotrexate, USP, 2.5 mg tablets

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in U.S.P. 23.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

NOV 13 1997

Methotrexate Tablets
2.5 mg Tablets
ANDA #40-233
Reviewer: Moo Park
Filename: 40233sd.d96

Duramed
Cincinnati, OH
Submission Date: 12/20/96

Review of an *in vivo* Bioequivalence Study and Dissolution Data

I. Objective

The objective of this study was to determine the bioequivalence of Methotrexate Tablets, USP, 2.5 mg, manufactured by Duramed Pharmaceuticals, Inc., relative to the listed drug product, Methotrexate Sodium Tablets, 2.5 mg, manufactured by Lederle Laboratories, in healthy, normal males under fasting conditions.

II. Background

Methotrexate is N-[4-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-L-glutamic acid. Methotrexate is an antimetabolite used in the treatment of neoplastic tumors as well as some non-neoplastic diseases such as severe psoriasis, and adult rheumatoid arthritis. The enzyme dihydrofolate reductase (DHFR) is the site of action for this antifolate drug. 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 nucleosides and thymidate. In this way, DNA and RNA synthesis, repair and cellular replication is disrupted.
The mechanism of action in rheumatoid arthritis is unknown. Methotrexate is an antimetabolite used in the treatment of certain neoplastic diseases (leukemia, lymphomas, mycosis fungoides, osteosarcoma), severe psoriasis, and adult rheumatoid arthritis. The most frequently reported adverse reactions include mouth sores, nausea, abdominal distress, and a decrease in the number of white blood cells. Oral dosing of methotrexate appears to be dose dependent. Peak serum levels are reached within 1 to 2 hours. At doses of 30 mg/m^2 or less, methotrexate is generally well absorbed with a mean bioavailability of about 60%. Methotrexate is metabolized via several routes including

partial metabolism by the intestinal flora, in addition to hepatic and intracellular metabolism. A small amount of metabolism to 7-hydroxymethotrexate may occur at doses commonly prescribed, but this metabolite is less effective in the competitive inhibition of DHFR. The drug is approximately 50% bound to serum proteins, primarily albumin. Renal excretion, specifically glomerular filtration and active tubular secretion, is the primary route of elimination. Nonlinear elimination due to saturation of renal tubular resorption can occur. Methotrexate therapy is available in tablets or injection. Methotrexate for oral administration is available only in tablets containing a quantity of methotrexate sodium equivalent to 2.5 mg of the base. Methotrexate is administered orally, IM or IV over courses of weeks to months depending on the indication and disease state. Dosages range from 2.5 mg every 12 hours to 15 or 30 mg per day.

III. Study Details

Protocol No. KDI-508

Applicant Duramed

Study sites

Investigator:

Study dates Period 1: 8/24/96 - 8/25/96
Period 2: 8/31/96 - 9/01/96

Study design This was an open-label, balanced, randomized, two period, single dose, crossover study in healthy, normal males. The protocol specified dosing of 26 volunteers with 26 to complete.

Subjects

Twenty-six healthy male subjects were recruited and 26 completed the crossover study. The subjects were:

- Age 18-40
- Weight within 15% of ideal body weight
- No clinically significant abnormalities
- Normal clinical laboratory values

Drug products

Test product: Methotrexate Tablets, USP, 2.5 mg, GA 194, Expiration Date: 5/98, Duramed Pharmaceuticals, Inc. Batch Size: (theoretical); 407,300 (actual yield) tablets

Reference Product: Methotrexate Sodium Tablets, 2.5 mg, Lot 397-336, Expiration Date: 11/97, Lederle Laboratories.

Dosing

In this study, subjects are dosed with 2 x 2.5 mg tablets twice, once for each period.

Food and fluid

Prior to each period there was an overnight fast of at least 10 hours. Water was consumed ad libitum except within 1 hour before and after dosing. Water (240 mL at room temperature) was consumed at the time of dosing. Four (4) hours after dosing a standardized meal was served. No other food or beverage was allowed from 12 hours prior to dosing until 4 hours after dosing. Meal plans were identical for all periods.

Housing

Subjects were admitted to the research center the evening prior to dosing and were discharged after the 24-hour post-dose blood sample was obtained. Subjects were discharged at the end of Period 2 following receipt of a post-study physical examination.

Washout

There was a one week washout period between the start of each of the dosing periods.

Blood samples	During each period, plasma samples were obtained from blood drawn into heparinized tubes at 0 (pre-dose), 0.25, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hours after administration of the dose. The blood samples were centrifuged at -4°C , plasma collected, flash frozen within 5 minutes of harvesting and stored at -20°C until shipped for analysis. See the *eport* for exceptions to draw times, which were incorporated into the statistical analyses.
IRB	Duramed secured the permission of the in writing on 7/9/96.
Informed consent	Subject Consent Form was signed by each subject who participated in the study.
Assay method for blood samples	
Analytes	Methotrexate
PK analysis	AUCT, AUCI, CMAX, TMAX, KE, and THALF were calculated.
Statistical analysis	90% confidence intervals were calculated for log-transformed AUCT, AUCI and CMAX.

IV. Bioanalytical Method Validation

Plasma methotrexate was analyzed using detection over a concentration range of ng/mL.

A. Pre-study Validation

The pre-study validation report for plasma methotrexate assay was prepared and signed as of 7/26/96.

Table IV-1. Pre-Study Validation for Plasma Methotrexate

Assay method:	internal standard was
Specificity:	No significant interference from endogenous components or other sources.
Sensitivity:	The limit of quantitation was set at 5 ng/mL for methotrexate.
Linearity:	Weighted ($1/C^2$) least squares regression was used. Standard curve was prepared in the concentration range of 5-500 ng/mL. Correlation coefficient was 0.9985.
Precision and accuracy:	Between assay for methotrexate quality control samples (5-400 ng/mL): 89.4-100.4% accuracy with 4.4-12.1% CV. Within assay for methotrexate quality control samples (5-400 ng/mL): 92.2-97.5% accuracy with 2.8-12.8% CV.
Recovery:	methotrexate: Absolute mean recovery of 63.2-72.3% with %CV of 10.6-14.0 for 10-400 ng/mL range. Internal standard (aminopterin): Absolute mean recovery of 46.0-59.9% with 9.6-17.1% CV.
Stability:	Long term stability for methotrexate: 3.5 month at -20°C. Stability data acceptable. Short term stability for methotrexate: 4 hours at RT. Stability data acceptable. Freeze-thaw stability for methotrexate: 3 cycles. Stability data acceptable. Extract stability for methotrexate: 48 hours at RT. Stability data acceptable.

B. Within-study Validation

Precision and accuracy of the assay of the quality control samples and back calculated standard curve samples used in the fasting study are shown in Table IV-2. The within-study

validation data are acceptable.

Table IV-2. Within-Study Precision and Accuracy
Methotrexate

Precision and accuracy:	Quality control samples (10-400 ng/mL): 95.8-101% accuracy with 2.83-14.8% CV. Standard curve samples (5-500 ng/mL): 99.5-100.8% accuracy with 4.82-9.9% CV.

V. Pharmacokinetic and Statistical Evaluation of Study Data

Subjects: All twenty-six healthy male subjects who enrolled completed the crossover study. Data from all subjects were used in the pharmacokinetic/statistical evaluation.

Medical events: A total of two medical events (2 for the reference product involving Subject #23.) were reported. No serious medical events were reported during the study.

Evaluation of study data: Reviewer recalculated all the pharmacokinetic parameters and statistics and the results of the recalculation are in agreement with the sponsor's submission.

1. Mean plasma methotrexate levels

Mean plasma methotrexate levels for the test and reference products under fasting conditions were comparable to each other as shown in Table V-1 and Fig. P-1. Peak mean plasma levels for the test and reference products were 128.9 ng/mL at 0.67 hour and 131.6 ng/mL at 0.83 hour, respectively.

TABLE V-1. MEAN PLASMA Methotrexate LEVELS FOR TEST AND REFERENCE PRODUCTS UNDER FASTING CONDITIONS
UNIT: PLASMA LEVEL=NG/ML TIME=HRS
MEAN1=TEST; MEAN2=REFERENCE; RMEAN12=MEAN1/MEAN2 RATIO
SD=STANDARD DEVIATION
Test Lot #GA194; Ref Lot #397-336

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.25	18.15	15.34	13.68	15.09	1.33
0.5	97.04	39.82	82.55	40.27	1.18
0.67	128.88	40.53	124.13	44.97	1.04
0.83	128.72	33.99	131.59	39.06	0.98
1	122.93	32.43	126.14	32.96	0.97
1.25	110.18	33.27	115.81	27.40	0.95
1.5	95.37	24.85	100.71	24.89	0.95
2	75.37	18.85	78.42	15.02	0.96
2.5	62.39	15.01	63.05	11.39	0.99
3	51.60	14.27	52.51	10.60	0.98
4	35.98	9.72	36.20	8.61	0.99
5	30.15	9.19	30.77	8.47	0.98
6	21.94	7.51	21.10	6.97	1.04
8	10.93	5.54	11.62	5.07	0.94
10	5.15	4.47	5.46	4.96	0.94
12	1.86	3.75	1.61	3.55	1.15
16	0.46	1.61	0.45	1.59	1.02
24	0.00	0.00	0.00	0.00	.

2. PK parameters and 90% confidence intervals

The arithmetic and geometric means for the PK parameters are shown in Table V-2. PK parameters, AUCT, AUCI, CMAX, LAUCT, LAUCI, and LCMAX for the test and reference products are comparable to each other. Their Test/Reference ratios range 0.97-1.01.

Table V-3 shows the LSMEANS for the test and reference products and the 90% confidence intervals for AUCT, AUCI and CMAX. The LSMEANS are comparable for the test and reference products. The Test/Reference ratios range 0.97-1.02. The 90% confidence intervals for the log-transformed AUCT, AUCI and CMAX are within the acceptable range of 80-125%.

No sequence effect was observed for LAUCT, LAUCI AND LCMAX.

TABLE V-2. ARITHMETIC/GEOMETRIC MEANS AND RATIOS
UNDER FASTING CONDITIONS
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG
MEAN1=TEST; MEAN2=REFERENCE; RMEAN12=MEAN1/MEAN2 RATIO
SD=STANDARD DEVIATION

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	433.58	95.14	428.75	95.08	1.01
AUCT	393.85	99.99	396.62	93.09	0.99
CMAX	144.29	34.61	146.83	29.38	0.98
KE	0.30	0.05	0.31	0.06	0.99
LAUCI	424.53	0.21	420.04	0.20	1.01
LAUCT	382.65	0.24	387.59	0.21	0.99
LCMAX	140.10	0.25	143.69	0.22	0.97
THALF	2.35	0.45	2.36	0.56	1.00
TMAX	0.88	0.32	0.97	0.40	0.91

TABLE V-3. LSMEANS AND 90% CONFIDENCE INTERVALS
UNDER FASTING CONDITIONS
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG
LSM1=TEST; LSM2=REFERENCE; RLSM12=LSM1/LSM2 RATIO
LOWCI12=LOWER 90% CI; UPPCI12=UPPER 90% CI

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	435.75	427.54	1.02	97.97	105.87
AUCT	393.85	396.62	0.99	94.83	103.77
CMAX	144.29	146.83	0.98	92.71	103.83
LAUCI	425.13	418.78	1.02	97.58	105.61
LAUCT	382.65	387.59	0.99	94.26	103.40
LCMAX	140.10	143.69	0.97	91.46	103.94

VI. Formulation and Dissolution Data

1. Formulation

The test formulation is shown in Table VI-1.

Table V-1. Test Formulation

Ingredient	Amount per tablet, mg
Methotrexate,	2.5
Lactose Monohydrate,	
Pregelatinized Starch,	
S	
Magnesium Stearate,	
Total weight	

2. Assay and content uniformity data

Table VI-2 shows the assay and content uniformity for the test and reference products.

Table VI-2. Assay and Content Uniformity

Product	Assay, %	Content Uniformity, % (%CV)
Test: Methotrexate Tablets, 2.5 mg Lot #GA194 Lot size: tablets		101.1 (3.0)
Reference: Methotrexate Sodium Tablets, 2.5 mg Lot #397-336 Exp: 11/97		99.4 (1.9)

3. Dissolution testing

USP23 dissolution method was used. The test and reference products met the USP specifications as shown in Table VI-3. The USP dissolution specifications are shown below:

Medium and Volume	0.1 N HCl; 900 mL
Apparatus and rpm	2 (paddle); 50 rpm
Time	45 min
Tolerances	NLT 75% (Q)

VII. Summary and Comments

1. **Pharmacokinetic and statistical evaluation:** Twenty-six healthy male subjects enrolled and all 26 completed the crossover study. Data from all 26 subjects were used in the pharmacokinetic/statistical evaluation. Peak mean plasma levels for the test and reference products were 128.9 ng/mL at 0.67 hour and 131.6 ng/mL at 0.83 hour, respectively. The LSMEANS are comparable for the test and reference products. The Test/Reference ratios range 0.97-1.02. The 90% confidence intervals for the log-transformed AUCT, AUCI and CMAX are within the acceptable range of 80-125%.

2. **Bioanalytical method validation:** Pre-study and within-study validation data are acceptable.

3. **Dissolution testing:** The test product, lot #GA194, met the USP dissolution specifications.

4. **Drug products:** The assay and content uniformity data for the test and reference products are acceptable. The batch size of the test product was ablets.

5. **Medical events:** A total of two medical events (2 for the reference product involving Subject #23.) were reported. No serious medical events were reported during the study.

VIII. Deficiency

None.

IX. Recommendations

1. The *in vivo* bioequivalence study conducted under fasting conditions by Duramed on its Methotrexate Tablets, 2.5 mg strength, lot #GA194, comparing it to Lederle's Methotrexate Sodium Tablets, 2.5 mg tablet, lot #397-336, has been found acceptable. The study demonstrates that Duramed's Methotrexate Tablets, 2.5 mg strength, is bioequivalent to the reference product, Lederle's Methotrexate Sodium Tablets, 2.5 mg tablet.

2. The USP dissolution testing conducted by Duramed on its Methotrexate Tablets, 2.5 mg strength, lot #GA194, is acceptable.

3. The USP dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of 0.1 N HCl at 37°C using USP 23 Apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than 75% of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

The firm should be informed of the recommendations.

/S/

Moo Park, Ph.D.
Chemist, Review Branch III
Division of Bioequivalence

/S/

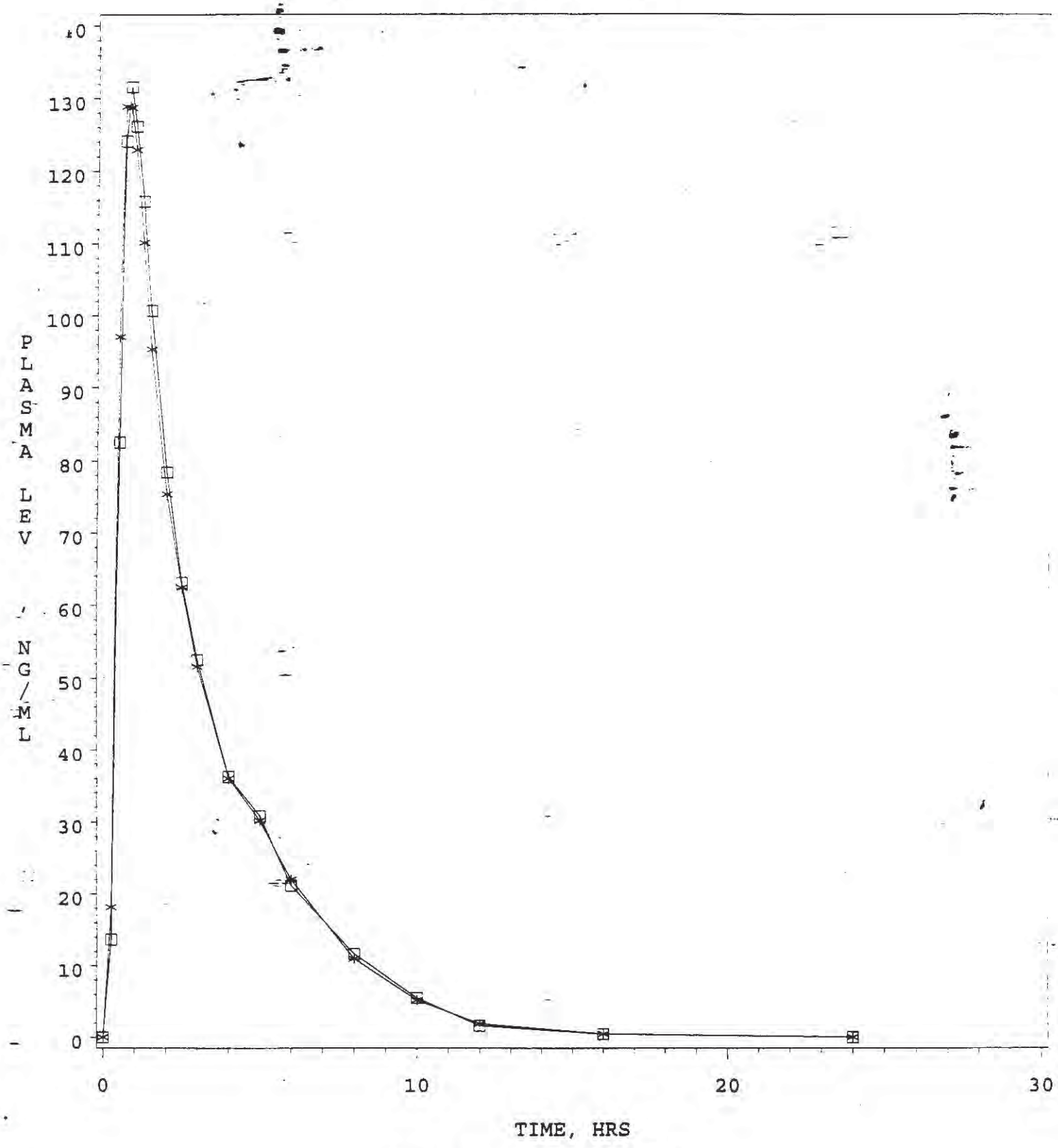
RD INITIALED RMHATRE
FT INITIALED RMHATRE
Ramakant M. Mhatre, Ph.D. 7/9/97
Team Leader, Review Branch III
Division of Bioequivalence

Concur: /S/ Date: 11/13/97
Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence

Table IV-3. *In Vitro* Dissolution Testing Data						
I. General Information						
Drug Product (Generic Name)	Methotrexate Tablets					
Strength	2.5 mg					
ANDA Number	40-233					
Applicant	Duramed					
Reference Drug Product	Lederle's Methotrexate Sodium Tablets, 2.5 mg					
II. USP Method for Dissolution Testing						
Medium and Volume	0.1 N HCl; 900 mL					
Apparatus and rpm	2 (paddle); 50 rpm					
Time	45 min					
Tolerances	NLT 75% (Q)					
Assay Method						
III. Dissolution Data (%)						
Time	Test Product Lot No: GA194 Strength: 2.5 mg No of Units: 12			Reference Product Lot No: 397-336 Strength: 2.5 mg No of Units: 12		
Min	Mean	Range	%CV	Mean	Range	%CV
5	83		8.8	21		14.1
10	94		5.1	48		6.9
15	95		5.2	76		7.3
45	96		4.5	100		2.2

FIG P- . PLASMA METHOTREXATE LEVELS

METHOTREXATE TABLETS, 2.5 MG, ANDA #40-233
UNDER FASTING CONDITIONS
DOSE=2 X 2.5 MG



BIOEQUIVALENCY - Acceptable

ANDA/AADA: 40-233 APPLICANT: Duramed

DRUG PRODUCT: Methotrexate 2.5mg tabs

1. **FASTING STUDY** (STF)
   Clinical: _____
   Analytical: _____
   Strengths: 2.5mg Acceptable
   Outcome: (AC) **IC UN NC**

2. **FOOD STUDY** (STP)
   Clinical: _____
   Analytical: _____
   Strengths: _____
   Outcome: AC IC UN NC

3. **MULTIPLE DOSE STUDY** (STM)
   Clinical: _____
   Analytical: _____
   Strengths: _____
   Outcome: AC IC UN NC

4. **DISSOLUTION DATA** (DIS)
   All Strengths
   Outcome: **AC IC UN NC**

5. **STUDY AMENDMENT** (STA)
   Strengths: _____
   Outcome: AC IC UN NC

6. **WAIVER** (WAI)
   Strengths: _____
   Outcome: AC IC UN NC

7. **DISSOLUTION WAIVER** (DIW)
   Strengths: _____
   Outcome: AC IC UN NC

8. **OTHER** (OTH) _____
   Strengths: _____
   Outcome: AC IC UN NC

9. **OTHER OPTIONS** (less common):
   Strengths: _____

   a. Protocol (PRO)
   b. Protocol Amendment (PRA)
   c. Protocol/Dissolution (PRD)
   d Special Dosage (STS)
   e. Study/Dissolution (STD)
   f. Bio study (STU)

   Outcome: AC IC UN NC

OUTCOME DECISIONS:

AC - Acceptable
NC - No Action
UN - Unacceptable (fatal flaw)
IC - Incomplete

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 40-233

ADMINISTRATIVE DOCUMENTS

APPROVAL SUMMARY PACKAGE

ANDA NUMBER: 40-233

FIRM: Duramed Pharmaceuticals, Inc.

DOSAGE FORM: Tablet

STRENGTHS: 2.5 mg

DRUG: Methotrexate Tablets

CGMP STATEMENT/EIR UPDATED STATUS:
EER status for all facilities listed in Section # 33 of CR # 4 of this ANDA is "Withhold" as of 6-30-98 by J.D. Ambrogia and there is no change in status since then.

BIO STUDY:
Acceptable as of sign off done on 1-16-98.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
MV is not required for the drug product. However, Philadelphia FDA District verified the methods for identification, assay, content uniformity and dissolution submitted in this ANDA.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?
Containers used in the stability studies are identical to those listed in container section.

LABELING:
FPL - acceptable per review completed by T. Watkins on 5-24-99.

STERILIZATION VALIDATION (IF APPLICABLE):
N/A

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?):
Methotrexate Tablets 2.5 mg (used for in-vivo bio studies and in-vitro dissolution studies): Lot # GA 194 (Size: Tablets).

Present status of Referenced DMF:

Referenced for is adequate per last review conducted by Steve Sherken on 12-11-97. No new information is submitted since this last review.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?)

Bio/stability Batches:

Methotrexate Tablets 2.5 mg: Lot # GA 194 (Size: Tablets).

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?

Production batch sizes post-approval to this ANDA are: Tablets and blets.

Manufacturing process for intended production size batch is same as used for the bio/stability batches.

Mujahid L. Shaikh /S/ 6/7/99
Review Chemist
Division of Chemistry I
OGD/CDER
5-28-99
Steve Sherken for Mike Smela/5/28/99 /S/ 6/7/99

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REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **40-233** Date of Submission: **October 9, 1998**

Applicant's Name: **Duramed Pharmaceuticals, Inc.**

Established Name: **Methotrexate Tablets USP, 2.5 mg**

Labeling Deficiencies:

1. CONTAINER (36s and 100s)

   Satisfactory in final.

2. INSERT

   Due to changes in the labeling of the reference listed drug, please revise your insert as follows:

   a. BOXED WARNING

      Include the following to appear as boxed warnings 8, 9, and 10:

      8. Like other cytotoxic drugs, methotrexate may induce "tumor lysis syndrome" in patients with rapidly growing tumors. Appropriate supportive and pharmacologic measures may prevent or alleviate this complication.

      9. Severe, occasionally fatal, skin reactions have been reported following single or multiple doses of methotrexate. Reaction have occurred within days of oral, intramuscular, intravenous, or intrathecal methotrexate administration. Recovery has been reported with discontinuation of therapy.(See **PRECAUTIONS, Organ System Toxicity**, *Skin*.)

      10. Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy.

b. PRECAUTIONS

I. Carcinogenesis, Mutagenesis, and Impairment of Fertility.

Delete "and" from this subsection title.

ii. Organ System Toxicity-Infection or Immunologic States

Revise the first sentence of paragraph two of this subsection to read as follows:

Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy.

iii. Organ System Toxicity-Renal

Include the following to appear immediately after the Pulmonary subsection.

Renal: High doses of methotrexate used in the treatment of osteosarcoma may cause renal damage leading to acute renal failure. Nephrotoxicity is due primarily to the precipitation of methotrexate and 7-hydroxymethotrexate in the renal tubules. Close attention to renal function including adequate hydration, urine alkalinization and measurement of serum methotrexate and creatinine levels are essential for safe administration.

iv. Organ System Toxicity-Skin

Include the following to appear immediately following the Organ System Toxicity-Renal Subsection:

Skin: Severe, occasionally fatal, dermatologic reactions, including toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, skin necrosis and erythema multiforme, have been reported in children and adults, within days of oral, intramuscular, intravenous, or intrathecal methotrexate administration. Reactions were noted after single or multiple, low, intermediate or high doses of

methotrexate in patients with neoplastic and non-neoplastic diseases.

c. ADVERSE REACTIONS

i. Include the following to appear immediately after the Alimentary System subsection:

Cardiovascular: pericarditis, pericardial effusion, hypotension, and thromboembolic events (including arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, thrombophlebitis, and pulmonary embolus).

ii. Central Nervous System-Revise the last sentence of this subsection to read as follows:

Following low doses, there have been occasional reports of transient subtle cognitive dysfunction, mood alteration, unusual cranial sensations, leukoencephalopathy, or encephalopathy.

iii. Include the following to appear immediately after the Central Nervous System subsection:

Infection: There have been case reports of sometimes fatal opportunistic infections in patients receiving methotrexate therapy for neoplastic and non-neoplastic diseases. *Pneumocystis carinii* pneumonia was the most common infection. Other reported infections included nocardiosis; histoplasmosis, cryptococcosis, Herpes zoster, H. simplex hepatitis, and disseminated H. simplex.

iv. Skin-Revise this subsection to read as follows:

...necrolysis, Stevens-Johnson syndrome, skin necrosis, and exfoliative dermatitis.

v. Urogenital System

A. Revise the first paragraph of this subsection to read as follows:

...dysfunction, vaginal discharge, and gynecomastia; infertility, abortion, fetal defects.

B. Delete "opportunistic infections" from the second paragraph of this subsection.

d. DOSAGE AND ADMINISTRATION

i. Neoplastic Diseases

A. Relocate the last sentence of paragraph one of this subsection to appear as the second paragraph under HANDLING AND DISPOSAL.

B. Include the following to appear as paragraph five of this subsection.

Leukemia: Acute lymphoblastic leukemia in pediatric patients and young adolescents is the most responsive to present day chemotherapy. In young adults and older patients, clinical remission is more difficult to obtain and early relapse is more common.

Please revise your package insert labeling, as instructed above, and submit 12 copies of final printed insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **ANDA 40233/000**
Stamp: **23-DEC-1996** Regulatory Due:
Applicant: **DURAMED PHARMS**
5040 LESTER RD
CINCINNATI, OH 45213

Priority: Org Code: **600**
Action Goal: District Goal: **23-FEB-1998**
Brand Name:
Established Name: **METHOTREXATE**
Generic Name:
Dosage Form: **TAB (TABLET)**
Strength: **2.5 MG**

FDA Contacts: **ID = 122344** **, Project Manager**
M. SMELA JR (HFD-625) 301-827-5848 , Team Leader

Overall Recommendation:

WITHHOLD on 30-JUN-1998 by J. D AMBROGIO (HFD-324) 301-827-0062
WITHHOLD on 08-MAY-1998 by R. WOODS (HFD-324) 301-827-0062

Establishment:
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **06-APR-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE OTHER TESTER**

Establishment:
DMF No:
AADA No:

)504

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **ASSIGNED INSPECTION TO IB**
Milestone Date: **12-APR-1999**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**
FINISHED DOSAGE OTHER TESTER
FINISHED DOSAGE PACKAGER

Establishment:
DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **07-APR-1999**
Decision: **ACCEPTABLE**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Reason: **BASED ON PROFILE**

Establishment:

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **06-APR-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE OTHER TESTER**
FINISHED DOSAGE OTHER TESTER

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 40-233

CORRESPONDENCE

DURAmed

The Art of Leadership...
The Science of Change

Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, Ohio 45213
(513) 731-9900

May 20, 1999

Mr. Douglas L. Sporn
Director, Office of Generic Drugs, CDER
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

[redacted] CORRESP
NC to Fax

RE: **ANDA 40-233: Methotrexate Tablets, USP, 2.5 mg**
Subject: **FACSIMILE AMENDMENT**

Dear Mr. Sporn:

Reference is made to your facsimile correspondence dated April 27, 1999 concerning deficiencies in our abbreviated new drug application (ANDA) #40-233 for Methotrexate Tablets, USP. We have noted the deficiencies cited and are amending the application, having responded to all of the deficiencies. For each item we first restate the deficiency then present our response or explanation. As requested, we have included a side-by-side comparison of our proposed labeling with our last submission.

This **Facsimile Amendment** is submitted in one (1) volume and includes two (2) copies, an archival copy and a review copy. In addition, a copy of the response minus the final printed labeling was faxed to the document control room at 301-827-4337.

We certify that a true copy of the technical section as described in 21 CFR 314.94 (d)(5) has been provided to the Food and Drug Administration, Atlanta District Office, Atlanta, Georgia.

Please direct any written communications regarding this ANDA to me at the above address. If you have any questions or require any additional information, please contact Ms. Annette Arlinghaus at (513) 731-9900, by fax at (513) 731-6482, or the undersigned at (513) 458-7274.

Sincerely,

Annette Arlinghaus /for

John R. Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs

Enclosures: completed Form FDA 356h

DURAmed

FPL

ORIG AMENDMENT

N/AC

Duramed Pharmaceuticals, Inc.
5040 Lester Road
Cincinnati, Ohio 45213
(513) 731-9900
(800) 543-8338

The Art of Leadership...
The Science of Change

October 9, 1998

Mr. Douglas L. Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: **ANDA 40-233: Methotrexate Tablets, USP, 2.5 mg**
Subject: **MAJOR AMENDMENT**

Dear Mr. Sporn:

Reference is made to your facsimile correspondence dated July 18, 1997 concerning deficiencies in our abbreviated new drug application (ANDA) #40-233 for Methotrexate Tablets, USP.

We have noted the deficiencies cited and are amending the application, having responded to all of the deficiencies. For each item we first restate the deficiency then present our response or explanation. As requested, we have included a side-by-side comparison of our proposed labeling with our last submission.

This **Major Amendment** is submitted in one (1) volume and includes two (2) copies, an archival copy and a review copy.

We certify that a true copy of the technical section as described in 21 CFR 314.94 (d)(5) has been provided to the Food and Drug Administration, Atlanta District Office, Atlanta, Georgia.

Please direct any written communications regarding this ANDA to me at the above address. If you have any questions or require any additional information, please contact Ms. Annette Arlinghaus at (513) 731-9900, by fax at (513) 731-6482, or the undersigned at (513) 458-7274.

Sincerely,

Annette Arlinghaus/for

John R. Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs

OCT 1998

Enclosures: completed Form FDA 356h

DURAmed

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Duramed Pharmaceuticals, Inc.
5040 Lester Road
Cincinnati, Ohio 45213
(513) 731-9900

April 16, 1997

NDA DRUG AMENDMENT

N/AC

Mr. Douglas L. Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 40-233 for Methotrexate Tablets, USP, 2.5 mg

Subject: **AMENDMENT - Addition of 36 count commercial package**

Dear Mr. Sporn:

Reference is made to your Refuse-to-File letter dated February 28, 1997. Our response to item 1 stated that we withdrew the 36 count commercial package due to lack of stability data. The data is now available and we are amending our application to include the 36 count package as a commercial package. The other applicable items specific to this package size were included in the original filing.

This **Amendment,** consisting of a two (2) page updated Stability Report (pages 1074 and 1075 of the original ANDA submission), now includes 1, 2 and 3 month AST, and 3 month RT results for the 36 count commercial package configuration.

This amendment includes two (2) copies, an archival copy and a review copy.

We certify that a true copy of this submission has been provided to the Food and Drug Administration, Atlanta District Office, Atlanta, Georgia.

If you have any questions, please feel free to contact Ms. Annette Arlinghaus or the undersigned by telephone at (513) 731-9900, or by fax at (513) 731-6482.

Sincerely,

John R. Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs

RECEIVED
APR 18 1997
GENERIC DRUGS

Enclosures: completed FDA 356h
stability tables

DURAMED
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The Science of Change

Duramed Pharmaceuticals, Inc.
5040 Lester Road
Cincinnati, Ohio 45213
(513) 731-9900

NDA ORIG AMENDMENT

March 13, 1997

Mr. Jerry Phillips
Director, Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville, MD 20857

RE: ANDA 40-233 for Methotrexate Tablets USP, 2.5 mg

Subject: **Amendment**

Dear Mr. Phillips:

Reference is made to your correspondence dated February 28, 1997 concerning minor administrative deficiencies in our Abbreviated New Drug Application 40-233 for Methotrexate Tablets USP, 2.5 mg. We have noted the deficiencies and are amending our application, having responded to all of the deficiencies. This amendment is formatted such that each deficiency is restated and then followed by our response.

This amendment includes two (2) copies, an archival copy and a review copy.

We certify that a true copy of this submission has been provided to the Food and Drug Administration, Atlanta District Office, Atlanta, Georgia.

If you have any questions, please contact Ms. Annette Arlinghaus or the undersigned by telephone at (513)-731-9900, or by fax at (513)-731-6482.

Sincerely,

John R. Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs

RECEIVED
MAR 14 1997
GENERIC DRUGS

ANDA 40-233

Duramed Pharmaceuticals, Inc.
Attention: John Repoza
5040 Lester Road
Cincinnati, OH 45213

APR 7

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to our "Refuse to File" letter dated February 28, 1997, and your amendment dated March 13, 1997.

NAME OF DRUG: Methotrexate Tablets USP, 2.5 mg

DATE OF APPLICATION: December 20, 1996

DATE OF RECEIPT: December 23, 1996

DATE ACCEPTABLE FOR FILING: March 14, 1997

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Sheila O'Keefe
Project Manager
(301) 594-0370

Sincerely yours,

/S/

Jerry Phillips 4/4/97
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 40-233

Duramed Pharmaceuticals, Inc.
Attention: John Repoza
5040 Lester Road
Cincinnati, OH 45213

FEB 28 '97

Dear Mr. Repoza:

Please refer to your abbreviated new drug application (ANDA) dated December 20, 1996 submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Methotrexate Tablets USP, 2.5 mg.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

Your stability data is incomplete. Please submit at least three months accelerated stability data on the largest and the smallest container sizes intended for market. The data for the 100 count package size is present, however, the data for the 36 count package is not complete, being comprised of only the initial data and no data for the 30-, 60- and 90-day stations.

Additionally, the dissolution data, as presented, does not include all the data necessary for a complete evaluation by the reviewer. In addition to the individual tablet data, means, range and relative standard deviation (RSD) at each time point and a description of the methodology being used, the dissolution report should also contain the lot numbers being tested, the designations "test preparation" and "reference preparation" are not adequate.

You have failed to completely package your test batch for lot GA194 in containers proposed for marketing. Please refer to the letters to industry from the Director, Office of Generic Drugs, dated November 8, 1991, and August 4, 1993. In addition, we refer you to the Office of Generic Drugs, Policy and Procedure Guide #41-91, dated February 8, 1995. Please provide documentation to confirm that the portion of the test batch packaged in the containers proposed for marketing is representative of the entire

batch. Such documentation should include testing results for in-process or packaged product that demonstrate homogeneity of the manufactured product.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Within 30 days of the date of this letter you may amend your application to include the above information or request, in writing, an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(a)(3) If you do so, the application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

Sheila O'Keefe
Project Manager
(301) 594-0370

Sincerely yours,

/S/

Jerry Phillips 2/25/97
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

DURAmed

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The Science of Change

Duramed Pharmaceuticals, Inc.
5040 Lester Road
Cincinnati, Ohio 45213
(513) 731-9900
(800) 543-8338

1/14/97

December 20, 1996

Mr. Douglas L. Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA for Methotrexate Tablets, USP, 2.5 mg

Dear Mr. Sporn:

Duramed Pharmaceuticals, Inc. (Duramed) submits today an original abbreviated new drug application (ANDA) seeking approval to market Methotrexate Tablets USP, 2.5 mg, that are bioequivalent to the reference drug, Lederle's Methotrexate Sodium Tablets, manufactured by Lederle pursuant to NDA # 08-085.

The facility for manufacturing of this dosage form is located at 2225 Centennial Drive in Gainesville, Georgia.

In accordance with the study protocol, approved by the Office of Generic Drugs (refer to documents included in Section VI), Duramed conducted one definitive *in vivo* bioequivalence study using 2.5 mg tablets.

Methotrexate Tablets, USP, 2.5 mg are stable and a two year expiration dating is requested for all package sizes. The two year expiration dating is supported by accelerated stability testing.

This ANDA is submitted in three (3) volumes. Duramed is filing an archival copy (blue folders) of the application that contains all the information required in the ANDA and a technical review copy (red folders) containing all the information in the archival copy with the exception of the Bioequivalence section. The Bioequivalence section (orange folders) contains the bioequivalence data as well a computer disk, in 3.5" format, containing ASCII files of the measured concentrations of the drug substance and the kinetic parameters for the bioequivalence study.

For more detailed information on the organization of this ANDA, please refer to the "Executive Summary - Organization of the ANDA" which follows this letter.

We certify that a true copy of the technical section described in 21 CFR 314.50 (d)(1), the chemistry, manufacturing, and controls section of this submission, has been provided to the Atlanta District Office of the Food and Drug Administration.

Please direct any written communications regarding this ANDA to me at the above address. If you have any questions or require any additional information, please feel free to contact Ms. Annette Arlinghaus at (513) 731-9900, or me at (513) 458-7294.

Sincerely,

John R. Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs

enclosures:
-Completed FDA Form 356h
-ANDA Submission

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40263

DRAFT FINAL PRINTED LABELING

Pharmaceuticals

Bioniar

METHOTREXATE INJECTION USP (Contains Preservative)

WARNINGS

METHOTREXATE SHOULD BE USED ONLY BY PHYSICIANS WHOSE KNOWLEDGE AND EXPERIENCE INCLUDE THE USE OF ANTIMETABOLITE THERAPY.

BECAUSE OF THE POSSIBILITY OF SERIOUS TOXIC REACTIONS (WHICH CAN BE FATAL):

METHOTREXATE SHOULD BE USED ONLY IN LIFE THREATENING NEOPLASTIC DISEASES, OR IN PATIENTS WITH PSORIASIS WITH SEVERE, RECALCITRANT, DISABLING DISEASE WHICH IS NOT ADEQUATELY RESPONSIVE TO OTHER FORMS OF THERAPY.

DEATHS HAVE BEEN REPORTED WITH THE USE OF METHOTREXATE IN THE TREATMENT OF MALIGNANCY AND PSORIASIS.

PATIENTS SHOULD BE CLOSELY MONITORED FOR BONE MARROW, LIVER, LUNG AND KIDNEY TOXICITIES. (See **PRECAUTIONS**)

PATIENTS SHOULD BE INFORMED BY THEIR PHYSICIAN OF THE RISKS INVOLVED AND BE UNDER A PHYSICIAN'S CARE THROUGHOUT THERAPY.

THE USE OF METHOTREXATE HIGH DOSE REGIMENS RECOMMENDED FOR OSTEOSARCOMA REQUIRES METICULOUS CARE. (See **DOSAGE AND ADMINISTRATION**.) HIGH DOSE REGIMENS FOR OTHER NEOPLASTIC DISEASES ARE INVESTIGATIONAL AND A THERAPEUTIC ADVANTAGE HAS NOT BEEN ESTABLISHED.

METHOTREXATE FORMULATIONS AND DILUENTS CONTAINING PRESERVATIVES MUST NOT BE USED FOR INTRATHECAL OR HIGH DOSE METHOTREXATE THERAPY.

1. Methotrexate has been reported to cause fetal death and/or congenital anomalies. Therefore, it is not recommended for women of childbearing potential unless there is clear medical evidence that the benefits can be expected to outweigh the considered risks. Pregnant women with psoriasis should not receive methotrexate. (See **CONTRAINDICATIONS**).

2. Methotrexate elimination is reduced in patients with impaired renal functions, ascites, or pleural effusions. Such patients require especially careful monitoring for toxicity, and require dose reduction or, in some cases, discontinuation of methotrexate administration.

3. Unexpectedly severe (sometimes fatal) bone marrow suppression and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high dosage) along with some nonsteroidal anti-inflammatory drugs (NSAIDs). (See **PRECAUTIONS**, Drug Interactions).

4. Methotrexate causes hepatotoxicity, fibrosis and cirrhosis, but generally only after prolonged use. Acutely, liver enzyme elevations are frequently seen. These are usually transient and asymptomatic, and also do not appear predictive of subsequent hepatic disease. Liver biopsy after sustained use often shows histologic changes, and fibrosis and cirrhosis have been reported; these latter lesions may not be preceded by symptoms or abnormal liver function tests in the psoriasis population. For this reason, periodic liver biopsies are usually recommended for psoriatic patients who are under long-term treatment. (See **PRECAUTIONS**, Organ System Toxicity, *Hepatic*).

5. Methotrexate-induced lung disease is a potentially dangerous lesion, which may occur acutely at any time during therapy and which has been reported at doses as low as 7.5 mg/week. It is not always fully reversible. Pulmonary symptoms (especially nonproductive cough) may require interruption of

6. Diarrhea and ulcerative stomatitis require interruption of therapy; otherwise, hemorrhagic enteritis and death from intestinal perforation may occur.

7. Malignant lymphomas, which may regress following withdrawal of methotrexate, may occur in patients receiving low-dose methotrexate and, thus, may not require cytotoxic treatment. Discontinue methotrexate first and, if the lymphoma does not regress, appropriate treatment should be instituted.

8. Like other cytotoxic drugs, methotrexate may induce "tumor lysis syndrome" in patients with rapidly growing tumors. Appropriate supportive and pharmacologic measures may prevent or alleviate this complication.

9. Severe, occasionally fatal, skin reactions have been reported following single or multiple doses of methotrexate. Reactions have occurred within days of oral, intramuscular, intravenous, or intrathecal methotrexate administration. Recovery has been reported with discontinuation of therapy (See **PRECAUTIONS, Organ System Toxicity**, *skin*.)

10. Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy.

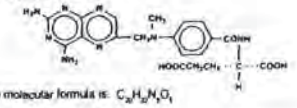
1999

DESCRIPTION

Methotrexate (formerly Amethopterin) is an antimetabolite used in the treatment of certain neoplastic diseases and severe psoriasis.

Chemically methotrexate is *N*-[4-[[(2,4-diamino-6-pteridinyl) methyl]methylamino]benzoyl]-L- glutamic acid.

The structural formula is:



The molecular formula is: $C_{20}H_{22}N_8O_5$

The molecular weight is: 454.45

Methotrexate Injection USP is sterile and non-pyrogenic and may be given by the intramuscular, intravenous or intra-arterial route. (See **DOSAGE AND ADMINISTRATION**). However, this preservative formulation contains Benzyl Alcohol and must not be used for intrathecal or high dose therapy.

Each mL contains methotrexate sodium equivalent to 25 mg methotrexate, Preservative: Benzyl Alcohol 0.90% w/v, and the following inactive ingredients: Sodium Chloride 0.26% w/v and Water for Injection qs ad 100% v. Sodium Hydroxide and/or Hydrochloric Acid may be added to adjust the pH during manufacture to 8.5 -8.7.

CLINICAL PHARMACOLOGY

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 nucleosides 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.

In psoriasis, the rate of production of epithelial cells in the skin is greatly increased over normal skin. This differential in proliferation rates is the basis for the use of methotrexate to control the psoriatic process.

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 resulting from gene amplification, or decreased polyglutamation of methotrexate. The actual mechanism of action is unknown.

Two Pediatric Oncology Group studies (one randomized and one non-randomized) demonstrated a significant improvement in relapse-free survival in patients with non-metastatic osteosarcoma, when high dose methotrexate with leucovorin rescue was used in combination with other chemotherapeutic agents following surgical resection of the primary tumor. These studies were not designed to demonstrate the specific contribution of high dose methotrexate/leucovorin rescue therapy to the efficacy of the combination. However, a contribution can be inferred from the reports of objective responses to this therapy in patients with metastatic osteosarcoma, and from reports of extensive tumor necrosis following preoperative administration of this therapy to patients with non-metastatic osteosarcoma.

Pharmacokinetics

Methotrexate is generally completely absorbed from parenteral routes of injection. After intramuscular injection, peak serum concentrations occur in 30 to 60 minutes.

Distribution- After intravenous administration, the initial volume of distribution is approximately 0.18 L/kg (18% of body weight) and steady- state volume of distribution is approximately 0.4 to 0.8 L/kg (40 to 80% of body weight). Methotrexate competes with reduced folates for active transport across cell membranes by means of a single carrier-mediated active transport process. At serum concentrations greater than 100 micromolar, passive diffusion becomes a major pathway by which effective intracellular concentrations can be achieved. Methotrexate in serum is approximately 50% protein bound. Laboratory studies demonstrate that it may be displaced from plasma albumin by various compounds including sulfonamides, salicylates, tetracyclines, chloramphenicol, and phenytoin.

Methotrexate does not penetrate the blood-cerebrospinal fluid barrier in therapeutic amounts when given parenterally.

Metabolism - After absorption, methotrexate undergoes hepatic and intracellular metabolism to polyglutamated forms which can be converted back to methotrexate by hydrolase activities. These polyglutamates act as inhibitors of dihydrofolate reductase and thymidylate synthesis. Small amounts of methotrexate polyglutamates may remain in tissues for extended periods. The retention and prolonged drug action of these active metabolites vary among different cells, tissues and tumors. The aqueous solubility of 7-hydroxymethotrexate is 2 to 5 fold lower than the parent compound. A small amount of metabolism to 7-hydroxymethotrexate may occur at doses commonly prescribed. Methotrexate is partially metabolized by intestinal flora after oral administration.

Half-Life - The terminal half-life reported for methotrexate is approximately three to ten hours for patients receiving treatment for psoriasis or low dose antineoplastic therapy (less than 30 mg/m²). For patients receiving high doses of methotrexate, the terminal half-life is eight to 15 hours.

Excretion - Renal excretion is the primary route of elimination and is dependent upon dosage and route of administration. With IV administration, 80% to 90% of the administered dose is excreted unchanged in the urine within 24 hours. There is limited biliary excretion amounting to 10% or less of the administered dose. Enterohepatic recirculation of methotrexate has been proposed.

Renal excretion occurs by glomerular filtration and active tubular secretion. Nonlinear elimination due to saturation of renal tubular reabsorption has been observed in psoriatic patients at doses between 7.5 and 30 mg. Impaired renal function, as well as concurrent use of drugs such as weak organic acids that also undergo tubular secretion, can markedly increase methotrexate serum levels. Excellent correlation has been reported between methotrexate clearance and endogenous creatinine clearance.

Methotrexate clearance rates vary widely and are generally at higher doses. Delayed drug clearance has been identified as one of the major factors responsible for methotrexate toxicity. It has been postulated that the toxicity of methotrexate for normal tissues is more dependent upon the duration of exposure to the drug rather than the peak level achieved. When a patient has delayed drug elimination due to compromised renal function, a third space effusion, or other causes, methotrexate serum concentrations may remain elevated for prolonged periods.

The potential for toxicity from high dose regimens or delayed excretion is reduced by the administration of leucovorin calcium during the final phase of methotrexate plasma elimination. Pharmacokinetic monitoring of methotrexate serum concentrations may help identify those patients at high risk for methotrexate toxicity and aid in proper adjustments of leucovorin dosing. Guidelines for monitoring serum methotrexate levels, and for adjustment of leucovorin dosing to reduce the risk of methotrexate toxicity, are provided below in **DOSAGE AND ADMINISTRATION**.

Methotrexate has been detected in human breast milk. The highest breast milk to plasma concentration ratio reached was 0.08.[1]

INDICATIONS AND USAGE

Neoplastic Diseases

Methotrexate is indicated in the treatment of gestational choriocarcinoma, chorioadenoma destruens and hydatidiform mole.

In acute lymphocytic leukemia, methotrexate is indicated in the pro-

prylaxis of meningeal leukemia and is used in maintenance therapy in combination with other chemotherapeutic agents.

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, 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.

Psoriasis
Methotrexate is indicated in the symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy, *but only when the diagnosis has been established, as by biopsy and/or after dermatologic consultation.* It is important to ensure that a psoriasis "flare" is not due to an undiagnosed concomitant disease affecting immune responses.

CONTRAINDICATIONS
Methotrexate can cause fetal death or teratogenic effects when administered to a pregnant woman. Methotrexate is contraindicated in pregnant patients with psoriasis and should be used in the treatment of neoplastic diseases only when the potential benefit outweighs the risk to the fetus. Women of childbearing potential should not be started on methotrexate until pregnancy is excluded and should be fully counseled on the serious risk to the fetus (see **PRECAUTIONS**) should they become pregnant while undergoing treatment. Pregnancy should be avoided if either partner is receiving methotrexate; during and for a minimum of three months after therapy for male patients, and during and for at least one ovulatory cycle after therapy for female patients. (See Boxed **WARNINGS**).

Because of the potential for serious adverse reactions from methotrexate in breast fed infants, it is contraindicated in nursing mothers.

Patients with psoriasis with alcoholism, alcoholic liver disease or other chronic liver disease should not receive methotrexate.

Patients with psoriasis who have overt or laboratory evidence of immunodeficiency syndromes should not receive methotrexate.

Patients with psoriasis who have preexisting blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anemia, should not receive methotrexate.

Patients with a known hypersensitivity to methotrexate should not receive the drug.

WARNINGS -SEE BOXED WARNINGS.

PRECAUTIONS
General
Methotrexate has the potential for serious toxicity (See Boxed **WARNINGS**). Toxic effects may be related in frequency and severity to dose or frequency of administration but have been seen at all doses. Because they can occur at any time during therapy, it is necessary to follow patients on methotrexate closely. Most adverse reactions are reversible if detected early. When such reactions do occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken. If necessary, this could include the use of leucovorin calcium (see **OVERDOSAGE**). If methotrexate therapy is reinstituted, it should be carried out with caution, with adequate consideration of further need for the drug and increased alertness as to possible recurrence of toxicity.

The clinical pharmacology of methotrexate has not been well studied in older individuals. Due to diminished hepatic and renal function as well as decreased folate stores in this population, relatively low doses should be considered, and these patients should be closely monitored for early signs of toxicity.

Information for Patients
Patients should be informed of the early signs and symptoms of toxicity, of the need to see their physician promptly if they occur, and the need for close follow-up, including periodic laboratory tests to monitor toxicity.

Both the physician and pharmacist should emphasize to the patient that the recommended dose is taken weekly in psoriasis, and that mistaken daily use of the recommended dose has led to fatal toxicity. Prescriptions should not be written or refilled on a PRN basis.

Patients should be informed of the potential benefit and risk in the use of methotrexate. The risk of effects on reproduction should be discussed with both male and female patients taking methotrexate.

Laboratory Tests
Patients undergoing methotrexate therapy should be closely monitored so that toxic effects are detected promptly. Baseline assessment should include a complete blood count with differential and platelet counts, hepatic enzymes, renal function tests and a chest X-ray. During therapy of psoriasis, monitoring of these parameters is recommended: hematology at least monthly, renal function and liver function every 1 to 2 months. More frequent monitoring is usually indicated during antineoplastic therapy. *During initial or changing doses*, or during periods of increased risk of elevated methotrexate blood levels (eg, dehydration), more frequent monitoring may also be indicated.

Transient liver function test abnormalities are observed frequently after methotrexate administration and are usually not cause for modification of methotrexate therapy. Persistent liver function test abnormalities, and/or depression of serum albumin may be indicators of serious liver toxicity and require evaluation. (See **PRECAUTIONS**, Organ System Toxicity, *Hepatic*).

A relationship between abnormal liver function tests and fibrosis or cirrhosis of the liver has not been established for patients with psoriasis.

Pulmonary function tests may be useful if methotrexate-induced lung disease is suspected, especially if baseline measurements are available.

Drug Interactions
Nonsteroidal anti-inflammatory drugs should not be administered prior to or concomitantly with the high doses of methotrexate used in the treatment of osteosarcoma. Concomitant administration of some NSAIDs with high dose methotrexate therapy has been reported to elevate and prolong serum methotrexate levels, resulting in deaths from severe hematologic and gastrointestinal toxicity.

Caution should be used when NSAIDs and salicylates are administered concomitantly with lower doses of methotrexate. These drugs have been reported to reduce the tubular secretion of methotrexate in an animal model and may enhance its toxicity.

Methotrexate is partially bound to serum albumin, and toxicity may be increased because of displacement by certain drugs, such as salicylates, phenylbutazone, phenytoin, and sulfonamides. Renal tubular transport is also diminished by probenecid, use of methotrexate with this drug should be carefully monitored.

In the treatment of patients with osteosarcoma, caution must be exercised if high-dose methotrexate is administered in combination with a potentially nephrotoxic chemotherapeutic agent (eg, cisplatin).

Oral antibiotics such as tetracycline, chloramphenicol, and nonabsorbable broad spectrum antibiotics, may decrease intestinal absorption of methotrexate or interfere with the enterohepatic circulation by inhibiting bowel flora and suppressing metabolism of the drug by bacteria.

Penicillins may reduce the renal clearance of methotrexate; increased serum concentrations of methotrexate with concomitant hematologic and gastrointestinal toxicity have been observed with low dose methotrexate. Use of methotrexate with penicillins should be carefully monitored.

Patients receiving concomitant therapy with methotrexate and etretinate or other retinoids should be monitored closely for possible higher risk of hepatotoxicity.

Methotrexate may decrease the clearance of theophylline; theophylline levels should be monitored when used concurrently with methotrexate.

Vitamin preparations containing folic acid or its derivatives may decrease responses to systemically administered methotrexate. Preliminary animal and human studies have shown that small quantities of intravenously administered leucovorin enter the CSF primarily as 5-methyltetrahydrofolate and, in humans, remain 1-3 orders of magnitude lower than the usual methotrexate concentrations following intrathecal administration. However, high doses of leucovorin may reduce the efficacy of intrathecally administered methotrexate.

Folate deficiency states may increase methotrexate toxicity. Trimethoprim/sulfamethoxazole has been reported rarely to increase bone marrow suppression in patients receiving methotrexate, probably by an additive antifolate effect.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No controled human data exist regarding the risk of neoplasia with methotrexate. Methotrexate has been evaluated in a number of animal studies for carcinogenic potential with inconclusive results. Although there is evidence that methotrexate causes chromosomal damage to animal somatic cells and human bone marrow cells, the clinical significance remains uncertain. Benefits should be weighed against the potential risk before using methotrexate alone or in combination with other drugs, especially in pediatric patients or young adults. Methotrexate causes embryotoxicity, abortion, and fetal defects in humans. It has also been reported to cause impairment of fertility, oligospermia and menstrual dysfunction in humans, during and for a short period after cessation of therapy.

Pregnancy : Teratogenic Effects, Pregnancy Category X.
Nursing Mothers
See **CONTRAINDICATIONS**.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established, other than in cancer chemotherapy.

Organ System Toxicity
Gastrointestinal: If vomiting, diarrhea, or stomatitis occur, which may result in dehydration, methotrexate should be discontinued until recovery occurs. Methotrexate should be used with extreme caution in the presence of peptic ulcer disease or ulcerative colitis.

Hematologic: Methotrexate can suppress hematopoiesis and cause anemia, leukopenia, and/or thrombocytopenia. In patients with malignancy and preexisting hematopoietic impairment, the drug should be used with caution, if at all.

In psoriasis, methotrexate should be stopped immediately if there is a significant drop in blood counts. In the treatment of neoplastic diseases, methotrexate should be continued only if the potential benefit warrants the risk of severe myelosuppression. Patients with profound granulocytopenia and fever should be evaluated immediately and usually require parenteral broad-spectrum antibiotic therapy.

Hepatic: Methotrexate has the potential for acute (elevated transaminases) and chronic (fibrosis and cirrhosis) hepatotoxicity. Chronic toxicity is potentially fatal, it generally has occurred after prolonged use (generally two years or more) and after a total dose of at least 1.5 grams. In studies in psoriatic patients, hepatotoxicity appeared to be a function of total cumulative dose and appeared to be enhanced by alcoholism, obesity, diabetes and advanced age. An accurate incidence rate has not been determined; the rate of progression and reversibility of lesions is not known. Special caution is indicated in the presence of preexisting liver damage or impaired hepatic function.

In psoriasis, liver function tests, including serum albumin, should be performed periodically prior to dosing but are often normal in the face of developing fibrosis or cirrhosis. These lesions may be detectable only by biopsy. The usual recommendation is to obtain a liver biopsy at 1) pretherapy or shortly after initiation of therapy (2-4 months), 2) a total cumulative dose of 1.5 grams, and 3) after each additional 1.0 to 1.5 grams. Moderate fibrosis or any cirrhosis normally leads to discontinuation of the drug; mild fibrosis normally suggests a repeat biopsy in 6 months. Milder histologic findings such as fatty change and low grade portal inflammation, are relatively common pretherapy. Although these mild changes are usually not a reason to avoid or discontinue methotrexate therapy, the drug should be used with caution.

Infection or Immunologic States: Methotrexate should be used with extreme caution in the presence of active infection, and is usually contraindicated in patients with overt or laboratory evidence of immunodeficiency syndromes. Immunization may be ineffective when given during methotrexate therapy. Immunization with live virus vaccines is generally not recommended. There have been reports of disseminated vaccinia infections after smallpox immunizations in patients receiving methotrexate therapy. Hypogammaglobulinemia has been reported rarely.

Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy. When a patient presents with pulmonary symptoms, the possibility of *Pneumocystis carinii* pneumonia should be considered.

Neurologic: There have been reports of leukoencephalopathy following intravenous administration of methotrexate to patients who have had craniospinal irradiation. Serious neurotoxicity, frequently manifested as generalized or focal seizures, has been reported with unexpectedly increased frequency among pediatric patients with acute lymphoblastic leukemia who were treated with intermediate-dose intravenous methotrexate (1 gm/m²). Symptomatic patients were commonly noted to have leukoencephalopathy and/or microangiopathic calcifications on diagnostic imaging studies. Chronic leukoencephalopathy has also been reported in patients who received repeated doses of high-dose methotrexate with leucovorin rescue even without cranial irradiation. Discontinuation of methotrexate does not always result in complete recovery.

A transient acute neurologic syndrome has been observed in patients treated with high dose regimens. Manifestations of this stroke-like encephalopathy may include confusion, hemiparesis, seizures and coma. The exact cause is unknown.

After the intrathecal use of methotrexate, the central nervous system toxicity which may occur can be classified as follows: acute chemical arachnoiditis manifested by such symptoms as headache, back pain, nuchal rigidity, and fever; sub-acute myelopathy characterized by paraparesis/paraplegia associated with involvement with one or more spinal nerve roots; chronic leukoencephalopathy manifested by confusion, irritability, somnolence, ataxia, dementia, seizures and coma. This condition can be progressive and even fatal.

Pulmonary: Pulmonary symptoms (especially a dry nonproductive cough) or a non-specific pneumonitis occurring during methotrexate therapy may be indicative of a potentially dangerous lesion and require interruption of treatment and careful investigation. Although clinically variable, the typical patient with methotrexate induced lung disease presents with fever, cough, dyspnea, hypoxemia, and an infiltrate on chest x-ray; infection needs to be excluded. This lesion can occur at all dosages.

Renal: High doses of methotrexate used in the treatment of osteosarcoma may cause renal damage leading to acute renal failure. Nephrotoxicity is due primarily to the precipitation of methotrexate and 7-hydroxymethotrexate in the renal tubules. Close attention to renal function including adequate hydration, urine alkalinization and measurement of serum methotrexate and creatinine levels are essential for safe administration.

Skin: Severe, occasionally fatal, dermatologic reactions, including toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, skin necrosis, and erythema multiforme, have been reported in children and adults, within days of oral, intramuscular, intravenous, or intrathecal methotrexate administration. Reactions were noted after single or multiple low, intermediate, or high doses of methotrexate in patients with neoplastic and non-neoplastic diseases.

Other precautions: Methotrexate should be used with extreme caution in the presence of debility.

Methotrexate exits slowly from third space compartments (eg, pleural effusions or ascites). This results in a prolonged terminal plasma half-life and unexpected toxicity. In patients with significant third space accumulations, it is advisable to evacuate the fluid before treatment and to monitor plasma methotrexate levels.

Lesions of psoriasis may be aggravated by concomitant exposure to ultraviolet radiation. Radiation dermatitis and sunburn may be "recalled" by the use of methotrexate.

ADVERSE REACTIONS

IN GENERAL, THE INCIDENCE AND SEVERITY OF ACUTE SIDE EFFECTS ARE RELATED TO DOSE AND FREQUENCY OF ADMINISTRATION. THE MOST SERIOUS REACTIONS ARE DISCUSSED ABOVE UNDER ORGAN SYSTEM TOXICITY IN THE PRECAUTION SECTION. THAT SECTION SHOULD ALSO BE CONSULTED WHEN LOOKING FOR INFORMATION ABOUT ADVERSE REACTIONS WITH METHOTREXATE.

The most frequently reported adverse reactions include ulcerative stomatitis, leukopenia, nausea, and abdominal distress. Other frequently reported adverse effects are malaise, undue fatigue, chills and fever, dizziness and decreased resistance to infection.

Other adverse reactions that have been reported with methotrexate are listed below by organ system. In the oncology setting, concomitant treatment and the underlying disease make specific attribution of a reaction to methotrexate difficult.

Alimentary System: gingivitis, pharyngitis, stomatitis, anorexia, nausea, vomiting, diarrhea, hematemesis, melena, gastrointestinal ulceration and bleeding, enteritis, pancreatitis.

Cardiovascular: pericarditis, pericardial effusion, hypotension, and thromboembolic events (including arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, thrombophlebitis, and pulmonary embolus).

Central Nervous System: headaches, drowsiness, blurred vision, Aphasia, hemiparesis, paresis and convulsions have also occurred following administration of methotrexate. Following low doses, there have been occasional reports of transient subtle cognitive dysfunction, mood alteration or unusual cranial sensations.

Infection: There have been case reports of sometimes fatal opportunistic infections in patients receiving methotrexate therapy for neoplastic and non-neoplastic diseases. *Pneumocycstis carinii* pneumonia was the most common infection. Other reported infections included nocardiosis, histoplasmosis, cryptococcosis, Herpes zoster, H. simplex hepatitis, and disseminated H. simplex.

Ophthalmic: conjunctivitis, serious visual changes of unknown etiology.

Pulmonary System: interstitial pneumonitis deaths have been reported, and chronic interstitial obstructive pulmonary disease has occasionally occurred.

Skin: erythematous rashes, pruritus, urticaria, photosensitivity, pigmentary changes, alopecia, ecchymosis, telangiectasia, acne, furunculosis, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, skin necrosis, and exfoliative dermatitis.

Urogenital System: severe nephropathy or renal failure, azotemia, cystitis, hematuria; defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, vaginal discharge, and gynecomastia; infertility, abortion, fetal defects.

Other rarer reactions to or attributed to the use of methotrexate such as nodulosis, vasculitis, arthralgia/myalgia, loss of libido/impotence, diabetes, osteoporosis, sudden death, reversible lymphomas and tumor lysis syndrome. Anaphylactoid reactions have been reported.

Adverse Reactions in Psoriasis:

There are no recent placebo-controlled trials in patients with psoriasis. There are two literature reports (Roenigk, 1969, and Nyfors, 1978) describing large series (n=204, 248) of psoriasis patients treated with methotrexate. Dosages ranged up to 25 mg per week and treatment was administered for up to four years. With the exception of alopecia, photosensitivity, and "burning of skin lesions" (each 3% to 10%), the adverse reaction rates in these reports were very similar to those in the rheumatoid arthritis studies.

OVERDOSAGE

Leucovorin is indicated to diminish the toxicity and counteract the effect of inadvertently administered overdosages of methotrexate. Leucovorin administration should begin as promptly as possible. As the time interval between methotrexate administration and leucovorin initiation increases, the effectiveness of leucovorin in counteracting toxicity decreases. Monitoring of the serum methotrexate concentration is essential in determining the optimal dose and duration of treatment with leucovorin.

In cases of massive overdosage, hydration and urinary alkalinization may be necessary to prevent the precipitation of methotrexate and/or its metabolites in the renal tubules. Neither hemodialysis nor peritoneal dialysis has been shown to improve methotrexate elimination.

Accidental intrathecal overdosage may require intensive systemic support, high dose systemic leucovorin, alkaline diuresis and rapid CSF drainage and ventriculolumbar perfusion.

DOSAGE AND ADMINISTRATION

Neoplastic Diseases

Oral administration in tablet form is often preferred when low doses are being administered since absorption is rapid and effective serum levels are obtained. Methotrexate injection may be given by the intramuscular, intravenous, or the intra-arterial route. However, this preserved formulation contains Benzyl Alcohol and must not be used for intrathecal or high dose therapy.

Choriocarcinoma and similar trophoblastic diseases: Methotrexate is administered orally or intramuscularly in doses of 15 to 30 mg daily for a five-day course. Such courses are usually repeated for 3 to 5 times as required, with rest periods of one or more weeks interposed between courses, until any manifesting toxic symptoms subside. The effectiveness of therapy is ordinarily evaluated by 24 hour quantitative analysis of urinary chorionic gonadotropin (hCG), which should return to normal or less than 50 IU/24 hr usually after the third or fourth course and usually be followed by a complete resolution of measurable lesions in 4 to 6 weeks. One to two courses of methotrexate after normalization of hCG is usually recommended. Before each course of the drug careful clinical assessment is essential. Cyclic combination therapy of methotrexate with other antitumor drugs has been reported as being useful.

Since hydatidiform mole may precede choriocarcinoma, prophylactic chemotherapy with methotrexate has been recommended.

Chorioadenoma destruens is considered to be an invasive form of hydatidiform mole. Methotrexate is administered in these disease states in doses similar to those recommended for choriocarcinoma.

Leukemia: Acute lymphoblastic leukemia in pediatric patients and young adolescents is the most responsive to present day chemotherapy. In young adults and older patients, clinical remission is more difficult to obtain and early relapse is more common.

Methotrexate alone or in combination with steroids was used initially for induction of remission in acute lymphoblastic leukemias. More recently corticosteroid therapy, in combination with other antileukemic drugs or in cyclic combinations with methotrexate included, has appeared to produce rapid and effective remissions. When used for induction, methotrexate in doses of 3.3 mg/m² in combination with 60 mg/m² of prednisone, given daily, produced remissions in 50% of patients treated, usually within a period of 4 to 6 weeks. Methotrexate in combination with other agents appears to be the drug of choice for securing maintenance of drug-induced remissions. When remission is achieved and supportive care has produced general clinical improvement, maintenance therapy is initiated, as follows: Methotrexate is administered 2 times weekly either by mouth or intramuscularly in total weekly doses of 30 mg/m². It has also been given in doses of 2.5 mg/kg intravenously every 14 days. If and when relapse does occur, reinduction of remission can again usually be obtained by repeating the initial induction regimen.

A variety of combination chemotherapy regimens have been used for both induction and maintenance therapy in acute lymphoblastic leukemia. The physician should be familiar with the new advances in antileukemic therapy.

Meningeal Leukemia: In the treatment of prophylaxis of meningeal leukemia, methotrexate must be administered intrathecally.

Preservative free methotrexate is diluted to a concentration of 1 mg/mL in an appropriate sterile, preservative free medium such as 0.9% Sodium Chloride Injection, USP.

The cerebrospinal fluid volume is dependent on age and not on body surface area. The CSF is at 40% of the adult volume at birth and reaches the adult volume in several years.

Intrathecal methotrexate administration at a dose of 12 mg/m² (maximum 15 mg) has been reported to result in low CSF methotrexate concentrations and reduced efficacy in pediatric patients and high concentrations and neurotoxicity in adults. The following dosage regimen is based on age instead of body surface area:

AGE (years)	DOSE (mg)
<1	6
1	8
2	10
3 or older	12

In one study in patients under the age of 40, this dosage regimen appeared to result in more consistent CSF methotrexate concentrations and less neurotoxicity. Another study in pediatric patients with acute lymphocytic leukemia compared this regimen to a dose of 12 mg/m² (maximum 15 mg), a significant reduction in the rate of CNS relapse was observed in the group whose dose was based on age.

Because the CSF volume and turnover may decrease with age, a dose reduction may be indicated in elderly patients.

For the treatment of meningeal leukemia, intrathecal methotrexate may be given at intervals of 2 to 5 days. However, administration at intervals of less than 1 week may result in increased subacute toxicity. Methotrexate is administered until the cell count of the cerebrospinal fluid returns to normal. At this point one additional dose is advisable. For prophylaxis against meningeal Leukemia, the dosage is the same as for treatment except for the intervals of administration. On this subject, it is advisable for the physician to consult the medical literature.

Untoward side effects may occur with any given intrathecal injection and are commonly neurological in character. Large doses may cause convulsions. Methotrexate given by the intrathecal route appears significantly in the systemic circulation and may cause systemic methotrexate toxicity. Therefore, systemic antileukemic therapy with the drug should be appropriately adjusted, reduced or discontinued. Focal leukemic involvement of the central nervous system may not respond to intrathecal chemotherapy and is best treated with radiotherapy.

Lymphomas. In Burkitt's tumor, Stages I-II, methotrexate has produced prolonged remissions in some cases. Recommended dosage is 10 to 25 mg/day orally for 4 to 8 days. In Stage III, methotrexate is commonly given concomitantly with other antitumor agents. Treatment in all stages usually consists of several courses of the drug interposed with 7 to 10 day rest periods. Lymphosarcomas in Stage III may respond to combined drug therapy with methotrexate given in doses of 0.625 to 2.5 mg/kg daily.

Mycosis fungoides. Therapy with methotrexate appears to produce clinical remissions in one-half of the cases treated. Dosage is usu-

ally 2.5 to 10 mg daily by mouth for weeks or months. Dose levels of drug adjustment of dose regimen by reduction or cessation of drug are guided by patient response and hematologic monitoring. Methotrexate has been given intramuscularly in doses of 50 mg once weekly or 25 mg 2 times weekly.

Osteosarcoma: An effective adjuvant chemotherapy regimen requires the administration of several cytotoxic chemotherapeutic agents. In addition to high dose methotrexate with leucovorin rescue, these agents may include doxorubicin, cisplatin, and the combination of bleomycin, cyclophosphamide and dactinomycin (BCD) in the doses and schedule shown in the table below. The starting dose for high-dose methotrexate treatment is 12 grams/m². If this dose is not sufficient to produce a peak serum methotrexate concentration of 1,000 micromolar (10^{-3} mol/L) at the end of the methotrexate infusion, the dose may be escalated to 15 grams/m² in subsequent treatments. If the patient is vomiting or is unable to tolerate oral medication, leucovorin is given IV or IM at the same dose and schedule.

Drug*	Dose*	Treatment Week* After Surgery
Methotrexate	12g/m² IV as 4 hour infusion (starting dose)	4,5,6,7,11,12,15 16,29,30,44,45
Leucovorin	15 mg orally every six hours for 10 doses starting at 24 hours after start of methotrexate infusion.	
Doxorubicin † as a single drug	30 mg/m² day IV x 3 days	8,17
Doxorubicin † Cisplatin †	50 mg/m² IV 100 mg/m² IV	20,23,33,36 20,23,33,36
Bleomycin †	15 units/m² IV x 2 days	2,13,26,39,42
Cyclophosphamide †	600 mg/m² IV x 2 days	2,13,26,39,42
Dactinomycin †	0.6 mg/m² IV x 2 days	2,13,26,39,42

* Link MP, Goorin AM, Miser AW, et al: The effect of adjuvant chemotherapy on relapse-free survival in patients with osteosarcoma of the extremity. *N Engl J of Med* 1986; 314(No 25) 1600-1606.

† See each respective package insert for full prescribing information. Dosage modifications may be necessary because of drug-induced toxicity.

When these higher doses of methotrexate are to be administered, the following safety guidelines should be closely observed.

GUIDELINES FOR METHOTREXATE THERAPY WITH LEUCOVORIN RESCUE

1. Administration of methotrexate should be delayed until recovery if:
   - the WBC count is less than 1500/microliter
   - the neutrophil count is less than 200/microliter
   - the platelet count is less than 75,000/microliter
   - the serum bilirubin level is greater than 1.2 mg/dL
   - the SGPT level is greater than 450 U
   - mucositis is present, until there is evidence of healing
   - persistent pleural effusion is present; this should be drained dry prior to infusion.

2. Adequate renal function must be documented.
   a. Serum creatinine must be normal, and creatinine clearance must be greater than 60 mL/min, before initiation of therapy.
   b. Serum creatinine must be measured prior to each subsequent course of therapy. If serum creatinine has increased by 50 % or more compared to a prior value, the creatinine clearance must be measured and documented to be greater than 60 mL/min (even if the serum creatinine is still within the normal range).

3. Patients must be well hydrated, and must be treated with sodium bicarbonate for urinary alkalinization.
   a. Administer 1,000 mL/m² of intravenous fluid over 6 hours prior to initiation of the methotrexate infusion. Continue hydration at 125 mL/m²/hr (3 liters/m²/day) during the methotrexate infusion, and for 2 days after the infusion has been completed.
   b. Alkalinize urine to maintain pH above 7.0 during methotrexate infusion and leucovorin calcium therapy. This can be accomplished by the administration of sodium bicarbonate orally or by incorporation into a separate intravenous solution.

4. Repeat serum creatinine and serum methotrexate 24 hours after starting methotrexate and at least once daily until the methotrexate level is below 5×10^{-8} mol/L (0.05 micromolar).

5. The table below provides guidelines for leucovorin calcium dosage based upon serum methotrexate levels. (See table below.†)

Patients who experience delayed early methotrexate elimination are likely to develop nonreversible oliguric renal failure. In addition to appropriate leucovorin therapy, these patients require continuing hydration and urinary alkalinization, and close monitoring of fluid and electrolyte status, until the serum methotrexate level has fallen to below 0.05 micromolar and the renal failure has resolved.

6. Some patients will have abnormalities in methotrexate elimination, or abnormalities in renal function following methotrexate administration, which are significant but less severe than the abnormalities described in the table below. These abnormalities may or may not be associated with significant clinical toxicity. If significant toxicity is observed, leucovorin rescue should be extended for an additional 24 hours (total 14 doses over 84 hours) in subsequent courses of therapy. The possibility that the patient is taking other medications which interact with methotrexate (eg, medications which may interfere with methotrexate binding to serum albumin, or elimination) should always be reconsidered when laboratory abnormalities or clinical toxicities are observed.

CAUTION: DO NOT ADMINISTER LEUCOVORIN INTRATHECALLY.

Psoriasis:
The patient should be fully informed of the risks involved and should be under constant supervision of the physician. (See Information for Patients Under **PRECAUTIONS**). Assessment of hematologic, hepatic, renal, and pulmonary function should be made by history, physical examination, and laboratory tests before beginning, periodically during, and before reinstituting methotrexate therapy. (See **PRECAUTIONS**). Appropriate steps should be taken to avoid conception during methotrexate therapy. (See **PRECAUTIONS and CONTRAINDICATIONS**).

All schedules should be continually tailored to the individual patient. An initial test dose may be given prior to the regular dosing schedule to detect any extreme sensitivity to adverse effects (See **ADVERSE REACTIONS**). Maximal myelosuppression usually occurs in seven to ten days.

Psoriasis: Recommended Starting Dose Schedule:

1. Weekly single IM or IV dosage schedule: 10 to 25 mg per week until adequate response is achieved.

2. Divided oral dose schedule: 2.5 mg at 12 hour intervals for three doses.

Dosages in each schedule may be gradually adjusted to achieve optimal clinical response; 30 mg/week should not ordinarily be exceeded.

Once optimal clinical response has been achieved, each dosage schedule should be reduced to the lowest possible amount of drug and to the longest possible rest period. The use of methotrexate may permit the return to conventional topical therapy, which should be encouraged.

HANDLING AND DISPOSAL

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[2-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

DILUTION INSTRUCTIONS FOR LIQUID METHOTREXATE INJECTION PRODUCT:

Methotrexate Injection USP, Isotonic Liquid, Contains Preservative

If desired, the solution may be further diluted with a compatible medium such as Sodium Chloride Injection. Storage for 24 hours at a temperature of 21 to 25°C results in a product which is within 90% of label potency.

HOW SUPPLIED

Methotrexate Injection USP, Isotonic Liquid, Contains Preservative

Each mL contains methotrexate sodium equivalent to 25 mg methotrexate.

2 mL 50 mg
10 mL 250mg

Store at controlled room temperature 15°-30°C (59°-86°F). **PROTECT FROM LIGHT.** RETAIN IN CARTON UNTIL CONTENTS ARE USED.

Rx only

Manufactured by:
Bigmar Pharmaceuticals SA
Barbengo, Switzerland

Manufactured for:
Bigmar, Inc.
Johnstown, OH 43031

Rev 05, November 1998

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†LEUCOVORIN RESCUE SCHEDULES FOLLOWING TREATMENT WITH HIGHER DOSES OF METHOTREXATE

Clinical Situation: Normal Methotrexate Elimination
Laboratory Findings: Serum methotrexate level approximately 10 micromolar at 24 hours after administration, 1 micromolar at 48 hours, and less than 0.2 micromolar at 72 hours.
Leucovorin Dosage and Duration: 15 mg PO, IM, or IV q 6 hours for 60 hours (10 doses starting at 24 hours after start of methotrexate infusion).

Clinical Situation: Delayed Late Methotrexate Elimination
Laboratory Findings: Serum methotrexate level remaining above 0.2 micromolar at 72 hours, and more than 0.05 micromolar at 96 hours after administration.
Leucovorin Dosage and Duration: Continue 15 mg PO, IM, or IV q six hours, until methotrexate level is less than 0.05 micromolar.

Clinical Situation: Delayed Early Methotrexate Elimination and/or Evidence of Acute Renal Injury
Laboratory Findings: Serum methotrexate level of 50 micromolar or more at 24 hours, or 5 micromolar or more at 48 hours after administration, OR, a 100% or greater increase in serum creatinine level at 24 hours after methotrexate administration, (eg, an increase from 0.5 mg/dL to a level of 1 mg/dL or more).
Leucovorin Dosage and Duration: 150 mg IV q three hours, until methotrexate level is less than 1 micromolar, then 15 mg IV q three hours until methotrexate level is less than 0.05 micromolar.

METHOTREXATE
INJECTION USP
CONTAINS PRESERVATIVE
50 mg
(25 mg/mL)
Sterile Isotonic Liquid
2 mL vial
NOT FOR INTRATHECAL USE
Rx only
Exp. Date
Lot #
METHOTREXATE
INJECTION USP
CONTAINS PRESERVATIVE
50 mg
(25 mg/mL)
Sterile Isotonic Liquid
Lot #
Exp. Date

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40265

DRAFT FINAL PRINTED LABELING

Pharmaceuticals

Bigmar

METHOTREXATE INJECTION USP (Preservative Free) Rx only

WARNINGS

METHOTREXATE SHOULD BE USED ONLY BY PHYSICIANS WHOSE KNOWLEDGE AND EXPERIENCE INCLUDE THE USE OF ANTIMETABOLITE THERAPY.

BECAUSE OF THE POSSIBILITY OF SERIOUS TOXIC REACTIONS (WHICH CAN BE FATAL):

METHOTREXATE SHOULD BE USED ONLY IN LIFE THREATENING NEOPLASTIC DISEASES, OR IN PATIENTS WITH PSORIASIS WITH SEVERE RECALCITRANT, DISABLING DISEASE WHICH IS NOT ADEQUATELY RESPONSIVE TO OTHER FORMS OF THERAPY.

DEATHS HAVE BEEN REPORTED WITH THE USE OF METHOTREXATE IN THE TREATMENT OF MALIGNANCY AND PSORIASIS.

PATIENTS SHOULD BE CLOSELY MONITORED FOR BONE MARROW, LIVER, LUNG AND KIDNEY TOXICITIES. (See **PRECAUTIONS**.)

PATIENTS SHOULD BE INFORMED BY THEIR PHYSICIAN OF THE RISKS INVOLVED AND BE UNDER A PHYSICIAN'S CARE THROUGHOUT THERAPY.

THE USE OF METHOTREXATE HIGH DOSE REGIMENS RECOMMENDED FOR OSTEOSARCOMA REQUIRES METICULOUS CARE. (See **DOSAGE AND ADMINISTRATION**.) HIGH DOSE REGIMENS FOR OTHER NEOPLASTIC DISEASES ARE INVESTIGATIONAL AND A THERAPEUTIC ADVANTAGE HAS NOT BEEN ESTABLISHED.

METHOTREXATE FORMULATIONS AND DILUENTS CONTAINING PRESERVATIVES MUST NOT BE USED FOR INTRATHECAL OR HIGH DOSE METHOTREXATE THERAPY.

1. Methotrexate has been reported to cause fetal death and/or congenital anomalies. Therefore, it is not recommended for women of childbearing potential unless there is clear medical evidence that the benefits can be expected to outweigh the considered risks. Pregnant women with psoriasis should not receive methotrexate. (See **CONTRAINDICATIONS**).

2. Methotrexate elimination is reduced in patients with impaired renal function, ascites, or pleural effusions. Such patients require especially careful monitoring for toxicity and require dose reduction or, in some cases, discontinuation of methotrexate administration.

3. Unexpectedly severe (sometimes fatal) bone marrow suppression and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high dosage) along with some nonsteroidal anti-inflammatory drugs (NSAIDs). (See **PRECAUTIONS**, *Drug Interactions*.)

4. Methotrexate causes hepatotoxicity, fibrosis and cirrhosis, but generally only after prolonged use. Acutely, liver enzyme elevations are frequently seen. These are usually transient and asymptomatic, and also do not appear predictive of subsequent hepatic disease. Liver biopsy after sustained use often shows histologic changes, and fibrosis and cirrhosis have been reported; these latter lesions may not be preceded by symptoms or abnormal liver function tests in the psoriasis population. For this reason, periodic liver biopsies are usually recommended for psoriatic patients who are under long-term treatment. (See **PRECAUTIONS**, Organ System Toxicity, *Hepatic*.)

5. Methotrexate-induced lung disease is a potentially dangerous lesion, which may occur acutely at any time during therapy and which has been reported at doses as low as 7.5 mg/week. It is not always fully reversible. Pulmonary symptoms (especially a dry, nonproductive cough) may require interruption or treatment and careful investigation.

6. Diarrhea and ulcerative stomatitis require interruption of therapy, otherwise, hemorrhagic enteritis and death from intestinal perforation may occur.

7. Malignant lymphomas, which may regress following withdrawal of methotrexate, may occur in patients receiving low-dose methotrexate and, thus may not require cytotoxic treatment. Discontinue methotrexate first and, if the lymphoma does not regress, appropriate treatment should be instituted.

8. Like other cytotoxic drugs, methotrexate may induce "tumor lysis syndrome" in patients with rapidly growing tumors. Appropriate supportive and pharmacologic measures may prevent or alleviate this complication.

9. Severe, occasionally fatal, skin reactions have been reported following single or multiple doses of methotrexate. Reaction have occurred within days of oral, intramuscular, intravenous, or intrathecal methotrexate administration. Recovery has been reported with discontinuation of therapy. (See **PRECAUTIONS**, **Organ System Toxicity**, *Skin*.)

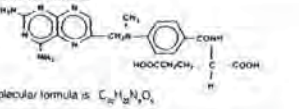
10. Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy.

DESCRIPTION

Methotrexate (formerly Amethopterin) is an antimetabolite used in the treatment of certain neoplastic diseases and severe psoriasis.

Chemically methotrexate is: *N*-[4-[[(2,4-diamino-6-pteridinyl) methyl]methylamino]benzoyl]-L-glutamic acid.

The structural formula is:



The molecular formula is $C_{20}H_{22}N_8O_5$

The molecular weight is 454.45

Methotrexate Injection USP is sterile and non-pyrogenic and may be given by the intramuscular, intravenous, intra-arterial or intrathecal route. (See **DOSAGE AND ADMINISTRATION**.)

Each mL contains methotrexate sodium equivalent to 25 mg methotrexate and the following inactive ingredients: Sodium Chloride 0.490% w/v and Water for Injection qs ad 100% v. Sodium Hydroxide and/or Hydrochloric Acid may be added to adjust the pH during manufacture to 8.5 - 8.7. The 2 mL, 4 mL, 8 mL, and 10 mL solutions contain approximately 0.43 mEq, 0.86 mEq, 1.72 mEq, and 2.15 mEq of Sodium per vial, respectively, and are isotonic solutions.

CLINICAL PHARMACOLOGY

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.

In psoriasis, the rate of production of epithelial cells in the skin is greatly increased over normal skin. This differential in proliferation rates is the basis for the use of methotrexate to control the psoriatic process.

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.

Two Pediatric Oncology Group studies (one randomized and one non-randomized) demonstrated a significant improvement

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in relapse-free survival in patients with non-metastatic osteosarcoma, when high dose methotrexate with leucovorin rescue was used in combination with other chemotherapeutic agents following surgical resection of the primary tumor. These studies were not designed to demonstrate the specific contribution of high dose methotrexate/leucovorin rescue therapy to the efficacy of the combination. However, a contribution can be inferred from the reports of objective responses to this therapy in patients with metastatic osteosarcoma, and from reports of extensive tumor necrosis following preoperative administration of this therapy to patients with non-metastatic osteosarcoma.

Pharmacokinetics

Absorption-Methotrexate is generally completely absorbed from parenteral routes of injection. After intramuscular injection, peak serum concentrations occur in 30 to 60 minutes.

Distribution- After intravenous administration, the initial volume of distribution is approximately 0.18 L/kg (18% of body weight) and steady-state volume of distribution is approximately 0.4 to 0.8 L/kg (40% to 80% of body weight). Methotrexate competes with reduced folates for active transport across cell membranes by means of a single carrier-mediated active transport process. At serum concentrations greater than 100 micromolar, passive diffusion becomes a major pathway by which effective intracellular concentrations can be achieved. Methotrexate in serum is approximately 50% protein bound. Laboratory studies demonstrate that it may be displaced from plasma albumin by various compounds including sulfonamides, salicylates, tetracyclines, chloramphenicol, and phenytoin.

Methotrexate does not penetrate the blood-cerebrospinal fluid barrier in therapeutic amounts when given parenterally. High CSF concentrations of the drug may be attained by intrathecal administration.

Metabolism - After absorption, methotrexate undergoes hepatic and intracellular metabolism to polyglutamated forms which can be converted back to methotrexate by hydrolase enzymes. These polyglutamates act as inhibitors of dihydrofolate reductase and thymidylate synthetase. Small amounts of methotrexate polyglutamates may remain in tissues for extended periods. The retention and prolonged drug action of these active metabolites vary among different cells, tissues and tumors. A small amount of metabolism to 7-hydroxymethotrexate may occur at doses commonly prescribed. Accumulation of this metabolite may become significant at the high doses used in osteogenic sarcoma. The aqueous solubility of 7-hydroxymethotrexate is 3 to 5 fold lower than the parent compound. Methotrexate is partially metabolized by intestinal flora after oral administration.

Half-Life - The terminal half-life reported for methotrexate is approximately three to ten hours for patients receiving treatment for psoriasis or low dose antineoplastic therapy (less than 30 mg/m²). For patients receiving high doses of methotrexate, the terminal half-life is eight to 15 hours.

Excretion - Renal excretion is the primary route of elimination, and is dependent upon dosage and route of administration. With IV administration, 80% to 90% of the administered dose is excreted unchanged in the urine within 24 hours. There is limited biliary excretion amounting to 10% or less of the administered dose. Enterohepatic recirculation of methotrexate has been proposed.

Renal excretion occurs by glomerular filtration and active tubular secretion. Nonlinear elimination due to saturation of renal tubular reabsorption has been observed in psoriatic patients at doses between 7.5 and 30 mg. Impaired renal function, as well as concurrent use of drugs such as weak organic acids that also undergo tubular secretion, can markedly increase methotrexate serum levels. Excellent correlation has been reported between methotrexate clearance and endogenous creatinine clearance.

Methotrexate clearance rates vary widely and are generally decreased at higher doses. Delayed drug clearance has been identified as one of the major factors responsible for methotrexate toxicity. It has been postulated that the toxicity of methotrexate for normal tissues is more dependent upon the duration of exposure to the drug rather than the peak level achieved. When a patient has delayed drug elimination due to compromised renal function, a third space effusion, or other causes, methotrexate serum concentrations may remain elevated for prolonged periods.

The potential for toxicity from high dose regimens or delayed excretion is reduced by the administration of leucovorin calcium during the final phase of methotrexate plasma elimination. Pharmacokinetic monitoring of methotrexate serum concentrations may help identify those patients at high risk for methotrexate toxicity and aid in proper adjustment of leucovorin dosing. Guidelines for monitoring serum methotrexate levels, and for adjustment of leucovorin dosing to reduce the risk of methotrexate toxicity, are provided below in **DOSAGE AND ADMINISTRATION**.

Methotrexate has been detected in human breast milk. The highest breast milk to plasma concentration ratio reached was 0.08:1.

INDICATIONS AND USAGE

Neoplastic Diseases

Methotrexate is indicated in the treatment of 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, 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.

Psoriasis

Methotrexate is indicated in the symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy, but only when the diagnosis has been established, as by biopsy and/or after dermatologic consultation. It is important to ensure that a psoriasis "flare" is not due to an undiagnosed concomitant disease affecting immune responses.

CONTRAINDICATIONS

Methotrexate can cause fetal death or teratogenic effects when administered to a pregnant woman. Methotrexate is contraindicated in pregnant women with psoriasis and should be used in the treatment of neoplastic diseases only when the potential benefit outweighs the risk to the fetus. Women of childbearing potential should not be started on methotrexate until pregnancy is excluded and should be fully counseled on the serious risk to the fetus (see **PRECAUTIONS**) should they become pregnant while undergoing treatment. Pregnancy should be avoided if either partner is receiving methotrexate, during and for a minimum of three months after therapy for male patients, and during and for at least one ovulatory cycle after therapy for female patients. (See Boxed **WARNINGS**).

Because of the potential for serious adverse reactions from methotrexate in breast fed infants, it is contraindicated in nursing mothers.

Patients with psoriasis with alcoholism, alcoholic liver disease or other chronic liver disease should not receive methotrexate.

Patients with psoriasis who have overt or laboratory evidence of immunodeficiency syndromes should not receive methotrexate.

Patients with psoriasis who have preexisting blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anemia, should not receive methotrexate.

Patients with a known hypersensitivity to methotrexate should not receive the drug.

WARNINGS -SEE BOXED WARNINGS.

PRECAUTIONS

General

Methotrexate has the potential for serious toxicity. (See Boxed **WARNINGS**). Toxic effects may be related in frequency and severity to dose or frequency of administration but have been seen at all doses. Because they can occur at any time during therapy, it is necessary to follow patients on methotrexate closely. Most adverse reactions are reversible if detected early. When such reactions do occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken. If necessary, this could include the use of leucovorin calcium (See **OVERDOSAGE**). If methotrexate therapy is reinstituted, it should be carried out with caution, with adequate consideration of further need for the drug and with increased alertness as to possible recurrence of toxicity.

The clinical pharmacology of methotrexate has not been well studied in older individuals. Due to diminished hepatic and renal function as well as decreased folate stores in this population, relatively low doses should be considered, and these patients should be closely monitored for early signs of toxicity.

Information for Patients

Patients should be informed of the early signs and symptoms of toxicity, of the need to see their physician promptly if they occur, and the need for close follow-up, including periodic laboratory tests to monitor toxicity.

Both the physician and pharmacist should emphasize to the patient that the recommended dose is taken weekly in psoriasis, and that mistaken daily use of the recommended dose has led to fatal toxicity. Prescriptions should not be written or refilled on a PRN basis.

Patients should be informed of the potential benefit and risk in the use of methotrexate. The risk of effects on reproduction should be discussed with both male and female patients taking methotrexate.

Laboratory Tests
Patients undergoing methotrexate therapy should be closely monitored so that toxic effects are detected promptly. Baseline assessment should include a complete blood count with differential and platelet counts, hepatic enzymes, renal function tests, and a chest X-ray. During therapy of psoriasis, monitoring of these parameters is recommended: hematology at least monthly; renal function and liver function every 1 to 2 months. More frequent monitoring is usually indicated during antineoplastic therapy. During initial or changing doses, or during periods of increased risk of elevated methotrexate blood levels (eg, dehydration), more frequent monitoring may also be indicated.

Transient liver function test abnormalities are observed frequently after methotrexate administration and are usually not cause for modification of methotrexate therapy. Persistent liver function test abnormalities, and/or depression of serum albumin may be indicators of serious liver toxicity and require evaluation. (See **PRECAUTIONS**, Organ System Toxicity, *Hepatic*.)

A relationship between abnormal liver function tests and fibrosis or cirrhosis of the liver has not been established for patients with psoriasis.

Pulmonary function tests may be useful if methotrexate-induced lung disease is suspected, especially if baseline measurements are available.

Drug Interactions
Nonsteroidal anti-inflammatory drugs should not be administered prior to or concomitantly with the high doses of methotrexate used in the treatment of osteosarcoma. Concomitant administration of some NSAIDs with high dose methotrexate therapy has been reported to elevate and prolong serum methotrexate levels, resulting in deaths from severe hematologic and gastrointestinal toxicity.

Caution should be used when NSAIDs and salicylates are administered concomitantly with lower doses of methotrexate. These drugs have been reported to reduce the tubular secretion of methotrexate in an animal model and may enhance its toxicity.

Methotrexate is partially bound to serum albumin, and toxicity may be increased because of displacement by certain drugs, such as salicylates, phenylbutazone, phenytoin, and sulfonamides. Renal tubular transport is also diminished by probenecid; use of methotrexate with this drug should be carefully monitored.

In the treatment of patients with osteosarcoma, caution must be exercised if high-dose methotrexate is administered in combination with a potentially nephrotoxic chemotherapeutic agent (eg, cisplatin).

Oral antibiotics such as tetracycline, chloramphenicol, and nonabsorbable broad spectrum antibiotics, may decrease intestinal absorption of methotrexate or interfere with the enterohepatic circulation by inhibiting bowel flora and suppressing metabolism of the drug by bacteria.

Penicillins may reduce the renal clearance of methotrexate; increased serum concentrations of methotrexate with concomitant hematologic and gastrointestinal toxicity have been observed with high and low dose methotrexate. Use of methotrexate with penicillins should be carefully monitored.

Patients receiving concomitant therapy with methotrexate and etretinate or other retinoids should be monitored closely for possible increased risk of hepatotoxicity.

Methotrexate may decrease the clearance of theophylline; theophylline levels should be monitored when used concurrently with methotrexate.

Vitamin preparations containing folic acid or its derivatives may decrease responses to systemically administered methotrexate. Preliminary animal and human studies have shown that small quantities of intravenously administered leucovorin enter the CSF primarily as 5-methyltetrahydrofolate and, in humans, remain 1 - 3 orders of magnitude lower than the usual methotrexate concentrations following intrathecal administration. However, high doses of leucovorin may reduce the efficacy of intrathecally administered methotrexate.

Folate deficiency states may increase methotrexate toxicity.

Trimethoprim/sulfamethoxazole has been reported rarely to increase bone marrow suppression in patients receiving methotrexate, probably by an additive antifolate effect.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No controlled human data exist regarding the risk of neoplasia with methotrexate. Methotrexate has been evaluated in a number of animal studies for carcinogenic potential with inconclusive results. Although there is evidence that methotrexate causes chromosomal damage to animal somatic cells and human bone marrow cells, the clinical significance remains uncertain. Benefits should be weighed against the potential risks before using methotrexate alone or in combination with other drugs, especially in pediatric patients or young adults. Methotrexate causes embryotoxicity, abortion, and fetal defects in humans. It has also been reported to cause impairment of fertility, oligospermia and menstrual dysfunction in humans, during and for a short period after cessation of therapy.

Pregnancy: Teratogenic Effects, Pregnancy Category X See **CONTRAINDICATIONS**.

Nursing Mothers
See **CONTRAINDICATIONS**.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established, other than in cancer chemotherapy.

Organ System Toxicity
Gastrointestinal: If vomiting, diarrhea, or stomatitis occur, which may result in dehydration, methotrexate should be discontinued until recovery occurs. Methotrexate should be used with extreme caution in the presence of peptic ulcer disease or ulcerative colitis.

Hematologic: Methotrexate can suppress hematopoiesis and cause anemia, leukopenia, and/or thrombocytopenia. In patients with malignancy and preexisting hematopoietic impairment the drug should be used with caution, if at all.

In psoriasis, methotrexate should be stopped immediately if there is a significant drop in blood counts. In the treatment of neoplastic diseases, methotrexate should be continued only if the potential benefit warrants the risk of severe myelosuppression. Patients with profound granulocytopenia and fever should be evaluated immediately and usually require parenteral broad-spectrum antibiotic therapy.

Hepatic: Methotrexate has the potential for acute (elevated transaminases) and chronic (fibrosis and cirrhosis) hepatotoxicity. Chronic toxicity is potentially fatal; it generally has occurred after prolonged use (generally two years or more) and after a total dose of at least 1.5 grams. In studies in psoriatic patients, hepatotoxicity appeared to be a function of total cumulative dose and appeared to be enhanced by alcoholism, obesity, diabetes and advanced age. An accurate incidence rate has not been determined, the rate of progression and reversibility of lesions is not known. Special caution is indicated in the presence of preexisting liver damage or impaired hepatic function.

In psoriasis, liver function tests, including serum albumin, should be performed periodically prior to dosing but are often normal in the face of developing fibrosis or cirrhosis. These lesions may be detectable only by biopsy. The usual recommendation is to obtain a liver biopsy at 1) pretherapy or shortly after initiation of therapy (2 - 4 months), 2) a total cumulative dose of 1.5 grams, and 3) after each additional 1.0 to 1.5 grams. Moderate fibrosis or any cirrhosis normally leads to discontinuation of the drug; mild fibrosis normally suggests a repeat biopsy in 6 months. Milder histologic findings such as fatty change and low grade portal inflammation, are relatively common pretherapy. Although these mild changes are usually not a reason to avoid or discontinue methotrexate therapy, the drug should be used with caution.

Infection or Immunologic States: Methotrexate should be used with extreme caution in the presence of active infection, and is usually contraindicated in patients with overt or laboratory evidence of immunodeficiency syndromes. Immunization may be ineffective when given during methotrexate therapy. Immunization with live virus vaccines is generally not recommended. There have been reports of disseminated vaccinia infections after smallpox immunizations in patients receiving methotrexate therapy. Hypogammaglobulinemia has been reported rarely.

Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy. When a patient presents with pulmonary symptoms, the possibility of *Pneumocystis carinii* pneumonia should be considered.

Neurologic: There have been reports of leukoencephalopathy following intravenous administration of methotrexate to patients who have had craniospinal irradiation. Serious neurotoxicity, frequently manifested as generalized or focal seizures, has been

reported with unexpectedly increased frequency among pediatric patients with acute lymphoblastic leukemia who were treated with intermediate-dose intravenous methotrexate (1 gm/m²). Symptomatic patients were commonly noted to have leukoencephalopathy and/or microangiopathic calcifications on diagnostic imaging studies. Chronic leukoencephalopathy has also been reported in patients who received repeated doses of high-dose methotrexate with leucovorin rescue even without cranial irradiation. Discontinuation of methotrexate does not always result in complete recovery.

A transient acute neurologic syndrome has been observed in patients treated with high dose regimens. Manifestations of this stroke-like encephalopathy may include confusion, hemiparesis, seizures and coma. The exact cause is unknown.

After the intrathecal use of methotrexate, the central nervous system toxicity which may occur can be classified as follows: acute chemical arachnoiditis manifested by such symptoms as headache, back pain, nuchal rigidity, and fever; sub-acute myelopathy characterized by paraparesis/paraplegia associated with involvement with one or more spinal nerve roots; chronic leukoencephalopathy manifested by confusion, irritability, somnolence, ataxia, dementia, seizures and coma. This condition can be progressive and even fatal.

Pulmonary: Pulmonary symptoms (especially a dry nonproductive cough) or a non-specific pneumonitis occurring during methotrexate therapy may be indicative of a potentially dangerous lesion and require interruption of treatment and careful investigation. Although clinically variable, the typical patient with methotrexate induced lung disease presents with fever, cough, dyspnea, hypoxemia, and an infiltrate on chest x-ray. Infection needs to be excluded. This lesion can occur at all dosages.

Renal: High doses of methotrexate used in the treatment of osteosarcoma may cause renal damage leading to acute renal failure. Nephrotoxicity is due primarily to the precipitation of methotrexate and 7-hydroxymethotrexate in the renal tubules. Close attention to renal function including adequate hydration, urine alkalinization and measurement of serum methotrexate and creatinine levels are essential for safe administration.

Skin: Severe, occasionally fatal, dermatologic reactions, including toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, skin necrosis and erythema multiforme, have been reported in children and adults, within days of oral, intramuscular, intravenous, or intrathecal methotrexate administration. Reactions were noted after single or multiple low, intermediate or high doses of methotrexate in patients with neoplastic and non-neoplastic diseases.

Other precautions: Methotrexate should be used with extreme caution in the presence of debility.

Methotrexate exits slowly from third space compartments (eg, pleural effusions or ascites). This results in a prolonged terminal plasma half-life and unexpected toxicity. In patients with significant third space accumulations, it is advisable to evacuate the fluid before treatment and to monitor plasma methotrexate levels.

Lesions of psoriasis may be aggravated by concomitant exposure to ultraviolet radiation. Radiation dermatitis and sunburn may be "recalled" by the use of methotrexate.

ADVERSE REACTIONS

IN GENERAL, THE INCIDENCE AND SEVERITY OF ACUTE SIDE EFFECTS ARE RELATED TO DOSE AND FREQUENCY OF ADMINISTRATION. THE MOST SERIOUS REACTIONS ARE DISCUSSED ABOVE UNDER ORGAN SYSTEM TOXICITY IN THE PRECAUTION SECTION. THAT SECTION SHOULD ALSO BE CONSULTED WHEN LOOKING FOR INFORMATION ABOUT ADVERSE REACTIONS WITH METHOTREXATE.

The most frequently reported adverse reactions include ulcerative stomatitis, leukopenia, nausea, and abdominal distress. Other frequently reported adverse effects are malaise, undue fatigue, chills and fever, dizziness and decreased resistance to infection.

Other adverse reactions that have been reported with methotrexate are listed below by organ system. In the oncology setting, concomitant treatment and the underlying disease make specific attribution of a reaction to methotrexate difficult.

Alimentary System: gingivitis, pharyngitis, stomatitis, anorexia, nausea, vomiting, diarrhea, hematemesis, melena, gastrointestinal ulceration and bleeding, enteritis, pancreatitis.

Cardiovascular: pericarditis, pericardial effusion, hypotension, and intramboembolic events (including arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, thrombophlebitis, and pulmonary emboli).

Central Nervous System: headaches, drowsiness, blurred vision. Aphasia, hemiparesis, paresis and convulsions have also occurred following administration of methotrexate. Following low doses, there have been occasional reports of transient subtle cognitive dysfunction, mood alteration, unusual cranial sensations, leukoencephalopathy, or encephalopathy.

Infection: There have been case reports of sometimes fatal opportunistic infections in patients receiving methotrexate therapy for neoplastic and non-neoplastic diseases. *Pneumocystis carinii* pneumonia was the most common infection. Other reported infections included nocardiosis, histoplasmosis, cryptococcosis, Herpes zoster, H. simplex hepatitis, and disseminated H. simplex.

Ophthalmic: conjunctivitis, serious visual changes of unknown etiology.

Pulmonary System: interstitial pneumonitis deaths have been reported, and chronic interstitial obstructive pulmonary disease has occasionally occurred.

Skin: erythematous rashes, pruritus, urticaria, photosensitivity, pigmentary changes, alopecia, ecchymosis, telangiectasia, acne, furunculosis, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, skin necrosis, and exfoliative dermatitis.

Urogenital System: severe nephropathy or renal failure, azotemia, cystitis, hematuria, defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, vaginal discharge, and gynecomastia, infertility, abortion, fetal defects.

Other rare reactions related to or attributed to the use of methotrexate such as nodulosis, vasculitis, arthralgia/myalgia, loss of libido/impotence, diabetes, osteoporosis, sudden death and reversible lymphomas. Anaphylactoid reactions have been reported.

Adverse Reactions in Psoriasis:
There are no recent placebo-controlled trials in patients with psoriasis. There are two literature reports (Roenigk, 1969, and Nyfors, 1978) describing large series (n=204, 248) of psoriasis patients treated with methotrexate. Dosages ranged up to 25 mg per week and treatment was administered for up to four years.

OVERDOSAGE

Leucovorin is indicated to diminish the toxicity and counteract the effect of inadvertently administered overdosages of methotrexate. Leucovorin administration should begin as promptly as possible. As the time interval between methotrexate administration and leucovorin initiation increases, the effectiveness of leucovorin in counteracting toxicity decreases. Monitoring of the serum methotrexate concentration is essential in determining the optimal dose and duration of treatment with leucovorin.

In cases of massive overdosage, hydration and urinary alkalinization may be necessary to prevent the precipitation of methotrexate and/or its metabolites in the renal tubules. Neither hemodialysis nor peritoneal dialysis has been shown to improve methotrexate elimination.

Accidental intrathecal overdosage may require intensive systemic support, high-dose systemic leucovorin, alkaline diuresis and rapid CSF drainage and ventriculolumbar perfusion.

DOSAGE AND ADMINISTRATION

Neoplastic Diseases
Oral administration in tablet form is often preferred when low doses are being administered since absorption is rapid and effective serum levels are obtained. Methotrexate injection may be given by the intramuscular, intravenous, intra-arterial, or intrathecal route.

Choriocarcinoma and similar trophoblastic diseases: Methotrexate is administered orally or intramuscularly in doses of 15 to 30 mg daily for a five-day course. Such courses are usually repeated for 3 to 5 times as required, with rest periods of one or more weeks interposed between courses, until any manifesting toxic symptoms subside. The effectiveness of therapy is ordinarily evaluated by 24-hour quantitative analysis of urinary chorionic gonadotropin (hCG), which should return to normal or less than 50 IU/24 hr usually after the third or fourth course and usually be followed by a complete resolution of measurable lesions in 4 to 6 weeks. One to two courses of methotrexate after normalization of hCG is usually recommended. Before each course of the drug careful clinical assessment is essential. Cyclic combination therapy of methotrexate with other antitumor drugs has been reported as being useful.

Since hydatidiform mole may precede choriocarcinoma, prophylactic chemotherapy with methotrexate has been recommended.

Chorioadenoma destruens is considered to be an invasive form of hydatidiform mole. Methotrexate is administered in these diseases

states in doses similar to those recommended for choriocarcinoma.

Leukemia: Acute lymphoblastic leukemia in pediatric patients and young adolescents is the most responsive to present day chemotherapy. In young adults and older patients, clinical remission is more difficult to obtain and early relapse is more common.

Methotrexate alone or in combination with steroids was used initially for induction of remission in acute lymphoblastic leukemias. More recently corticosteroid therapy, in combination with other antileukemic drugs or in cyclic combinations with methotrexate included, has appeared to produce rapid and effective remissions. When used for induction, methotrexate in doses of 3.3 mg/m² in combination with 60 mg/m² of prednisone, given daily, produced remissions in 50% of patients treated, usually within a period of 4 to 6 weeks. Methotrexate in combination with other agents appears to be the drug of choice for securing maintenance of drug-induced remissions. When remission is achieved and supportive care has produced general clinical improvement, maintenance therapy is initiated, as follows: Methotrexate is administered 2 times weekly either by mouth or intramuscularly in total weekly doses of 30 mg/m². It has also been given in doses of 2.5 mg/kg intravenously every 14 days. If and when relapse does occur, reinduction of remission can again usually be obtained by repeating the initial induction regimen.

A variety of combination chemotherapy regimens have been used for both induction and maintenance therapy in acute lymphoblastic leukemia. The physician should be familiar with the new advances in antileukemic therapy.

Meningeal Leukemia: In the treatment or prophylaxis of meningeal leukemia, methotrexate must be administered intrathecally. Preservative free methotrexate is diluted to a concentration of 1 mg/mL in an appropriate sterile, preservative free medium such as 0.9% Sodium Chloride Injection, USP.

The cerebrospinal fluid volume is dependent on age and not on body surface area. The CSF is at 40% of the adult volume at birth and reaches the adult volume in several years.

Intrathecal methotrexate administration at a dose of 12 mg/m² (maximum 15 mg) has been reported to result in low CSF methotrexate concentrations and reduced efficacy in pediatric patients and high concentrations and neurotoxicity in adults. The following dosage regimen is based on age instead of body surface area:

AGE (years)	DOSE (mg)
< 1	6
1	8
2	10
3 or older	12

In one study in patients under the age of 40, this dosage regimen appeared to result in more consistent CSF methotrexate concentrations and less neurotoxicity. Another study in pediatric patients with acute lymphocytic leukemia compared this regimen to a dose of 12 mg/m² (maximum 15 mg), a significant reduction in the rate of CNS relapse was observed in the group whose dose was based on age.

Because the CSF volume and turnover may decrease with age, a dose reduction may be indicated in elderly patients.

For the treatment of meningeal leukemia, intrathecal methotrexate may be given at intervals of 2 to 5 days. However, administration at intervals of less than 1 week may result in increased subacute toxicity. Methotrexate is administered until the cell count of the cerebrospinal fluid returns to normal. At this point one additional dose is advisable. For prophylaxis against meningeal leukemia, the dosage is the same as for treatment except for the intervals of administration. On this subject, it is advisable for the physician to consult the medical literature.

Untoward side effects may occur with any given intrathecal injection and are commonly neurological in character. Large doses may cause convulsions. Methotrexate given by the intrathecal route appears significantly in the systemic circulation and may cause systemic methotrexate toxicity. Therefore, systemic antileukemic therapy with the drug should be appropriately adjusted, reduced or discontinued. Focal leukemic involvement of the central nervous system may not respond to intrathecal chemotherapy and is best treated with radiotherapy.

Lymphomas: In Burkitt's tumor, Stages I-II, methotrexate has produced prolonged remissions in some cases. Recommended dosage is 10 to 25 mg/day orally for 4 to 8 days. Stage III, methotrexate is commonly given concomitantly with other antitumor agents. Treatment in all stages usually consists of several courses of the drug interposed with 7 to 10 day rest periods. Lymphosarcomas in Stage III may respond to combined drug therapy with methotrexate given in doses of 0.625 to 2.5 mg/kg daily.

Mycosis Fungoides: Therapy with methotrexate appears to produce clinical remissions in one half of the cases treated. Dosage is usually 2.5 to 10 mg daily by mouth for weeks or months. Dose levels of drug and adjustment of dose regimen by reduction or cessation of drug are guided by patient response and hematologic monitoring. Methotrexate has been given intramuscularly in doses of 50 mg once weekly or 25 mg 2 times weekly.

Osteosarcoma: An effective adjuvant chemotherapy regimen requires the administration of several cytotoxic chemotherapeutic agents. In addition to high-dose methotrexate with leucovorin rescue, these agents may include doxorubicin, cisplatin, and the combination of bleomycin, cyclophosphamide and dactinomycin (BCD) in the doses and schedule shown in the table below. The starting dose for high-dose methotrexate treatment is 12 grams/m². If this dose is not sufficient to produce a peak serum methotrexate concentration of 1,000 micromolar (10^{-3} mol/L) at the end of the methotrexate infusion, the dose may be escalated to 15 grams/m² in subsequent treatments. If the patient is vomiting or is unable to tolerate oral medication, leucovorin is given IV or IM at the same dose and schedule.

Drug[a] Week[a]	Dose[a]	Treatment After Surgery
Methotrexate 15, 16, 29,30,44,45	12g/m² IV as 4 hour infusion (starting dose)	4,5,8,7,11,12,
Leucovorin	15 mg orally every six hours for 10 doses starting at 24 hours after start of methotrexate infusion.	
Doxorubicin[b] as a single drug	30 mg/m² day IV x 3 days	8,17
Doxorubicin[b]	50 mg/m² IV	20,23,33,36
Cisplatin[b]	100 mg/m² IV	20,23,33,36
Bleomycin[b]	15 units/m² IV x 2 days	2,13,26,39,42
Cyclophosphamide[b]	600 mg/m² IV x 2 days.	2,13,26,39,42
Dactinomycin[b]	0.6 mg/m² IV x 2 days.	2,13,26,39,42

[a] Link MP, Goorin AM, Miser AW, et al. The effect of adjuvant chemotherapy on relapse-free survival in patients with osteosarcoma of the extremity. *N Engl J of Med* 1986; 314(No.25):1600-1606.

[b] See each respective package insert for full prescribing information. Dosage modifications may be necessary because of drug-induced toxicity.

When these higher doses of methotrexate are to be administered, the following safety guidelines should be closely observed:

GUIDELINES FOR METHOTREXATE THERAPY WITH LEUCOVORIN RESCUE

1. Administration of methotrexate should be delayed until recovery if:
   - the WBC count is less than 1500/microliter
   - the neutrophil count is less than 200/microliter
   - the platelet count is less than 75,000/microliter
   - the serum bilirubin level is greater than 1.2 mg/dl
   - the SGPT level is greater than 450 U
   - mucositis is present, until there is evidence of healing
   - persistent pleural effusion is present; this should be drained dry prior to infusion.
2. Adequate renal function must be documented:
   a. Serum creatinine must be normal, and creatinine clearance must be greater than 60 mL/min, before initiation of therapy.
   b. Serum creatinine must be measured prior to each subsequent course of therapy. If serum creatinine has increased by 50 % or more compared to a prior value, the creatinine clearance must be measured and documented to be greater than 60 mL/min (even if the serum creatinine is still within the normal range).
3. Patients must be well hydrated, and must be treated with sodium bicarbonate for urinary alkalinization:
   a. Administer 1,000 mL/m² of intravenous fluid over 6 hours prior to initiation of the methotrexate infusion. Continue hydration at 125 mL/m²/hr (3 liters/m²/day) during the methotrexate infusion, and for 2 days after the infusion has been completed.
   b. Alkalinize urine to maintain pH above 7.0 during methotrexate infusion and leucovorin calcium therapy. This can be accomplished by the administration of sodium bicarbonate orally or by incorporation into a separate intravenous solution.
4. Repeat serum creatinine and serum methotrexate 24 hours after starting methotrexate and at least once daily until the methotrexate level is below 5×10^{-8} mol/L (0.05 micromolar).
5. The table below provides guidelines for leucovorin calcium dosage based upon serum methotrexate levels. (See table below.[1])

Patients who experience delayed early methotrexate elimination are likely to develop nonreversible oliguric renal failure. In addition to appropriate leucovorin therapy, these patients require continuing hydration and urinary alkalinization, and dose monitoring of fluid and electrolyte status, until the serum methotrexate level has fallen to below 0.05 micromolar and the renal failure has resolved.

6. Some patients will have abnormalities in methotrexate elimination, or abnormalities in renal function following methotrexate administration, which are significant but less severe than the abnormalities described in the table below. These abnormalities may or may not be associated with significant clinical toxicity. If significant clinical toxicity is observed, leucovorin rescue should be extended for an additional 24 hours (total 14 doses over 84 hours) in subsequent courses of therapy. The possibility that the patient is taking other medications which interact with methotrexate (eg, medications which may interfere with methotrexate binding to serum albumin, or elimination) should always be reconsidered when laboratory abnormalities or clinical toxicities are observed.

CAUTION: DO NOT ADMINISTER LEUCOVORIN INTRATHECALLY.

Psoriasis:
The patient should be fully informed of the risks involved and should be under constant supervision of the physician. (See Information for Patients Under **PRECAUTIONS**). Assessment of hematologic, hepatic, renal, and pulmonary function should be made by history, physical examination, and laboratory tests before beginning, periodically during, and before reinstituting methotrexate therapy. (See **PRECAUTIONS**) Appropriate steps should be taken to avoid conception during methotrexate therapy. (See **PRECAUTIONS AND CONTRAINDICATIONS**).

All schedules should be continually tailored to the individual patient. An initial test dose may be given prior to the regular dosing schedule to detect any extreme sensitivity to adverse effects (See **ADVERSE REACTIONS**). Maximal myelosuppression usually occurs in seven to ten days.

Psoriasis, Recommended Starting Dose Schedule:

1. Weekly single oral IM or IV dosage schedule: 10 to 25 mg per week until adequate response is achieved.

2. Divided oral dose schedule: 2.5 mg at 12 hour intervals for three doses.

Dosages in each schedule may be gradually adjusted to achieve optimal clinical response; 30 mg/week should not ordinarily be exceeded.

Once optimal clinical response has been achieved, each dosage schedule should be reduced to the lowest possible amount of drug and to the longest possible rest period. The use of methotrexate may permit the return to conventional topical therapy, which should be encouraged.

HANDLING AND DISPOSAL

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[2-9] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

DILUTION INSTRUCTIONS FOR LIQUID METHOTREXATE INJECTION PRODUCT:

Methotrexate Injection USP, Isotonic Liquid, Preservative Free, for Single Use Only

If desired, the solution may be further diluted immediately prior to use with an appropriate sterile, preservative free medium such as 5% Dextrose Solution, or Sodium Chloride Injection.

HOW SUPPLIED

Methotrexate Injection USP, Isotonic Liquid, Preservative Free, for Single Use Only

Each mL contains methotrexate sodium equivalent to 25 mg methotrexate.

2 mL vial 50 mg
4 mL vial 100 mg
8 mL vial 200 mg
10 mL vial 250 mg

See package insert for routes of administration.

Rx only

Store at controlled room temperature 15-30°C (59°-86°F). Retain in carton until time of use. Protect from light.

Manufactured by:
Bigmar Pharmaceuticals SA
Barbengo, Switzerland

Manufactured for:
Bigmar, Inc.
Johnstown, OH 43031

Rev 05- November 1998

REFERENCES

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LEUCOVORIN RESCUE SCHEDULES FOLLOWING TREATMENT WITH HIGHER DOSES OF METHOTREXATE

Clinical Situation: Normal Methotrexate Elimination
Laboratory Findings: Serum methotrexate level approximately micromolar at 24 hours after administration, 1 micromolar at hours, and less than 0.2 micromolar at 72 hours.
Leucovorin Dosage and Duration: 15 mg PO, IM, or IV hours for 60 hours (10 doses starting at 24 hours after start methotrexate infusion)

Clinical Situation: Delayed Late Methotrexate Elimination
Laboratory Findings: Serum methotrexate level remaining ab 0.2 micromolar at 72 hours, and more than 0.05 micromolar a hours after administration.
Leucovorin Dosage and Duration: Continue 15 mg PO, IM, o q 6 hours, until methotrexate level is than 0.05 micromolar.

Clinical Situation: Delayed Early Methotrexate Elimination an Evidence of Acute Renal Injury.
Laboratory Findings: Serum methotrexate level of 50 microm or more at 24 hours, or 5 micromolar or more at 48 hours a administration, OR a 100% or greater increase in serum creati level at 24 hours after methotrexate administration (eg, an increa from 0.5 mg/dL to a level of 1 mg/dL or more).
Leucovorin Dosage and Duration: 150 mg IV q 3 hours, methotrexate level is less than 1 micromolar; then 15 mg IV hours until methotrexate level is less than 0.05 micromolar.

METHOTREXATE INJECTION USP
(PRESERVATIVE FREE)
250 mg
(25 mg/mL)
Sterile Isotonic Liquid

FEB 2 6 1999

APPROVED

Bigmar Pharmaceuticals

See package insert for routes of administration.

8 mL single dose vial

Sterile Isotonic Liquid

METHOTREXATE INJECTION USP
(PRESERVATIVE FREE)

Rx only

Inactive ingredients: Sodium Chloride 0.490% w/v and Water for Injection. Sodium hydroxide and/or hydrochloric acid may be added to adjust pH to 8.5 - 8.7 during manufacture.

Each mL contains methotrexate sodium equivalent to 25 mg methotrexate.

Usual Dosage: Consult package insert for dosage and full prescribing information.

Usual Dosage: Consult package insert for dosage and full prescribing information.

Each mL contains methotrexate sodium equivalent to 25 mg methotrexate.

Inactive ingredients: Sodium Chloride 0.490% w/v and Water for Injection. Sodium hydroxide and/or hydrochloric acid may be added to adjust pH to 8.5 - 8.7 during manufacture.

Rx only

METHOTREXATE INJECTION USP
(PRESERVATIVE FREE)
250 mg
(25 mg/mL)
Sterile Isotonic Liquid
10 mL single dose vial
See package insert for routes of administration.

Pharmaceuticals
Bigmar

FEB 2 6 1999

METHOTREXATE INJECTION USP
(PRESERVATIVE FREE)

Sterile Isotonic Liquid

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OH 43031

...EXATE
...N USP
...ATIVE FREE)

Sterile Isotonic Liquid
2 mL single dose vial
See package insert for routes of administration.

Pharmaceuticals
Bigmar

FEB 2 6 1999

Lot #
Exp. Date

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40266

DRAFT FINAL PRINTED LABELING

Pharmaceuticals

Bigmar

METHOTREXATE FOR INJECTION USP

WARNINGS

METHOTREXATE SHOULD BE USED ONLY BY PHYSICIANS WHOSE KNOWLEDGE AND EXPERIENCE INCLUDE THE USE OF ANTIMETABOLITE THERAPY.

BECAUSE OF THE POSSIBILITY OF SERIOUS TOXIC REACTIONS (WHICH CAN BE FATAL)

METHOTREXATE SHOULD BE USED ONLY IN LIFE THREATENING NEOPLASTIC DISEASES, OR IN PATIENTS WITH PSORIASIS WITH SEVERE RECALCITRANT, DISABLING DISEASE WHICH IS NOT ADEQUATELY RESPONSIVE TO OTHER FORMS OF THERAPY.

DEATHS HAVE BEEN REPORTED WITH THE USE OF METHOTREXATE IN THE TREATMENT OF MALIGNANCY AND PSORIASIS.

PATIENTS SHOULD BE CLOSELY MONITORED FOR BONE MARROW, LIVER, LUNG AND KIDNEY TOXICITIES. (See **PRECAUTIONS**.)

PATIENTS SHOULD BE INFORMED BY THEIR PHYSICIAN OF THE RISKS INVOLVED AND BE UNDER A PHYSICIAN'S CARE THROUGHOUT THERAPY.

THE USE OF METHOTREXATE HIGH DOSE REGIMENS *RECOMMENDED FOR OSTEOSARCOMA REQUIRES METICULOUS CARE.* (See **DOSAGE AND ADMINISTRATION**.) *HIGH DOSE REGIMENS FOR OTHER NEOPLASTIC DISEASES ARE IN-VESTIGATIONAL AND A THERAPEUTIC ADVANTAGE HAS NOT BEEN ESTABLISHED.*

METHOTREXATE FORMULATIONS AND DILUENTS CONTAINING PRESERVATIVES MUST NOT BE USED FOR INTRATHECAL OR HIGH DOSE METHOTREXATE THERAPY.

1. Methotrexate has been reported to cause fetal death and/or congenital anomalies. Therefore, it is not recommended for women of childbearing potential unless there is clear medical evidence that the benefits can be expected to outweigh the considered risks. Pregnant women with psoriasis should not receive methotrexate. (See **CONTRAINDICATIONS**).

2. Methotrexate elimination is reduced in patients with impaired renal function, ascites, or pleural effusions. Such patients require especially careful monitoring for toxicity, and require dose reduction or, in some cases, discontinuation of methotrexate administration.

3. Unexpectedly severe (sometimes fatal) bone marrow suppression and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high dosage) along with some nonsteroidal anti-inflammatory drugs (NSAIDs). (See **PRECAUTIONS**, Drug Interactions).

4. Methotrexate causes hepatotoxicity, fibrosis and cirrhosis, but generally only after prolonged use. Acutely, liver enzyme elevations are frequently seen. These are usually transient and asymptomatic, and also do not appear predictive of subsequent hepatic disease. Liver biopsy after sustained use often shows histologic changes, and fibrosis and cirrhosis have been reported; these latter lesions may not be preceded by symptoms or abnormal liver function tests in the psoriasis population. For this reason, periodic liver biopsies are usually recommended for psoriatic patients who are under long-term treatment. (See **PRECAUTIONS**, Organ System Toxicity, Hepatic.)

5. Methotrexate-induced lung disease is a potentially dangerous lesion, which may occur acutely at any time during therapy and which has been reported at doses as low as 7.5 mg/week. It is not always fully reversible. Pulmonary symptoms (especially a dry, nonproductive cough) may require interruption of treatment and careful investigation.

6. Diarrhea and ulcerative stomatitis require interruption of therapy; otherwise, hemorrhagic enteritis and death from intestinal perforation may occur.

7. Malignant lymphomas, which may regress following withdrawal of methotrexate, may occur in patients receiving low-dose methotrexate and, thus may not require cytotoxic treatment. Discontinue methotrexate first and, if the lymphoma does not regress, appropriate treatment should be instituted.

8. Like other cytotoxic drugs, methotrexate may induce "tumor lysis syndrome" in patients with rapidly growing tumors. Appropriate supportive and pharmacologic measures may prevent or alleviate this complication.

9. Severe, occasionally fatal, skin reactions have been reported following single or multiple doses of methotrexate. Reactions have occurred within days of oral, intramuscular, intravenous, or intrathecal methotrexate administration. Recovery has been reported with discontinuation of therapy. (See **PRECAUTIONS**, Organ System Toxicity, *skin*.)

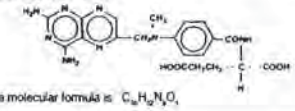
10. Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia may occur with methotrexate therapy.

DESCRIPTION

Methotrexate (formerly Amethopterin) is an antimetabolite used in the treatment of certain neoplastic diseases and severe psoriasis.

Chemically methotrexate is *N*-[4-[[(2,4-diamino-6-pteridinyl) methyl]methylamino]benzoyl]-L-glutamic acid.

The structural formula is



The molecular formula is $C_{20}H_{22}N_8O_5$.

The molecular weight is 454.45.

Methotrexate for Injection, is sterile and non-pyrogenic and may be given by the intramuscular, intravenous, intra-arterial, or intrathecal route. (See **DOSAGE AND ADMINISTRATION**)

Each vial contains methotrexate sodium equivalent to 1 g methotrexate. Contains no preservative. Sodium hydroxide and/or hydrochloric acid may be added to adjust the pH during manufacture to 8.5-8.7. The 1 g vial contains approximately 7mEq of sodium.

CLINICAL PHARMACOLOGY

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.

In psoriasis, the rate of production of epithelial cells in the skin is greatly increased over normal skin. This differential in proliferation rates is the basis for the use of methotrexate to control the psoriatic process.

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 dihyrofolic acid reductase resulting from gene amplification, or decreased polyglutamation of methotrexate. The actual mechanism of action is unknown.

Two Pediatric Oncology Group studies (one randomized and one non-randomized) demonstrated a significant improvement in relapse-free survival in patients with non-metastatic osteosarcoma, when high dose methotrexate with leucovorin rescue was used in combination with other chemotherapeutic agents following surgical resection of the primary tumor. These studies were not designed to demonstrate the specific contribution of high dose methotrexate/leucovorin rescue therapy to the efficacy of the combination. However, a contribution can be inferred from the reports of objective responses to this therapy in patients with metastatic osteosarcoma, and from reports of extensive tumor necrosis following preoperative administration of this therapy to patients with non-metastatic osteosarcoma.

Pharmacokinetics

Absorption-Methotrexate is generally completely absorbed from parenteral routes of injection. After intramuscular injection, peak serum concentrations occur in 30 to 60 minutes.

Distribution- After intravenous administration, the initial volume of distribution is approximately 0.18 L/kg (18% of body weight) and steady-state volume of distribution is approximately 0.4 to 0.6 L/kg (40% to 60% of body weight). Methotrexate competes with reduced folates for active transport across cell membranes by means of a single carrier-mediated active transport process. At serum concentrations greater than 100 micromolar, passive diffusion becomes a major pathway by which effective intracellular concentrations can be achieved. Methotrexate in serum is approximately 50% protein bound. Laboratory studies demonstrate that it may be displaced from plasma albumin by various compounds including sulfonamides, salicylates, tetracyclines, chloramphenicol, and phenytoin.

Methotrexate does not penetrate the blood-cerebrospinal fluid barrier in therapeutic amounts when given parenterally. High CSF concentrations of the drug may be attained by intrathecal administration.

Metabolism - After absorption, methotrexate undergoes hepatic and intracellular metabolism to polyglutamated forms which can be converted back to methotrexate by hydrolase enzymes. These polyglutamates act as inhibitors of dihydrofolate reductase and thymidylate synthetase. Small amounts of methotrexate polyglutamates may remain in tissues for extended periods. The retention and prolonged drug action of these active metabolites vary among different cells, tissues and tumors. A small amount of metabolism to 7-hydroxymethotrexate may occur at doses commonly prescribed. Accumulation of this metabolite may become significant at the high doses used in osteogenic sarcoma. The aqueous solubility of 7-hydroxymethotrexate is 3 to 5 fold lower than the parent compound. Methotrexate is partially metabolized by intestinal flora after oral administration.

Half-Life - The terminal half-life reported for methotrexate is approximately three to ten hours for patients receiving treatment for psoriasis or low dose antineoplastic therapy (less than 30 mg/m^2). For patients receiving high doses of methotrexate, the terminal half-life is eight to 15 hours.

Excretion - Renal excretion is the primary route of elimination, and is dependent upon dosage and route of administration. With IV administration, 80% to 90% of the administered dose is excreted unchanged in the urine within 24 hours. There is limited biliary excretion amounting to 10% or less of the administered dose. Enterohepatic recirculation of methotrexate has been proposed.

Renal excretion occurs by glomerular filtration and active tubular secretion. Nonlinear elimination due to saturation of renal tubular reabsorption has been observed in psoriatic patients at doses between 7.5 and 30 mg. Impaired renal function, as well as concurrent use of drugs such as weak organic acids that also undergo tubular secretion, can markedly increase methotrexate serum levels. Excellent correlation has been reported between methotrexate clearance and endogenous creatinine clearance.

Methotrexate clearance rates vary widely and are generally decreased at higher doses. Delayed drug clearance has been identified as one of the major factors responsible for methotrexate toxicity. It has been postulated that the toxicity of methotrexate for normal tissues is more dependent upon the duration of exposure to the drug rather than the peak level achieved. When a patient has delayed drug elimination due to compromised renal function, a third space effusion, or other causes, methotrexate serum concentrations may remain elevated for prolonged periods.

The potential for toxicity from high dose regimens or delayed excretion is reduced by the administration of leucovorin calcium during the final phase of methotrexate plasma elimination. Pharmacokinetic monitoring of methotrexate serum concentrations may help identify those patients at high risk for methotrexate toxicity and aid in proper adjustment of leucovorin dosing. Guidelines for monitoring serum methotrexate levels, and for adjustment of leucovorin dosing to reduce the risk of methotrexate toxicity are provided below in **DOSAGE AND ADMINISTRATION**.

Methotrexate has been detected in human breast milk. The highest breast milk to plasma concentration ratio reached was 0.08:1.

INDICATIONS AND USAGE

Neoplastic Diseases

Methotrexate is indicated in the treatment of 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, 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.

Psoriasis

Methotrexate is indicated in the symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy, *but only when the diagnosis has been established, as by biopsy and/or after dermatologic consultation.* It is important to ensure that a psoriasis "flare" is not due to an undiagnosed concomitant disease affecting immune responses.

CONTRAINDICATIONS

Methotrexate can cause fetal death or teratogenic effects when administered to a pregnant woman. Methotrexate is contraindicated in pregnant women with psoriasis and should be used in the treatment of neoplastic diseases only when the potential benefit outweighs the risk to the fetus. Women of childbearing potential should not be started on methotrexate until pregnancy is excluded and should be fully counseled on the serious risk to the fetus (see **PRECAUTIONS**) should they become pregnant while undergoing treatment. Pregnancy should be avoided if either partner is receiving methotrexate; during and for a minimum of three months after therapy for male patients, and during and for at least one ovulatory cycle after therapy for female patients. (See Boxed **WARNINGS**.)

Because of the potential for serious adverse reactions from methotrexate in breast fed infants, it is contraindicated in nursing mothers.

Patients with psoriasis with alcoholism, alcoholic liver disease or other chronic liver disease should not receive methotrexate.

Patients with psoriasis who have overt or laboratory evidence of immunodeficiency syndromes should not receive methotrexate.

Patients with psoriasis who have preexisting blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anemia, should not receive methotrexate.

Patients with a known hypersensitivity to methotrexate should not receive the drug.

WARNINGS -SEE BOXED WARNINGS.

PRECAUTIONS

General

Methotrexate has the potential for serious toxicity (See Boxed **WARNINGS**). Toxic effects may be related in frequency and severity to dose or frequency of administration but have been seen at all doses. Because they can occur at any time during therapy, it is necessary to follow patients on methotrexate closely. Most adverse reactions are reversible if detected early. When such reactions do occur, the drug should be reduced in dosage or discontinued as appropriate corrective measures should be taken. If necessary, this could include the use of leucovorin calcium (See **OVERDOSAGE**). If methotrexate therapy is reinstituted, it should be carried out with caution, with adequate consideration of further need for the drug and with increased alertness as to possible recurrence of toxicity.

The clinical pharmacology of methotrexate has not been well studied in older individuals. Due to diminished hepatic and renal function as well as decreased folate stores in this population, relatively low doses should be considered, and these patients should be closely monitored for early signs of toxicity.

Information for Patients

Patients should be informed of the early signs and symptoms of toxicity, of the need to see their physician promptly if they occur, and the need for close follow-up, including periodic laboratory tests to monitor toxicity.

Both the physician and pharmacist should emphasize to the patient that the recommended dose is taken weekly in psoriasis and that mistaken daily use of the recommended dose has led to fatal toxicity. Prescriptions should not be written or refilled on a PRN basis.

Patients should be informed of the potential benefit and risk in the use of methotrexate. The risk of effects on reproduction should

discussed with both male and female patients taking methotrexate.

Laboratory Tests
Patients undergoing methotrexate therapy should be closely monitored so that toxic effects are detected promptly. Baseline assessment should include a complete blood count with differential and platelet counts, hepatic enzymes, renal function tests, and a chest X-ray. During therapy of psoriasis, monitoring of these parameters is recommended: hematology at least monthly, renal function and liver function every 1 to 2 months. More frequent monitoring is usually indicated during antineoplastic therapy. During initial or changing doses, or during periods of increased risk of elevated methotrexate blood levels (eg, dehydration), more frequent monitoring may also be indicated.

Transient liver function test abnormalities are observed frequently after methotrexate administration and are usually not cause for modification of methotrexate therapy. Persistent liver function test abnormalities, and/or depression of serum albumin may be indicators of serious liver toxicity and require evaluation. (See **PRECAUTIONS**, Organ System Toxicity, *Hepatic*.)

A relationship between abnormal liver function tests and fibrosis or cirrhosis of the liver has not been established for patients with psoriasis.

Pulmonary function tests may be useful if methotrexate-induced lung disease is suspected, especially if baseline measurements are available.

Drug Interactions
Nonsteroidal anti-inflammatory drugs should not be administered prior to or concomitantly with the high doses of methotrexate used in the treatment of osteosarcoma. Concomitant administration of some NSAIDs with high dose methotrexate therapy has been reported to elevate and prolong serum methotrexate levels, resulting in deaths from severe hematologic and gastrointestinal toxicity.

Caution should be used when NSAIDs and salicylates are administered concomitantly with lower doses of methotrexate. These drugs have been reported to reduce the tubular secretion of methotrexate in an animal model and may enhance its toxicity.

Methotrexate is partially bound to serum albumin, and toxicity may be increased because of displacement by certain drugs, such as salicylates, phenylbutazone, phenytoin, and sulfonamides. Renal tubular transport is also diminished by probenecid; use of methotrexate with this drug should be carefully monitored.

In the treatment of patients with osteosarcoma, caution must be exercised if high-dose methotrexate is administered in combination with a potentially nephrotoxic chemotherapeutic agent (eg, cisplatin).

Oral antibiotics such as tetracycline, chloramphenicol, and nonabsorbable broad spectrum antibiotics, may decrease intestinal absorption of methotrexate or interfere with the enterohepatic circulation by inhibiting bowel flora and suppressing metabolism of the drug by bacteria.

Penicillins may reduce the renal clearance of methotrexate; increased serum concentrations of methotrexate with concomitant hematologic and gastrointestinal toxicity have been observed with high and low dose methotrexate. Use of methotrexate with penicillins should be carefully monitored.

Patients receiving concomitant therapy with methotrexate and etretinate or other retinoids should be monitored closely for possible increased risk of hepatotoxicity.

Methotrexate may decrease the clearance of theophylline; theophylline levels should be monitored when used concurrently with methotrexate.

Vitamin preparations containing folic acid or its derivatives may decrease responses to systemically administered methotrexate. Preliminary animal and human studies have shown that small quantities of intravenously administered leucovorin enter the CSF primarily as 5-methyltetrahydrofolate and, in humans, remain 1 - 3 orders of magnitude lower than the usual methotrexate concentrations following intrathecal administration. However, high doses of leucovorin may reduce the efficacy of intrathecally administered methotrexate.

Folate deficiency states may increase methotrexate toxicity. Trimethoprim/sulfamethoxazole has been reported rarely to increase bone marrow suppression in patients receiving methotrexate, probably by an additive antifolate effect.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No controlled human data exist regarding the risk of neoplasia with methotrexate. Methotrexate has been evaluated in a number of animal studies for carcinogenic potential with inconclusive results.

Although there is evidence that methotrexate causes chromosomal damage to animal somatic cells and human bone marrow cells, the clinical significance remains uncertain. Benefits should be weighed against the potential risks before using methotrexate alone or in combination with other drugs, especially in pediatric patients or young adults. Methotrexate causes embryotoxicity, abortion, and fetal defects in humans. It has also been reported to cause impairment of fertility, oligospermia and menstrual dysfunction in humans, during and for a short period after cessation of therapy.

Pregnancy: Teratogenic Effects, Pregnancy Category X
See **CONTRAINDICATIONS**.

Nursing Mothers
See **CONTRAINDICATIONS**.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established, other than in cancer chemotherapy.

Organ System Toxicity
Gastrointestinal: If vomiting, diarrhea, or stomatitis occur, which may result in dehydration, methotrexate should be discontinued until recovery occurs. Methotrexate should be used with extreme caution in the presence of peptic ulcer disease or ulcerative colitis.

Hematologic: Methotrexate can suppress hematopoiesis and cause anemia, leukopenia, and/or thrombocytopenia. In patients with malignancy and preexisting hematopoietic impairment the drug should be used with caution, if at all.

In psoriasis, methotrexate should be stopped immediately if there is a significant drop in blood counts. In the treatment of neoplastic diseases, methotrexate should be continued only if the potential benefit warrants the risk of severe myelosuppression. Patients with profound granulocytopenia and fever should be evaluated immediately and usually require parenteral broad-spectrum antibiotic therapy.

Hepatic: Methotrexate has the potential for acute (elevated transaminases) and chronic (fibrosis and cirrhosis) hepatotoxicity. Chronic toxicity is potentially fatal; it generally has occurred after prolonged use (generally two years or more) and after a total dose of at least 1.5 grams. In studies in psoriatic patients, hepatotoxicity appeared to be a function of total cumulative dose and appeared to be enhanced by alcoholism, obesity, diabetes and advanced age. An accurate incidence rate has not been determined; the rate of progression and reversibility of lesions is not known. Special caution is indicated in the presence of preexisting liver damage or impaired hepatic function.

In psoriasis, liver function tests, including serum albumin, should be performed periodically prior to dosing but are often normal in the face of developing fibrosis or cirrhosis. These lesions may be detectable only by biopsy. The usual recommendation is to obtain a liver biopsy at 1) pretherapy or shortly after initiation of therapy (2 - 4 months), 2) a total cumulative dose of 1.5 grams, and 3) after each additional 1.0 to 1.5 grams. Moderate fibrosis or any cirrhosis normally leads to discontinuation of the drug; mild fibrosis normally suggests a repeat biopsy in 6 months. Milder histologic findings such as fatty change and low grade portal inflammation, are relatively common pretherapy. Although these mild changes are usually not a reason to avoid or discontinue methotrexate therapy, the drug should be used with caution.

Infection or Immunologic States: Methotrexate should be used with extreme caution in the presence of active infection, and is usually contraindicated in patients with overt or laboratory evidence of immunodeficiency syndromes. Immunization may be ineffective when given during methotrexate therapy. Immunization with live virus vaccines is generally not recommended. There have been reports of disseminated vaccinia infections after smallpox immunizations in patients receiving methotrexate therapy. Hypogammaglobulinemia has been reported rarely.

Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy. When a patient presents with pulmonary symptoms, the possibility of *Pneumocystis carinii* pneumonia should be considered.

Neurologic: There have been reports of leukoencephalopathy following intravenous administration of methotrexate to patients who have had craniospinal irradation. Serious neurotoxicity, frequently manifested as generalized or focal seizures, has been reported with unexpectedly increased frequency among pediatric patients with acute lymphoblastic leukemia who were treated with intermediate-dose intravenous methotrexate (1 gm/m²). Symptomatic patients were commonly noted to have leukoencephalopathy and/or microangiopathic calcifications on diagnostic imaging studies. Chronic leukoencephalopathy has also been reported in patients who received repeated doses of high-dose methotrexate with leucovorin rescue even without

cranial irradation. Discontinuation of methotrexate does not always result in complete recovery.

A transient acute neurologic syndrome has been observed in patients treated with high dose regimens. Manifestations of this stroke-like encephalopathy may include confusion, hemiparesis, seizures and coma. The exact cause is unknown.

After the intrathecal use of methotrexate, the central nervous system toxicity which may occur can be classified as follows: acute chemical arachnoiditis manifested by such symptoms as headache, back pain, nuchal rigidity, and fever; sub-acute myelopathy characterized by paraparesis/paraplegia associated with involvement with one or more spinal nerve roots; chronic leukoencephalopathy manifested by confusion, irritability, somnolence, ataxia, dementia, seizures and coma. This condition can be progressive and even fatal.

Pulmonary: Pulmonary symptoms (especially a dry nonproductive cough) or a non-specific pneumonitis occurring during methotrexate therapy may be indicative of a potentially dangerous lesion and require interruption of treatment and careful investigation. Although clinically variable, the typical patient with methotrexate induced lung disease presents with fever, cough, dyspnea, hypoxemia, and an infiltrate on chest x-ray. Infection needs to be excluded. This lesion can occur at all dosages.

Renal: High doses of methotrexate used in the treatment of osteosarcoma may cause renal damage leading to acute renal failure. Nephrotoxicity is due primarily to the precipitation of methotrexate and 7-hydroxymethotrexate in the renal tubules. Close attention to renal function including adequate hydration, urine alkalinization and measurement of serum methotrexate and creatinine levels are essential for safe administration.

Skin: Severe, occasionally fatal, dermatologic reactions, including toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, skin necrosis, and erythema multiforme, have been reported in children and adults, within days of oral, intramuscular, intravenous, or intrathecal methotrexate administration. Reactions were noted after single or multiple low, intermediate, or high doses of methotrexate in patients with neoplastic and non-neoplastic diseases.

Other precautions: Methotrexate should be used with extreme caution in the presence of debility.

Methotrexate exits slowly from third space compartments (eg, pleural effusions or ascites). This results in a prolonged terminal plasma half-life and unexpected toxicity. In patients with significant third space accumulations, it is advisable to evacuate the fluid before treatment and to monitor plasma methotrexate levels.

Lesions of psoriasis may be aggravated by concomitant exposure to ultraviolet radiation. Radiation dermatitis and sunburn may be "recalled" by the use of methotrexate.

ADVERSE REACTIONS

IN GENERAL, THE INCIDENCE AND SEVERITY OF ACUTE SIDE EFFECTS ARE RELATED TO DOSE AND FREQUENCY OF ADMINISTRATION. THE MOST SERIOUS REACTIONS ARE DISCUSSED ABOVE UNDER ORGAN SYSTEM TOXICITY IN THE PRECAUTION SECTION. THAT SECTION SHOULD ALSO BE CONSULTED WHEN LOOKING FOR INFORMATION ABOUT ADVERSE REACTIONS WITH METHOTREXATE.

The most frequently reported adverse reactions include ulcerative stomatitis, leukopenia, nausea, and abdominal distress. Other frequently reported adverse effects are malaise, undue fatigue, chills and fever, dizziness and decreased resistance to infection.

Other adverse reactions that have been reported with methotrexate are listed below by organ system. In the oncology setting, concomitant treatment and the underlying disease make specific attribution of a reaction to methotrexate difficult.

Alimentary System: gingivitis, pharyngitis, stomatitis, anorexia, nausea, vomiting, diarrhea, hematemesis, melena, gastrointestinal ulceration and bleeding, enteritis, pancreatitis.

Cardiovascular: pericarditis, pericardial effusion, hypotension, and thromboembolic events (including arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, thrombophlebitis, and pulmonary embolus).

Central Nervous System: headaches, drowsiness, blurred vision, Aphasia, hemiparesis, paresis and convulsions have also occurred following administration of methotrexate. Following low doses, there have been occasional reports of transient subtle cognitive dysfunction, mood alteration or unusual cranial sensations.

Infection: There have been case reports of sometimes fatal opportunistic infections in patients receiving methotrexate therapy for neoplastic and non-neoplastic diseases. *Pneumocystis carinii* monia was the most common infection. Other reported infec included nocardiosis, histoplasmosis, cryptococcosis, Herpes z H. simplex hepatitis, and disseminated H. simplex.

Ophthalmic: conjunctivitis, serious visual changes of unknown eti

Pulmonary System: interstitial pneumonitis deaths have bee ported, and chronic interstitial obstructive pulmonary disease occasionally occurred.

Skin: erythematous rashes, pruritus, urticaria, photosens ity, pigmentary changes, alopecia, ecchymosis, telangiectc acne, furunculosis, erythema multiforme, toxic epider necrolysis, Stevens-Johnson syndrome, skin necrosis, exfoliative dermatitis.

Urogenital System: severe nephropathy or renal failure, azotei cystitis, hematuria, defective oogenesis or spermatogenesis, t sient oligospermia, menstrual dysfunction, vaginal discharge, gynecomastia; infertility, abortion, fetal defects.

Other rarer reactions related to or attributed to the use of me otrexate such as nodulosis, vasculitis, arthralgia/myalgia, l of libido/impotence, diabetes, osteoporosis, sudden death, versible lymphomas, and tumor lysis syndrome. Anaphylact reactions have been reported.

Adverse Reactions in Psoriasis:

There are no recent placebo-controlled trials in patients with pso sis. There are two literature reports (Roenigk, 1969, and Nyl 1978) describing large series (n=204, 248) of psoriasis patie treated with methotrexate. Dosages ranged up to 25 mg per we and treatment was administered for up to four years. With the ception of alopecia, photosensitivity and "burning of skin lesio (each 3% to 10%), the adverse reaction rates in these reports we very similar to those in the rheumatoid arthritis studies.

OVERDOSAGE

Leucovorin is indicated to diminish the toxicity and counteract t effect of inadvertently administered overdosages of methotrexat Leu-covorin administration should begin as promptly as possibl As the time interval between methotrexate administration and le covorin ini-tiation increases, the effectiveness of leucovorin i counteracting toxicity decreases. Monitoring of the serum methot exate concentra-tion is essential in determining the optimal dos and duration of treatment with leucovorin.

In cases of massive overdosage, hydration and urinary alkalinizat tion may be necessary to prevent the precipitation of methotrexat and/or its metabolites in the renal tubules. Neither hemodialysis nor perito-neal dialysis has been shown to improve methotrexate elimination.

Accidental intrathecal overdosage may require intensive systemic support, high-dose systemic leucovorin, alkaline diuresis and rapid CSF drainage and ventriculolumbar perfusion.

DOSAGE AND ADMINISTRATION

Neoplastic Diseases

Oral administration in tablet form is often preferred when low doses are being administered since absorption is rapid and effective serum levels are obtained. Methotrexate for Injection may be given by the intramuscular, intravenous, intra-arterial, or in-trathecal route.

Choriocarcinoma and similar trophoblastic diseases: Methotrexate is administered orally or intramuscularly in doses of 15 to 30 mg daily for a five-day course. Such courses are usually repeated for 3 to 5 times as required, with rest periods of one or more weeks interposed between courses, until any manifesting toxic symptoms subside. The effectiveness of therapy is ordinarily evaluated by 24 hour quantita-tive analysis of urinary chorionic gonadotropin (hCG), which should return to normal or less than 50 IU/24 hr usually after the third or fourth course and usually be followed by a complete resolution of measurable lesions in 4 to 6 weeks. One to two courses of methotr-exate after normalization of hCG is usually recommended. Before each course of the drug careful clinical assessment is essential. Cy-clic combination therapy of methotrexate with other antitumor drugs has been reported as being useful.

Since hydatidiform mole may precede choriocarcinoma, prophylactic chemotherapy with methotrexate has been recommended.

Chorioadenoma destruens is considered to be an invasive form of hydatidiform mole. Methotrexate is administered in these disease states in doses similar to those recommended for choriocarcinoma.

Leukemia: Acute lymphoblastic leukemia in pediatric patients and young adolescents is the most responsive to present day chemotherapy. In young adults and older patients, clinical remission is more difficult to obtain and early relapse is more common.

Methotrexate alone or in combination with steroids was used initially for induction of remission in acute lymphoblastic leukemias. More recently corticosteroid therapy, in combination with other antileukemic drugs or in cyclic combinations with methotrexate included, has appeared to produce rapid and effective remissions. When used for induction, methotrexate in doses of 3.3 mg/m² in combination with 60 mg/m² of prednisone, given daily, produced remissions in 50% of patients treated, usually within a period of 4 to 8 weeks. Methotrexate in combination with other agents appears to be the drug of choice for securing maintenance of drug-induced remissions. When remission is achieved and supportive care has produced general clinical improvement, maintenance therapy is initiated, as follows: Methotrexate is administered 2 times weekly either by mouth or intramuscularly in total weekly doses of 30 mg/m². It has also been given in doses of 2.5 mg/kg intravenously every 14 days. If and when relapse does occur, reinduction of remission can again usually be obtained by repeating the initial induction regimen.

A variety of combination chemotherapy regimens have been used for both induction and maintenance therapy in acute lymphoblastic leukemia. The physician should be familiar with the new advances in antileukemic therapy.

Meningeal Leukemia: In the treatment or prophylaxis of meningeal leukemia, methotrexate must be administered intrathecally. Preservative free methotrexate is diluted to a concentration of 1 mg/mL in an appropriate sterile, preservative free medium such as 0.9% Sodium Chloride Injection.

The cerebrospinal fluid volume is dependent on age and not on body surface area. The CSF is at 40% of the adult volume at birth and reaches the adult volume in several years.

Intrathecal methotrexate administration at a dose of 12 mg/m² (maximum 15 mg) has been reported to result in low CSF methotrexate concentrations and reduced efficacy in pediatric patients and high concentrations and neurotoxicity in adults. The following dosage regimen is based on age instead of body surface area.

AGE (years)	DOSE (mg)
< 1	6
1	8
2	10
3 or older	12

In one study in patients under the age of 40, this dosage regimen appeared to result in more consistent CSF methotrexate concentrations and less neurotoxicity. Another study in pediatric patients with acute lymphocytic leukemia compared this regimen to a dose of 12 mg/m² (maximum 15 mg), a significant reduction in the rate of CNS relapse was observed in the group whose dose was based on age.

Because the CSF volume and turnover may decrease with age, a dose reduction may be indicated in elderly patients.

For the treatment of meningeal leukemia, intrathecal methotrexate may be given at intervals of 2 to 5 days. However, administration at intervals of less than 1 week may result in increased subacute toxicity. Methotrexate is administered until the cell count of the cerebrospinal fluid returns to normal. At this point one additional dose is advisable. For prophylaxis against meningeal leukemia, the dosage is the same as for treatment except for the intervals of administration. On this subject, it is advisable for the physician to consult the medical literature.

Untoward side effects may occur with any given intrathecal injection and are commonly neurological in character. Large doses may cause convulsions. Methotrexate given by the intrathecal route appears significantly in the systemic circulation and may cause systemic methotrexate toxicity. Therefore, systemic antileukemic therapy with the drug should be appropriately adjusted, reduced or discontinued. Focal leukemic involvement of the central nervous system may not respond to intrathecal chemotherapy and is best treated with radiotherapy.

Lymphomas: In Burkitt's tumor, Stages I-II, methotrexate has produced prolonged remissions in some cases. Recommended dosage is 10 to 25 mg/day orally for 4 to 8 days. In Stage III, methotrexate is commonly given concomitantly with other antitumor agents. Treatment in all stages usually consists of several courses of the drug interposed with 7 to 10 day rest periods. Lymphosarcomas in Stage III may respond to combined drug therapy with methotrexate given in doses of 0.625 to 2.5 mg/kg daily.

Mycosis Fungoides: Therapy with methotrexate appears to produce clinical remissions in one half of the cases treated. Dosage is usually 2.5 to 10 mg daily by mouth for weeks or months. Dose levels of drug and adjustment of dose regimen by reduction or cessation of drug are guided by patient response and hematologic monitoring. Methotrexate has been given intramuscularly in doses of 50 mg once weekly or 25 mg 2 times weekly.

Osteosarcoma: An effective adjuvant chemotherapy regimen requires the administration of several cytotoxic chemotherapeutic agents. In addition to high-dose methotrexate with leucovorin rescue, these agents may include doxorubicin, cisplatin, and the combination of bleomycin, cyclophosphamide and dactinomycin (BCD) in the doses and schedule shown in the table below. The starting dose for high-dose methotrexate treatment is 12 grams/m². If this dose is not sufficient to produce a peak serum methotrexate concentration of 1,000 micromolar (10^{-3} mol/L) at the end of the methotrexate infusion, the dose may be escalated to 15 grams/m² in subsequent treatments. If the patient is vomiting or is unable to tolerate oral medication, leucovorin is given IV or IM at the same dose and schedule.

Drug* Dose* After Surgery	Treatment Week	
Methotrexate	12g/m² IV as 4 hour infusion (starting dose)	4,5,6,7,11,12, 15, 16, 29,30,44,45
Leucovorin	15 mg orally every six hours for 10 doses starting at 24 hours after start of methotrexate infusion.	
Doxorubicin† as a single drug	30 mg/m² day IV ± 3 days	8,17
Doxorubicin† Cisplatin†	50 mg/m² IV 100 mg/m² IV	20,23,33,36 20,23,33,36
Bleomycin†	15 units/m² IV ± 2 days	2,13,26,39,42
Cyclophosphamide†	600 mg/m² IV ± 2 days	2,13,26,39,42
Dactinomycin†	0.6 mg/m² IV ± 2 days	2,13,26,39,42

* Link MP, Goorin AM, Miser AW, et al: The effect of adjuvant chemotherapy on relapse-free survival in patients with osteosarcoma of the extremity. *N Engl J of Med* 1986; 314(No.25):1600-1606

†See each respective package insert for full prescribing information. Dosage modifications may be necessary because of drug-induced toxicity.

When these higher doses of methotrexate are to be administered, the following safety guidelines should be closely observed.

GUIDELINES FOR METHOTREXATE THERAPY WITH LEUCOVORIN RESCUE

1. Administration of methotrexate should be delayed until recovery if:
   - the WBC count is less than 1500/microliter
   - the neutrophil count is less than 200/microliter
   - the platelet count is less than 75,000/microliter
   - the serum bilirubin level is greater than 1.2 mg/dl
   - the SGPT level is greater than 450 U
   - mucositis is present, until there is evidence of healing
   - persistent pleural effusion is present, this should be drained dry prior to infusion.
2. Adequate renal function must be documented.
   a. Serum creatinine must be normal, and creatinine clearance must be greater than 60 mL/min, before initiation of therapy.
   b. Serum creatinine must be measured prior to each subsequent course of therapy. If serum creatinine has increased by 50 % or more compared to a prior value, the creatinine clearance must be measured and documented to be greater than 60 mL/min (even if the serum creatinine is still within the normal range).
3. Patients must be well hydrated, and must be treated with sodium bicarbonate for urinary alkalinization.
   a. Administer 1,000 mL/m² of intravenous fluid over 6 hours prior to initiation of the methotrexate infusion. Continue hydration at 125 mL/m²/hr (3 liters/m²/day) during the methotrexate infusion, and for 2 days after the infusion has been completed.
   b. Alkalinize urine to maintain pH above 7.0 during methotrexate infusion and leucovorin calcium therapy. This can be accomplished by the administration of sodium bicarbonate orally or by incorporation into a separate intravenous solution.
4. Repeat serum creatinine and serum methotrexate 24 hours after starting methotrexate and at least once daily until the methotrexate level is below 5×10^{-8} mol/L (0.05 micromolar).
5. The table below provides guidelines for leucovorin calcium dosage based upon serum methotrexate levels. (See table below.†)

Patients who experience delayed early methotrexate elimination are likely to develop nonreversible oliguric renal failure. In addition to appropriate leucovorin therapy, these patients require continuing hydration and urinary alkalinization, and close monitoring of fluid and electrolyte status, until the serum methotrexate level has fallen to be-low 0.05 micromolar and the renal failure has resolved.

6. Some patients will have abnormalities in methotrexate elimination, or abnormalities in renal function following methotrexate adminis-tration, which are significant but less severe than the abnormalities described in the table below. These abnormalities may or may not be associated with significant clinical toxicity. If significant clinical toxicity is observed, leucovorin rescue should be extended for an additional 24 hours (total 14 doses over 84 hours) in subsequent courses of therapy. The possibility that the patient is taking other medications which interact with methotrexate (eg, medications which may interfere with methotrexate binding to serum albumin, or elimi-nation) should always be reconsidered when laboratory abnormalities or clinical toxicities are observed.

CAUTION: DO NOT ADMINISTER LEUCOVORIN INTRATHECALLY.

Psoriasis:
The patient should be fully informed of the risks involved and should be under constant supervision of the physician. (See Information for Patients Under **PRECAUTIONS**). Assessment of hematologic, hepatic, renal, and pulmonary function should be made by history, physical examination, and laboratory tests before beginning, periodically during, and before reinstituting methotrexate therapy. (See **PRECAUTIONS**). Appropriate steps should be taken to avoid conception during methotrexate therapy. (See **PRECAUTIONS AND CONTRAINDICATIONS**).

All schedules should be continually tailored to the individual patient. An initial test dose may be given prior to the regular dosing schedule to detect any extreme sensitivity to adverse effects (See **ADVERSE REACTIONS**). Maximal myelosuppression usually occurs in seven to ten days.

Psoriasis: Recommended Starting Dose Schedule

1. Weekly single oral IM or IV dosage schedule: 10 to 25 mg per week until adequate response is achieved.

2. Divided oral dose schedule: 2.5 mg at 12 hour intervals for three doses.

Dosages in each schedule may be gradually adjusted to achieve optimal clinical response: 30 mg/week should not ordinarily be exceeded.

Once optimal clinical response has been achieved, each dosage schedule should be reduced to the lowest possible amount of drug and to the longest possible rest period. The use of methotrexate may permit the return to conventional topical therapy, which should be encouraged.

HANDLING AND DISPOSAL

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. ** There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

RECONSTITUTION OF LYOPHILIZED POWDER

Reconstitute immediately prior to use.

Methotrexate for Injection should be reconstituted with an appropriate sterile preservative free medium such as 5% Dextrose Solution, or Sodium Chloride Injection. **The 1 gram vial should be reconstituted with 19.4 mL to a concentration of 50 mg/mL.** When high doses of methotrexate are administered by IV infusion, the total dose is diluted in 5% Dextrose Solution.

For intrathecal injection, reconstitute to a concentration of 1 mg/mL with an appropriate sterile, preservative free medium such as Sodium Chloride Injection.

HOW SUPPLIED

Methotrexate for Injection USP, Lyophilized, Preservative Free, for Single Use Only.

Each 1 g vial of lyophilized powder contains methotrexate sodium equivalent to 1 g methotrexate.

1 g vial

Store at controlled room temperature 15-30°C (59°-86°F). Protect From Light. Retain in carton until time of use. Discard unused portion.

See package insert for routes of administration.

Rx only

Manufactured by:
Bigmar Pharmaceuticals SA
Barbengo, Switzerland

Manufactured for:
Bigmar, Inc.
Johnstown, OH 43031

Rev 06, November 1998

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†LEUCOVORIN RESCUE SCHEDULES FOLLOWING TREATMENT WITH HIGHER DOSES OF METHOTREXATE

Clinical Situation: Normal Methotrexate Elimination
Laboratory Findings: Serum methotrexate level approximately micromolar at 24 hours after administration, 1 micromolar at hours, and less than 0.2 micromolar at 72 hours.
Leucovorin Dosage and Duration: 15 mg PO, IM, or IV hours for 60 hours (10 doses starting at 24 hours after star methotrexate infusion).

Clinical Situation: Delayed Late Methotrexate Elimination
Laboratory Findings: Serum methotrexate level remaining ab 0.2 micromolar at 72 hours, and more than 0.05 micromolar at hours after administration.
Leucovorin Dosage and Duration: Continue 15 mg PO, IM, o q 6 hours, until methotrexate level is than 0.05 micromolar.

Clinical Situation: Delayed Early Methotrexate Elimination a or Evidence of Acute Renal Injury.
Laboratory Findings: Serum methotrexate level of 50 micron lar or more at 24 hours, or 5 micromolar or more at 48 hours af admin-istration, OR a 100% or greater increase in serum cre nine level at 24 hours after methotrexate administration (eg, increase from 0.5 mg/dL to a level of 1 mg/dL or more).
Leucovorin Dosage and Duration: 150 mg IV q 3 hours, un meth-otrexate level is less than 1 micromolar, then 15 mg IV q hours until methotrexate level is less than 0.05 micromolar.

METHOTREXATE
FOR INJECTION USP
1 g
Lyophilized
PRESERVATIVE FREE

METHOTREXATE
FOR INJECTION USP

1 g

Lyophilized
PRESERVATIVE FREE

1 g Single Dose Vial Sterile

See package insert for routes of administration.

Pharmaceuticals Bigmar

Usual Dosage: Consult package insert for dosage and full prescribing information.

Each vial contains lyophilized Methotrexate Sodium equivalent to 1000 mg methotrexate and approximately 7 mEq of sodium.

Inactive ingredients: Sodium hydroxide and/or hydrochloric acid may be added to adjust pH to 8.5 - 8.7 during manufacture.

Rx only

METHOTREXATE
FOR INJECTION USP

1 g

Lyophilized
PRESERVATIVE FREE

1 g Single Dose Vial Sterile

See package insert for routes of administration.

Pharmaceuticals Bigmar

Store between 15° - 30°C (59° - 86°F). **PROTECT FROM LIGHT.** Retain in carton until time of use. Discard unused portion.

Reconstitute immediately prior to use with 19.4 mL of an appropriate sterile, preservative-free medium to a concentration of 50 mg/mL.

WARNING: SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION AND BOXED WARNINGS.

Manufactured by:
Bigmar Pharmaceuticals SA
Barbengo, Switzerland

Manufactured for:
Bigmar, Inc.
Johnstown, OH 43031

Lot #
Exp. Date

METHOTREXATE
FOR INJECTION USP

1 g

Lyophilized
PRESERVATIVE FREE

1 g Single Dose Vial **Sterile**
See package insert for routes of administration.

Rx only

Usual Dosage: Consult package insert for dosage and full prescribing information.

Reconstitute immediately prior to use with 19.4 mL of an appropriate sterile, preservative-free medium to a concentration of 50 mg/mL.

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Manufactured by:
Bigmar Pharmaceuticals SA
Barbengo, Switzerland

Manufactured for:
Bigmar, Inc.
Johnstown, OH 43031

Lot # Exp. Date
FEB 26 1999

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 40-385

Name:	Trexall Tablets (Methotrexate Tablets USP)
Sponsor:	Barr Laboratories, Inc.
Approval Date:	March 21, 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-385

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-385

APPROVAL LETTER

ANDA 40-385

MAR 21 2001

Barr Laboratories, Inc.
Attention: Christine Mundkur
2 Quaker Road
P.O. Box 2900
Pomona, NY 10970

Dear Madam:

This is in reference to your abbreviated new drug application dated July 23, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Trexall® Tablets (Methotrexate Tablets USP), 5 mg, 7.5 mg, 10 mg, and 15 mg.

Reference is also made to your amendments dated October 7, 1999, and February 15, and February 22, 2001.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The drug product, Trexall® Tablets (Methotrexate Tablets USP), 5 mg, 7.5 mg, 10 mg, and 15 mg, can be expected to have the same therapeutic effect as equivalent doses of the listed drug product which the Agency relied upon as the basis of safety and effectiveness. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print.

Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Gary Buehler 3/22/01
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 40-385
Division File
Field Copy
HFD-610/R. West
HFD-210/B. Poole
HFD-330
HFD-205

Endorsements:
HFD-625/E.Schaefer/
HFD-625/M.Smela/
HFD-617/M.Dillahunt/3/8/01
HFD-613/A.Payne/
HFD-613/J.Grace/

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F/T by: DJ 3/8/01

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-385

APPROVED LABELING

Rx only

MAR 21 2001

APPROVED

21009270101

Trexall™

(methotrexate tablets, USP)

Revised JANUARY 2001
21009270101

WARNINGS:

METHOTREXATE SHOULD BE USED ONLY BY PHYSICIANS WHOSE KNOWLEDGE AND EXPERIENCE INCLUDE THE USE OF ANTIMETABOLITE THERAPY.

BECAUSE OF THE POSSIBILITY OF SERIOUS TOXIC REACTIONS (WHICH CAN BE FATAL):

METHOTREXATE SHOULD BE USED ONLY IN LIFE THREATENING NEOPLASTIC DISEASES, OR IN PATIENTS WITH PSORIASIS OR RHEUMATOID ARTHRITIS WITH SEVERE, RECALCITRANT, DISABLING DISEASE WHICH IS NOT ADEQUATELY RESPONSIVE TO OTHER FORMS OF THERAPY.

DEATHS HAVE BEEN REPORTED WITH THE USE OF METHOTREXATE IN THE TREATMENT OF MALIGNANCY, PSORIASIS, AND RHEUMATOID ARTHRITIS.

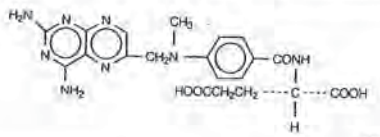
PATIENTS SHOULD BE CLOSELY MONITORED FOR BONE MARROW, LIVER, LUNG AND KIDNEY TOXICITIES. (See **PRECAUTIONS**.)

PATIENTS SHOULD BE INFORMED BY THEIR PHYSICIAN OF THE RISKS INVOLVED AND BE UNDER A PHYSICIAN'S CARE THROUGHOUT THERAPY.

1. Methotrexate has been reported to cause fetal death and/or congenital anomalies. Therefore, it is not recommended for women of childbearing potential unless there is clear medical evidence that the benefits can be expected to outweigh the considered risks. Pregnant women with psoriasis or rheumatoid arthritis should not receive methotrexate. (See **CONTRAINDICATIONS**.)
2. Methotrexate elimination is reduced in patients with impaired renal function, ascites, or pleural effusions. Such patients require especially careful monitoring for toxicity, and require dose reduction or, in some cases, discontinuation of methotrexate administration.
3. Unexpectedly severe (sometimes fatal) bone marrow suppression and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high dosage) along with some nonsteroidal anti-inflammatory drugs (NSAIDs). (See **PRECAUTIONS, Drug Interactions**.)
4. Methotrexate causes hepatotoxicity, fibrosis and cirrhosis, but generally only after prolonged use. Acutely, liver enzyme elevations are frequently seen. These are usually transient and asymptomatic, and also do not appear predictive of subsequent hepatic disease. Liver biopsy after sustained use often shows histologic changes, and fibrosis and cirrhosis have been reported; these latter lesions may not be preceded by symptoms or abnormal liver function tests in the psoriasis population. For this reason, periodic liver biopsies are usually recommended for psoriatic patients who are under long-term treatment. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid arthritis population. (See **PRECAUTIONS, Organ System Toxicity**, *Hepatic*.)
5. Methotrexate-induced lung disease is a potentially dangerous lesion, which may occur acutely at any time during therapy and which has been reported at doses as low as 7.5 mg/week. It is not always fully reversible. Pulmonary symptoms (especially a dry, nonproductive cough) may require interruption of treatment and careful investigation.
6. Diarrhea and ulcerative stomatitis require interruption of therapy; otherwise, hemorrhagic enteritis and death from intestinal perforation may occur.
7. Malignant lymphomas, which may regress following withdrawal of methotrexate, may occur in patients receiving low-dose methotrexate and, thus, may not require cytotoxic treatment. Discontinue methotrexate first and, if the lymphoma does not regress, appropriate treatment should be instituted.
8. Like other cytotoxic drugs, methotrexate may induce "tumor lysis syndrome" in patients with rapidly growing tumors. Appropriate supportive and pharmacologic measures may prevent or alleviate this complication.
9. Severe, occasionally fatal, skin reactions have been reported following single or multiple doses of methotrexate. Reactions have occurred within days of oral, intramuscular, intravenous, or intrathecal methotrexate administration. Recovery has been reported with discontinuation of therapy. (See **PRECAUTIONS, Organ System Toxicity**, *Skin*.)
10. Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy.
11. Methotrexate given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.

DESCRIPTION:

Trexall™ (methotrexate tablets, USP) (formerly Amethopterin) is an antimetabolite used in the treatment of certain neoplastic diseases, severe psoriasis, and adult rheumatoid arthritis. Chemically methotrexate is *N*-[4[[(2,4-diamino-6-pteridinyl) methyl] methyl-amino]benzoyl]-L-glutamic acid. The structural formula is:



$C_{20}H_{22}N_8O_5$ Molecular Weight: 454.45

Trexall™ (methotrexate tablets), for oral administration, are available in 5 mg, 7.5 mg, 10 mg and 15 mg strengths in bottles of 30's, 60's and 100's.

Each 5 mg tablet contains an amount of methotrexate sodium equivalent to 5 mg of methotrexate.

Each 7.5 mg tablet contains an amount of methotrexate sodium equivalent to 7.5 mg of methotrexate.

Each 10 mg tablet contains an amount of methotrexate sodium equivalent to 10 mg of methotrexate.

Each 15 mg tablet contains an amount of methotrexate sodium equivalent to 15 mg of methotrexate.

In addition, each tablet contains the following inactive ingredients: anhydrous lactose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, pregelatinized starch, sodium carbonate monohydrate and talc.

The 5 mg also contains: crospovidone, D&C yellow no. 10 aluminum lake, FD&C blue no. 1 aluminum lake, FD&C yellow no. 6 aluminum lake, polysorbate 80, and titanium dioxide.

The 7.5 mg also contains: crospovidone, FD&C blue no.1 aluminum lake, polysorbate 80, and titanium dioxide.

The 10 mg also contains: crospovidone, FD&C red no. 40 aluminum lake, polysorbate 80, and titanium dioxide.

The 15 mg also contains: crospovidone, FD&C blue no. 2 aluminum lake, FD&C red no. 40 aluminum lake, polysorbate 80, and titanium dioxide.

CLINICAL PHARMACOLOGY:

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.

The mechanism of action in rheumatoid arthritis is unknown; it may affect immune function. Two reports describe *in vitro* methotrexate inhibition of DNA precursor uptake by stimulated mononuclear cells, and another describes, in animal polyarthritis partial correction by methotrexate of spleen cell hyporesponsiveness and suppressed IL 2 production. Other laboratories, however, have been unable to demonstrate similar effects. Clarification of methotrexate's effect on immune activity and its relation to rheumatoid immunopathogenesis await further studies.

In patients with rheumatoid arthritis, effects of methotrexate on articular swelling and tenderness can be seen as early as 3 to 6 weeks. Although methotrexate clearly ameliorates symptoms of inflammation (pain, swelling, stiffness), there is no evidence that it induces remission of rheumatoid arthritis nor has a beneficial effect been demonstrated on bone erosions and other radiologic changes which result in impaired joint use, functional disability, and deformity.

Most studies of methotrexate in patients with rheumatoid arthritis have been of short duration (3 to 6 months).

Limited data from long-term studies indicate that an initial clinical improvement is maintained for at least two years with continued therapy.

In psoriasis, the rate of production of epithelial cells in the skin is greatly increased over normal skin. This differential in proliferation rates is the basis for the use of methotrexate to control the psoriatic process.

Pharmacokinetics:

Absorption: In adults, oral absorption appears to be dose dependent. Peak serum levels are reached within one to two hours. At doses of 30 mg/m^2 or less, methotrexate is generally well absorbed with a mean bioavailability of about 60%. The absorption of doses greater than 80 mg/m^2 is significantly less, possibly due to a saturation effect.

In leukemic pediatric patients, oral absorption has been reported to vary widely (23% to 95%). A twenty fold difference between highest and lowest peak levels (C_{MAX}: 0.11 to 2.3 micromolar after a 20 mg/m^2 dose) has been reported. Significant interindividual variability has also been noted in time to peak concentration (T_{MAX}: 0.67 to 4 hours after a 15 mg/m^2 dose) and fraction of dose absorbed. Food has been shown to delay absorption and reduce peak concentration.

Distribution: After intravenous administration, the initial volume of distribution is approximately 0.18 L/kg (18% of body weight) and steady-state volume of distribution is approximately 0.4 to 0.8 L/kg (40 to 80% of body weight). Methotrexate competes with reduced folates for active transport across cell membranes by means of a single carrier-mediated active transport process. At serum concentrations greater than 100 micromolar, passive diffusion becomes a major pathway by which effective intracellular concentrations can be achieved. Methotrexate in serum is approximately 50% protein bound. Laboratory studies demonstrate that it may be displaced from plasma albumin by various compounds including sulfonamides, salicylates, tetracyclines, chloramphenicol, and phenytoin.

Methotrexate does not penetrate the blood-cerebrospinal fluid barrier in therapeutic amounts when given orally or parenterally. High CSF concentrations of the drug may be attained by intrathecal administration.

In dogs, synovial fluid concentrations after oral dosing were higher in inflamed than uninflamed joints. Although salicylates did not interfere with this penetration, prior prednisone treatment reduced penetration into inflamed joints to the level of normal joints.

Metabolism: After absorption, methotrexate undergoes hepatic and intracellular metabolism to polyglutamated forms which can be converted back to methotrexate by hydrolase enzymes. These polyglutamates act as inhibitors of dihydrofolate reductase and thymidylate synthetase. Small amounts of methotrexate polyglutamates may remain in tissues for extended periods. The retention and prolonged drug action of these active metabolites vary among different cells, tissues and tumors. A small amount of metabolism to 7-hydroxymethotrexate may occur at doses commonly prescribed. The aqueous solubility of 7-hydroxymethotrexate is 3 to 5 fold lower than the parent compound. Methotrexate is partially metabolized by intestinal flora after oral administration.

Half-Life: The terminal half-life reported for methotrexate is approximately three to ten hours for patients receiving treatment for psoriasis, or rheumatoid arthritis or low dose antineoplastic therapy (less than 30 mg/m^2). For patients receiving high doses of methotrexate, the terminal half-life is eight to 15 hours.

Excretion: Renal excretion is the primary route of elimination, and is dependent upon dosage and route of administration. With IV administration, 80% to 90% of the administered dose is excreted unchanged in the urine within 24 hours. There is limited biliary excretion amounting to 10% or less of the administered dose. Enterohepatic recirculation of methotrexate has been proposed.

Renal excretion occurs by glomerular filtration and active tubular secretion. Nonlinear elimination due to saturation of renal tubular reabsorption has been observed in psoriatic patients at doses between 7.5 and 30 mg. Impaired renal function, as well as concurrent use of drugs such as weak organic acids that also undergo tubular secretion, can markedly increase methotrexate serum levels. Excellent correlation has been reported between methotrexate clearance and endogenous creatinine clearance.

Methotrexate clearance rates vary widely and are generally decreased at higher doses. Delayed drug clearance has been identified as one of the major factors responsible for methotrexate toxicity. It has been postulated that the toxicity of methotrexate for normal tissues is more dependent upon the duration of exposure to the drug rather than the peak level achieved. When a patient has delayed drug elimination due to compromised renal function, a third space effusion, or other causes, methotrexate serum concentrations may remain elevated for prolonged periods.

Methotrexate has been detected in human breast milk. The highest breast milk to plasma concentration ratio reached was 0.08:1.

INDICATIONS AND USAGE:

Neoplastic Diseases:

Trexall™ (methotrexate tablets) are indicated in the treatment of gestational choriocarcinoma, chorioadenoma destruens and hydatidiform mole.

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, 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.

Psoriasis:

Trexall™ (methotrexate tablets) are indicated in the symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy, *but only when the diagnosis has been established, as by biopsy and/or after dermatologic consultation.* It is important to ensure that a psoriasis "flare" is not due to an undiagnosed concomitant disease affecting immune responses.

Rheumatoid Arthritis:

Trexall™ (methotrexate tablets) are indicated in the management of selected adults with severe, active, classical or definite rheumatoid arthritis (ARA criteria) who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of first-line therapy including full dose NSAIDs and usually a trial of at least one or more disease-modifying antirheumatic drugs.

Aspirin, nonsteroidal anti-inflammatory agents, and/or low dose steroids may be continued, although the possibility of increased toxicity with concomitant use of NSAIDs including salicylates has not been fully explored (see **PRECAUTIONS, Drug Interactions**). Steroids may be reduced gradually in patients who respond to methotrexate. Combined use of methotrexate with gold, penicillamine, hydroxychloroquine, sulfasalazine, or cytotoxic agents, has not been studied and may increase the incidence of adverse effects. Rest and physiotherapy as indicated should be continued.

CONTRAINDICATIONS:

Methotrexate can cause fetal death or teratogenic effects when administered to a pregnant woman. Methotrexate is contraindicated in pregnant women with psoriasis or rheumatoid arthritis and should be used in the treatment of neoplastic diseases only when the potential benefit outweighs the risk to the fetus. Women of childbearing potential should not be started on methotrexate until pregnancy is excluded and should be fully counseled on the serious risk to the fetus (see **PRECAUTIONS**) should they become pregnant while undergoing treatment. Pregnancy should be avoided if either partner is receiving methotrexate; during and for a minimum of three months after therapy for male patients, and during and for at least one ovulatory cycle after therapy for female patients. (See Boxed **WARNINGS.**)

Because of the potential for serious adverse reactions from methotrexate in breast fed infants, it is contraindicated in nursing mothers.

Patients with psoriasis or rheumatoid arthritis with alcoholism, alcoholic liver disease or other chronic liver disease should not receive methotrexate.

Patients with psoriasis or rheumatoid arthritis who have overt or laboratory evidence of immunodeficiency syndromes should not receive methotrexate.

Patients with psoriasis or rheumatoid arthritis who have preexisting blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia or significant anemia, should not receive methotrexate.

Patients with a known hypersensitivity to methotrexate should not receive the drug.

WARNINGS:

See Boxed **WARNINGS.**

PRECAUTIONS:

General:

Methotrexate has the potential for serious toxicity. (See Boxed **WARNINGS.**) Toxic effects may be related in frequency and severity to dose or frequency of administration but have been seen at all doses. Because they can occur at any time during therapy, it is necessary to follow patients on methotrexate closely. Most adverse reactions are reversible if detected early. When such reactions do occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken. If necessary, this could include the use of leucovorin calcium and/or acute, intermittent hemodialysis with a high-flux dialyzer. (See **OVERDOSAGE.**) If methotrexate therapy is reinstituted, it should be carried out with caution, with adequate consideration of further need for the drug and with increased alertness as to possible recurrence of toxicity.

The clinical pharmacology of methotrexate has not been well studied in older individuals. Due to diminished hepatic and renal function as well as decreased folate stores in this population, relatively low doses should be considered, and these patients should be closely monitored for early signs of toxicity.

Information for Patients:

Patients should be informed of the early signs and symptoms of toxicity, of the need to see their physician promptly if they occur, and the need for close follow-up, including periodic laboratory tests to monitor toxicity.

Both the physician and pharmacist should emphasize to the patient that the recommended dose is taken weekly in rheumatoid arthritis and psoriasis, and that mistaken daily use of the recommended dose has led to fatal toxicity. Prescriptions should not be written or refilled on a PRN basis.

Patients should be informed of the potential benefit and risk in the use of methotrexate. The risk of effects on reproduction should be discussed with both male and female patients taking methotrexate.

Laboratory Tests:

Patients undergoing methotrexate therapy should be closely monitored so that toxic effects are detected promptly. Baseline assessment should include a complete blood count with differential and platelet counts, hepatic enzymes, renal function tests, and a chest X-ray. During therapy of rheumatoid arthritis and psoriasis, monitoring of these parameters is recommended: hematology at least monthly, renal function and liver function every 1 to 2 months. More frequent monitoring is usually indicated during antineoplastic therapy. *During initial or changing doses,* or during periods of increased risk of elevated methotrexate blood levels (e.g., dehydration), more frequent monitoring may also be indicated.

Transient liver function test abnormalities are observed frequently after methotrexate administration and are usually not cause for modification of methotrexate therapy. Persistent liver function test abnormalities, and/or depression of serum albumin may be indicators of serious liver toxicity and require evaluation. (See **PRECAUTIONS, Organ System Toxicity,** *Hepatic.*)

A relationship between abnormal liver function tests and fibrosis or cirrhosis of the liver has not been established for patients with psoriasis. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid arthritis population.

Pulmonary function tests may be useful if methotrexate-induced lung disease is suspected, especially if baseline measurements are available.

Drug Interactions:

Concomitant administration of some NSAIDs with high dose methotrexate therapy has been reported to elevate and prolong serum methotrexate levels, resulting in deaths from severe hematologic and gastrointestinal toxicity.

Caution should be used when NSAIDs or salicylates are administered concomitantly with lower doses of methotrexate. These drugs have been reported to reduce the tubular secretion of methotrexate in an animal model and may enhance its toxicity.

Despite the potential interactions, studies of methotrexate in patients with rheumatoid arthritis have usually included concurrent use of constant dosage regimens of NSAIDs, without apparent problems. It should be appreciated, however, that the doses used in rheumatoid arthritis (7.5 to 15 mg/week) are somewhat lower than those used in psoriasis and that larger doses could lead to unexpected toxicity.

Methotrexate is partially bound to serum albumin, and toxicity may be increased because of displacement by certain drugs, such as salicylates, phenylbutazone, phenytoin, and sulfonamides. Renal tubular transport is also diminished by probenecid; use of methotrexate with this drug should be carefully monitored.

Oral antibiotics such as tetracycline, chloramphenicol, and nonabsorbable broad spectrum antibiotics, may decrease intestinal absorption of methotrexate or interfere with the enterohepatic circulation by inhibiting bowel flora and suppressing metabolism of the drug by bacteria.

Penicillins may reduce the renal clearance of methotrexate; increased serum concentrations of methotrexate with concomitant hematologic and gastrointestinal toxicity have been observed with high and low dose methotrexate. Use of methotrexate with penicillins should be carefully monitored.

The potential for increased hepatotoxicity when methotrexate is administered with other hepatotoxic agents has not been evaluated. However, hepatotoxicity has been reported in such cases. Therefore, patients receiving concomitant therapy with methotrexate and other potential hepatotoxins (e.g., azathioprine, retinoids, sulfasalazine) should be closely monitored for possible increased risk of hepatotoxicity.

Methotrexate may decrease the clearance of theophylline; theophylline levels should be monitored when used concurrently with methotrexate.

Vitamin preparations containing folic acid or its derivatives may decrease responses to systemically administered methotrexate. Preliminary animal and human studies have shown that small quantities of intravenously administered leucovorin enter the CSF primarily as 5-methyltetrahydrofolate and, in humans, remain 1-3 orders of magnitude lower than the usual methotrexate concentrations following intrathecal administration. However, high doses of leucovorin may reduce the efficacy of intrathecally administered methotrexate.

Folate deficiency states may increase methotrexate toxicity.

Trimethoprim/sulfamethoxazole has been reported rarely to increase bone marrow suppression in patients receiving methotrexate, probably by an additive antifolate effect.

Carcinogenesis, Mutagenesis, and Impairment of Fertility:

No controlled human data exist regarding the risk of neoplasia with methotrexate. Methotrexate has been evaluated in a number of animal studies for carcinogenic potential with inconclusive results. Although there is evidence that methotrexate causes chromosomal damage to animal somatic cells and human bone marrow cells, the clinical significance remains uncertain. Non-Hodgkin's lymphoma and other tumors have been reported in patients receiving low-dose oral methotrexate. However, there have been instances of malignant lymphoma arising during treatment with low-dose oral methotrexate, which have regressed completely following withdrawal of methotrexate, without requiring active anti-lymphoma treatment. Benefits should be weighed against the potential risks before using methotrexate alone or in combination with other drugs, especially in pediatric patients or young adults. Methotrexate causes embryotoxicity, abortion, and fetal defects in humans. It has also been reported to cause impairment of fertility, oligospermia and menstrual dysfunction in humans, during and for a short period after cessation of therapy.

Pregnancy:

Psoriasis and rheumatoid arthritis: Methotrexate is in Pregnancy Category X. See **CONTRAINDICATIONS.**

Nursing Mothers:

See **CONTRAINDICATIONS.**

Pediatric Use:

Safety and effectiveness in pediatric patients have not been established, other than in cancer chemotherapy.

Organ System Toxicity:

Gastrointestinal: If vomiting, diarrhea, or stomatitis occur, which may result in dehydration, methotrexate should be discontinued until recovery occurs. Methotrexate should be used with extreme caution in the presence of peptic ulcer disease or ulcerative colitis.

Hematologic: Methotrexate can suppress hematopoiesis and cause anemia, leukopenia, and/or thrombocytopenia. In patients with malignancy and preexisting hematopoietic impairment, the drug should be used with caution, if at all. In controlled clinical trials in rheumatoid arthritis (n=128), leukopenia (WBC <3000/mm^3) was seen in 2 patients, thrombocytopenia (platelets <100,000/mm^3) in 6 patients, and pancytopenia in 2 patients.

In psoriasis and rheumatoid arthritis, methotrexate should be stopped immediately if there is a significant drop in blood counts. In the treatment of neoplastic diseases, methotrexate should be continued only if the potential benefit warrants the risk of severe myelosuppression. Patients with profound granulocytopenia and fever should be evaluated immediately and usually require parenteral broad-spectrum antibiotic therapy.

Hepatic: Methotrexate has the potential for acute (elevated transaminases) and chronic (fibrosis and cirrhosis) hepatotoxicity. Chronic toxicity is potentially fatal; it generally has occurred after prolonged use (generally two years or more) and after a total dose of at least 1.5 grams. In studies in psoriatic patients, hepatotoxicity appeared to be a function of total cumulative dose and appeared to be enhanced by alcoholism, obesity, diabetes and advanced age. An accurate incidence rate has not been determined; the rate of progression and reversibility of lesions is not known. Special caution is indicated in the presence of preexisting liver damage or impaired hepatic function.

(Over)

In psoriasis, liver function tests, including serum albumin, should be performed periodically prior to dosing but are often normal in the face of developing fibrosis or cirrhosis. These lesions may be detectable only by biopsy. The usual recommendation is to obtain a liver biopsy at 1) pretherapy or shortly after initiation of therapy (2-4 months), 2) a total cumulative dose of 1.5 grams, and 3) after each additional 1.0 to 1.5 grams. Moderate fibrosis or any cirrhosis normally leads to discontinuation of the drug; mild fibrosis normally suggests a repeat biopsy in 6 months. Milder histologic findings such as fatty change and low grade portal inflammation are relatively common pretherapy. Although these mild changes are usually not a reason to avoid or discontinue methotrexate therapy, the drug should be used with caution.

In rheumatoid arthritis, age at first use of methotrexate and duration of therapy have been reported as risk factors for hepatotoxicity; other risk factors, similar to those observed in psoriasis, may be present in rheumatoid arthritis but have not been confirmed to date. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in this population. There is a combined reported experience in 217 rheumatoid arthritis patients with liver biopsies both before and during treatment (after a cumulative dose of at least 1.5 g) and in 714 patients with a biopsy only during treatment. There are 64 (7%) cases of fibrosis and 1 (0.1%) cases of cirrhosis. Of the 64 cases of fibrosis, 60 were deemed mild. The reticulin stain is more sensitive for early fibrosis and its use may increase these figures. It is unknown whether even longer use will increase these risks.

Liver function tests should be performed at baseline and at 4-8 week intervals in patients receiving methotrexate for rheumatoid arthritis. Pretreatment liver biopsy should be performed for patients with a history of excessive alcohol consumption, persistently abnormal baseline liver function test values or chronic hepatitis B or C infection. During therapy, liver biopsy should be performed if there are persistent liver function test abnormalities or there is a decrease in serum albumin below the normal range (in the setting of well controlled rheumatoid arthritis).

If the results of a liver biopsy show mild changes (Roenigk grades I, II, IIIa), methotrexate may be continued and the patient monitored as per recommendations listed above. Methotrexate should be discontinued in any patient who displays persistently abnormal liver function tests and refuses liver biopsy or in any patient whose liver biopsy shows moderate to severe changes (Roenigk grade IIIb or IV).[2]

Infection or Immunologic States: Methotrexate should be used with extreme caution in the presence of active infection, and is usually contraindicated in patients with overt or laboratory evidence of immunodeficiency syndromes. Immunization may be ineffective when given during methotrexate therapy. Immunization with live virus vaccines is generally not recommended. There have been reports of disseminated vaccinia infections after smallpox immunization in patients receiving methotrexate therapy. Hypogammaglobulinemia has been reported rarely.

Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy. When a patient presents with pulmonary symptoms, the possibility of *Pneumocystis carinii* pneumonia should be considered.

Neurologic: There have been reports of leukoencephalopathy following intravenous administration of methotrexate to patients who have had craniospinal irradiation. Serious neurotoxicity, frequently manifested as generalized or local seizures, has been reported with unexpectedly increased frequency among pediatric patients with acute lymphoblastic leukemia who were treated with intermediate-dose intravenous methotrexate (1 gm/m^2). Symptomatic patients were commonly noted to have leukoencephalopathy and/or microangiopathic calcifications on diagnostic imaging studies. Chronic leukoencephalopathy has also been reported in patients who received repeated doses of high-dose methotrexate with leucovorin rescue even without cranial irradiation. Discontinuation of methotrexate does not always result in complete recovery.

A transient acute neurologic syndrome has been observed in patients treated with high dosage regimens. Manifestations of this stroke-like encephalopathy may include confusion, hemiparesis, seizures and coma. The exact cause is unknown.

Pulmonary: Pulmonary symptoms (especially a dry nonproductive cough) or a nonspecific pneumonitis occurring during methotrexate therapy may be indicative of a potentially dangerous lesion and require interruption of treatment and careful investigation. Although clinically variable, the typical patient with methotrexate induced lung disease presents with fever, cough, dyspnea, hypoxemia, and an infiltrate on chest X-ray; infection needs to be excluded. This lesion can occur at all dosages.

Renal: High doses of methotrexate used in the treatment of osteosarcoma may cause renal damage leading to acute renal failure. Nephrotoxicity is due primarily to the precipitation of methotrexate and 7-hydroxymethotrexate in the renal tubules. Close attention to renal function including adequate hydration, urine alkalinization and measurement of serum methotrexate and creatinine levels are essential for safe administration.

Skin: Severe, occasionally fatal, dermatologic reactions, including toxic epidermal necrolysis, Stevens-Johnson Syndrome, exfoliative dermatitis, skin necrosis, and erythema multiforme, have been reported in children and adults, within days of oral, intramuscular, intravenous, or intrathecal methotrexate administration. Reactions were noted after single or multiple, low intermediate or high doses of methotrexate in patients with neoplastic and non-neoplastic diseases.

Other Precautions: Methotrexate should be used with extreme caution in the presence of debility.

Methotrexate exits slowly from third-space compartments (e.g., pleural effusions or ascites). This results in a prolonged terminal plasma half-life and unexpected toxicity. In patients with significant third-space accumulations, it is advisable to evacuate the fluid before treatment and to monitor plasma methotrexate levels.

Lesions of psoriasis may be aggravated by concomitant exposure to ultraviolet radiation. Radiation dermatitis and sunburn may be "recalled" by the use of methotrexate.

ADVERSE REACTIONS:

IN GENERAL, THE INCIDENCE AND SEVERITY OF ACUTE SIDE EFFECTS ARE RELATED TO DOSE AND FREQUENCY OF ADMINISTRATION. THE MOST SERIOUS REACTIONS ARE DISCUSSED ABOVE UNDER ORGAN SYSTEM TOXICITY IN THE PRECAUTION SECTION. THAT SECTION SHOULD ALSO BE CONSULTED WHEN LOOKING FOR INFORMATION ABOUT ADVERSE REACTIONS WITH METHOTREXATE.

The most frequently reported adverse reactions include ulcerative stomatitis, leukopenia, nausea, and abdominal distress. Other frequently reported adverse effects are malaise, undue fatigue, chills and fever, dizziness and decreased resistance to infection.

Other adverse reactions that have been reported with methotrexate are listed below by organ system. In the oncology setting, concomitant treatment and the underlying disease make specific attribution of a reaction to methotrexate difficult.

Alimentary System: Gingivitis, pharyngitis, stomatitis, anorexia, nausea, vomiting, diarrhea, hematemesis, melena, gastrointestinal ulceration and bleeding, enteritis, pancreatitis.

Cardiovascular: Pericarditis, pericardial effusion, hypotension, and thromboembolic events (including arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, thrombophlebitis, and pulmonary embolus).

Central Nervous System: Headaches, drowsiness, blurred vision. Aphasia, hemiparesis, paresis and convulsions have also occurred following administration of methotrexate. Following low doses, there have been occasional reports of transient subtle cognitive dysfunction, mood alteration, unusual cranial sensation, leukoencephalopathy, or encephalopathy.

Infection: There have been case reports of sometimes fatal opportunistic infections in patients receiving methotrexate therapy for neoplastic and non-neoplastic diseases. *Pneumocystis carinii* pneumonia was the most common infection. Other reported infections included nocardiosis, histoplasmosis, cryptococcosis, *Herpes zoster*, *H. simplex* hepatitis, and disseminated *H. simplex*.

Ophthalmic: Conjunctivitis, serious visual changes of unknown etiology.

Pulmonary System: Interstitial pneumonitis deaths have been reported, and chronic interstitial obstructive pulmonary disease has occasionally occurred.

Skin: Erythematous rashes, pruritus, urticaria, photosensitivity, pigmentary changes, alopecia, ecchymosis, telangiectasia, acne, furunculosis, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson Syndrome, skin necrosis, and exfoliative dermatitis.

Urogenital System: Severe nephropathy or renal failure, azotemia, cystitis, hematuria; defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, vaginal discharge, and gynecomastia; infertility, abortion, fetal defects.

Other rarer reactions related to or attributed to the use of methotrexate such as nodulosis, vasculitis, arthralgia/myalgia, loss of libido/impotence, diabetes, osteoporosis, sudden death, reversible lymphomas, tumor lysis syndrome, soft tissue necrosis and osteonecrosis. Anaphylactoid reactions have been reported.

Adverse Reactions in Double-Blind Rheumatoid Arthritis Studies:

The approximate incidences of methotrexate-attributed (i.e., placebo rate subtracted) adverse reactions in 12 to 18 week double-blind studies of patients (n=128) with rheumatoid arthritis treated with low-dose oral (7.5 to 15 mg/week) pulse methotrexate, are listed below. Virtually all of these patients were on concomitant nonsteroidal anti-inflammatory drugs and some were also taking low dosages of corticosteroids.

Incidence greater than 10%: Elevated liver function tests 15%, nausea/vomiting 10%.

Incidence 3% to 10%: Stomatitis, thrombocytopenia, (platelet count less than 100,000/mm^3).

Incidence 1% to 3%: Rash/pruritus/dermatitis, diarrhea, alopecia, leukopenia (WBC less than 3000/mm^3), pancytopenia, dizziness.

No pulmonary toxicity was seen in these two trials. Thus, the incidence is probably less than 2.5% (95% C.L.). Hepatic histology was not examined in these short-term studies (see **PRECAUTIONS**).

Other less common reactions included decreased hematocrit, headache, upper respiratory infection, anorexia, arthralgias, chest pain, coughing, dysuria, eye discomfort, epistaxis, fever, infection, sweating, tinnitus, and vaginal discharge.

Adverse Reactions in Psoriasis:

There are no recent placebo-controlled trials in patients with psoriasis. There are two literature reports (Roenigk, 1969 and Nyfors, 1978) describing large series (n=204, 248) of psoriasis patients treated with methotrexate. Dosages ranged up to 25 mg per week and treatment was administered for up to four years. With the exception of alopecia, photosensitivity, and "burning of skin lesions" (each 3% to 10%), the adverse reaction rates in these reports were very similar to those in the rheumatoid arthritis studies.

Rarely, painful plaque erosions may appear (Pearce, HP and Wilson, BB: *Am Acad Dermatol* 35:835-838, 1996).

OVERDOSAGE:

Leucovorin is indicated to diminish the toxicity and counteract the effect of inadvertently administered overdosages of methotrexate. Leucovorin administration should begin as promptly as possible. As the time interval between methotrexate administration and leucovorin initiation increases, the effectiveness of leucovorin in counteracting toxicity decreases. Monitoring of the serum methotrexate concentration is essential in determining the optimal dose and duration of treatment with leucovorin.

In cases of massive overdosage, hydration and urinary alkalinization may be necessary to prevent the precipitation of methotrexate and/or its metabolites in the renal tubules. Generally speaking, neither hemodialysis nor peritoneal dialysis have been shown to improve methotrexate elimination. However, effective clearance of methotrexate has been reported with acute, intermittent hemodialysis using a high-flux dialyzer. (Wall, SM et al: *AM J Kidney Dis* 28(6):846-854, 1996).

DOSAGE AND ADMINISTRATION:

Neoplastic Diseases:

Oral administration in tablet form is often preferred when low doses are being administered since absorption is rapid and effective serum levels are obtained.

Choriocarcinoma and similar trophoblastic diseases: Methotrexate is administered orally or intramuscularly in doses of 15 to 30 mg daily for a five-day course. Such courses are usually repeated for 3 to 5 times as required, with rest periods of one or more weeks interposed between courses, until any manifesting toxic symptoms subside. The effectiveness of therapy is ordinarily evaluated by 24-hour quantitative analysis of urinary chorionic gonadatropin (hCG), which should return to normal or less than 50 IU/24 hr usually after the third or fourth course and usually be followed by a complete resolution of measurable lesions in 4 to 6 weeks. One to two courses of methotrexate after normalization of hCG is usually recommended. Before each course of the drug careful clinical assessment is essential. Cyclic combination therapy of methotrexate with other antitumor drugs has been reported as being useful.

Since hydatidiform mole may precede choriocarcinoma, prophylactic chemotherapy with methotrexate has been recommended.

Chorioadenoma destruens is considered to be an invasive form of hydatidiform mole. Methotrexate is administered in these disease states in doses similar to those recommended for choriocarcinoma.

Leukemia: Acute lymphoblastic leukemia in pediatric patients is the most responsive to present-day chemotherapy. In young adults and older patients, clinical remission is more difficult to obtain and early relapse is more common.

Methotrexate alone or in combination with steroids was used initially for induction of remission in acute lymphoblastic leukemias. More recently corticosteroid therapy, in combination with other antileukemic drugs or in cyclic combinations with methotrexate included, has appeared to produce rapid and effective remissions. When used for induction, methotrexate in doses of 3.3 mg/m^2 in combination with 60 mg/m^2 of prednisone, given daily, produced remissions in 50% of patients treated, usually within a period of 4 to 6 weeks. Methotrexate in combination with other agents appears to be the drug of choice for securing maintenance of drug-induced remissions. When remission is achieved and supportive care has produced general clinical improvement, maintenance therapy is initiated, as follows: Methotrexate is administered 2 times weekly either by mouth or intramuscularly in total weekly doses of 30 mg/m^2. It has also been given in doses of 2.5 mg/kg intravenously every 14 days. If and when relapse does occur, reinduction of remission can again usually be obtained by repeating the initial induction regimen.

A variety of combination chemotherapy regimens have been used for both induction and maintenance therapy in acute lymphoblastic leukemia. The physician should be familiar with the new advances in antileukemic therapy.

Lymphomas: In Burkitt's tumor, Stages I-II, methotrexate has produced prolonged remissions in some cases. Recommended dosage is 10 to 25 mg/day orally for 4 to 8 days. In Stage III, methotrexate is commonly given concomitantly with other antitumor agents. Treatment in all stages usually consists of several courses of the drug interposed with 7 to 10 day rest periods. Lymphosarcomas in Stage III may respond to combined drug therapy with methotrexate given in doses of 0.625 to 2.5 mg/kg daily.

Mycosis fungoides: Therapy with methotrexate appears to produce clinical remissions in one-half of the cases treated. Dosage is usually 2.5 to 10 mg daily by mouth for weeks or months. Dose levels of drug and adjustment of dose regimen by reduction or cessation of drug are guided by patient response and hematologic monitoring. Methotrexate has also been given intramuscularly in doses of 50 mg once weekly or 25 mg, 2 times weekly.

Psoriasis and Rheumatoid Arthritis:

The patient should be fully informed of the risks involved and should be under constant supervision of the physician (see **Information for Patients** under **PRECAUTIONS**). Assessment of hematologic, hepatic, renal, and pulmonary function should be made by history, physical examination, and laboratory tests before beginning, periodically during, and before reinstituting methotrexate therapy (see **PRECAUTIONS**). Appropriate steps should be taken to avoid conception during methotrexate therapy (see **PRECAUTIONS** and **CONTRAINDICATIONS**).

Weekly therapy may be instituted to provide doses over a range of 5 mg to 15 mg administered as a single weekly dose. All schedules should be continually tailored to the individual patient. An initial test dose may be given prior to the regular dosing schedule to detect any extreme sensitivity to adverse effects (see **ADVERSE REACTIONS**). Maximal myelosuppression usually occurs in seven to ten days.

Psoriasis: Recommended Starting Dose Schedules:

1. Weekly single oral, IM or IV dosage schedule: 10 to 25 mg per week until adequate response is achieved.
2. Divided oral dose schedule: 2.5 mg at 12-hour intervals for three doses.

Dosages in each schedule may be gradually adjusted to achieve optimal clinical response; 30 mg/week should not ordinarily be exceeded.

Once optimal clinical response has been achieved, each dosage schedule should be reduced to the lowest possible amount of drug and to the longest possible rest period. The use of methotrexate may permit the return to conventional topical therapy, which should be encouraged.

Rheumatoid Arthritis: Recommended Starting Dosage Schedules:

1. Single oral doses of 7.5 mg once weekly.
2. Divided oral dosages of 2.5 mg at 12-hour intervals for 3 doses given as a course once weekly.

Dosages in each schedule may be adjusted gradually to achieve an optimal response, but not ordinarily to exceed a total weekly dose of 20 mg. Limited experience shows a significant increase in the incidence and severity of serious toxic reactions, especially bone marrow suppression, at doses greater than 20 mg/wk.

Once response has been achieved, each schedule should be reduced, if possible, to the lowest possible effective dose.

Therapeutic response usually begins within 3 to 6 weeks and the patient may continue to improve for another 12 weeks or more.

The optimal duration of therapy is unknown. Limited data available from long-term studies indicate that the initial clinical improvement is maintained for at least two years with continued therapy. When methotrexate is discontinued, the arthritis usually worsens within 3 to 6 weeks.

HANDLING AND DISPOSAL:

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED:

Trexall™ (methotrexate tablets, USP) are available as:

5 mg: Green, oval-shaped, film-coated, scored, biconvex tablet. Debossed with **b** on one side and **927/5** on the other side. Each 5 mg tablet contains an amount of methotrexate sodium equivalent to 5 mg of methotrexate.

Available in bottles of:

30 NDC 0555-0927-01
60 NDC 0555-0927-09
100 NDC 0555-0927-02

7.5 mg: Blue, oval-shaped, film-coated, scored, biconvex tablet. Debossed with **b** on one side and **928/7½** on the other side. Each 7.5 mg tablet contains an amount of methotrexate sodium equivalent to 7.5 mg of methotrexate.

Available in bottles of:

30 NDC 0555-0928-01
60 NDC 0555-0928-09
100 NDC 0555-0928-02

10 mg: Pink, oval-shaped, film-coated, scored, biconvex tablet. Debossed with **b** on one side and **929/10** on the other side. Each 10 mg tablet contains an amount of methotrexate sodium equivalent to 10 mg of methotrexate.

Available in bottles of:

30 NDC 0555-0929-01
60 NDC 0555-0929-09
100 NDC 0555-0929-02

15 mg: Purple, oval-shaped, film-coated, scored, biconvex tablet. Debossed with **b** on one side and **945/15** on the other side. Each 15 mg tablet contains an amount of methotrexate sodium equivalent to 15 mg of methotrexate.

Available in bottles of:

30 NDC 0555-0945-01
60 NDC 0555-0945-09
100 NDC 0555-0945-02

Dispense with a child-resistant closure in a well-closed container as defined in the USP.
Store at controlled room temperature 15°-30°C (59°-86°F).
Protect from light.

REFERENCES:

1. Controlling occupational exposure to hazardous drugs (OSHA Work-Practice Guidelines). *Am J Health Syst Pharm* 1996; 53:1669-1685.
2. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, US Government Printing Office, Washington, DC 20402.
3. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. *JAMA*, 1985; 253(11):1590-1592.
4. National Study Commission on Cytotoxic Exposure - Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, Sc D, Chairman, National Study Commisssion on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston Massachusetts 02115.
5. Clinical Oncological Society of Australia: Guidelines and recommendations for safe handling of antineoplastic agents. *Med J Australia* 1983; 1:426-428.
6. Jones RB, et al. Safe handling of chemotherapeutic agents: A report from the Mount Sinai Medical Center. Ca - *A Cancer Journal for Clinicians* Sept/Oct 1983; 258-263.
7. American Society of Hospital Pharmacists technical assistance bulletin on handling cytotoxic and hazardous drugs. *Am J Hosp Pharm* 1990; 47:1033-1049.
8. OSHA Work-Practice Guidelines for Personnel Dealing with Cytotoxic (Antineoplastic) Drugs. *Am J Hosp Pharm*, 1986; 43:1193-1204.

Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970

Marketed by:
DuPont Pharma
Wilmington, DE 19880

Revised JANUARY 2001
BR-927, 928, 929, 945

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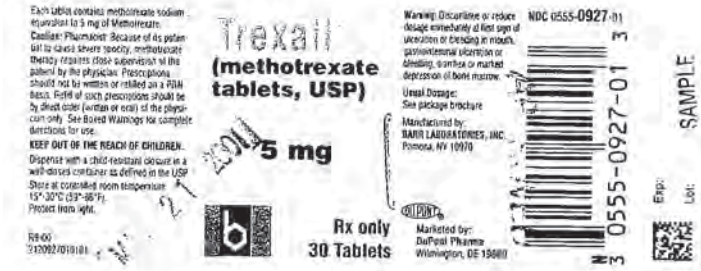
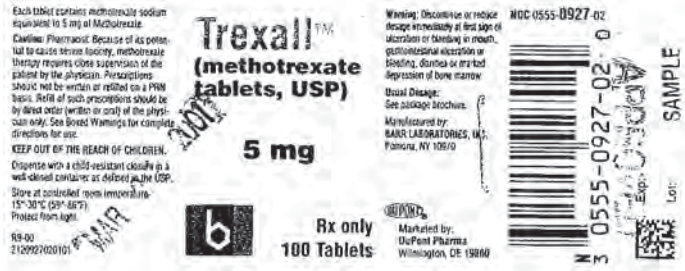
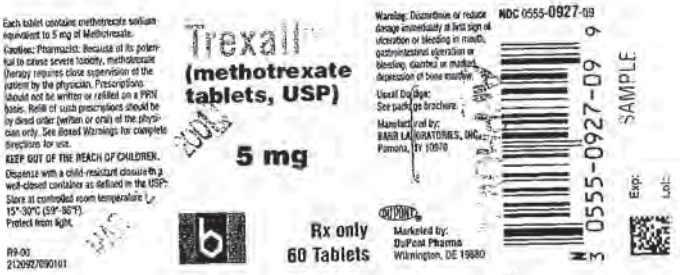
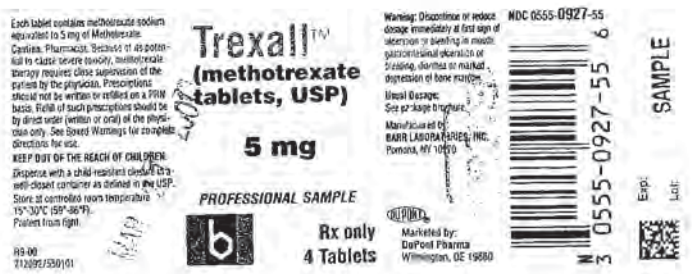
Approved

3/21/01









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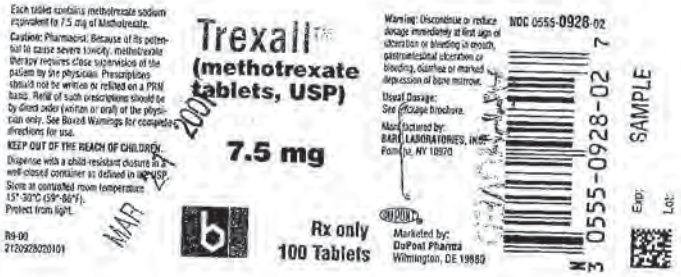
Each tablet contains methotrexate sodium equivalent to 7.5 mg of Methotrexate.
Caution: Pharmacist: Because of its potential to cause severe toxicity, methotrexate therapy requires close supervision of the patient by the physician. Prescriptions should not be written or refilled on a PRN basis. Refill of such prescriptions should be by direct order (written or oral) of the physician only. See Boxed Warnings for complete directions for use.
KEEP OUT OF THE REACH OF CHILDREN.
Dispense with a child-resistant closure in a well-closed container as defined in the USP.
Store at controlled room temperature 15°-30°C (59°-86°F).
Protect from light.
R9-00
2120928020101
Trexall™
(methotrexate tablets, USP)
7.5 mg
Rx only
100 Tablets
Warning: Discontinue or reduce dosage immediately at first sign of ulceration or bleeding in mouth, gastrointestinal ulceration or bleeding, diarrhea or marked depression of bone marrow.
Usual Dosage:
See package brochure.
Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970
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Wilmington, DE 19880
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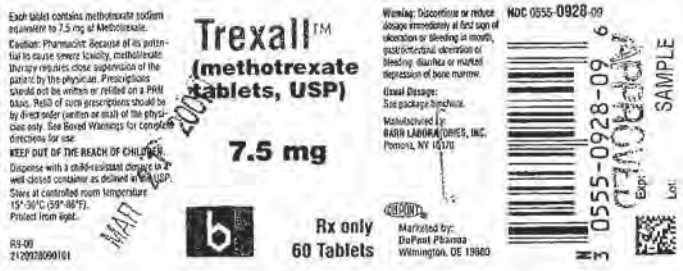
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Store at controlled room temperature 15°-30°C (59°-86°F).
Protect from light.
R9-00
2120928090101
Trexall™
(methotrexate tablets, USP)
7.5 mg
Rx only
60 Tablets
Warning: Discontinue or reduce dosage immediately at first sign of ulceration or bleeding in mouth, gastrointestinal ulceration or bleeding, diarrhea or marked depression of bone marrow.
Usual Dosage:
See package brochure.
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Pomona, NY 10970
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Wilmington, DE 19880
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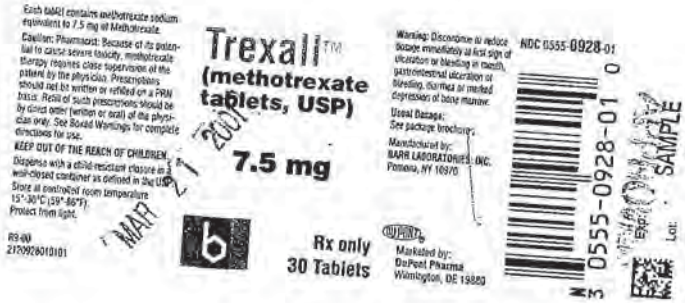
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Store at controlled room temperature 15°-30°C (59°-86°F).
Protect from light.
R9-00
2120928010101
Trexall™
(methotrexate tablets, USP)
7.5 mg
Rx only
30 Tablets
Warning: Discontinue or reduce dosage immediately at first sign of ulceration or bleeding in mouth, gastrointestinal ulceration or bleeding, diarrhea or marked depression of bone marrow.
Usual Dosage:
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Manufactured by:
BARR LABORATORIES, INC.
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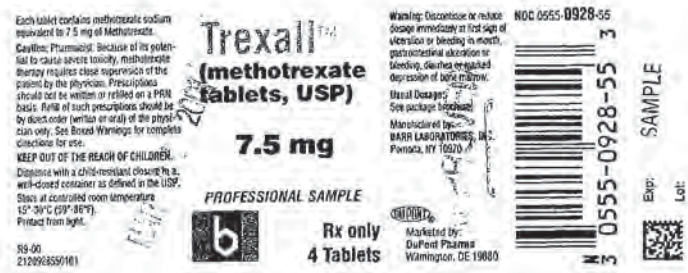
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Store at controlled room temperature 15°-30°C (59°-86°F).
Protect from light.
R9-00
2120928550101
Trexall™
(methotrexate tablets, USP)
7.5 mg
PROFESSIONAL SAMPLE
Rx only
4 Tablets
Warning: Discontinue or reduce dosage immediately at first sign of ulceration or bleeding in mouth, gastrointestinal ulceration or bleeding, diarrhea or marked depression of bone marrow.
Usual Dosage:
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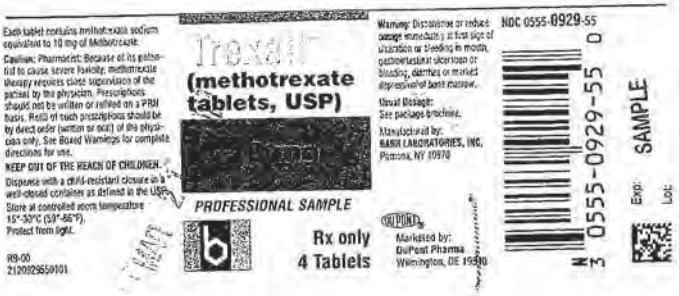
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R9-00
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Trexall
(methotrexate tablets, USP)
PROFESSIONAL SAMPLE
Rx only
4 Tablets
Warning: Discontinue or reduce dosage immediately at first sign of ulceration or bleeding in mouth, gastrointestinal ulceration or bleeding, diarrhea or marked depression of bone marrow.
Usual Dosage:
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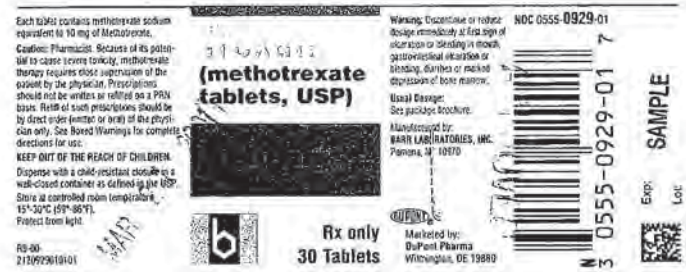
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KEEP OUT OF THE REACH OF CHILDREN.
Dispense with a child-resistant closure as a well-closed container as defined in the USP.
Store at controlled room temperature 15°-30°C (59°-86°F).
Protect from light.
R9-00
2120929619101
(methotrexate tablets, USP)
Rx only
30 Tablets
Warning: Discontinue or reduce dosage immediately at first sign of ulceration or bleeding in mouth, gastrointestinal ulceration or bleeding, diarrhea or marked depression of bone marrow.
Usual Dosage:
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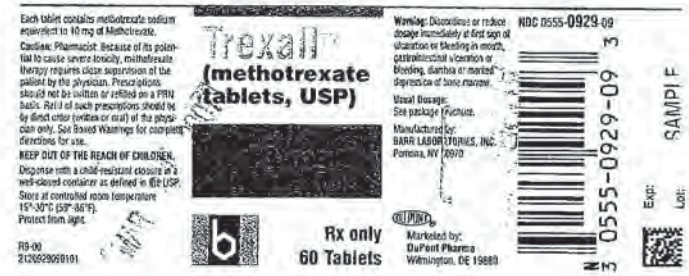
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KEEP OUT OF THE REACH OF CHILDREN.
Dispense with a child-resistant closure in a well-closed container as defined in the USP.
Store at controlled room temperature 15°-30°C (59°-86°F).
Protect from light.
R9-00
2120929059101
Trexall
(methotrexate tablets, USP)
Rx only
60 Tablets
Warning: Discontinue or reduce dosage immediately at first sign of ulceration or bleeding in mouth, gastrointestinal ulceration or bleeding, diarrhea or marked depression of bone marrow.
Usual Dosage:
See package brochure.
Manufactured by:
BARR LABORATORIES, INC.
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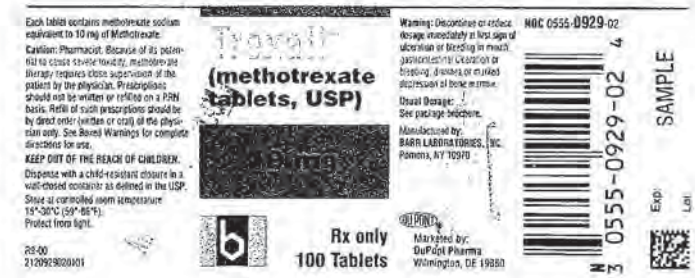
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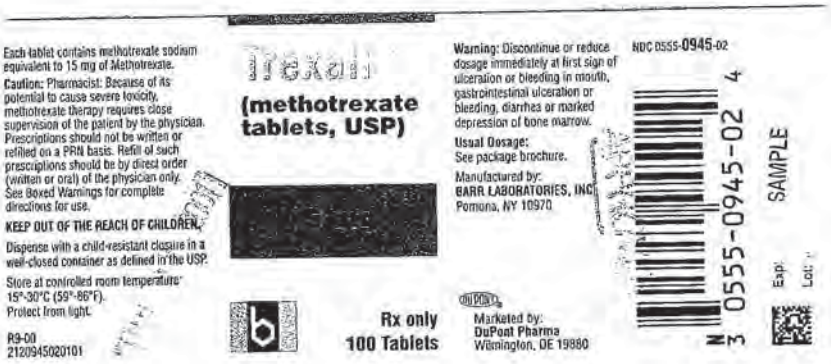
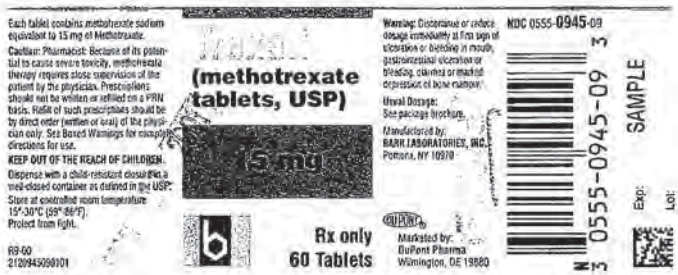
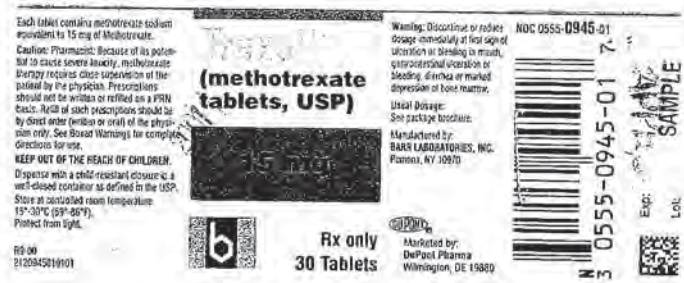
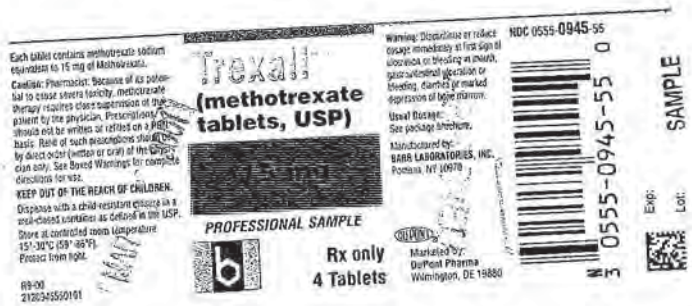
Protect from light.
R9-00
2120929029101
Trexall
(methotrexate tablets, USP)
Rx only
100 Tablets
Warning: Discontinue or reduce dosage immediately at first sign of ulceration or bleeding in mouth, gastrointestinal ulceration or bleeding, diarrhea or marked depression of bone marrow.
Usual Dosage:
See package brochure.
Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970
Marketed by:
DuPont Pharma
Wilmington, DE 19880
NDC 0555-0929-02
0555-0929-02
SAMPLE
Exp:
Lot:

40-385

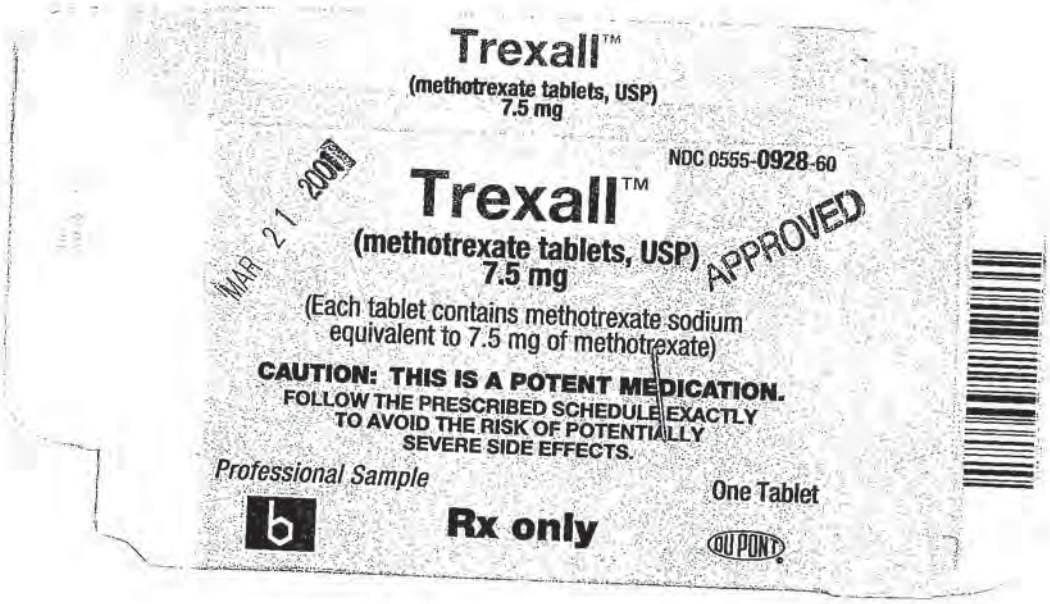

Each tablet contains methotrexate sodium equivalent to 15 mg of Methotrexate.
Caution: Pharmacist: Because of its potential to cause severe toxicity, methotrexate therapy requires close supervision of the patient by the physician. Prescriptions should not be written or refilled on a PRN basis. Refill of such prescriptions should be by direct order (written or oral) of the physician only. See Boxed Warnings for complete directions for use.
KEEP OUT OF THE REACH OF CHILDREN.
Dispense with a child-resistant closure in a well-closed container as defined in the USP.
Store at controlled room temperature 15°-30°C (59°-86°F).
Protect from light.
R9-00
2120945020101
Trexall
(methotrexate tablets, USP)
Rx only
100 Tablets
Warning: Discontinue or reduce dosage immediately at first sign of ulceration or bleeding in mouth, gastrointestinal ulceration or bleeding, diarrhea or marked depression of bone marrow.
Usual Dosage:
See package brochure.
Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970
Marketed by:
DuPont Pharma
Wilmington, DE 19880
NDC 0555-0945-02
3 0555-0945-02 4
SAMPLE
Exp:
Lot:

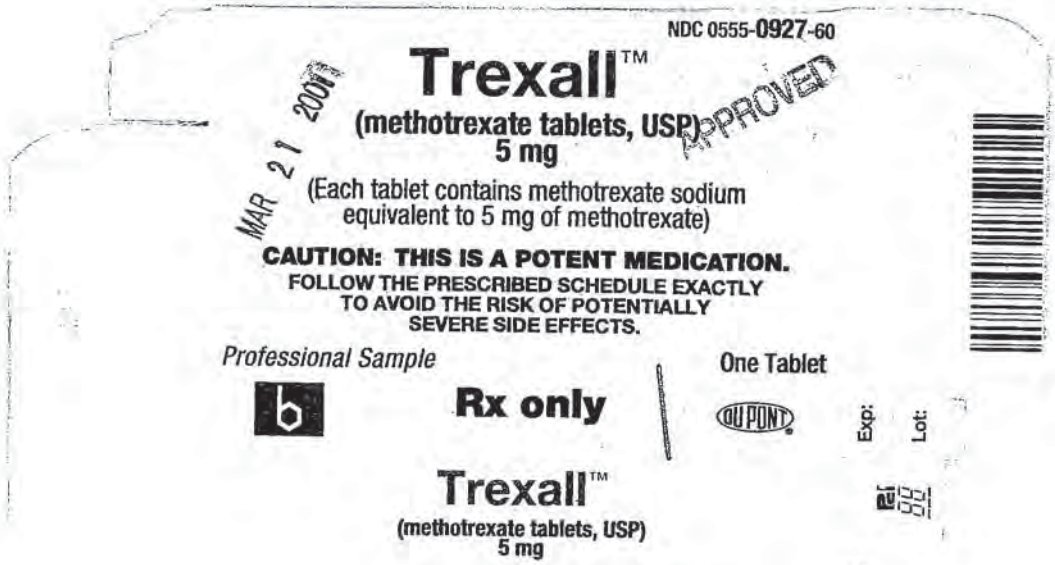

Each tablet contains methotrexate sodium equivalent to 15 mg of Methotrexate.
Caution: Pharmacist: Because of its potential to cause severe toxicity, methotrexate therapy requires close supervision of the patient by the physician. Prescriptions should not be written or refilled on a PRN basis. Refill of such prescriptions should be by direct order (written or oral) of the physician only. See Boxed Warnings for complete directions for use.
KEEP OUT OF THE REACH OF CHILDREN.
Dispense with a child-resistant closure in a well-closed container as defined in the USP.
Store at controlled room temperature 15°-30°C (59°-86°F).
Protect from light.
R9-00
2120945090101
Trexall
(methotrexate tablets, USP)
15 mg
Rx only
60 Tablets
Warning: Discontinue or reduce dosage immediately at first sign of ulceration or bleeding in mouth, gastrointestinal ulceration or bleeding, diarrhea or marked depression of bone marrow.
Usual Dosage:
See package brochure.
Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970
Marketed by:
DuPont Pharma
Wilmington, DE 19880
NDC 0555-0945-09
3 0555-0945-09 3
SAMPLE
Exp:
Lot:

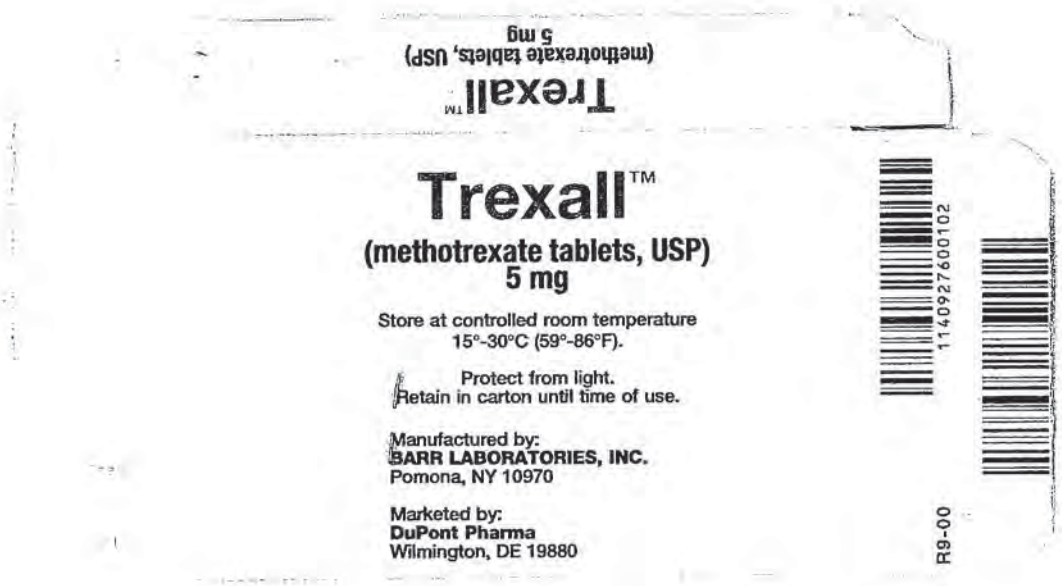

Each tablet contains methotrexate sodium equivalent to 15 mg of Methotrexate.
Caution: Pharmacist: Because of its potential to cause severe toxicity, methotrexate therapy requires close supervision of the patient by the physician. Prescriptions should not be written or refilled on a PRN basis. Refill of such prescriptions should be by direct order (written or oral) of the physician only. See Boxed Warnings for complete directions for use.
KEEP OUT OF THE REACH OF CHILDREN.
Dispense with a child-resistant closure in a well-closed container as defined in the USP.
Store at controlled room temperature 15°-30°C (59°-86°F).
Protect from light.
R9-00
2120945010101
Trexall
(methotrexate tablets, USP)
15 mg
Rx only
30 Tablets
Warning: Discontinue or reduce dosage immediately at first sign of ulceration or bleeding in mouth, gastrointestinal ulceration or bleeding, diarrhea or marked depression of bone marrow.
Usual Dosage:
See package brochure.
Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970
Marketed by:
DuPont Pharma
Wilmington, DE 19880
NDC 0555-0945-01
3 0555-0945-01 7
SAMPLE
Exp:
Lot:

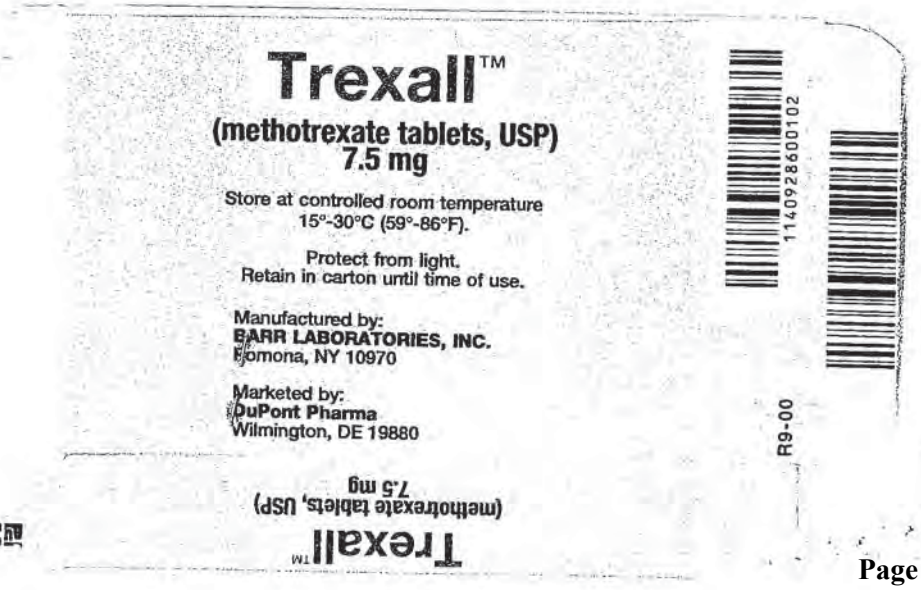

Each tablet contains methotrexate sodium equivalent to 15 mg of Methotrexate.
Caution: Pharmacist: Because of its potential to cause severe toxicity, methotrexate therapy requires close supervision of the patient by the physician. Prescriptions should not be written or refilled on a PRN basis. Refill of such prescriptions should be by direct order (written or oral) of the physician only. See Boxed Warnings for complete directions for use.
KEEP OUT OF THE REACH OF CHILDREN.
Dispense with a child-resistant closure in a well-closed container as defined in the USP.
Store at controlled room temperature 15°-30°C (59°-86°F).
Protect from light.
R9-00
2120945550101
Trexall
(methotrexate tablets, USP)
15 mg
PROFESSIONAL SAMPLE
Rx only
4 Tablets
Warning: Discontinue or reduce dosage immediately at first sign of ulceration or bleeding in mouth, gastrointestinal ulceration or bleeding, diarrhea or marked depression of bone marrow.
Usual Dosage:
See package brochure.
Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970
Marketed by:
DuPont Pharma
Wilmington, DE 19880
NDC 0555-0945-55
3 0555-0945-55 0
SAMPLE
Exp:
Lot:

40-385


Trexall™
(methotrexate tablets, USP)
7.5 mg
NDC 0555-0928-60
Trexall™
(methotrexate tablets, USP)
7.5 mg
MAR 21 2001
APPROVED
(Each tablet contains methotrexate sodium equivalent to 7.5 mg of methotrexate)
CAUTION: THIS IS A POTENT MEDICATION.
FOLLOW THE PRESCRIBED SCHEDULE EXACTLY TO AVOID THE RISK OF POTENTIALLY SEVERE SIDE EFFECTS.
Professional Sample
b
Rx only
One Tablet
DUPONT


NDC 0555-0927-60
Trexall™
(methotrexate tablets, USP)
5 mg
MAR 21 2001
APPROVED
(Each tablet contains methotrexate sodium equivalent to 5 mg of methotrexate)
CAUTION: THIS IS A POTENT MEDICATION.
FOLLOW THE PRESCRIBED SCHEDULE EXACTLY TO AVOID THE RISK OF POTENTIALLY SEVERE SIDE EFFECTS.
Professional Sample
b
Rx only
One Tablet
DUPONT
Exp:
Lot:
Trexall™
(methotrexate tablets, USP)
5 mg

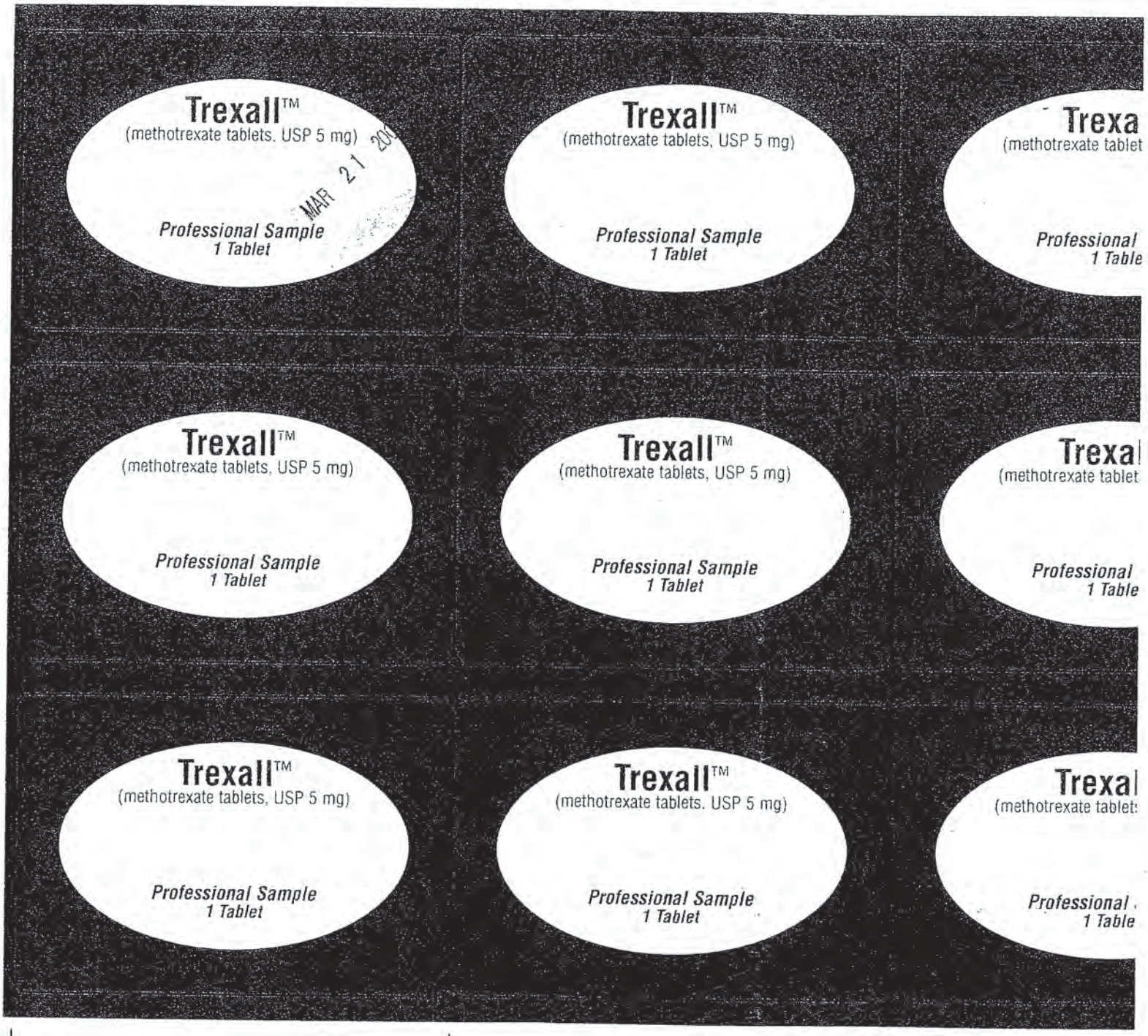

Trexall™
(methotrexate tablets, USP)
5 mg
Trexall™
(methotrexate tablets, USP)
5 mg
Store at controlled room temperature
15°-30°C (59°-86°F).
Protect from light.
Retain in carton until time of use.
Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970
Marketed by:
DuPont Pharma
Wilmington, DE 19880
11409276001 02
R9-00


Trexall™
(methotrexate tablets, USP)
7.5 mg
Trexall™
(methotrexate tablets, USP)
7.5 mg
Store at controlled room temperature
15°-30°C (59°-86°F).
Protect from light.
Retain in carton until time of use.
Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970
Marketed by:
DuPont Pharma
Wilmington, DE 19880
11409286001 02
R9-00

10-385

9 Labels

VINYL HEATSEAL (FRONT/FOIL) SIDE



3.125" 3.125" 3.125"

9.375"

8

GREEN PMS 365

LAVENDAR PMS 2573

NON-VINYL (BACK/PAPER) SIDE

(Each tablet contains methotrexate sodium equivalent to 5 mg of methotrexate)

CAUTION: THIS IS A POTENT MEDICATION. FOLLOW THE PRESCRIBED SCHEDULE EXACTLY TO AVOID THE RISK OF POTENTIALLY SEVERE SIDE EFFECTS.

Push through tablet from the other side.

Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970

Marketed by:
DuPont Pharma
Wilmington, DE 19880

R9-00

(Each tablet contains methotrexate sodium equivalent to 5 mg of methotrexate)

CAUTION: THIS IS A POTENT MEDICATION. FOLLOW THE PRESCRIBED SCHEDULE EXACTLY TO AVOID THE RISK OF POTENTIALLY SEVERE SIDE EFFECTS.

Push through tablet from the other side.

Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970

Marketed by:
DuPont Pharma
Wilmington, DE 19880

R9-00

(Each tablet contains methotrexate sodium equivalent to 5 mg of methotrexate)

CAUTION: THIS IS A POTENT MEDICATION. FOLLOW THE PRESCRIBED SCHEDULE EXACTLY TO AVOID THE RISK OF POTENTIALLY SEVERE SIDE EFFECTS.

Push through tablet from the other side.

Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970

Marketed by:
DuPont Pharma
Wilmington, DE 19880

R9-00

(Each tablet contains methotrexate sodium equivalent to 5 mg of methotrexate)

CAUTION: THIS IS A POTENT MEDICATION. FOLLOW THE PRESCRIBED SCHEDULE EXACTLY TO AVOID THE RISK OF POTENTIALLY SEVERE SIDE EFFECTS.

Push through tablet from the other side.

Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970

Marketed by:
DuPont Pharma
Wilmington, DE 19880

R9-00

(Each tablet contains methotrexate sodium equivalent to 5 mg of methotrexate)

CAUTION: THIS IS A POTENT MEDICATION. FOLLOW THE PRESCRIBED SCHEDULE EXACTLY TO AVOID THE RISK OF POTENTIALLY SEVERE SIDE EFFECTS.

Push through tablet from the other side.

Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970

Marketed by:
DuPont Pharma
Wilmington, DE 19880

R9-00

(Each tablet contains methotrexate sodium equivalent to 5 mg of methotrexate)

CAUTION: THIS IS A POTENT MEDICATION. FOLLOW THE PRESCRIBED SCHEDULE EXACTLY TO AVOID THE RISK OF POTENTIALLY SEVERE SIDE EFFECTS.

Push through tablet from the other side.

Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970

Marketed by:
DuPont Pharma
Wilmington, DE 19880

R9-00

.079"
3.125"
3.125"
9.375"

40-385

NDC 0555-**0927**-60

Trexall™

(methotrexate tablets, USP)
5 mg

(Each tablet contains methotrexate sodium equivalent to 5 mg of methotrexate)

NDC 0555-**0927**-60

Trexall™

(methotrexate tablets, USP)
5 mg

(Each tablet contains methotrexate sodium equivalent to 5 mg of methotrexate)

CAUTION: THIS IS A POTENT MEDICATION. FOLLOW THE PRESCRIBED SCHEDULE EXACTLY TO AVOID THE RISK OF POTENTIALLY SEVERE SIDE EFFECTS.

SAMPLE

MAR 21 2000
APPROVED

Rx only

Professional Samples

10 Samples x 1
5 mg Tablet

b

DUPONT

R9-00
2140927600102

NDC 0555-**0927**-60

Trexall™

(methotrexate tablets, USP)
5 mg

(Each tablet contains methotrexate sodium equivalent to 5 mg of methotrexate)

10 Samples x 1
5 mg Tablet

Trexall™

(methotrexate tablets, USP)
5 mg

(Each tablet contains methotrexate sodium equivalent to 5 mg of methotrexate)

Usual Dosage: See package brochure.

Store at controlled room temperature 15°-30°C (59°-86°F).

Protect from light.

Retain in carton until time of use.

Professional Samples

10 Samples x 1
5 mg Tablet

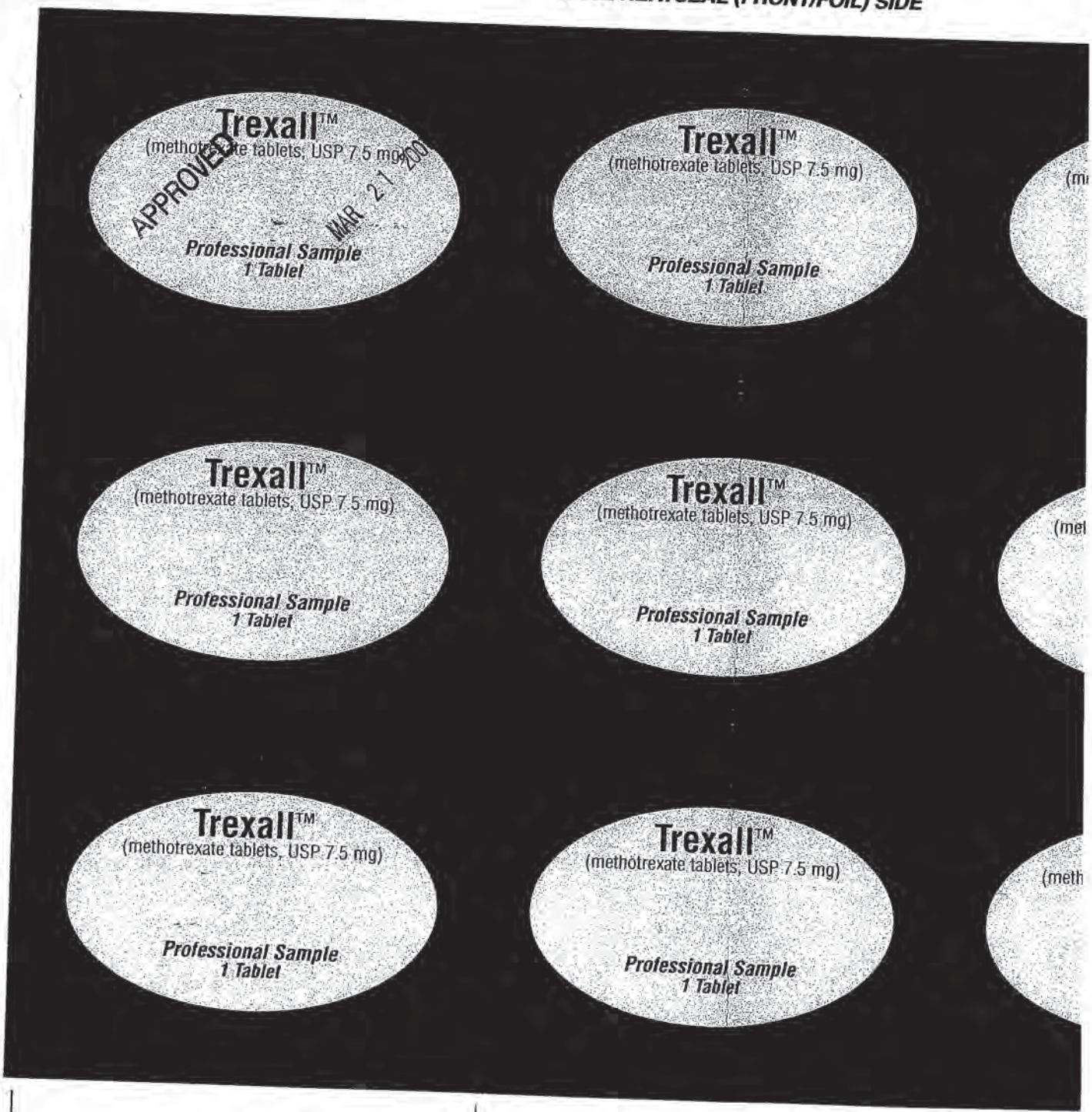
Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970

Marketed by:
DuPont Pharma
Wilmington, DE 19880

40-385

9 L

VINYL HEATSEAL (FRONT/FOIL) SIDE



NON-VINYL (BACK/PAPER) SIDE

sodium equivalent
rexate)

ICATION. FOLLOW
CTLY TO AVOID THE
DE EFFECTS.

side.

(Each tablet contains methotrexate sodium equivalent to 7.5 mg of methotrexate)

CAUTION: THIS IS A POTENT MEDICATION. FOLLOW THE PRESCRIBED SCHEDULE EXACTLY TO AVOID THE RISK OF POTENTIALLY SEVERE SIDE EFFECTS.

Push through tablet from the other side.

Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970

Marketed by:
DuPont Pharma
Wilmington, DE 19880

R9-00

(Each tablet contains methotrexate sodium equivalent to 7.5 mg of methotrexate)

CAUTION: THIS IS A POTENT MEDICATION. FOLLOW THE PRESCRIBED SCHEDULE EXACTLY TO AVOID THE RISK OF POTENTIALLY SEVERE SIDE EFFECTS.

Push through tablet from the other side.

Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970

Marketed by:
DuPont Pharma
Wilmington, DE 19880

R9-00

sodium equivalent
exate)

CATION. FOLLOW
CTLY TO AVOID THE
DE EFFECTS.

side.

(Each tablet contains methotrexate sodium equivalent to 7.5 mg of methotrexate)

CAUTION: THIS IS A POTENT MEDICATION. FOLLOW THE PRESCRIBED SCHEDULE EXACTLY TO AVOID THE RISK OF POTENTIALLY SEVERE SIDE EFFECTS.

Push through tablet from the other side.

Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970

Marketed by:
DuPont Pharma
Wilmington, DE 19880

R9-00

(Each tablet contains methotrexate sodium equivalent to 7.5 mg of methotrexate)

CAUTION: THIS IS A POTENT MEDICATION. FOLLOW THE PRESCRIBED SCHEDULE EXACTLY TO AVOID THE RISK OF POTENTIALLY SEVERE SIDE EFFECTS.

Push through tablet from the other side.

Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970

Marketed by:
DuPont Pharma
Wilmington, DE 19880

R9-00

odium equivalent
xate)

ATION. FOLLOW
TLY TO AVOID THE
E EFFECTS.

ide.

(Each tablet contains methotrexate sodium equivalent to 7.5 mg of methotrexate)

CAUTION: THIS IS A POTENT MEDICATION. FOLLOW THE PRESCRIBED SCHEDULE EXACTLY TO AVOID THE RISK OF POTENTIALLY SEVERE SIDE EFFECTS.

Push through tablet from the other side.

Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970

Marketed by:
DuPont Pharma
Wilmington, DE 19880

R9-00

(Each tablet contains methotrexate sodium equivalent to 7.5 mg of methotrexate)

CAUTION: THIS IS A POTENT MEDICATION. FOLLOW THE PRESCRIBED SCHEDULE EXACTLY TO AVOID THE RISK OF POTENTIALLY SEVERE SIDE EFFECTS.

Push through tablet from the other side.

Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970

Marketed by:
DuPont Pharma
Wilmington, DE 19880

R9-00

3.125"

3.125"

9.375"

3

NDC 0555-**0928**-60

Trexall™

(methotrexate tablets, USP)
7.5 mg

(Each tablet contains methotrexate sodium equivalent to 7.5 mg of methotrexate)

NDC 0555-**0928**-60

Trexall™

(methotrexate tablets, USP)
7.5 mg

(Each tablet contains methotrexate sodium equivalent to 7.5 mg of methotrexate)

CAUTION: THIS IS A POTENT MEDICATION. FOLLOW THE PRESCRIBED SCHEDULE EXACTLY TO AVOID THE RISK OF POTENTIALLY SEVERE SIDE EFFECTS.

Rx only

Professional Samples 10 Samples x 1
7.5 mg Tablet

b

DUPONT®

Pull tab to open

R9-00
21409286001O2

NDC 0555-**0928**-60

Trexall™

(methotrexate tablets, USP)
7.5 mg

(Each tablet contains methotrexate sodium equivalent to 7.5 mg of methotrexate)

10 Samples x 1
7.5 mg Tablet

Trexall™

(methotrexate tablets, USP)
7.5 mg

(Each tablet contains methotrexate sodium equivalent to 7.5 mg of methotrexate)

Usual Dosage: See package brochure.

Store at controlled room temperature 15°-30°C (59°-86°F).

Protect from light.

Retain in carton until time of use.

2140928600102

Professional Samples 10 Samples x 1
7.5 mg Tablet

Manufactured by:
BARR LABORATORIES, INC.
Pomona, NY 10970

Marketed by:
DuPont Pharma
Wilmington, DE 19880

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-385

LABELING REVIEW(S)

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 40-385 **Date of Submission: July 23, 1999**
Applicant's Name: Barr Laboratories, Inc.
Established Name: Methotrexate Tablets USP, 5 mg and 15 mg
Proposed Proprietary Name: ———
Labeling Deficiencies:

1. GENERAL COMMENTS – Your proposed proprietary name has been found unacceptable based on 21 CFR 201.10(c)(5). It sounds like or looks like the following proprietary names already on the market: Mesnex® and Mezlin®. Please remove it from all labels and labeling.

2. CONTAINER (30's and 60's)

   i. Caution- Revise the second and third sentences in this section to read as follows:

   Prescriptions should not be written or refilled on a PRN basis. Refill of prescriptions should be by direct order (written or oral) of the physician only. See Boxed Warnings for complete directions for use.

   ii. Include the statement "KEEP OUT OF REACH OF CHILDREN."

3. UNIT DOSE BLISTER (1's)- See comment under GENERAL COMMENTS.

4. UNIT DOSE BLISTER CARTON (1 x 5 mg, and ' ———)- See comments under GENERAL COMMENTS and (ii) under CONTAINER.

5. PROFESSIONAL SAMPLE DISPENSER (10 x 1[5 mg] and ' ———)- See comments under GENERAL COMMENTS and (ii) under CONTAINER.

6. INSERT
   a. Revise your insert to be in accord with the most recent labeling for the reference listed drug, Methotrexate Tablets USP (Lederle; NDA# 08-085/S0048; approved October 29, 1999). The labeling may be obtained from Freedom of Information or the following website – http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html.
   b. See comment under GENERAL COMMENTS.

Please revise your labels and labeling, as instructed above, and submit 4 copies of draft labels and labeling. We will not request final print labels and labeling until a determination has been made regarding the acceptability of your proposed proprietary name.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes- http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained.

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: (30's and 60's)
Unit Dose Blister (1's)
Unit Dose Blister Carton (1 x 5 mg, and ' ———

Physician's sample Dispenser (10 x 1[5 mg] and ———— Satisfactory as of July 23, 1999 submission.

Professional Package Insert Labeling: Satisfactory as of July 23, 1999 submission.

Revisions needed post-approval:

BASIS OF APPROVAL:
Was this approval based upon a petition? Yes
What is the RLD on the 356(h) form: Methotrexate Sodium Tablets

NDA Number: 08-085/S-048
NDA Drug Name: Methotrexate Sodium Tablets
NDA Firm: Lederle Laboratories

Date of Approval of NDA Insert and supplement #: October 29, 1999
Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels in jacket.

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.	X		
Do you find the name objectionable? List reasons in FTR, If so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?	X	X	
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?	X		
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			

Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?	X		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?	X		
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility Information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

FOR THE RECORD:

1. The reference listed drug for this product is Methotrexate Sodium Tablets, 2.5 mg (Lederle; NDA#08-085/S-048; Approved October 29, 1999.
2. The firm cites suitability petition docket number 97P-0279/CP1, approved August 22, 1997, as the basis for the 5 mg and 15 mg strength submission. See Vol. 1.1, page 02-00005.
3. The firm certifies there are no patents/exclusivities in effect for this drug product. See Vol. 1.1, page 03-00001.
4. The product is manufactured by Barr Laboratories, Inc., 2150 Perrowville Road, Forest, VA 24551. See Vol. 1.2, page 09-00002.
5. Outside firms are utilized for testing only. See Vol. 1.2, page 10-00002.
6. Container/Closure

   30's – bottle: 75 cc, HDPE, White, Wide mouth, Round 33/400,
   Cap: Metal, with Inner liner 33/400, (Two-piece ' —— CRC)
   Filler: 12 grams cotton

   60's (5mg)- bottle: 75 cc, HDPE, White, Wide mouth, Round 33/400
   Cap: Metal, with Inner liner 33/400, (Two-piece ' —— CRC)
   Filler: 12 grams cotton

   60's (15mg)- bottle: 120 cc HDPE, White, Wide mouth, Round 38/400
   Cap: Metal with ' ——, 38/400
   Filler: 16 grams cotton

   1 Tablet Blister Card for 5 mg and —— strength Physician sample :
   Film: ——
   Foil: ——— , aluminum foil. ——
   See Vol. 1.3, page 13-00003.
7. Product Line:
   2.5 mg – (36's, 100's, 500's, and a Dose pack) [approved under separate ANDA]
   5 mg - (30's and 60's)
   15 mg – (30's and 60's)
   See Vol. 1.1, page 05-00016.

8. Components/Composition
Innovator:
Active: Methotrexate Sodium equivalent to 2.5 mg Methotrexate
Inactive: Lactose
Magnesium Stearate
Pregelatinized Starch
And possibly corn starch
Applicant:
Active: Methotrexate 5 mg or 15 mg
Inactive:Sodium Carbonate
Microcrystalline Cellulose
Anhydrous Lactose
Pregelatinized Starch
Crospovidone
Talc
Magnesium Stearate
5 mg only – [redacted] titanium dioxide, polyethylene glycol, FD&C Blue No 1 aluminum lake, Polysorbate 80, D&C Yellow No 10 aluminum lake, FD&C Yellow No 6 aluminum lake)
15 mg only-[redacted] titanium dioxide, [redacted], FD&C Blue No 2 aluminum lake, FD&C Red No 40 aluminum lake, Polysorbate 80)
See Vol. 1.1, page 07-0002

9. Storage/Dispensing
NDA: Store at 25°C (77°F); excursions permitted to 15° - 30°C (59° - 86°F) [see USP controlled Room Temperature]. Protect from light.
ANDA: Dispense with a child-resistant closure in a well-closed container as defined in USP. Store at controlled room temperature 15° - 30°C (59° - 86°F). Protect from light.
USP: Preserve in well-closed containers. A unit-of-use container contains a quantity of tablets sufficient to provide one week's therapy as indicated in the labeling.
Labeling: When packaged in a unit-of-use container, the label indicates the total amount of methotrexate present as one week's supply. See Vol. 1.1, page 05-00016.

Date of Review: September 22, 1999
Date of Submission: July 23, 1999

Reviewer: JWatkins **Date:** 12/21/99

Team Leader: John Grace **Date:** 12/21/1999

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cc:
ANDA: 40-385
DUP/DIVISION FILE
HFD-613/TWatkins/JGrace (no cc)
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Review

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 40-385 **Date of Submission: April 14, 2000**
Applicant's Name: Barr Laboratories, Inc.
Established Name: Methotrexate Tablets USP, 5 mg, 7.5 mg, 10mg and 15 mg
Proposed Proprietary Name: ———, TREXALL™, and ———
Labeling Deficiencies:

1. GENERAL COMMENTS – Your proposed proprietary names are under review. We defer comment at this time.

2. CONTAINER (30's, 60's and 100's)
   i. Storage Temperature Recommendation- include "Protect from light.".
   ii. Warnings- Delete " ———————————

3. PHYSICIAN'S SAMPLE BOTTLE (4's) – See comments under CONTAINER.

4. PHYSICIAN'S SAMPLE UNIT DOSE BLISTER (1's)- See GENERAL COMMENTS.

5. PHYSICIAN'S SAMPLE UNIT DOSE BLISTER CARTON (1's)- See GENERAL COMMENTS.

6. PHYSICIAN'S SAMPLE DISPENSER (10 unit dose cartons per dispenser)-See comments under GENERAL COMMENTS.

7. INSERT
   a. See GENERAL COMMENTS.
   b. INDICATIONS AND USAGE
      i. Neoplastic Diseases – Delete ' ———————————
   c. PRECAUTIONS (Information for Patients) – Second paragraph- Delete the penultimate sentence which reads, " ——— Your product is not ←———————
   d. PRECAUTIONS (Organ System Toxicity; Neurologic) – Include the following to appear as the second and third sentences of paragraph one of this subsection:

      Serious neurotoxicity, frequently manifested as generalized or focal seizures, has been reported with unexpectedly increased frequency among pediatric patients with acute lymphoblastic leukemia who were treated with intermediate-dose intravenous methotrexate (1 gm/m^2). Symptomatic patients were commonly noted to have leukoencephalopathy and/or microangiopathic calcifications on diagnostic imaging studies.

      NOTE: Although you are not seeking approval for the indication referenced above, we feel that it is important information for safe use of the drug. Although seizures are only documented in this situation, it may be reasonable that this could occur in other situations.

   e. ADVERSE REACTIONS (Adverse reactions in Psoriasis) – Include the following to appear as the last sentence in this subsection:

      Rarely, painful plaque erosions may appear (Pearce, HP and Wilson, BB: *Am Acad Dermatol* 35" 835-838, 1996).

f. DOSAGE AND ADMINISTRATION (Psoriasis and Rheumatoid Arthritis) Revise the second paragraph of this subsection to read as follows:

Weekly therapy may be instituted to provide doses over a range of 5 mg to 15 mg administered as a single weekly dose. All schedules should be continually tailored to the individual patient. An initial test dose may be given prior to the regular dosing schedule to detect any extreme sensitivity to adverse effects (see **ADVERSE REACTIONS**). Maximal myelosuppression usually occurs in seven to ten days.

Please revise your labels and labeling, as instructed above, and submit 4 copies of draft labels and labeling. We will not request final print labels and labeling until a determination has been made regarding the acceptability of your proposed proprietary name.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes- http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained.

Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? Yes
Container Labels: (30's, 60's and 100's)
Professional sample bottle labels (4's)
Unit Dose Blister (1's)
Unit Dose Blister Carton (1 tablet per carton)
Physician's sample Dispenser (10 Unit dose cartons per dispenser) Satisfactory as of July 23, 1999 submission.
Professional Package Insert Labeling: Satisfactory as of July 23, 1999 submission.

BASIS OF APPROVAL:
Was this approval based upon a petition? Yes
What is the RLD on the 356(h) form: Methotrexate Sodium Tablets
NDA Number: 08-085/S-048
NDA Drug Name: Methotrexate Sodium Tablets
NDA Firm: Lederle Laboratories
Date of Approval of NDA Insert and supplement #: October 29, 1999
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels in jacket.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.	X		
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		X	
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?	X		
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	

Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?	X		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?	X		
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

FOR THE RECORD:

1. The reference listed drug for this product is Methotrexate Sodium Tablets, 2.5 mg (Lederle; NDA#08-085/S-048; Approved October 29, 1999.
2. The firm cites suitability petition docket number 97P-0279/CP1, approved August 22, 1997, as the basis for the 5 mg, 7.5 mg,10 mg and 15 mg strength submission. See Vol. 1.1 & 4.1, page 02-00005.
3. The firm certifies there are no patents/exclusivities in effect for this drug product. See Vol. 1.1, page 03-00001.
4. The product is manufactured by Barr Laboratories, Inc., 2150 Perrowville Road, Forest, VA 24551. See Vol. 1.2, page 09-00002.
5. Outside firms are utilized for testing only. See Vol. 1.2, page 10-00002.
6. Container/Closure
   30's – bottle: 75 cc, HDPE, White, Wide mouth, Round 33/400, Cap: Metal, with Inner liner 33/400, (Two-piece ——— CRC), Filler: 12 grams cotton
   60's (5mg)- bottle: 75 cc, HDPE, White, Wide mouth, Round 33/400, Cap: Metal, with Inner liner 33/400, (Two-piece ——— CRC), Filler: 12 grams cotton
   60's (15mg)- bottle: 120 cc HDPE, White, Wide mouth, Round 38/400, Cap: Metal with ———, 38/400 Filler: 16 grams cotton
   1 Tablet Blister Card for 5 mg and ——— strength Physician sample : Film: ———, Foil: ——— aluminum foil, ———. See Vol. 1.3, page 13-00003.
7. Product Line:
   2.5 mg – (36's, 100's, 500's, and a Dose pack) [approved under separate ANDA]
   5 mg - (30's, 60's and 100's) plus physician's sample bottle of 4's and unit dose blister of 1's.
   7.5 mg- (30's, 60's and 100's) plus physician's sample bottle of 4's and unit dose blister of 1's.
   10 mg- 30's, 60's and 100's) plus physician's sample bottle of 4's ———
   15 mg – (30's and 60's) plus physician's sample bottle of 4's ———
   See Vol. 1.1, page 05-00016.
8. Components/Composition
   Innovator:
   Active: Methotrexate Sodium equivalent to 2.5 mg Methotrexate
   Inactive: Lactose, Magnesium Stearate, Pregelatinized Starch, And possibly corn starch
   Applicant:
   Active: Methotrexate 5 mg or 15 mg
   Inactive:Sodium Carbonate, Microcrystalline Cellulose, Anhydrous Lactose, Pregelatinized Starch, Crospovidone, Talc, Magnesium Stearate
   5 mg only – ———, titanium dioxide, ——— FD&C Blue No 1 aluminum lake, Polysorbate 80, D&C Yellow No 10 aluminum lake, FD&C Yellow No 6 aluminum lake)
   15 mg only- ———, titanium dioxide, ——— FD&C Blue No 2 aluminum lake, FD&C Red No 40 aluminum lake, Polysorbate 80)
   See Vol. 1.1, page 07-0002
9. Storage/Dispensing
   NDA: Store at 25°C (77°F); excursions permitted to 15° - 30°C (59° - 86°F) [see USP controlled Room

Temperature]. Protect from light.
ANDA: Dispense with a child-resistant closure in a well-closed container as defined in USP. Store at controlled room temperature 15° - 30°C (59° - 86°F). Protect from light.
USP: Preserve in well-closed containers. A unit-of-use container contains a quantity of tablets sufficient to provide one week's therapy as indicated in the labeling.
Labeling: When packaged in a unit-of-use container, the label indicates the total amount of methotrexate present as one week's supply. See Vol. 1.1, page 05-00016.

Date of Review: April 19, 2000
Date of Submission: April 14, 2000

Reviewer: J. Watts **Date:** 5/3/2000
Team Leader: **Date:** 5-17-2000

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cc: ANDA: 40-385
DUP/DIVISION FILE
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Review

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ON ORIGINAL

APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 40-385 **Date of Submission: Jan. 12, 2001 & Feb 2, 2001**
Applicant's Name: Barr Laboratories, Inc.
Established Name: Methotrexate Tablets USP, 5 mg, 7.5 mg, 10mg and 15 mg
Proprietary Name: TREXALL™

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? Yes TRADE NAME "TREXALL" APPROVED BY AGENCY.

Container Labels: 5 mg, 7.5 mg, 10 mg, 15 mg (30's, 60's and 100's)- Satisfactory in FPL as of Jan. 12, 2001.

Professional sample bottle labels (4's): 5 mg, 7.5 mg, 10 mg, 15 mg (4's) Satisfactory in FPL as of Jan. 12, 2001.

Professional sample Unit Dose Blister: 5 mg, 7.5 mg (1's) Satisfactory in FPL as of Jan. 12, 2001.

Professional sample Unit Dose Blister Carton: 5 mg, 7.5 mg (1 tablet per carton) Satisfactory in FPL as of Jan. 12, 2001.

Physician's sample Dispenser (10 Unit dose cartons per dispenser): 5 mg, 7.5 mg- Satisfactory in FPL as of Jan. 12, 2001

Professional Package Insert Labeling: (R /Jan2001) Satisfactory in FPL as of February 2, 2001
Revision needed post approval: Revise according to S-046/ AP 11/8/2000 or latest approved.
BASIS OF APPROVAL:
Was this approval based upon a petition? Yes
What is the RLD on the 356(h) form: Methotrexate Sodium Tablets
NDA Number: 08-085/S-048. CSO cannot provide S-046 make changes post approval.
NDA Drug Name: Methotrexate Sodium Tablets
NDA Firm: Lederle Laboratories
Date of Approval of NDA Insert and supplement #: October 29, 1999
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels in jacket.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.	X		
Do you find the name objectionable? List reasons in FTR, If so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		X	
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?	X		
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	

Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?	X		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?	X		
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

FOR THE RECORD:

1. The reference listed drug for this product is Methotrexate Sodium Tablets, 2.5 mg (Lederle; NDA#08-085/S-048; Approved October 29, 1999. CSO cannot provide S-046 at this time more changes and FPL needed of RLD.
2. The firm cites suitability petition docket number 97P-0279/CP1, approved August 22, 1997, as the basis for the 5 mg, 7.5 mg,10 mg and 15 mg strength submission. See Vol. 1.1 & 4.1, page 02-00005.
3. The firm certifies there are no patents/exclusivities in effect for this drug product. See Vol. 1.1, page 03-00001.
4. The product is manufactured by Barr Laboratories, Inc., 2150 Perrowville Road, Forest, VA 24551. See Vol. 1.2, page 09-00002.
5. Outside firms are utilized for testing only. See Vol. 1.2, page 10-00002.
6. Container/Closure
   30's – bottle: 75 cc, HDPE, White, Wide mouth, Round 33/400, Cap: Metal, with Inner liner 33/400, (Two-piece ——— CRC), Filler: 12 grams cotton
   60's (5mg)- bottle: 75 cc, HDPE, White, Wide mouth, Round 33/400, Cap: Metal, with Inner liner 33/400, (Two-piece ——— CRC), Filler: 12 grams cotton
   60's (15mg)- bottle: 120 cc HDPE, White, Wide mouth, Round 38/400, Cap: Metal with ———, 38/400 Filler: 16 grams cotton
   1 Tablet Blister Card for 5 mg ——— strength Physician sample : Film: ———, Foil: ——— aluminum foil, ——— See Vol. 1.3, page 13-00003.

7. Product Line:
   2.5 mg – (36's, 100's, 500's, and a Dose pack) [approved under separate ANDA]
   5 mg - (30's, 60's and 100's) plus physician's sample bottle of 4's and unit dose blister of 1's.
   7.5 mg- (30's, 60's and 100's) plus physician's sample bottle of 4's and unit dose blister of 1's.
   10 mg- 30's, 60's and 100's) plus Dr. sample bottle of 4's and unit dose blister of 1's. Deleted ——— 1/12/01
   15 mg – (30's and 60's) plus Dr. sample bottle of 4's and unit dose blister of 1's. Deleted ———and added 100s
   See Vol. 1.1, page 05-00016. January 12, 2001
8. Components/Composition
   Innovator:
   Active: Methotrexate Sodium equivalent to 2.5 mg Methotrexate
   Inactive: Lactose, Magnesium Stearate, Pregelatinized Starch, And possibly corn starch
   Applicant:
   Active: Methotrexate 5 mg or 15 mg
   Inactive:Sodium Carbonate, Microcrystalline Cellulose, Anhydrous Lactose, Pregelatinized Starch, Crospovidone, Talc, Magnesium Stearate
   5 mg only – ———————————————————, titanium dioxide, ———————
   FD&C Blue No 1 aluminum lake, Polysorbate 80, D&C Yellow No 10 aluminum lake, FD&C Yellow No 6 aluminum lake)
   15 mg only- ———————————————————— titanium dioxide, ———————
   FD&C Blue No 2 aluminum lake, FD&C Red No 40 aluminum lake, Polysorbate 80)
   See Vol. 1.1, page 07-0002
9. Storage/Dispensing
   NDA: Store at 25°C (77°F); excursions permitted to 15° - 30°C (59° - 86°F) [see USP controlled Room Temperature]. Protect from light.
   ANDA: Dispense with a child-resistant closure in a well-closed container as defined in USP. Store at controlled room temperature 15° - 30°C (59° - 86°F). Protect from light.
   USP: Preserve in well-closed containers. A unit-of-use container contains a quantity of tablets sufficient to provide one week's therapy as indicated in the labeling.
   Labeling: When packaged in a unit-of-use container, the label indicates the total amount of methotrexate present as one week's supply. See Vol. 1.1, page 05-00016.
10. The professional sample sizes are not listed in the HOW SUPPLIED section of the insert.
11. Theresa apparently called the firm on August 8, 200 to inform the applicant that their trade name Trexall was accepted by the Agency. The applicant reconfirmed by calling in November 16, 2000. Theresa confirmed the acceptability of trexall. See vol 5.1 response form applicant. Writer unable to find record of telephone conversation or Agency approval letter. Will accept the response from applicant at this time.

Date of Review: Jan. 31, 2001 & Feb. 8, 2001 **Date of Submission: Jan. 12, 2001 & Feb 2, 2001**
Reviewer: Angela Payne **Date: 1/31/01 & 2/8/2001**
Team Leader: John Grace **Date:**

John Grace 2/12/2001

cc: ANDA: 40-385
DUP/DIVISION FILE
HFD-613/APayne/JGrace (no cc)
V:\FIRMSAM\BARR\LTRS&REV\40385ap.l
Review

A Payne 2/8/01

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-385

CHEMISTRY REVIEW(S)

U:\ESD\cmc\40385\BRL9901.004

1. CHEMISTRY REVIEW NO. 1

2. ANDA # **40385**

3. NAME AND ADDRESS OF APPLICANT
Barr Laboratories, Inc.
Attention: Christine Mundkur
2 Quaker Road
PO Box 2900
Pomona, NY 10970-0519

4. LEGAL BASIS FOR SUBMISSION
ANDA Suitability Petition for change in strength
Innovator Product: Methotrexate Sodium Tablets, 2.5 mg (base)
Innovator Company: ESI Lederle Inc., NDA 8085
Patent Expiration Date: Past
Exclusivity: None

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
——— However, the labeling reviewer will inform Barr that the proposed proprietary name is unacceptable.

7. NONPROPRIETARY NAME
Methotrexate Tablets, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Vol.	Submission date	Submission type
A1.1 – 1.10	**07/23/99**	**Original**
(A1.2 – 1.7 are Bio)		
A2.1	**08/06/99**	**NC – CMC electronic submission**
"	**09/08/99**	**Telecon re Bio facilities**
"	**09/20/99**	**NC – List of Bio facilities**
"	**09/21/99**	**"Acceptable for Filing" letter**
A3.1	**10/07/99**	**Bio telephone amendment**

10. PHARMACOLOGICAL CATEGORY
antineoplastic, antirheumatic and antipsoriatic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

Approved ANDA 81-099, Methotrexate Tablets USP, 2.5 mg, Barr Laboratories, Inc.

Bio-IND 15-304, Methotrexate Tablets USP, 15 mg, Barr Laboratories, Inc.

DMF number	DMF type	DMF holder	LOA(s)
	III: Packaging		
	III: Packaging		
	III: Packaging		
	III: Packaging		
	II: Drug Substance		
	III: Packaging		
	III: Packaging		
	III: Packaging		
	III: Packaging		
	III: Packaging		

See DMF Checklist for further details.

13. DOSAGE FORM
tablet

14. STRENGTH

Strength	Strength units
15	mg (base)
5	mg (base)

15. CHEMICAL NAME AND STRUCTURE

Methotrexate. L-Glutamic acid, *N*-[4-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-. $C_{20}H_{22}N_8O_5$. 454.45. 59-05-2.

16. RECORDS AND REPORTS N/A

17. COMMENTS

There are **deficiencies** in the following Review Points:

23.A, 23.B, 25, 28.A, 28.B, 29

The conditions of the **other disciplines** are as follows:

25. MANUFACTURING AND PROCESSING (Microbiology)

This is not a sterile product.

31. SAMPLES AND RESULTS

The drug substance and drug product are in USP 24.

32. LABELING

The labeling in the original submission was found **not satisfactory** by Ms. Teresa Watkins 12/21/99. Vol. A1.1

33. ESTABLISHMENT INSPECTION

An EER was submitted 9/21/99. The facilities were found **acceptable** 2/28/2000.

34. BIOEQUIVALENCE STATUS

The Bio review has not been completed, as of 2/28/2000.

18. CONCLUSIONS AND RECOMMENDATIONS

ANDA 40-385 is **NOT APPROVED – MAJOR AMENDMENT** requested.

19.	REVIEWER:	DATE COMPLETED:	DATE REVISED:
	Eugene L. Schaefer, Ph.D.	2/28/2000	3/6/2000

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CHEMISTRY REVIEW #1

cc: ANDA 40-385
DIV FILE
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ES 3/8/2000

Endorsements:

HFD-625/ELSchaefer, Chemist/3-6-00
HFD-625/MSmela, Chemistry Team Leader/3-7-00 MSmela 3/8/00
HFD-617/MDillahunt, Project Manager/3-7-00 MDillahunt 3/8/00

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CHEMISTRY REVIEW - Not APPROVABLE - Major

1. CHEMISTRY REVIEW NO. 2 2. ANDA # 40385

3. NAME AND ADDRESS OF APPLICANT
Barr Laboratories, Inc.
Attention: Christine Mundkur
2 Quaker Road
PO Box 2900
Pomona, NY 10970-0519

4. LEGAL BASIS FOR SUBMISSION
Approved ANDA Suitability Petition for change in strength

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
——— However, the labeling reviewer informed Barr that the proposed proprietary name is unacceptable. Barr has proposed ———Trexall, and ——— The labeling reviewer has requested a consult from HFD-400.

7. NONPROPRIETARY NAME
Methotrexate Tablets, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

A1.1 – 1.10 (A1.1 & 1.8 – 1.10 are Chem) (A1.2 – 1.7 are Bio)	07/23/99	Original
A2.1	09/21/99	"Acceptable for Filing" letter
A3.1	10/07/99	Bio telephone amendment
A1.1	03/09/00	NA – Major
"	03/23/00	Fax from Barr re packaging and stability
"	03/28/00	Telecon re 3/23
A4.1 – 4.5	04/14/00	Major amendment
A4.1	08/09/00	Labeling comments to firm via voicemail

In addition to responding to deficiencies, Barr is adding two new strengths, 7.5 mg and 10 mg, and an alternate source of DS, ———

Barr is providing documentation for the manufacture of the new strengths with DS from the same source, ————————, which was used for making the original exhibit batches of the 5 mg and 15 mg tablets.

Barr has made a new exhibit batch of 15 mg tablets with the ———material, and has put this new batch on the stability program. They are providing comparative dissolution profiles of the 15 mg batches made from the two sources of DS, in the Bio section on pages 06-00033 to 06-00038.

10. PHARMACOLOGICAL CATEGORY
antineoplastic, antirheumatic and antipsoriatic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

Approved ANDA 81-099, Methotrexate Tablets USP, 2.5 mg, Barr Laboratories, Inc.

Bio-IND 15-304, Methotrexate Tablets USP, 15 mg, Barr Laboratories, Inc.

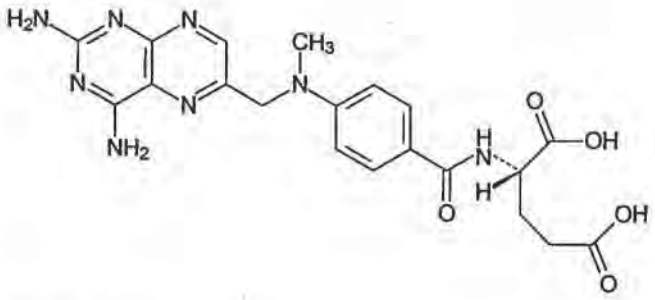
See DMF Checklist.

13. DOSAGE FORM
tablet

14. STRENGTHS 5 mg, 7.5 mg, 10 mg, 15 mg

15. CHEMICAL NAME AND STRUCTURE

Methotrexate. L-Glutamic acid, *N*-[4-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-. $C_{20}H_{22}N_8O_5$. 454.45. 59-05-2.



16. RECORDS AND REPORTS N/A

17. COMMENTS

There are **deficiencies** in the following Review Points:

22, 25, 28.A, 28.B, 29

The conditions of the **other disciplines** are as follows:

25. MANUFACTURING AND PROCESSING (Microbiology)

This is not a sterile product.

31. SAMPLES AND RESULTS

The drug substance and drug product are in USP 24.

32. LABELING

The labeling in the amendment of 4/14/00 was found **not satisfactory** by Ms. Teresa Watkins 5/17/00. Vol. A4.1

33. ESTABLISHMENT INSPECTION

An EER was submitted 9/21/99. The facilities were found acceptable 2/28/2000. However, **a new EER must be submitted to provide for the new drug substance manufacturer** described on page 08-00004 of the amendment of 4/14/00:

34. BIOEQUIVALENCE STATUS

No further questions for 5 mg and 15 mg tablets, 2/16/00.

No further questions for 7.5 mg and 10 mg tablets, 6/1/00.

18. CONCLUSIONS AND RECOMMENDATIONS

ANDA 40-385 is **NOT APPROVED – MINOR AMENDMENT** requested.

19.	REVIEWER:	DATE COMPLETED:	REVISED:
	Eugene L. Schaefer, Ph.D.	10/24/2000	10/27/00

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ON ORIGINAL

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CHEMISTRY REVIEW #2

1. CHEMISTRY REVIEW NO. 3 2. ANDA # 40385

3. NAME AND ADDRESS OF APPLICANT
Barr Laboratories, Inc.
Attention: Christine Mundkur
2 Quaker Road
PO Box 2900
Pomona, NY 10970-0519

4. LEGAL BASIS FOR SUBMISSION
Approved ANDA Suitability Petition for change in strengths (4)

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
——— in the original submission was unacceptable. Trexall™ in the minor amendment of 1/12/01 is acceptable.

7. NONPROPRIETARY NAME
Methotrexate Tablets, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

A1.1 – 1.10 (A1.1 & 1.8 – 1.10 are Chem) (A1.2 – 1.7 are Bio)	07/23/99	Original
A2.1	09/21/99	"Acceptable for Filing" letter
A3.1	10/07/99	Bio telephone amendment
A1.1	03/09/00	NA – Major
"	03/23/00	Fax from Barr re packaging and stability
"	03/28/00	Telecon re 3/23
A4.1 – 4.5 (A4.2 is labeling)	04/14/00	Major amendment
A4.1	08/09/00	Labeling comments to firm via voicemail
"	11/13/00	NA – Minor
A5.1 – 5.3 (5.2 & 5.3 are labeling.)	01/12/01	Minor amendment

Barr added two new strengths, 7.5 mg and 10 mg, and an alternate source of DS, ——— in the major amendment of 4/14/00.

10. PHARMACOLOGICAL CATEGORY 11. Rx or OTC
antineoplastic, antirheumatic and antipsoriatic Rx

12. RELATED IND/NDA/DMF(s)

Approved ANDA 81-099, Methotrexate Tablets USP, 2.5 mg, Barr Laboratories, Inc.

Bio-IND 15-304, Methotrexate Tablets USP, 15 mg, Barr Laboratories, Inc.

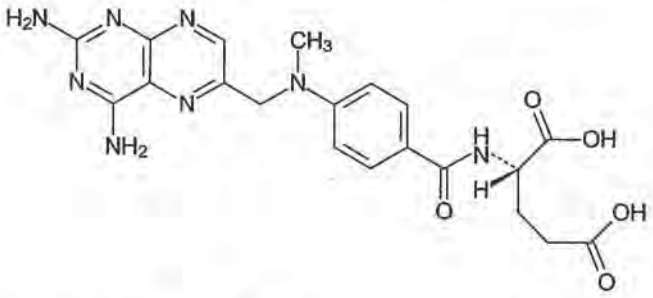
See DMF Checklist.

13. DOSAGE FORM
tablet

14. STRENGTHS 5 mg, 7.5 mg, 10 mg, 15 mg

15. CHEMICAL NAME AND STRUCTURE

Methotrexate. L-Glutamic acid, *N*-[4-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-. $C_{20}H_{22}N_8O_5$. 454.45. 59-05-2.



16. RECORDS AND REPORTS N/A

17. COMMENTS

There are **deficiencies** in the following Review Points:

28.A, 28.B, 29

The conditions of the **other disciplines** are as follows:

25. MANUFACTURING AND PROCESSING (Microbiology)

This is not a sterile product.

31. SAMPLES AND RESULTS

The drug substance and drug product are in USP 24.

32. LABELING

The labeling reviewer is preparing an approval summary, as of 1/31/01.

33. ESTABLISHMENT INSPECTION

The facilities, including [redacted], were found acceptable 10/30/2000.

34. BIOEQUIVALENCE STATUS

No further questions for 5 mg and 15 mg tablets, 2/16/00.

No further questions for 7.5 mg and 10 mg tablets, 6/1/00.

18. CONCLUSIONS AND RECOMMENDATIONS

ANDA 40-385 is **NOT APPROVED – MINOR AMENDMENT** requested.

19. REVIEWER: Eugene L. Schaefer, Ph.D.

DATE COMPLETED: 1/31/01

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CHEMISTRY REVIEW #3

cc: ANDA 40-385
DUP
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ES 2/2/01

Endorsements:

HFD-625/ELSchaefer, Chemist/1/31/01
HFD-625/MSmela, Chemistry Team Leader/2/1/01 MSmela 2/5/01
HFD-617/MDillahunt, Project Manager/2/2/01 MDillahunt 2/2/01
F/t by: DJ 2/2/01
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CHEMISTRY REVIEW - Not APPROVABLE - Minor

APPEARS THIS WAY
ON ORIGINAL

1. CHEMISTRY REVIEW NO. 4 2. ANDA # 40385

3. NAME AND ADDRESS OF APPLICANT
Barr Laboratories, Inc.
Attention: Christine Mundkur
2 Quaker Road
PO Box 2900
Pomona, NY 10970-0519

4. LEGAL BASIS FOR SUBMISSION
Approved ANDA Suitability Petition for change in strengths (4)

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
[redacted] in the original submission was unacceptable. Trexall™ in the minor amendment of 1/12/01 is acceptable.

7. NONPROPRIETARY NAME
Methotrexate Tablets, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

A1.1 – 1.10 (A1.1 & 1.8 – 1.10 are Chem) (A1.2 – 1.7 are Bio)	07/23/99	Original
A2.1	09/21/99	"Acceptable for Filing" letter
A3.1	10/07/99	Bio telephone amendment
A1.1	03/09/00	NA – Major
"	03/23/00	Fax from Barr re packaging and stability
"	03/28/00	Telecon re 3/23
A4.1 – 4.5 (A4.2 is labeling)	04/14/00	Major amendment
A4.1	08/09/00	Labeling comments to firm via voicemail
"	11/13/00	NA – Minor
A5.1 – 5.3 (5.2 & 5.3 are labeling.)	01/12/01	Minor amendment
A5.1	02/02/01	NC – Labeling
"	02/06/01	NA-Minor
"	02/08/01	Fax from Barr re 02/06/01*
"	02/13/01	Chem telecon re 02/06/01*
"	02/15/01	Minor amendment*
"	02/21/01	Chem telecon re 02/06/01*
"	02/22/01	Minor amendment*

* The subjects of Chemistry Review #4

Barr added two new strengths, 7.5 mg and 10 mg, and an alternate source of DS, ——in the major amendment of 4/14/00. Barr withdrew ——in the minor amendment of 2/22/01.

10. PHARMACOLOGICAL CATEGORY
antineoplastic, antirheumatic and antipsoriatic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

Approved ANDA 81-099, Methotrexate Tablets USP, 2.5 mg, Barr Laboratories, Inc.

Bio-IND 15-304, Methotrexate Tablets USP, 15 mg, Barr Laboratories, Inc.

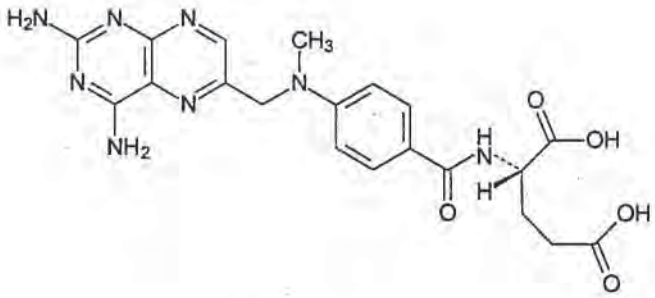
See DMF Checklist.

13. DOSAGE FORM
tablet

14. STRENGTHS 5 mg, 7.5 mg, 10 mg, 15 mg

15. CHEMICAL NAME AND STRUCTURE

Methotrexate. L-Glutamic acid, *N*-[4-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-. $C_{20}H_{22}N_8O_5$. 454.45. 59-05-2.



16. RECORDS AND REPORTS N/A

17. COMMENTS

All chemistry deficiencies have been resolved.

The conditions of the **other disciplines** are as follows:

25. MANUFACTURING AND PROCESSING (Microbiology)

This is not a sterile product.

31. SAMPLES AND RESULTS

The drug substance and drug product are in USP 24.

32. LABELING

The labeling reviewer prepared an approval summary on 2/8/01.

33. ESTABLISHMENT INSPECTION

The facilities were found acceptable 10/30/2000.

34. BIOEQUIVALENCE STATUS

No further questions for 5 mg and 15 mg tablets, 2/16/00.

No further questions for 7.5 mg and 10 mg tablets, 6/1/00.

18. CONCLUSIONS AND RECOMMENDATIONS

ANDA 40-385 can be **APPROVED**.

19. REVIEWER: Eugene L. Schaefer, Ph.D.

DATE COMPLETED: 3/7/01

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CHEMISTRY REVIEW #4

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

None

cc: ANDA 40-385

DIV FILE
Field Copy

Endorsements:

HFD-625/ELSchaefer, Chemist/3/7/01
HFD-625/MSmela, Chemistry Team Leader/3/7/01
HFD-617/MDillahunt, Project Manager/3/8/01
F/T by: DJ 3/8/01
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CHEMISTRY REVIEW - APPROVED

ANDA APPROVAL SUMMARY

ANDA: 40-385	CHEMIST: Eugene L. Schaefer, Ph.D.	DATE: 3/7/01
DRUG PRODUCT: Methotrexate		
FIRM: Barr Laboratories, Inc.		
DOSAGE FORM: Tablets, USP	STRENGTHS: 5 mg, 7.5 mg, 10 mg, 15 mg	
cGMP: The facilities were found acceptable on 10/30/00.		
BIO: No further questions 2/16/00 and 6/1/00.		
VALIDATION - (Description of dosage form received by FDA lab same as in firm's ANDA?): N/A DS and DP are in USP 24.		
STABILITY: The containers in the stability studies are identical to those in the container section.		
LABELING: Container, carton, and insert labeling were approved by Angela Payne on 2/8/01.		
STERILIZATION VALIDATION (If applicable): N/A		
SIZE OF BIO BATCH (Firm's source of NDS ok?): Yes, DMF —— OK. ——— 15-mg tablets		
SIZE OF STABILITY BATCHES (If different from bio batch, were they manufactured via the same process?): Yes 5 mg: ——— tablets 7.5 mg: ——— tablets 10 mg: ——— tablets 15 mg: ——— tablets		
PROPOSED PRODUCTION BATCHES-MANUFACTURING PROCESS SAME?: Yes 5 mg: ——— tablets 7.5 mg: ——— tablets 10 mg: ——— tablets 15 mg: ——— tablets		
Signature of chemist: Eugene L. Schaefer 3/9/01 Eugene L. Schaefer, Ph.D.	Signature of Team Leader: Michael Smela 3/12/01	

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-385

BIOEQUIVALENCE REVIEW(S)

Methotrexate Sodium	**Barr Laboratories**
15 mg and 5 mg Tablets	Pomona, N.Y.
ANDA # 40-385	Submission Date:
Reviewer: André Jackson	July 23, 1999
	October 7, 1999

V:\Firmsam\Barr\Ltr&Rev\40385SDW.799

Review of A Bioavailability Study on the 15 mg Tablet and Request for Waiver of the 5 mg Tablet and Dissolution Data

RLD: Methotrexate Sodium Tablets 2.5 mg

BACKGROUND:

The firm filed a suitability petition on July 7, 1997 for the submission of 5 mg, 7.5 mg, 10 mg, 12.5 mg and 15 mg methotrexate sodium tablets. The petition was granted and the firm has submitted a study on the 15 mg strength and a request for waiver on the 5 mg strength. The other strengths were withdrawn.

INTRODUCTION:

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

In adults, oral absorption appears to be dose dependent. Peak serum levels are reached within one to two hours. At doses of 30 mg/m(squared) or less, methotrexate is generally well absorbed with a mean bioavailability of about 60%. The absorption of doses greater than 80 mg/m(squared) is significantly less, possibly due to a saturation effect. Food has been shown to delay absorption and reduce peak concentration.

The terminal half-life reported for methotrexate is approximately three to ten hours for patients receiving treatment for psoriasis, or rheumatoid arthritis or low dose

antineoplastic therapy (less than 30 mg/m(squared)). For patients receiving high doses of methotrexate, the terminal half-life is 8 to 15 hours.

The potential for toxicity from high dose regimens or delayed excretion is reduced by the administration of leucovorin calcium during the final phase of methotrexate plasma elimination. Pharmacokinetic monitoring of methotrexate serum concentrations may help identify those patients at high risk for methotrexate toxicity and aid in proper adjustment of leucovorin dosing.

STUDY OBJECTIVE

The study objective is to determine the bioavailability of a test formulation (Methotrexate Tablets, USP 15 mg, Barr Laboratories, Inc.: 1 x 15 mg) relative to a reference formulation (Methotrexate Sodium Tablets, 2.5 mg, ESI Lederle, Inc.: 6x 2.5 mg) after administration of an equal 15mg single dose to male and female patients with mild to severe psoriasis under fasting conditions.

Fasting Study:

Study Facility Information:

Clinical Facilities:	1. 2. 3.
Principal Investigator:	1. 2. 3.
Clinical Study Date:	Period I / Period II 1.GRI 10/31/98 / 11/14/98 GRII 1/9/99 / 1/23/99 2.GRI 11/23/98 / 12/7/98 GRII 12/3/98 / 12/17/98 3.GRI 12/2/98 / 12/17/98 GRII 1/8/99 / 1/22/99
Analytical Facility:	

Principal Investigator:	[redacted]
Analytical Study Dates:	December 4, 1998-February 22, 1999
Storage Period:	90 days

Study Design:

Protocol No.:	9801 A Single Dose, Fasting Bioequivalence Study Comparing Barr Lab's 15 mg methotrexate sodium 15 mg tablet with 6 x 2.5 mg Lederle methotrexate sodium tablets
Design Type:	Crossover
Randomized:	Y
No. of Sequences:	2
Number of Clinical Sites:	3
Number of Groups/Site:	2
No. of Treatment Periods/Site:	2
No. of Treatments/Site:	2
Washout Period:	14 days
Single, Multiple, Food:	Single

Subjects:

Patients with Mild to Severe Psoriasis:	Y
IRB Approval:	Y
Informed Consent Obtained:	Y
No. of Subjects Enrolled:	38 (22 males,16 females)
Inclusion/Exclusion criteria	vol:1.1 ; pages: 85-87

Special Procedures: Forty-eight hours after methotrexate administration in period II, patients were provided with Leucovorin Calcium tablets (2 x 5 mg) to be taken every 6 hours for four doses(to minimize the risk of myelosuppression).

Housing: Evening prior to each drug administration until 36 hours after dosing on day 2.

Treatment Information:

Treatment:	A	B
Test or Reference:	Test	Reference
Product Name:	Methotrexate sodium	Methotrexate sodium
Strength:	15 mg	2.5 mg
Manufacturer:	Barr Laboratories	ESI Lederle
Batch/Lot No.:	409457R01	457-037
Exhibit Batch Size:	[redacted]	N/A
Expiration Date:	N/A	6/2000
Content Uniformity	95.4%	99.7%
Assay	96.1%	98.7%
Dose Administered:	1 x 15 mg Tablet	6 x 2.5 mg Tablets
Length of Fasting:	10 hr overnight	10 hr overnight

Dosing:

After an overnight fast of ten hours, each subject randomly (Randomization Code in Table 1) received either a test product or a reference product with 240 mL of water. Standard meals were provided at 4 and 10 hours after dosing. Water was not permitted for 1 hour before and 2 hours after dosing in each dosing period.

Table 1. RANDOMIZATION SCHEDULE

Site	Period I	Period II	Subjects
1.GRI	A	B	1,6,7,11
GRII	B	A	2,3,5,9,12,13
2.GRI	A	B	14,15,18,20,23, 24,21,33
GRII	B	A	16,17,19,22,34

3.GRI	A	B	26,27,30,48
GRII	B	A	28,46,67,70

Blood Sampling:

No. of time points	22
Time points	0,0.25,0.5,0.75,1,1.5,2,2.5,3,3.5,4,5,6,7, 8,10,12,16,24,30,36 and 48 hrs

The blood samples were centrifuged and plasma samples were separated and stored at -20°C until analyzed.

The following table gives the formulation for 15 mg Tablet

Ingredient	mg
Core:	
Methotrexate, USP[a]	15

Coated tablet weight (target)

---

a. Theoretical quantities are based on the Methotrexate, USP assay at 100%.
b. Stated quantity weighed but only partially retained in product after chemical reaction.
c. Dependent on Methotrexate, USP assay.
d. Used but not retained, except as allowed in .
e. Theoretical value based on 3% weight gain.

Analytical Method

The plasma samples were assayed for methotrexate by .

The details of the analytical method for methotrexate are presented in Table 2:

Table 2: Validation data for methotrexate.

Parameter	
Method	
Internal Standard	
Sensitivity/LOQ	
Linearity (Standard curve samples)	
Quality Control (QC) Samples	
Precision of Standards (%CV)	
Precision of QC Samples (%CV)	
Accuracy of Standards (%)	
Accuracy of QC Samples (%)	
Stability	
Freeze-thaw	

Processed Sample Stability at RT	
Long term at -25° C	
Recovery Low Med High	

STATISTICAL ANALYSIS:

AUCL was calculated from zero time to the last non-zero concentration CT. AUCinf, was calculated by extrapolation of AUCL to time infinity by adding CT/K, to AUCL, The elimination rate constant (K) was estimated by linear least squares fitting of the logarithm of the concentrations over the log-linear terminal phase of the concentration versus time profile. Half-life (HL=0.693/K,), maximum concentration attained (Cpeak) and the time of maximum concentration (Tmax) were also calculated. AUCL, AUCI, Cpeak and log transformed AUCL, AUCI and Cpeak was analyzed by Analysis of Variance (ANOVA) with effects for treatments, sequence of dosing, subjects within sequence, study period and study site in the statistical model.

The two one-sided hypotheses at the alpha=0.05 level of significance were tested for AUCL, AUCinf, Cpeak in original scale and after log transformation, by constructing the 90% confidence intervals for the differences between the test and the reference least squares means, and were reported relative to the reference means.

Pharmacokinetics/Statistical Analysis

Results

Of the 38 healthy, adult subjects enrolled in the study, 36 subjects successfully completed both phases of the study. Subject 25 withdrew prior to period 2 dosing. Patient 37 was lost to follow up and the last sample was obtained at the 48

hour time point in period 1.

Table 3. Mean plasma levels of 36 subjects. Values are mean ± sd.

	TEST		REFERENCE	
HOUR0	0.00	0.00	0.41	1.59
HOUR0.25	14.45	18.43	20.21	19.73
HOUR0.5	123.67	89.73	113.04	86.73
HOUR0.75	208.62	101.16	204.26	128.47
HOUR1	265.97	118.74	235.34	128.45
HOUR1.5	296.07	101.39	255.62	106.39
HOUR2	258.33	75.61	248.67	64.52
HOUR2.5	212.93	62.87	233.80	68.23
HOUR3	179.07	49.83	186.60	41.54
HOUR3.5	150.83	41.65	177.58	84.22
HOUR4	119.25	27.58	156.91	73.48
HOUR5	95.21	19.96	105.30	29.30
HOUR6	68.50	13.62	78.42	18.88
HOUR7	52.54	13.27	59.19	15.06
HOUR8	40.89	10.44	48.59	16.26
HOUR10	28.72	9.90	31.90	9.91
HOUR12	16.68	5.36	18.79	6.81
HOUR16	6.79	5.12	7.92	5.17
HOUR24	0.74	1.96	0.82	2.17
HOUR30	0.38	1.47	0.46	1.80
HOUR36	0.36	1.39	0.36	1.41
HOUR48	0.00	0.00	0.00	0.00

Table 4: Mean for test and reference products (N=36). Values are mean ± sd.

	TEST		REFERENCE		RATIO(T/R)
CPEAK ng/mL	347.69	106.37	342.83	79.01	1.01
LCPEAK ng/mL	5.81	0.28	5.81	0.23	1.00[3]
AUCL[1] ng/mL x hr	1235.73	280.24	1310.73	294.18	0.94
LAUCL ng/mL x hr	7.09	0.23	7.16	0.22	0.93

AUCI[2] ng/mL x hr	1282.12	285.52	1358.21	296.46	0.94
LAUCI ng/mL x hr	7.13	0.23	7.19	0.21	0.94
TMAX hr	1.43	0.56	1.69	0.80	---
KEL hr-1	0.23	0.06	0.22	0.05	---
THALF hr	3.29	0.89	3.42	0.91	---

1.AUC 0 to last measured concentration
2.AUC to time infinity
3.Ratio of geometric means

Table 5: 90% CI for pharmacokinetic parameters with site*trt interaction in the model

LCPEAK	93.2-105.9
LAUCL	88.7-97.3
LAUCI	89.3-97.2

ALL CALCULATIONS WERE VERIFIED BY THE REVIEWER

SUBJECTS DID NOT EXHIBIT CPEAK AT THE FIRST NON-ZERO TIME POINT NOR WAS CPEAK OBSERVED AT FIRST MEASURABLE TIME POINT IN THIS STUDY.

Adverse Events

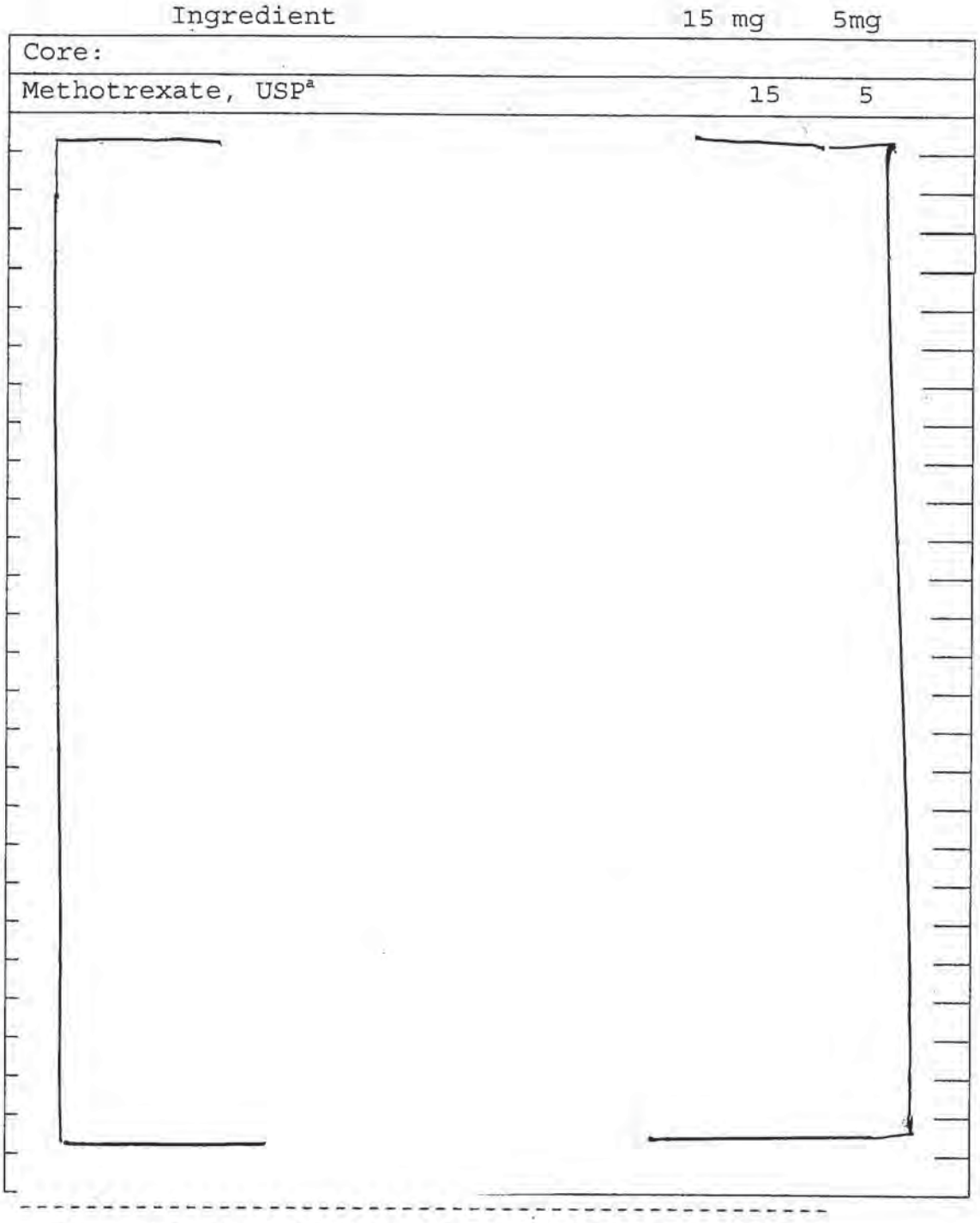
Adverse effects are summarized in Table 3 , vol. 1.2, pages 13-14. The effects were mainly headache and appeared to be equally distributed between test and reference products.

Sample Repeats

Three hundred and eleven out of the one thousand six hundred and twenty-six samples analyzed (19.1%) were reanalyzed. They are listed in volume 1.3, page 62. Most re-analyses were a result of problems with the quality controls.

The following table gives the comparative formulations for the

15 mg and 5 mg Tablets.



Ingredient	15 mg	5mg
Core:		
Methotrexate, USP[a]	15	5

a Theoretical quantities are based on the Methotrexate, USP assay at 100%.
b Stated quantity weighed but only partially retained in product after chemical reaction.

10

c.Dependent on Methotrexate, USP assay.
d.Used but not retained, except as allowed in
[redacted].
e.Theoretical value based on 3% weight gain.

IN-VITRO DISSOLUTION TESTING

The dissolution testing for the test and reference products was conducted using 0.1N HCL as the dissolution media using USP 23 apparatus 2 (Paddle) at 50 rpm. This is a USP method.

Comments:

1. The ANOVA with the interaction term site*trt was significant at the $p<0.1$ level for LAUCL and LAUCI. Therefore the study was analyzed with the site*trt interaction term retained in the model. 90% CI's for this model were within the 80-125% limit.

2.The appended tables for each site shows the reason for the significant site*trt interaction was that site three had higher mean values for LAUC. However since sites 1 and 2 were similar the analysis combining all 3 sites was within the CI limits.

3.The PDR labeling for methotrexate contains the following statement " Food has been shown to delay absorption and reduce peak concentration". However, the Division of Bioequivalence has not required a food effects study for this product for three marketed generic products (ANDA # 81099-Barr ; ANDA # 40-054-Roxanne and ANDA # 81235-Mylan). Two other products reviewed by the Division (ANDA # [redacted] and ANDA # 40-233-Duramed) and not yet approved also did not require food studies. However, there is no information on a possible food effect at the 15 mg dosage level for methotrexate. Two recent references, J.Rheumatol. 1995, April, 22, 630-632 and Arthritis-Rheum. 1992, July, 35, 761-764 (the latter at a dose of 7.5 mg, i.e., 3x2.5 mg tablets) showed no food effects looked at the effects of food on methotrexate. Both studies concluded that there was no food effect which raises additional questions related to the effects of food based upon the statement in the labeling.

4.A survey of PDR labeling for several orally administered anti cancer drugs (list appended to this review) did not report that food had any effect on their absorption. Therefore it appears that the food effect presented in methotrexate labeling may be an exception.

5.The regulatory history of the methotrexate studies reviewed by the Division of Bioequivalence and their status is appended to the review. This data is based upon COMIS. There was no food study requirement for the studies submitted to the Division of Bioequivalence.

RECOMMENDATIONS:

1.The fasting bioavailability study conducted by Barr Laboratories on its 15 mg, methotrexate sodium tablet(lot 409457R01 comparing it to ESI Lederle's methotrexate sodium tablet 6 x 2.5 mg tablets, lot number 457037 has been found to be acceptable to the Division of Bioequivalence. The study demonstrates that Barr Laboratories' 15 mg, methotrexate sodium tablet is bioavailable to 6 x 2.5 mg ESI Lederle's methotrexate sodium tablets.

2.The in vitro dissolution testing conducted on the 15 mg methotrexate sodium tablet has been found to be acceptable.

3. The dissolution testing conducted by Barr on its 5 mg, methotrexate sodium tablet, lot 409277R01 is acceptable. The firm has conducted an acceptable in vivo bioavailabilty study comparing its 15 mg tablet of the test product with 6 x 2.5 mg tablets of the reference product methotrexate sodium manufactured by ESI Lederle. The formulation for the 5 mg strength is proportionally similar to the 15 mg strength of the test product which underwent bioavailability testing. The waiver of the in vivo bioavailibility study requirements for the 5 mg tablet is granted. The 5 mg tablet of the test product is therefore deemed to be bioavailable to 2 x 2.5 mg methotrexate sodium tablets manufactured by ESI Lederle.

4.The dissolution testing should be incorporated into the firm's manufacturing and controls programs. The dissolution testing should be conducted in 900 ml of 0.1N HCL at 37°C using USP XXIII apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

NLT 75% of methotrexate is dissolved in 45 min

André J. Jackson, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang
FT INITIALED YCHuang Date 2/8/2000

Concur Date 2/16/00
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

ANDA 40-385 (original, duplicate), HFD 652(Jackson), Drug file, Division File, HFD-650(Division Director).
Appendix, Attachments

Table 6. In Vitro Dissolution Testing

Drug (Generic Name): Methotrexate sodium
Dose Strengths:5 mg and 15 mg
ANDA No.:40-385
Firm: Barr
Submission Date: July 23, 1999
File Name:40385SDW.799

I. Conditions for Dissolution Testing:

USP XXIII Basket: Paddle: x RPM: 50
No. Units Tested: 12
Medium: 0.1N HCL
Wavelength: 306 nm
Volume: 900 mL
Specifications:
NLT 75% in 45 min
Reference Drug: Methotrexate sodium
Assay Methodology: UV Spectroscopy

THIS IS A USP METHOD

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 409277R01 Strength(mg) 5			Reference Product Lot # 457-037 Strength(mg) 2.5		
	Mean	Range	%CV	Mean	Range	%CV
10	87	77-92	6.3	52	49-56	4.7
20	88	80-93	5.2	97	94-100	2.2
30	89	82-93	4.5	99	96-104	2.8
45	91	84-94	4.2	100	97-105	2.9
75	92	87-95	3.2	99	96-104	2.6
Sampling Times (Minutes)	Test Product Lot # 409457R01 Strength(mg) 15			Reference Product Lot # 457-037 Strength(mg) 2.5		
	Mean	Range	%CV	Mean	Range	%CV
10	89	76-95	7.2	52	49-56	4.7
20	91	81-95	5.0	97	94-100	2.2
30	92	83-96	4.4	99	96-104	2.8
45	92	84-95	3.8	100	97-105	2.9
75	93	85-96	3.5	99	96-104	2.6

APPENDIX

Site 1

Variable	N	Mean TEST	Std	Mean REFERENCE	Std	Ratio (TEST/REFERENCE)
CPEAK ng/mL	15	335.53	103.80	331.27	82.72	
LCPEAK ng/mL	15	5.77	0.31	5.77	0.26	1.0
AUCL ng/mL x hr	15	1229.71	241.65	1305.83	227.08	
LAUCL ng/mL x hr	15	7.09	0.21	7.16	0.18	0.93
AUCI ng/mL x hr	15	1274.51	246.81	1347.00	223.56	
LAUCI ng/mL x hr	15	7.13	0.21	7.19	0.17	0.94
TMAX hr	15	1.34	0.43	1.98	0.91	
KEL hr-1	15	0.21	0.05	0.23	0.05	
THALF hr	15	3.42	0.87	3.24	0.83	

Site 2

Variable	N	Mean TEST	Std	Mean REFERENCE	Std	Ratio (TEST/REFERENCE)
CPEAK ng/mL	13	365.54	132.97	345.46	89.33	
LCPEAK ng/mL	13	5.85	0.31	5.82	0.25	1.03
AUCL ng/mL x hr	13	1194.19	267.17	1179.85	244.33	
LAUCL ng/mL x hr	13	7.06	0.23	7.05	0.21	1.01
AUCI ng/mL x hr	13	1235.75	261.60	1231.02	246.61	
LAUCI ng/mL x hr	13	7.10	0.22	7.10	0.20	1.00
TMAX hr	13	1.44	0.66	1.16	0.36	
KEL hr-1	13	0.24	0.06	0.20	0.05	
THALF hr	13	2.98	0.64	3.63	1.07	

Site 3

Variable	N	Mean	Std	Mean	Std	Ratio (TEST/REFERENCE)
CPEAK ng/mL	8	341.50	61.30	360.25	56.57	
LCPEAK ng/mL	8	5.82	0.18	5.88	0.15	0.94
AUCL ng/mL x hr	8	1314.51	378.35	1532.59	372.99	
LAUCL ng/mL x hr	8	7.15	0.29	7.31	0.22	0.85
AUCI ng/mL x hr	8	1371.73	393.90	1585.91	381.64	
LAUCI ng/mL x hr	8	7.19	0.29	7.35	0.22	0.85
TMAX hr	8	1.56	0.62	2.00	0.71	
KEL hr-1	8	0.22	0.07	0.21	0.05	
THALF hr	8	3.53	1.21	3.42	0.79	

APPEARS THIS WAY
ON ORIGINAL

CC: ANDA 40385
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)
HFD-652/Reviewer
HFD-652/Bio Team Leader
HFD-617/Project Manager
HFD-650/Dale Conner 2/16/00

V:\Firmsam\Barr\Ltr&Rev\40385SDW.799

BIOAVAILABILITY - ACCEPTABLE Submission Date: July 23, 1999

1. **FASTING STUDY** (STF) o/c Strength: 15 mg Tablet

Clinical: 1.
2.
3.

Analytical:

Outcome: AC

2. **Dissolution WAIVER** (DIW) Strength: 5 mg Tablet
o/c **Outcome: AC**

Submission Date: October 7, 1999

3. **STUDY AMENDMENT** (STA) Strength: 15 mg
Disk and Additional
Information **Outcome: AC**

3.1
Gene Sharpe

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA 40-385 APPLICANT: Barr Laboratories

DRUG PRODUCT: Methotrexate 15 mg and 5 mg Tablets

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 24.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 40-385 SPONSOR : Barr Laboratories

DRUG AND DOSAGE FORM : Methotrexate Sodium Tablets

STRENGTH(S) : **15 mg and 5 mg**
TYPES OF STUDIES : Single Dose

CLINICAL STUDY SITE(S) :1
2.
3.

ANALYTICAL SITE(S) :

STUDY SUMMARY : See Review

DISSOLUTION : See Submission

DSI INSPECTION STATUS

Inspection needed: YES / NO	Inspection status:	Inspection results:
First Generic ~~X~~	Inspection requested: (date)	
New facility X	Inspection completed: (date)	
For cause		
Other		

PRIMARY REVIEWER : Andre Jackson BRANCH : I

INITIAL : DATE : 2/9/2000

TEAM LEADER : Y.C. Huang BRANCH : I

INITIAL : DATE : 2/9/2000

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : DATE : 2/16/00

4.1 Smelva

Methotrexate Sodium
15 mg, 10mg, 7.5mg
and 5 mg Tablets
ANDA # 40-385

Barr Laboratories
Pomona, N.Y.
Submission Date:
April 14, 2000

Reviewer: André Jackson
V:\Firmsam\Barr\Ltr&Rev\40385A.400

Review of A Study Amendment for the 15 mg Bioequivalence Study: A Request for Dissolution Waiver for 10 mg and 7.5 mg Tablets

RLD: Methotrexate Sodium Tablets 2.5 mg

BACKGROUND:

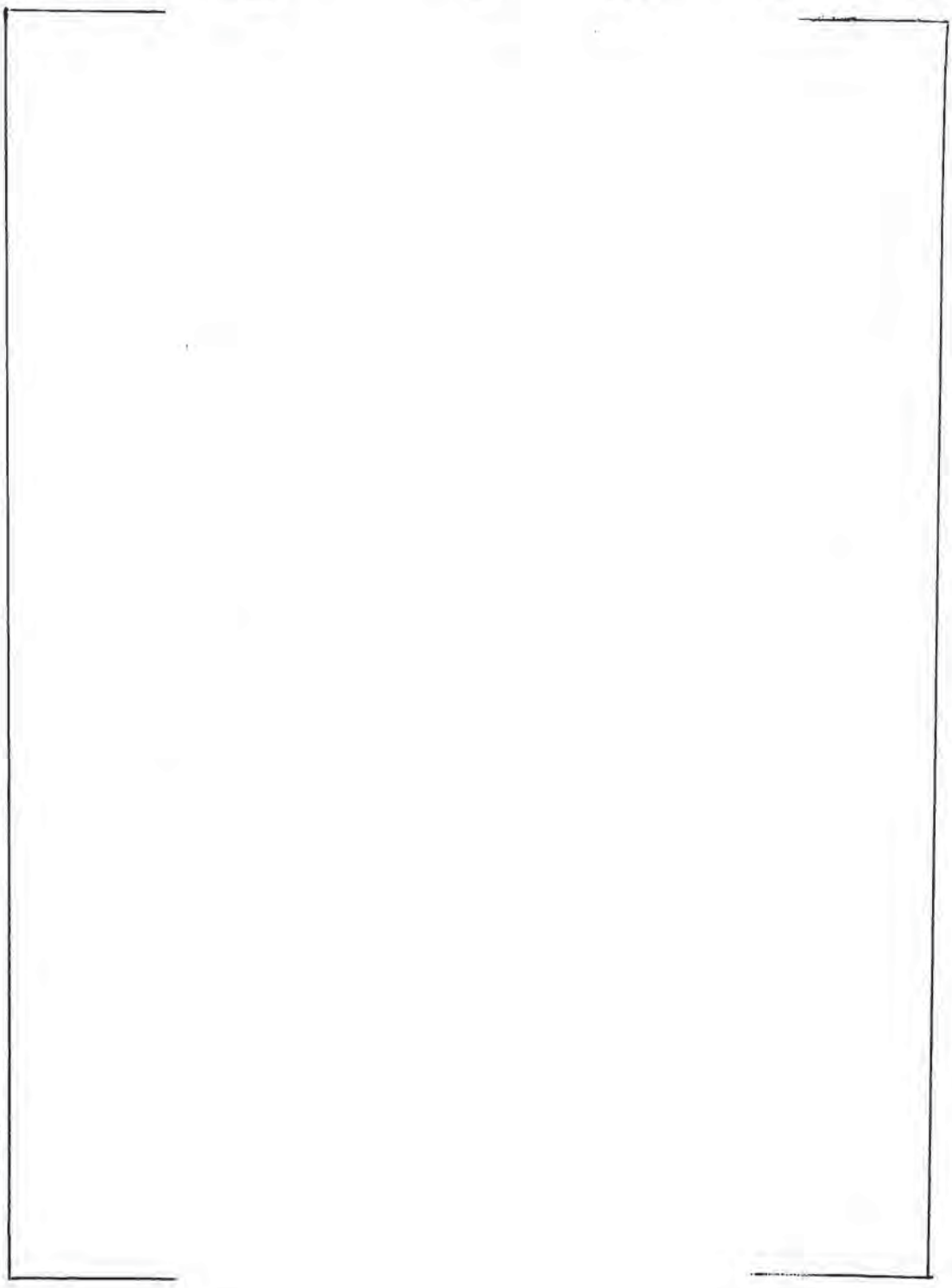
The firm filed a suitability petition on July 7, 1997 for the submission of 5 mg, 7.5 mg, 10 mg, 12.5 mg and 15 mg methotrexate sodium tablets. The petition was granted and the firm has submitted a study on the 15 mg strength and a request for waiver on the 5 mg strength. The other strengths were withdrawn. The 15 mg study was reviewed and found to be acceptable by the Division of Bioequivalence but the approval is pending in OGD. Barr has submitted the current request for waiver for 10 mg and 7.5 mg tablets based upon the submitted 15 mg study. In addition, Barr is also submitting documentation to provide for an alternate source of drug substance. In accordance with FDA Policy and Procedure Guide #22-90, "Interim Policy on Exemptions to the Batch-Size and Production Condition Requirements for Non-Antibiotic, Solid Oral-Dosage Form Drug Products Supporting Proposed ANDAs" (9/13/90). Barr made one batch of the 15 mg strength (bioequivalency batch strength) with the ——— material and placed it into its stability program (controlled room temperature and accelerated conditions). In addition, a dissolution profile was generated comparing the enclosed ——— material test batch with Barr's ——————— material bioequivalency batch.

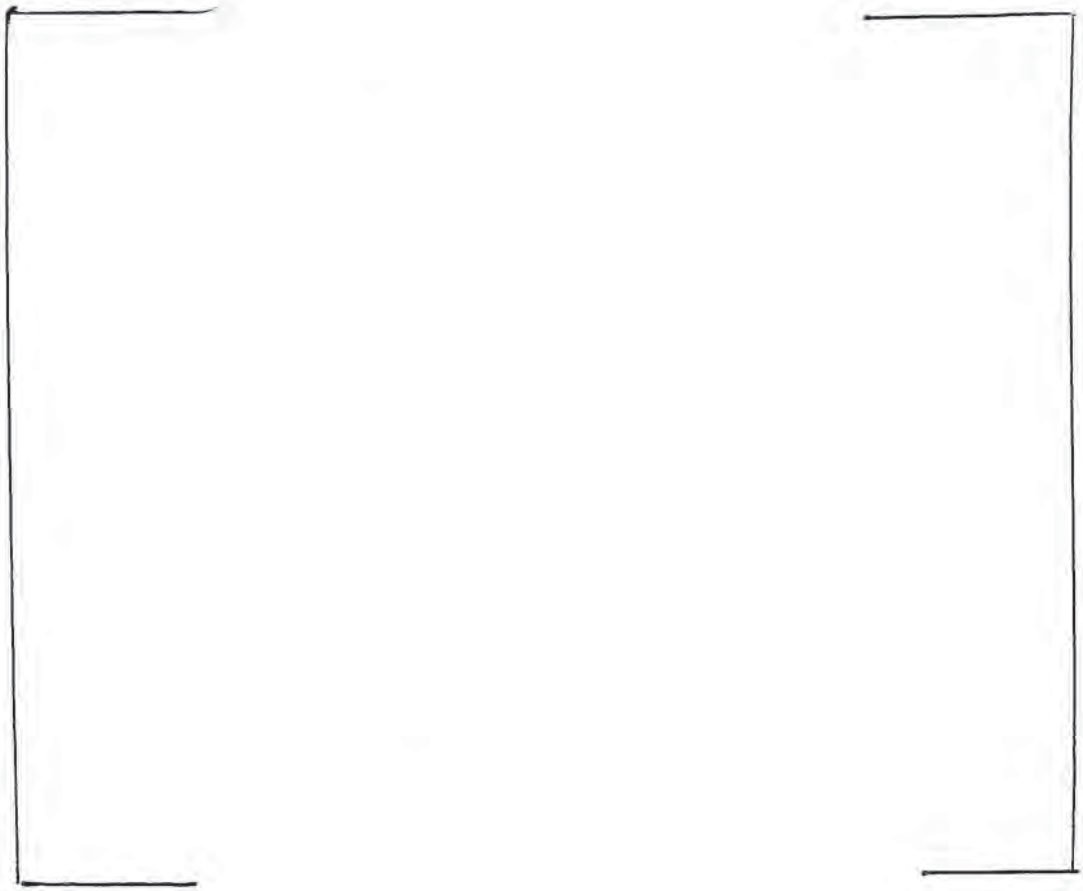
Formulation data

The following table compares the formulation (mg/dose) of Methotrexate Tablets, USP 7.5 mg, 10

mg with that of the 5 mg and 15 mg (bioequivalence) strengths submitted in the original application.

Ingredient	5 mg	7.5 mg	10 Mg	15 mg
Core:				
Methotrexate, USP[a]	5	7.5	10	15





Comments:

1. The active and inactive ingredients and their concentrations for the 10 mg and 7.5 mg tablets are compositionally proportional to the 15 mg tablet which underwent a bioequivalence study.

2. Pursuant to 21 CFR 320.22(d)(2) the request for waiver of the in vivo bioequivalence requirements for the 10 mg and 7.5 mg tablets may be granted based upon the final approval of the 15 mg bioequivalence study by OGD.

3. The f2 values for the dosage strengths were estimated to be:

Tablet Strength	vs Reference Strength	Tablet Strength	vs Test 15 mg Strength
15 mg	35.23	10 mg	70.9

10 mg	40.83	7.5 mg	62.1
7.5 mg	39.61	-----	
5 mg	35.36	-----	

These values were calculated using the mean data since the per cent coefficients of variation for the earlier time points were less than 20% and other time points were also less than 10%. The F2 values versus the same strength reference are below 50. However, the F2 values using the test product 15 mg tablet (i.e., biostudy strength) as the reference are above 50. In both cases, the F2 values are not problematic since 90% dissolution is achieved within 20 min.

4. The firm submitted dissolution data comparing the 10 mg strength with 4x2.5 mg tablets of the reference and the 7.5 mg strength compared to 3x2.5 mg reference tablets. The results were similar to those versus 1 tablet of reference.

5. The dissolution data submitted for the 15 mg tablet manufactured from the alternate source, ———, is comparable to that from the original source ———.

RECOMMENDATIONS:

1. The dissolution testing conducted by Barr on its 10 mg methotrexate sodium tablet, lot 409299R01 and its 7.5 mg, methotrexate sodium tablet, lot 409289R01 and is acceptable. The firm has conducted an acceptable in vivo bioavailabilty study comparing its 15 mg tablet of the test product with 6 x 2.5 mg tablets of the reference product methotrexate sodium manufactured by ESI Lederle. The formulations for the 10 mg and 7.5 mg strengths are proportionally similar to the 15 mg strength of the test product which underwent bioavailability testing. The waiver of the in vivo bioavailibility study requirements for the 10 mg and 7.5 mg tablet is granted pending approval of the 15 mg study by OGD.

2. The dissolution testing for the 15 mg tablet lot # 409459R01 of the test Barr product manufactured with the ——— drug substance comparing it to the 15 mg tablet lot #

409457R01 of the Barr product manufactured with the ——— drug substance and used in the bioequivalence study is acceptable. The waiver of the in vivo bioavailibility study requirements for the Barr methotrexate 15 mg tablet product manufactured with the ——— drug substance is granted pending approval of the 15 mg study by OGD.

2.The dissolution testing should be incorporated into the firm's manufacturing and controls programs. The dissolution testing should be conducted in 900 ml of 0.1N HCL at 37°C using USP XXIV apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

NLT 75% of methotrexate is dissolved in 45 min

André J. Jackson, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang
FT INITIALED YCHuang

Date 5/23/2000

Concur:

Date 6/1/00

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

ANDA 40-385 (original, duplicate), HFD 652(Jackson), Drug file, Division File, HFD-650(Division Director).

Dissolution Conditions:

USP XX~~III~~ IV Basket: Paddle: x RPM: 50
No. Units Tested: 12
Medium: 0.1N HCL
Wavelength: 306 nm
Volume: 900 mL
Specifications:
NLT 75% in 45 min
Reference Drug: Methotrexate sodium
Assay Methodology: UV Spectroscopy
THIS IS A USP METHOD

IN-Vitro COMPARATIVE DISSOLUTION STUDY

Sampling Times (Minutes)	Test Product Lot # 409289R01 Strength 7.5 mg					Reference Product Lot # 457-037 Strength 2.5 mg					
	% Dissolved						% Dissolved				
Sample No.	10 min.	20 min.	30 min.	45 min.	75* min.	Sample No.	10 min.	20 min.	30 min.	45 min.	75* min.
1						1					
2						2					
3						3					
4						4					
5						5					
6						1					
7						7					
8						8					
9						9					
10						10					
11						11					
12						12					
Mean	89	92	94	95	96	Mean	57	94	95	93	94
Max	95	98	99	100	101	Max.	60	101	98	98	100
Min.	81	86	88	90	91	Min.	53	90	91	75	8 3
%RSD.	4.6	4	3.7	3.3	3	%RSD.	4.8	2.9	2.2	6.8	5

*Additional time point at the same rotation speed.

IN-Vitro COMPARATIVE DISSOLUTION STUDY

Sampling Times (Minutes)	Test Product Lot # 409299R01 Strength 10 mg					Reference Product Lot # 457-037 Strength 2.5 mg					
	% Dissolved						% Dissolved				
Sample No.	10 min	20 mm.	30 min.	45 min.	75* min.	Sample No.	10 min.	20 min.	30 min.	45 min.	75* min
1						1					
2						2					
3						3					
4						4					
5						5					
6						6					
7						7					
8						8					
9						9					
10						10					
11						11					
12						12					
Mean	87	90	92	93	95	Mean	57	94	95	93	94
Max.	93	96	97	98	99	Max.	60	101	98	98	100
Min.	78	84	86	88	90	Min.	53	90	91	75	83
%RSD.	5.9	4.6	3.9	3.7	3.2	%RSD.	4.8	2.9	2.2	6.8	5

*Additional time point at the same rotation speed.

Sampling Times (Minutes)	Test Product Lot # 409459R01 Strength 15 mg					Reference Product Lot # 409457R01 Strength 15 mg					
	% Dissolved					% Dissolved					
Sample No.	10 min.	20 min.	30 min.	45 min.	75* min.	Sample No.	10 min.	20 min.	30 min.	45 min.	75* min.
1						1					
2						2					
3						3					
4						4					
5						5					
6						1					
7						7					
8						8					
9						9					
10						10					
11						11					
12						12					
Mean	92	94	95	96	96	Mean	83	88	89	90	91
Max	94	95	96	97	97	Max.	95	96	96	96	96
Min.	85	93	94	94	95	Min.	69	80	82	83	8 5
%RSD.	2.5	0.8	0.8	0.9	0.8	%RSD.	10.1	5.6	5.0	4.4	3.7

APPEARS THIS WAY

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA 40-385 APPLICANT: Barr Laboratories

DRUG PRODUCT: Methotrexate 15mg, 10mg, 7.5mg and 5.0mg Tablets

The Division of Bioequivalence has completed its review and has no further questions at this time.

However, the waiver can not be granted until the 15 mg tablet has been approved.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 24.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

#2

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 40-385 SPONSOR :Barr Laboratories, Inc.

DRUG AND DOSAGE FORM : Methotrexate Sodium Tablets

STRENGTH(S) : 15mg, 10 mg, 7.5 mg and 5.0 mg

TYPES OF STUDIES : Single Dose BA study on 15 mg / waiver on 10 mg 7.5 mg and 5 mg

CLINICAL STUDY SITE(S) :1.

2.

3.

ANALYTICAL SITE(S) :

STUDY SUMMARY : See Review(Approval was pending DSI inspection completed on (9/29/2000)

DISSOLUTION : See Submission

DSI : Acceptable Y/N

DSI INSPECTION STATUS

Inspection needed: YES / NO	Inspection status:	Inspection results:
First Generic ____	Inspection requested: (date)	
New facility ____	Inspection completed: (date)	
For cause ____		
Other ____		

PRIMARY REVIEWER : Andre Jackson BRANCH : I

INITIAL : a/j DATE : 12/4/2000

TEAM LEADER : Y.C. Huang BRANCH : I

INITIAL : YCH DATE : 12/4/2000

for DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : Barbara McCall DATE : 12/5/00

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-385

ADMINISTRATIVE DOCUMENTS

a request for

EDL
3/6/01

RECORD OF TELEPHONE CONVERSATION

Barr Laboratories received a minor amendment on 2/6/01. The firm submitted a fax to the Agency to request a telecon to discuss comment 2 of the deficiency letter. (see attached fax).

Mike Smela reviewed the fax and I telephoned the firm and left the following voice mail message for Mr. Sharif Ahmed: It is policy to require full term data if accelerated show adverse trends.

DATE February 13, 2001
ANDA NUMBER 40-385
IND NUMBER
TELECON
INITIATED BY **SPONSOR X** **FDA**
PRODUCT NAME Methotrexate Tablets USP
FIRM NAME Barr Laboratories
NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD Sharif Ahmed
TELEPHONE NUMBER (913) 353-8476
SIGNATURE M.Dillahunt M Dillahunt 2/13/01

V:\FIRMSAM\BARR\TELECONS\40385tcon.4.doc

CC: ANDA 40-385
Chem Div I, T-con Notebook

a request for

ESS

3/6/01

RECORD OF TELEPHONE CONVERSATION

Barr Laboratories received a minor amendment on 2/6/01. The firm submitted a fax to the Agency to request a telecon to discuss comment 2 of the deficiency letter. (see attached fax) even though they already have submitted a response.

Ms. Christine Mundkur of Barr Laboratories stated she needed clarification regarding comment#2. Ms. Mundkur stated there was no trending down in CRT for the 5 mg and 15 mg of the original batches. Ms. Mundkur felt this data could be used to support stability for the 7.5 mg, 10 mg and 15 mg strengths of the alternate vendor.
Mr. Smela informed her the Agency does not allow generic firms to matrix strengths at this time.
Mr. Smela stated that it is policy to require full term data if accelerated data show adverse trends.

Mr. Smela stated that the firm had the option of reducing their expiration date, and or/withdrawing the alternate supplier.

The firm questioned what is meant by adverse trend.
Mr. Smela stated ICH has a definition for significant change in the stability guidance, however it is currently not implemented in OGD and a significant change is defined on a case by case basis.

Mr. Smela also informed the firm the chemistry reviewer is on leave for 2 weeks. If there is no additional information submitted to their application regarding comment 2, the firm will likley receive another not approvable letter.

Ms. Mundkur stated the firm will amend the ANDA before 2 weeks.

DATE
February 21, 2001

ANDA NUMBER
40-385

IND NUMBER

TELECON

INITIATED BY

SPONSOR X

FDA

PRODUCT NAME
Methotrexate Tablets USP

FIRM NAME
Barr Laboratories

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Sharif Ahmed
Christine Mundkur

TELEPHONE NUMBER
(913) 353-8476

SIGNATURE

M.Smela M.Smela 2/21/01
M.Dillahunt 2/21/01

V:\FIRMSAM\BARR\TELECONS\40385tcon.5.doc
CC: ANDA 40-385
Chem Div I, T-con Notebook

Telecon

RECORD OF TELEPHONE CONVERSATION

The firm received a major amendment on 3/9/2000. The firm submitted a fax to the Agency on 3/23/2000 requesting a telecon to discuss chemistry comment #14. (see attached fax)

Please provide stability data for both tablet strengths packaged in the actual container sizes, 30's and 60's, and using the same closure, CRC, that will be used for marketing. It is not acceptable to bracket stability studies using presentations that are not proposed in the ANDA nor intended market.

Mike Smela informed the firm the stability data pre and post approval should include the smallest and largest container/closure proposed for marketing. The firm can bracket container/closures as long as they are the same, except for size including closures and liners.
Mr. Smela also informed the firm that their post approval stability protocol must be consistent with any changes made in the ANDA. Labeling is also needed for all container/ closures.

The firm had a question about the tradename they propose to use for their product.
Mr. Smela referred the firm to contact John Grace for questions about the tradename.

DATE
March 28, 2000

ANDA NUMBER
40-385

IND NUMBER

TELECON

INITIATED BY

X **SPONSOR**

FDA

PRODUCT NAME
Methotrexate Tablets 5mg and 15 mg

FIRM NAME
Barr Laboratories

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Christine Mundker
Sharif Ahmed

TELEPHONE NUMBER
(914) 353-8432

SIGNATURE
M.Dillahunt 5/25/00
M.Smela

V:\FIRMSAM\BARR\TELECONS\40385.tcon3.doc

.CC: ANDA 40-385
Division File
Chem Div I, T-con Notebook

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-385

CORRESPONDENCE

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

July 23, 1999

505(b)(2)(A) 04
9/21/99

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

REFERENCE: ABBREVIATED NEW DRUG APPLICATION
METHOTREXATE TABLETS, USP
5 MG AND 15 MG

In accordance with the regulations promulgated under 505 (j) of the Food, Drug and Cosmetic Act, and as amended, Barr Laboratories, Inc. is submitting this Abbreviated New Drug Application for Methotrexate Tablets, USP 5 mg and 15 mg.

On June 24, 1999, the Office of Generic Drugs refused to file Barr's ANDA 40-370 for Methotrexate Tablets, USP 5 mg, 7.5 mg, 10 mg and 15 mg on the ground that one batch of each strength were not made with the primary source of drug substance. At this time, Barr is submitting this application for Methotrexate Tablets, USP 5 mg and 15 mg, containing supporting data from one batch of each strength manufactured with a single source of drug substance.

Barr's Abbreviated New Drug Application for Methotrexate Tablets, USP 5 mg and 15 mg is based on a suitability petition, Docket No 97P-0279/CP1, filed by Pitney, Hardin, Kipp & Szuch for Methotrexate Sodium Tablets, 5 mg, 7.5 mg, 10 mg, 12.5 mg and 15 mg (base) and approved by the Agency on August 22, 1997.

The application is provided in duplicate, as an archival copy, and a review copy. The archival copy of the application is contained in blue binders and consists of 10 volumes. The chemistry, manufacturing and controls part of the review copy is contained in red binders and consists of 4 volumes. The bioequivalence part of the review copy is contained in orange binders and consists of 7 volumes.

Included in this application and in accordance with the Generic Drug Enforcement Act of 1992, are Debarment Certification Statements from Barr and outside contractors. A Field Copy of this application has been forwarded to the Maryland District Office. A Field Copy Certification is also provided in this application.

Certifications of financial interests and arrangements of clinical investigators conducting the bioequivalence study are provided in Section VI.

The CMC section of this application will be provided in electronic format within 30 days from this date. Barr Laboratories, Inc. will, at that time, provide a declaration that the information in the electronic submission is the same as the information provided in the paper submission.

METHOTREXATE TABLETS, USP
5 MG AND 15 MG

The format of this application is in accordance with Office of Generic Drug's Guidance for Industry: Organization of an ANDA, dated February 1999. The information submitted in this application is also in accordance with the October 14, 1994 communication from Dr. Janet Woodcock, (CDER) and Mr. Ronald Chesemore (ORA).

If you have any questions concerning this application, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859. Your earliest acknowledgment to this application will be very much appreciated.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality
and Regulatory Counsel

mb

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

August 6, 1999

NEW CORRESP

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

40 - 385
RW

REFERENCE: METHOTREXATE TABLETS, USP
5 MG AND 15 MG
AMENDMENT: CMC ELECTRONIC SUBMISSION

Reference is made to our Abbreviated New Drug Application submitted July 23, 1999 under 505(j) of the Food, Drug and Cosmetic Act for Methotrexate Tablets, USP 5 mg and 15 mg.

As indicated in our original application, Barr Laboratories, Inc. is amending the above referenced application to provide the CMC electronic submission. The CMC electronic submission is contained on a single diskette labeled "ESD & Companion Document". A backup diskette containing identical information is also provided. The ESD file is named "Brl9901.003" and the MicroSoft Word Companion Document file is named "Brl9901.004".

Barr Laboratories, Inc. declares that the information provided in the electronic submission is the same as the information provided in the paper submission.

A copy of this letter has been forwarded to the Baltimore District Office.

If you have any questions concerning this application, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859. Your earliest acknowledgment to this application will be very much appreciated.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur

Christine Mundkur
Vice President, Quality
and Regulatory Counsel

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
AUG 1999

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

September 20, 1999

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NEW CORRESP
NC

REFERENCE: ANDA 40-385
METHOTREXATE TABLETS, USP
5 MG AND 15 MG
GENERAL CORRESPONDENCE

Reference is made to our Abbreviated New Drug Application 40-385 for Methotrexate Tablets, USP 5 mg and 15 mg, submitted on July 23, 1999. Reference is also made to the September 8, 1999 discussion with Lt. Gregory Davis of the Office of Generic Drugs.

As requested by the Agency, following is a list of sites used in conducting the bioequivalence study for Methotrexate Tablets, 15 mg.

	Facilities	**Function**
1.	[redacted]	Clinical Site
2.		Clinical Site
3.		Clinical Site
4.		Clinical Site
5.		Laboratory for Screening and Safety Tests
6.		Laboratory for Screening and Safety Tests

	Facilities	Function
7.	[redacted]	Laboratory for Screening and Safety Tests
8.		Laboratory for Screening and Safety Tests
9.		Bio-analytical method development and validation, bio-analytical testing and statistical analysis

If you have any questions concerning this correspondence, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality
and Regulatory Counsel

2.1

ANDA 40-385

Barr Laboratories, Inc.
Attention: Christine Mundkur
2 Quaker Road
P.O. Box 2900
Pomona, NY 10970

SEP 21 1999

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the telephone conversation dated September 8, 1999 and your correspondence dated September 20, 1999.

NAME OF DRUG: Methotrexate Tablets USP, 5 mg and 15 mg

DATE OF APPLICATION: July 23, 1999

DATE (RECEIVED) ACCEPTABLE FOR FILING: July 28, 1999

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Michelle Dillahunt
Project Manager
(301) 827-5848

Sincerely yours,

for

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 40-385
cc: DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-92
HFD-615/M.Bennett
Endorsement:
HFD-615/NMahmud, Chief, RSB _____ date 9/21/99
HFD-615, GDavis, CSO _____ date 9/21/99
HFD-600, MSmela, Sup. Chem. _____ date
Word File v:\firmsam\barr\ltrs&rev\40385.ack
FT\njg\9\21\99
ANDA Acknowledgment Letter!

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773
Attn: Elaine Hu

October 7, 1999

NDA DRUG AMENDMENT
KB

REFERENCE: ANDA 40-385
METHOTREXATE TABLETS, USP
5 MG AND 15 MG
TELEPHONE BIOEQUIVALENCE AMENDMENT

Reference is made to our Abbreviated New Drug Application 40-385 for Methotrexate Tablets, USP 5 mg and 15 mg, submitted on July 23, 1999. Reference is also made to the September 23, 1999 discussion with Elaine Hu of the Office of Generic Drugs.

As requested by the Agency, Barr is providing a revised diskette and a backup copy that contain the two additional fields for the study sites and groups to the tables containing the pharmacokinetic data and are provided in Attachment 1. Comprehensive lists of clinical sites and their function related to the bioequivalence study for Methotrexate Tablets, 15 mg have also been clarified and are provided in Attachment 2.

If you have any questions concerning this correspondence, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality
and Regulatory Counsel

CENTER FOR DRUG
RECD
OCT 0 8 1999

MAJOR AMENDMENT

ANDA 40-385

MAR 9 2000

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Barr Laboratories, Inc. PHONE: (914) 362-1100

ATTN: Christine Mundkur FAX: (914) 353-3859

FROM: Michelle Dillahunt PROJECT MANAGER (301) 827–5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated July 23, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methotrexate Tablets USP, 5 mg and 15 mg .

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (4 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MAJOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If this represents a second or greater occasion upon which significant (MAJOR) deficiencies have been identified, please contact the Project Manager within 30 days for further clarification or assistance.

SPECIAL INSTRUCTIONS:

CMC and Labeling Comments Included

X:\new\ogdadmin\macros\faxmaj.frm

5/9/00 MM

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information from

3/9/2000 FDA FAX

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 40-385 Date of Submission: July 23, 1999
Applicant's Name: Barr Laboratories, Inc.
Established Name: Methotrexate Tablets USP, 5 mg and 15 mg
Proposed Proprietary Name: ———
Labeling Deficiencies:

1. GENERAL COMMENTS – Your proposed proprietary name has been found unacceptable based on 21 CFR 201.10(c)(5). It sounds like or looks like the following proprietary names already on the market: ———. Please remove it from all labels and labeling.

2. CONTAINER (30's and 60's)

   i. Caution- Revise the second and third sentences in this section to read as follows:

   Prescriptions should not be written or refilled on a PRN basis. Refill of prescriptions should be by direct order (written or oral) of the physician only. See Boxed Warnings for complete directions for use.

   ii. Include the statement "KEEP OUT OF REACH OF CHILDREN."

3. UNIT DOSE BLISTER (1's)- See comment under GENERAL COMMENTS.

4. UNIT DOSE BLISTER CARTON (1 x 5 mg, and ——— - See comments under GENERAL COMMENTS and (ii) under CONTAINER.

5. PROFESSIONAL SAMPLE DISPENSER (10 x 1[5 mg] and ——— - See comments under GENERAL COMMENTS and (ii) under CONTAINER.
6. INSERT
   a. Revise your insert to be in accord with the most recent labeling for the reference listed drug, Methotrexate Tablets USP (Lederle; NDA# 08-085/S0048; approved October 29, 1999). The labeling may be obtained from Freedom of Information or the following website – http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html.
   b. See comment under GENERAL COMMENTS.

Please revise your labels and labeling, as instructed above, and submit 4 copies of draft labels and labeling. We will not request final print labels and labeling until a determination has been made regarding the acceptability of your proposed proprietary name.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes- http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained.

Robert L. West, M.S., R.Ph
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

barr Laboratories, Inc.

2 Quaker Road
P.O. Box 2900
Pomona, NY 10970
914-362-1100

Fax Transmission

Date: March 23, 2000

To: Michelle Dilahunt
Project Manager, OGD

Phone Number: (301) 827-5848
Fax Number: (301) 594 -0180

From: Sharif Ahmed
Manager of Regulatory Affairs
Barr Laboratories, Inc.

Phone Number: (913) 353-8476
Fax Number: (914) 353-3859

Pages 1

Message:

Reference is made to our ANDA 40-385 for Methotrexate Tablets, USP 5 mg and 15 mg submitted on July 23, 1999. Reference is also made to a Major Amendment dated March 9, 2000. We are sending this facsimile to request a discussion with the review branch concerning comment 14.

In view of a recent partnership agreement with DuPont Pharmaceuticals, Barr has revised its marketing strategy for Methotrexate Tablets, 5 mg and 15 mg. Once approved, DuPont will market Methotrexate Tablets, 5 mg and 15 mg. According to this arrangement, Barr would like to manufacture Methotrexate Tablets, 5 mg and 15 mg in containers of 4, 30, 60 and 100 tablets [redacted] containers of 4 tablets [redacted] will be used as professional samples. The containers of 30, 60 and 100 tablets will be sold in the market. Therefore, Barr would be seeking approval for the Methotrexate Tablets, 5 mg and 15 mg in containers of 4, 30, 60 and 100 tablets [redacted]

The submission batches of Methotrexate Tablets, USP 5 mg and 15 mg were packaged in containers of 4 tablets and 100 tablets. The same container closure system was used for the packaging of these two configurations. The stability data generated for these packaging configurations brackets the packaging configurations proposed for commercial production.

Since Barr would now be seeking approval for all of the above mentioned package sizes, we believe this meets requirements for submission of stability data. However, we would like to confirm if this addresses the reviewer's concern expressed in comment 14. We will appreciate if you would arrange a teleconference with the review branch.

Verification Name/Number: _____

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

April 14, 2000

ORIG AMENDMENT
N/Ac

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

REFERENCE: **ANDA 40-385**
Methotrexate Tablets, USP 5 mg and 15 mg
Additional Strengths: Methotrexate Tablets, USP 7.5 mg and 10 mg
MAJOR AMEDMENT

Reference is made to our Abbreviated New Drug Application 40-385, submitted on July 23, 1999, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Methotrexate Tablets, USP 5 mg and 15 mg. Reference is also made to your facsimile dated March 9, 2000. The deficiencies identified in the facsimile and our responses are as follows:

CHEMISTRY DEFICIENCIES

A. Deficiencies

COMMENT 1:

[redacted]

RESPONSE:

[redacted]

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information from

4/14/2000 BARR LETTER

COMMENT

Please revise your labels and labeling, as instructed above, and submit 4 copies of draft labels and labeling. We will not request final print labels and labeling until determination has been made regarding the acceptability of your proposed proprietary name.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes- http:/www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.04 (a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained.

RESPONSE:

As requested by the Agency, Barr is providing 4 copies of draft labeling in Section V. To facilitate review, and in accordance with 21 CFR 314.04 (a)(8)(iv), side-by-side comparisons of our proposed labeling with the previously submitted labeling are provided in Section IV.

APPEARS THIS WAY
ON ORIGINAL

The CMC and Bioequivalence section of this application will be provided in electronic format within 30 days from this date. Barr Laboratories, Inc. will, at that time, provide a declaration that the information in the electronic submission is the same as the information provided in the paper submission.

A Field Copy of this application has been forwarded to the Baltimore and Philadelphia District Offices. A Field Copy Certification is also provided.

This completes the present Major Amendment. If you have any questions, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and Regulatory Counsel

MINOR AMENDMENT

NOV 13 2000

ANDA 40-385

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Barr Laboratories, Inc.

TEL: (914) 362-1100

ATTN: Christine Mundkur

FAX: ~~(914)~~ (845) 353-3859

FROM: Michelle Dillahunt

PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated July 23, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methotrexate Tablets USP, 5 mg, 7.5 mg, 10 mg 15 mg.

Reference is also made to your amendment dated April 14, 2000.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (5 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS: Chemistry and labeling Comments Included.

11/9/00

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information from

11/13/2000 FDA FAX

8. [redacted]

9.

10.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Your response must also address the labeling deficiencies.

2. A satisfactory establishment evaluation is necessary for approval. We have requested an evaluation from the Office of Compliance.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

January 12, 2001

N/AM

ORIG AMENDMENT

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

REFERENCE: **ANDA 40-385**
METHOTREXATE TABLETS, USP 5 MG, 7.5 MG, 10 MG & 15 MG
MINOR AMENDMENT

Reference is made to our Abbreviated New Drug Application 40-385 dated July 23, 1999 and submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Methotrexate Tablets, USP 5 mg, 7.5 mg, 10 mg and 15 mg. Reference is also made to your facsimile dated March 9, 2000, Barr's major amendment dated April 14, 2000 and your facsimile dated November 13, 2000. The deficiencies identified in the November 13, 2000 facsimile and our responses are as follows:

A. DEFICIENCIES

COMMENT 1:

DMF _____ has been found deficient. The DMF holder has been notified by separate letter. Please respond to this deficiency only after you have learned that the DMF holder has responded.

RESPONSE:

_____ the holder of DMF ____ has responded to the deficiencies on January 12, 2001.

COMMENT 2:

DMF _____ ., has been found deficient. The DMF holder has been notified by separate letter. Please respond to this deficiency only after you have learned that the DMF holder has responded.

RESPONSE:

_____, the holder of DMF ____ has responded to the deficiencies on November 13, 2000.

MW 1-22-01

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of trade secret and/or

confidential commercial

information from

1/12/2001 BARR LETTER

LABELING DEFICIENCIES:

COMMENT 1:

GENERAL COMMENTS – Your proposed proprietary names are under review. We defer comment at this time.

COMMENT 2:

CONTAINER (30's, 60's and 100's)

i. Storage Temperature Recommendation – include "Protect from light.".

ii. Warnings – Delete '[redacted].

COMMENT 3:

PHYSICIAN'S SAMPLE BOTTLE (4's) – See comments under CONTAINER.

COMMENT 4:

PHYSICIAN'S SAMPLE UNIT DOSE BLISTER (1's) – See GENERAL COMMENTS.

COMMENT 5:

PHYSICIANS'S SAMPLE UNIT DOSE BLISTER CARTON (1's) – See GENERAL COMMENTS.

COMMENT 6:

PHYSICIAN'S SAMPLE DISPENSER (10 unit dose cartons per dispenser) – See comments under GENERAL COMMENTS.

COMMENT 7:

INSERT

a. See GENERAL COMMENTS.

b. INDICATIONS AND USAGE

i. Neoplastic Diseases – Delete [redacted]

c. PRECAUTIONS (Information for Patients) – Second paragraph – Delete the penultimate sentence which reads, "[redacted] Your product is not [redacted]

d. PRECAUTIONS (Organ System Toxicity; Neurologic) – Include the following to appear as the second and third sentences of paragraph one of this subsection:

Serious neurotoxicity, frequently manifested as generalized or focal seizures, has been reported with unexpectedly increased frequency among pediatric patients with acute lymphoblastic leukemia who were treated with intermediate – dose intravenous methotrexate (1 gm/m^2). Symptomatic patients were commonly noted to have leukoencephalopathy and/or microangiopathic calcifications on diagnostic imaging studies.

COMMENT 7 (continued)

NOTE: Although you are not seeking approval for the indication referenced above, we feel that it is important information for safe use of the drug. Although seizures are only documented in this situation, it may be reasonable that this could occur in other situations.

e. **ADVERSE REACTIONS (Adverse reactions in Psoriasis) – Include the following to appear as the last sentence in this subsection:**

Rarely, painful plaque erosions may appear (Pearce, HP and Wilson, BB: *Am Acad Dermatol* 35" 835-838, 1996).

f. **DOSAGE AND ADMINISTRATION (Psoriasis and Rheumatoid Arthritis) Revise the second paragraph of this subsection to read as follows:**

Weekly therapy may be instituted to provide doses over a range of 5 mg to 15 mg administered as a single weekly dose. All schedules should be continually tailored to the individual patient. An initial test dose may be given prior to the regular dosing schedule to detect any extreme sensitivity to adverse effects (see ADVERSE REACTIONS). Maximal myelosuppression usually occurs in seven to ten days.

Please revise your labels and labeling, as instructed above, and submit 4 copies of draft labels and labeling. We will not request final print labels and labeling until a determination has been made regarding the acceptability of your proposed proprietary name.

RESPONSE:

Barr has revised the labels and labeling as requested by the Agency. Please note that Barr received a telephone call on August 8, 2000 from Ms Theresa Watkins of Labeling Review Branch regarding the review of our proposed proprietary names. Ms Watkins informed that Trexall™ was found to be acceptable by the review committee. Upon receipt of this comment letter, Barr contacted Ms Watkins on November 16, 2000 to confirm the status of the proposed proprietary name. Ms Watkins confirmed that the proprietary name Trexall™ has been approved by the Agency and Barr could submit final printed labeling. Based on our discussion with Ms Theresa Watkins, we are providing final printed labeling in this amendment in Attachment 7. Side by side comparisons of the final printed labeling for Trexall™ with the previously submitted draft labeling for Trexall™ are also provided.

This amendment will be provided in electronic format within 30 days from the date of this letter. Barr Laboratories, Inc. will at that time, provide a declaration that the information in the electronic submission is the same as the information provided in the paper submission.

A Field Copy of this amendment has been forwarded to the Baltimore District Office. A Field Copy Certification is also provided.

This completes the present Minor Amendment. If you have any questions, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and Regulatory Counsel

Document Certification

Barr Laboratories, Inc. hereby certifies that field copy of this Minor Amendment for Methotrexate Tablets, USP 5 mg, 7.5 mg, 10 mg and 15 mg is being submitted to the Baltimore District office of the FDA. Barr Laboratories, Inc. further certifies that the field copy is a true copy of the material submitted to the Agency.

Christine Mundkur
Vice President, Quality and Regulatory Counsel
Barr Laboratories, Inc.

Jan. 12, 2001
Date

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

February 2, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NEW CORRESP
NC

REFERENCE: **ANDA 40-385**
METHOTREXATE TABLETS, USP 5 MG, 7.5 MG, 10 MG & 15 MG
GENERAL CORRESPONDENCE

Reference is made to our Abbreviated New Drug Application 40-385 dated July 23, 1999 and submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Methotrexate Tablets, USP 5 mg, 7.5 mg, 10 mg and 15 mg. Reference is also made to your facsimile dated November 13, 2000 and Barr's minor amendment dated January 12, 2001.

As per a discussion between Ms. Angela Payne of the Labeling Review Branch, OGD, and Sharif Ahmed of Barr Laboratories, Inc. on February 2, 2001, we are submitting this correspondence to provide a revised package brochure.

Please note that in the labeling deficiency comment 7 d. of the November 13, 2000 facsimile, FDA requested the following:

> d. **PRECAUTIONS (Organ System Toxicity; Neurologic) – Include the following to appear as the second and third sentences of paragraph one of this subsection:**
>
> **Serious neurotoxicity, frequently manifested as generalized or focal seizures, has been reported with unexpectedly increased frequency among pediatric patients with acute lymphoblastic leukemia who were treated with intermediate – dose intravenous methotrexate (1 gm/m^2). Symptomatic patients were commonly noted to have leukoencephalopathy and/or microangiopathic calcifications on diagnostic imaging studies.**

Barr mistakenly "replaced" the second and third sentences of the paragraph with the above sentences instead of "adding" them and submitted the labeling in the January 12, 2001 minor amendment. Barr is now submitting corrected labeling that includes the two sentences that were mistakenly replaced. A side by side comparison of the affected sections of the previous labeling and the proposed labeling is provided along with 12 copies of final print labeling.

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
FEB – 5 2001
OGD

We apologize for the mistake. If you have any questions, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and Regulatory Counsel

MINOR AMENDMENT

ANDA 40-385

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

FEB 6 2001

TO: APPLICANT: Barr Laboratories, Inc. TEL: (845) 362-1100

ATTN: Christine Mundkur FAX: (845) 353-3859

FROM: Michelle Dillahunt PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated July 23, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methotrexate Tablets USP, 5 mg, 7.5 mg, 10 mg, and 15 mg.

Reference is also made to your amendment(s) dated: January 12, 2001.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (1 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

2/6/01 MD

FEB 16 XXX

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-385 APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Methotrexate Tablets USP, 5mg, 7.5mg, 10mg, 15mg.

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1.

2.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

barr Laboratories, Inc.

2 Quaker Road
P.O. Box 2900
Pomona, NY 10970
914-362-1100

Fax Transmission

Date: February 8, 2001

To: Michelle Dillahunt
Project Manager
Phone Number: (301) 827-5848
Fax Number: (301) 594-0180

From: Sharif Ahmed
Manager of Regulatory Affairs
Phone Number: (913) 353-8476
Fax Number: (914) 353-3859

Number of Pages (including cover): 9

Message:

Please refer to our pending application ANDA 40-385 for Methotrexate Tablets, USP 5 mg, 7.5 mg, 10 mg and 15 mg and the deficiency letter of February 6, 2001. We would like to discuss comment 2 with the chemistry reviewer or the team leader. We want to make sure we understand the reason for Agency's concern expressed in this comment before we respond to this deficiency.

I will appreciate if you would set up a conference call. Please call us at (845) 353-8432 some time tomorrow morning or at your convenience. Christine Mundkur, Vice President of Quality and Regulatory Counsel and Sharif Ahmed, Manager of Regulatory Affairs will participate in the discussion. Please confirm when you will be calling so we will make ourselves available.

Sincerely,
Sharif Ahmed

Verification Name/Number: _____

MD
Pls advise them it is policy to require full term data if accelerated show adverse trends. If they still want TCon, set up for [illegible] since I do not know my [illegible]

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

February 15, 2001

NDA ORIG AMENDMENT
N/Am

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

REFERENCE: **ANDA 40-385**
METHOTREXATE TABLETS, USP 5 MG, 7.5 MG, 10 MG & 15 MG
MINOR AMENDMENT

Reference is made to our Abbreviated New Drug Application 40-385 dated July 23, 1999 and submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Methotrexate Tablets, USP 5 mg, 7.5 mg, 10 mg and 15 mg. Reference is also made to your facsimile dated March 9, 2000, Barr's major amendment dated April 14, 2000, your facsimile dated November 13, 2000, Barr's minor amendment dated January 12, 2001 and your facsimile dated February 6, 2001. The deficiencies identified in the February 6, 2001 facsimile and our responses are as follows:

A. DEFICIENCIES

COMMENT 1:

[redacted]

RESPONSE:

Following the Agency comment we reviewed our response to comment 7 and found that the statements made in the response was not accurate. We apologize for the inadvertent mistake and any confusion this may have caused. Following is a clarification regarding the validation study and response to the Agency comment 7.

[redacted]

Redacted 2 page(s)

of trade secret and/or

confidential commercial

information from

2/15/2001 BARR LETTER

Document Certification

Barr Laboratories, Inc. hereby certifies that a field copy of this Minor Amendment for Methotrexate Tablets, USP 5 mg, 7.5 mg, 10 mg and 15 mg is being submitted to the Baltimore District office of the FDA. Barr Laboratories, Inc. further certifies that the field copy is a true copy of the material submitted to the Agency.

Christine Mundkur
Vice President, Quality and Regulatory Counsel
Barr Laboratories, Inc.

2/15/01
Date

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

February 22, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NDA ORIG AMENDMENT

REFERENCE: **ANDA 40-385**
METHOTREXATE TABLETS, USP 5 MG, 7.5 MG, 10 MG & 15 MG
AMENDMENT TO FEBRUARY 15 MINOR AMENDMENT

Reference is made to our Abbreviated New Drug Application 40-385 dated July 23, 1999 and submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Methotrexate Tablets, USP 5 mg, 7.5 mg, 10 mg and 15 mg. Reference is also made to your facsimile dated March 9, 2000, Barr's major amendment dated April 14, 2000, your facsimile dated November 13, 2000, Barr's minor amendment dated January 12, 2001, your facsimile dated February 6, 2001 and Barr's minor amendment dated February 15, 2001.

Reference is also made to a conference call with Michael Smela, Jr. and Michelle Dillahunt of the Office of Generic Drugs and Christine Mundkur and Sharif Ahmed of Barr Laboratories, Inc. concerning the February 6, 2001 deficiency letter and Barr's response to that. Following the discussion, Barr decided to amend the February 15, 2001 minor amendment.

The deficiencies identified in the February 6, 2001 facsimile and Barr's amended responses are as follows:

A. DEFICIENCIES

COMMENT 1:

[redacted]

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
FEB 23 2001
OGD

RESPONSE:

Following the Agency comment we reviewed our response to comment 7 and found that the statements made in the response was not accurate. We apologize for the inadvertent mistake and any confusion this may have caused. Following is a clarification regarding the validation study and response to the Agency comment 7.

[redacted]

Redacted 1 page(s)

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information from

2/22/2001 BARR LETTER

At this time, Barr also requests to withdraw the additional drug substance source of ——————— without prejudice to filing at a future date.

The updated stability data for the 5 mg and 15 mg through 36 months, 7.5 mg and 10 mg through 18 months are provided in Attachment 1.

A field copy of this amendment has been forwarded to the Baltimore District Office. A Field Copy Certification is also provided.

This completes the present amendment. If you have any questions, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and Regulatory Counsel

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use OTREXUP™ safely and effectively. See full prescribing information for OTREXUP.

OTREXUP (methotrexate) injection, for subcutaneous use
Initial U.S. Approval: 1953

WARNING: SEVERE TOXIC REACTIONS, INCLUDING EMBRYO-FETAL TOXICITY AND DEATH
See full prescribing information for complete boxed warning.
• Serious toxic reactions and death have been reported with the use of methotrexate. Patients should be closely monitored for bone marrow, liver, lung, skin, and kidney toxicities (5.1).
• Methotrexate has been reported to cause fetal death and/or congenital anomalies and is contraindicated in pregnancy (4, 5.2).
• Unexpectedly severe (sometimes fatal) bone marrow suppression, aplastic anemia, and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high dosage) along with some nonsteroidal anti-inflammatory drugs (NSAIDs) (5.1).
• Hepatotoxicity, fibrosis, and cirrhosis may occur after prolonged use (5.1).
• Methotrexate may cause interstitial pneumonitis at any time during therapy and has been reported at low doses. Pulmonary symptoms (especially a dry, nonproductive cough) may require interruption of treatment and careful investigation (5.1).
• Diarrhea, ulcerative stomatitis, hemorrhagic enteritis, and death from intestinal perforation may occur (5.1).
• Severe, occasionally fatal, skin reactions have been reported (5.1).
• Potentially fatal opportunistic infections may occur (5.1).

----------RECENT MAJOR CHANGES----------
Dosage and Administration (2) 11/2014

----------INDICATIONS AND USAGE----------
Otrexup is a folate analog metabolic inhibitor indicated for the:
- Management of patients with severe, active rheumatoid arthritis (RA) and polyarticular juvenile idiopathic arthritis (pJIA), who are intolerant of or had an inadequate response to first-line therapy (1.1)
- Symptomatic control of severe, recalcitrant, disabling psoriasis in adults who are not adequately responsive to other forms of therapy (1.2)

Limitation of Use
Otrexup is not indicated for the treatment of neoplastic diseases (1 3).

----------DOSAGE AND ADMINISTRATION----------
- Otrexup is for once weekly subcutaneous use only. Administer Otrexup in the abdomen or thigh. (2.1)
- Use another formulation of methotrexate for patients requiring oral, intramuscular, intravenous, intra-arterial, or intrathecal dosing, doses less than 7.5 mg per week, doses above 25 mg per week, high-dose regimens, or dose adjustments of less than 5 mg increments (2.1)
- Starting doses of methotrexate:
  - RA: 7.5 mg once weekly (2.2)
  - pJIA: 10 mg/m^2 once weekly (2.2)
  - Psoriasis: 10 to 25 mg once weekly of an oral, intramuscular, subcutaneous, or intravenous formulation (2.3)
- Adjust dose gradually to achieve an optimal response (2.2, 2.3)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: Single-dose auto-injector delivering 0.4 mL of methotrexate in the following dosage strengths: 7 5 mg, 10 mg, 15 mg, 20mg, and 25 mg (3).

----------CONTRAINDICATIONS----------
- Pregnancy (4)
- Nursing mothers (4)
- Alcoholism or liver disease (4)
- Immunodeficiency syndromes (4)
- Preexisting blood dyscrasias (4)
- Hypersensitivity to methotrexate (4)

----------WARNINGS AND PRECAUTIONS----------
- Organ system toxicity: Potential for serious toxicity. Only for use by physicians experienced in antimetabolite therapy (5.1).
- Embryo-fetal toxicity: Exclude pregnancy before treatment. Avoid pregnancy if either partner is receiving Otrexup. Advise males to avoid pregnancy for a minimum of three months after therapy and females to avoid pregnancy for at least one ovulatory cycle after therapy (5.2).
- Effects on reproduction: May cause impairment of fertility, oligospermia and menstrual dysfunction (5.3)
- Laboratory tests: Monitor complete blood counts, renal function and liver function tests (5.4).
- Risks from improper dosing: Mistaken daily use has led to fatal toxicity (5.5)
- Patients with impaired renal function, ascites, or pleural effusions: Elimination is reduced (5.6).
- Dizziness and fatigue: May impair ability to drive or operate machinery (5.7)

----------ADVERSE REACTIONS----------
Common adverse reactions are: nausea, abdominal pain, dyspepsia, stomatitis/mouth sores, rash, nasopharyngitis, diarrhea, liver function test abnormalities, vomiting, headache, bronchitis, thrombocytopenia, alopecia, leucopenia, pancytopenia, dizziness, photosensitivity, and "burning of skin lesions" (6).

To report SUSPECTED ADVERSE REACTIONS, contact Antares at 1-855-Otrexup (1-855-687-3987) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Aspirin, NSAIDs, and steroids: concomitant use may elevate and prolong serum methotrexate levels and cause increased toxicity (7.1)
- Proton pump inhibitors concomitant use may elevate and prolong serum methotrexate levels and cause increased toxicity (7.2)

----------USE IN SPECIFIC POPULATIONS----------
- Pediatric use: Safety and efficacy of methotrexate, including Otrexup, have not been established in pediatric patients with psoriasis. Safety and efficacy of Otrexup have not been established in pediatric patients with malignancy (8.4)
- Geriatric use: Use caution in dose selection (8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

---

FULL PRESCRIBING INFORMATION

WARNING: SEVERE TOXIC REACTIONS, INCLUDING EMBRYO-FETAL TOXICITY AND DEATH

Otrexup should be used only by physicians whose knowledge and experience include the use of antimetabolite therapy. Because of the possibility of serious toxic reactions (which can be fatal), Otrexup should be used only in patients with psoriasis or rheumatoid arthritis with severe, recalcitrant, disabling disease which is not adequately responsive to other forms of therapy. Deaths have been reported with the use of methotrexate in the treatment of malignancy, psoriasis, and rheumatoid arthritis. Patients should be closely monitored for bone marrow, liver, lung, skin, and kidney toxicities. Patients should be informed by their physician of the risks involved and be under a physician's care throughout therapy *[see Warnings and Precautions (5.1)]*.

1. Methotrexate has been reported to cause fetal death and/or congenital anomalies.

Therefore, Otrexup is not recommended for females of childbearing potential unless there is clear medical evidence that the benefits can be expected to outweigh the considered risks *[see Warnings and Precautions (5.2)]*. Otrexup is contraindicated in pregnant women *[see Contraindications (4)]*.

2. Methotrexate elimination is reduced in patients with impaired renal functions, ascites, or pleural effusions. Such patients require especially careful monitoring for toxicity, and require dose reduction or, in some cases, discontinuation of Otrexup administration *[see Warnings and Precautions (5.6)]*.

3. Unexpectedly severe (sometimes fatal) bone marrow suppression, aplastic anemia, and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high dosage) along with some nonsteroidal anti-inflammatory drugs (NSAIDs) *[see Warnings and Precautions (5.1) and Drug Interactions (7.1)]*.

4. Methotrexate causes hepatotoxicity, fibrosis and cirrhosis, but generally only after prolonged use. Acutely, liver enzyme elevations are frequently seen. These are usually transient and asymptomatic, and also do not appear predictive of subsequent hepatic disease. Liver biopsy after sustained use often shows histologic changes, and fibrosis and cirrhosis have been reported; these latter lesions may not be preceded by symptoms or abnormal liver function tests in the psoriasis population. For this reason, periodic liver biopsies are usually recommended for psoriatic patients who are under long-term treatment. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid arthritis population *[see Warnings and Precautions (5.1)]*.

5. Methotrexate-induced lung disease, including acute or chronic interstitial pneumonitis, is a potentially dangerous lesion, which may occur acutely at any time during therapy and has been reported at low doses. It is not always fully reversible and fatalities have been reported. Pulmonary symptoms (especially a dry, nonproductive cough) may require interruption of treatment and careful investigation *[see Warnings and Precautions (5.1)]*.

6. Diarrhea and ulcerative stomatitis require interruption of therapy: otherwise, hemorrhagic enteritis and death from intestinal perforation may occur *[see Warnings and Precautions (5.1)]*.

7. Malignant lymphomas, which may regress following withdrawal of methotrexate, may occur in patients receiving low-dose methotrexate and, thus, may not require cytotoxic treatment. Discontinue Otrexup first and, if the lymphoma does not regress, appropriate treatment should be instituted *[see Warnings and Precautions (5.8)]*.

8. Like other cytotoxic drugs, methotrexate may induce "tumor lysis syndrome" in patients with rapidly growing tumors *[see Warnings and Precautions (5.9)]*.

9. Severe, occasionally fatal, skin reactions have been reported following single or multiple doses of methotrexate. Reactions have occurred within days of oral, intramuscular, intravenous, or intrathecal methotrexate administration. Recovery has been reported with discontinuation of therapy *[see Warnings and Precautions (5.1)]*.

10. Potentially fatal opportunistic infections, especially *Pneumocystis jiroveci* pneumonia, may occur with methotrexate therapy *[see Warnings and Precautions (5.1)]*.

11. Methotrexate given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis *[see Warnings and Precautions (5.10)]*.

1 INDICATIONS AND USAGE

1.1 Rheumatoid Arthritis including Polyarticular Juvenile Idiopathic Arthritis

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

1.2 Psoriasis

Otrexup is indicated in adults for the symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy, but only when the diagnosis has been established, as by biopsy and/or after dermatologic consultation. It is important to ensure that a psoriasis "flare" is not due to an undiagnosed concomitant disease affecting immune responses.

1.3 Limitation of Use

Otrexup is not indicated for the treatment of neoplastic diseases.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosing Information

Otrexup is a single-dose auto-injector for once-weekly subcutaneous use only *[see Warnings and Precautions (5.5)]*. Administer Otrexup in the abdomen or the thigh. Otrexup is available in the following dosage strengths: 7.5, 10, 15, 20 and 25 mg. Use another formulation of methotrexate for alternative dosing in patients who require oral, intramuscular, intravenous, intra-arterial, or intrathecal dosing, doses less than 7.5 mg per week, doses more than 25 mg per week, high-dose regimens, or dose adjustments between the available doses.

2.2 Rheumatoid Arthritis including Polyarticular Juvenile Idiopathic Arthritis

Recommended starting dose of methotrexate:

Adult RA: 7.5 mg once weekly.

pJIA: 10 mg/m^2 once weekly.

For patients switching from oral methotrexate to Otrexup, consider any differences in bioavailability between oral and subcutaneously administered methotrexate *[see Clinical Pharmacology (12.3)]*.

Dosages may be adjusted gradually to achieve an optimal response. Limited experience shows a significant increase in the incidence and severity of serious toxic reactions, especially bone marrow suppression, at doses greater than 20 mg/wk in adults. Although there is experience with doses up to 30 mg/m^2/wk in children, there are too few published data to assess how doses over 20 mg/m^2/wk might affect the risk of serious toxicity in children. Experience does suggest, however, that children receiving 20 to 30 mg/m^2/wk (0.65 to 1.0 mg/kg/wk) may have better absorption and fewer gastrointestinal side effects if methotrexate is administered either intramuscularly or subcutaneously.

Therapeutic response usually begins within 3 to 6 weeks and the patient may continue to improve for another 12 weeks or more.

The optimal duration of therapy is unknown. Limited data available from long-term studies in adults indicate that the initial clinical improvement is maintained for at least two years with continued therapy. When methotrexate is discontinued, the arthritis usually worsens within 3 to 6 weeks.

The patient should be fully informed of the risks involved and should be under constant supervision of the physician. Assessment of hematologic, hepatic, renal, and pulmonary function should be made by history,

physical examination, and laboratory tests before beginning, periodically during, and before reinstituting Otrexup therapy *[see Warnings and Precautions (5.4)]*. Females of childbearing potential should not be started on Otrexup until pregnancy is excluded *[see Contraindications (4) and Warnings and Precautions (5.2)]*

All schedules should be continually tailored to the individual patient. An initial test dose may be given prior to the regular dosing schedule to detect any extreme sensitivity to adverse effects.

Maximal myelosuppression usually occurs in seven to ten days.

2.3 Psoriasis

Recommended starting dose of methotrexate:

Psoriasis: single weekly oral, intramuscular, subcutaneous, or intravenous doses of 10-25 mg.

For patients switching from oral methotrexate to Otrexup, consider any differences in bioavailability between oral and subcutaneously administered methotrexate *[see Clinical Pharmacology (12.3)]*.

Dosage may be gradually adjusted to achieve optimal clinical response; 30 mg/week should not ordinarily be exceeded. Once optimal clinical response has been achieved, the dosage should be reduced to the lowest possible amount of drug and to the longest possible rest period. The use of Otrexup may permit the return to conventional topical therapy, which should be encouraged.

2.4 Administration and Handling

Otrexup is an auto-injector intended for subcutaneous use under the guidance and supervision of a physician.

Patients may self-inject with Otrexup if a physician determines that it is appropriate, if they have received proper training in how to prepare and administer the correct dose, and if they receive medical follow-up, as necessary. A trainer device is available for training purposes.

Visually inspect Otrexup for particulate matter and discoloration prior to administration. Do not use Otrexup if the seal is broken.

Handle and dispose of Otrexup consistent with recommendations for handling and disposal of cytotoxic drugs[1].

3 DOSAGE FORMS AND STRENGTHS

Otrexup is an injection available as an autoinjector that administers a single 0.4 mL dose of methotrexate solution in the following dosage strengths:

- 7.5 mg/0.4 mL methotrexate
- 10 mg/0.4 mL methotrexate
- 15 mg/0.4 mL methotrexate
- 20 mg/0.4 mL methotrexate
- 25 mg/0.4 mL methotrexate

4 CONTRAINDICATIONS

Otrexup is contraindicated in the following:

• Pregnancy

Otrexup can cause fetal death or teratogenic effects when administered to a pregnant woman.

Otrexup is contraindicated in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.1)]*.

•Nursing Mothers

Because of the potential for serious adverse reactions from methotrexate in breast fed infants, Otrexup is contraindicated in nursing mothers *[see Use in Specific Populations (8.3)]*.

•Alcoholism or Liver Disease

Patients with alcoholism, alcoholic liver disease or other chronic liver disease [see *Warnings and Precautions (5.1)*].

• Immunodeficiency Syndromes

Patients who have overt or laboratory evidence of immunodeficiency syndromes [*see Warnings and Precautions (5.1)*].

• Preexisting Blood Dyscrasias

Patients who have preexisting blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anemia *[see Warnings and Precautions (5.1)]*.

•Hypersensitivity

Patients with a known hypersensitivity to methotrexate. Severe hypersensitivity reactions have been observed with methotrexate use *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1 and 6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Organ System Toxicity

Otrexup should be used only by physicians whose knowledge and experience include the use of antimetabolite therapy. Because of the possibility of serious toxic reactions (which can be fatal), Otrexup should be used only in patients with psoriasis or rheumatoid arthritis with severe, recalcitrant, disabling disease which is not adequately responsive to other forms of therapy.

Deaths have been reported with the use of methotrexate in the treatment of malignancy, psoriasis, and rheumatoid arthritis. Patients should be closely monitored for bone marrow, liver, lung and kidney toxicities.

Otrexup has the potential for serious toxicity. Toxic effects may be related in frequency and severity to dose or frequency of administration but have been seen at all doses. Because they can occur at any time during therapy, it is necessary to follow patients on Otrexup closely. Most adverse reactions are reversible if detected early. When such reactions do occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken. If necessary, this could include the use of leucovorin calcium and/or acute, intermittent hemodialysis with a high-flux dialyzer [see *Overdosage (10)*]. If Otrexup therapy is reinstituted, it should be carried out with caution, with adequate consideration of further need for the drug and increased alertness as to possible recurrence of toxicity. The clinical pharmacology of methotrexate has not been well studied in older individuals. Due to diminished hepatic and renal function as well as decreased folate stores in this population, relatively low doses should be considered, and these patients should be closely monitored for early signs of toxicity *[see Use in Specific Populations (8.5)]*.

Gastrointestinal:

Diarrhea and ulcerative stomatitis require interruption of therapy: otherwise, hemorrhagic enteritis and death from intestinal perforation may occur.

If vomiting, diarrhea, or stomatitis occur, which may result in dehydration, Otrexup should be discontinued until recovery occurs. Otrexup should be used with extreme caution in the presence of peptic ulcer disease or ulcerative colitis.

Unexpectedly severe (sometimes fatal) gastrointestinal toxicity has been reported with concomitant administration of methotrexate (usually in high dosage) along with some nonsteroidal anti-inflammatory drugs (NSAIDs*) [see Drug Interactions (7.1)]*.

Hematologic:

Otrexup can suppress hematopoiesis and cause anemia, aplastic anemia, pancytopenia, leukopenia, neutropenia, and/or thrombocytopenia. In patients with preexisting hematopoietic impairment, Otrexup should be used with caution, if at all. In controlled clinical trials conducted with another formulation of methotrexate in rheumatoid arthritis (n=128), leukopenia (WBC <3000/mm^3) was seen in 2 patients, thrombocytopenia (platelets <100,000/mm^3) in 6 patients, and pancytopenia in 2 patients.

Otrexup should be stopped immediately if there is a significant drop in blood counts. Patients with profound granulocytopenia and fever should be evaluated immediately and usually require parenteral broad-spectrum antibiotic therapy.

Unexpectedly severe (sometimes fatal) bone marrow suppression and aplastic anemia have been reported with concomitant administration of methotrexate (usually in high dosage) along with some nonsteroidal anti-inflammatory drugs (NSAIDs) *[see Drug Interactions (7.1)]*.

Hepatic:

Otrexup has the potential for acute (elevated transaminases) and chronic (fibrosis and cirrhosis) hepatotoxicity. Chronic toxicity is potentially fatal; it generally has occurred after prolonged use (generally two years or more) and after a total dose of at least 1.5 grams. In studies in psoriatic patients, hepatotoxicity appeared to be a function of total cumulative dose and appeared to be enhanced by alcoholism, obesity, diabetes and advanced age. An accurate incidence rate has not been determined; the rate of progression and reversibility of lesions is not known. Special caution is indicated in the presence of preexisting liver damage or impaired hepatic function.

In psoriasis, liver function tests, including serum albumin, should be performed periodically prior to dosing but are often normal in the face of developing fibrosis or cirrhosis. These lesions may be detectable only by biopsy. The usual recommendation is to obtain a liver biopsy at 1) pretherapy or shortly after initiation of therapy (2 to 4 months), 2) a total cumulative dose of 1.5 grams, and 3) after each additional 1.0 to 1.5 grams. Moderate fibrosis or any cirrhosis normally leads to discontinuation of the drug; mild fibrosis normally suggests a repeat biopsy in 6 months.

Milder histologic findings such as fatty change and low grade portal inflammation, are relatively common pretherapy. Although these mild changes are usually not a reason to avoid or discontinue Otrexup therapy, the drug should be used with caution.

In rheumatoid arthritis, age at first use of methotrexate and duration of therapy have been reported as risk factors for hepatotoxicity; other risk factors, similar to those observed in psoriasis, may be present in rheumatoid arthritis but have not been confirmed to date. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in this population. There is a combined reported experience in 217 rheumatoid arthritis patients with liver biopsies both before and during treatment (after a cumulative dose of at least 1.5 g) and in 714 patients with a biopsy only during treatment. There are 64 (7%) cases of fibrosis and 1 (0.1%) case of cirrhosis. Of the 64 cases of fibrosis, 60 were deemed mild. The reticulin stain is more sensitive for early fibrosis and its use may increase these figures. It is unknown whether even longer use will increase these risks.

Liver function tests should be performed at baseline at 4 to 8 week intervals in patients receiving Otrexup for rheumatoid arthritis. Pretreatment liver biopsy should be performed for patients with a history of excessive alcohol consumption, persistently abnormal baseline liver function test values or chronic hepatitis B or C infection. During therapy, liver biopsy should be performed if there are persistent liver function test abnormalities or there is a decrease in serum albumin below the normal range (in the setting of well controlled rheumatoid arthritis).

If the results of a liver biopsy show mild changes (Roenigk, grades I, II, IIIa), Otrexup may be continued and the patient monitored as per recommendations listed above. Otrexup should be discontinued in any patient who displays persistently abnormal liver function tests and refuses liver biopsy or in any patient whose liver biopsy shows moderate to severe changes (Roenigk grade IIIb or IV).

Infection or Immunologic States:

Otrexup should be used with extreme caution in the presence of active infection, and is contraindicated in patients with overt or laboratory evidence of immunodeficiency syndromes.

Immunization may be ineffective when given during Otrexup therapy. Immunization with live virus vaccines is generally not recommended. There have been reports of disseminated vaccinia infections after smallpox

immunizations in patients receiving methotrexate therapy. Hypogammaglobulinemia has been reported rarely.

Potentially fatal opportunistic infections, especially *Pneumocystis jiroveci* pneumonia, may occur with Otrexup therapy. When a patient presents with pulmonary symptoms, the possibility of *Pneumocystis jiroveci* pneumonia should be considered.

Neurologic:

There have been reports of leukoencephalopathy following intravenous administration of methotrexate to patients who have had craniospinal irradiation. Serious neurotoxicity, frequently manifested as generalized or focal seizures, has been reported with unexpectedly increased frequency among pediatric patients with acute lymphoblastic leukemia who were treated with intermediate-dose intravenous methotrexate (1 gm/m^2). Symptomatic patients were commonly noted to have leukoencephalopathy and/or microangiopathic calcifications on diagnostic imaging studies. Chronic leukoencephalopathy has also been reported in patients who received repeated doses of high-dose methotrexate with leucovorin rescue even without cranial irradiation.

Discontinuation of methotrexate does not always result in complete recovery. A transient acute neurologic syndrome has been observed in patients treated with high dose regimens. Manifestations of this stroke-like encephalopathy may include confusion, hemiparesis, transient blindness, seizures and coma. The exact cause is unknown. After the intrathecal use of methotrexate, the central nervous system toxicity which may occur can be classified as follows: acute chemical arachnoiditis manifested by such symptoms as headache, back pain, nuchal rigidity, and fever; sub-acute myelopathy characterized by paraparesis/paraplegia associated with involvement with one or more spinal nerve roots; chronic leukoencephalopathy manifested by confusion, irritability, somnolence, ataxia, dementia, seizures and coma. This condition can be progressive and even fatal.

Pulmonary:

Methotrexate-induced lung disease, including acute or chronic interstitial pneumonitis, is a potentially dangerous lesion, which may occur acutely at any time during therapy and has been reported at low doses. It is not always fully reversible and fatalities have been reported.

Pulmonary symptoms (especially a dry nonproductive cough) or a non-specific pneumonitis occurring during Otrexup therapy may be indicative of a potentially dangerous lesion and require interruption of treatment and careful investigation. Although clinically variable, the typical patient with methotrexate induced lung disease presents with fever, cough, dyspnea, hypoxemia, and an infiltrate on chest X-ray; infection (including pneumonia) needs to be excluded. This lesion can occur at all dosages.

Renal:

Otrexup may cause renal damage that may lead to acute renal failure. High doses of methotrexate used in the treatment of osteosarcoma may cause renal damage leading to acute renal failure. Nephrotoxicity is due primarily to the precipitation of methotrexate and 7- hydroxymethotrexate in the renal tubules. Close attention to renal function including adequate hydration, urine alkalinization and measurement of serum methotrexate and creatinine levels are essential for safe administration.

Skin:

Severe, occasionally fatal, dermatologic reactions, including toxic epidermal necrolysis, Stevens-

Johnson syndrome, exfoliative dermatitis, skin necrosis, and erythema multiforme, have been reported in children and adults, within days of oral, intramuscular, intravenous, or intrathecal methotrexate administration. Reactions were noted after single or multiple low, intermediate, or high doses of methotrexate in patients with neoplastic and non-neoplastic diseases.

Lesions of psoriasis may be aggravated by concomitant exposure to ultraviolet radiation.

Radiation dermatitis and sunburn may be “recalled” by the use of methotrexate.

Other precautions:

Otrexup should be used with extreme caution in the presence of debility.

Methotrexate exits slowly from third space compartments (e.g., pleural effusions or ascites). This results in a prolonged terminal plasma half-life and unexpected toxicity. In patients with significant third space accumulations, it is advisable to evacuate the fluid before treatment and to monitor plasma methotrexate levels.

5.2 Embryo-Fetal Toxicity

Methotrexate has been reported to cause fetal death and/or congenital anomalies. Therefore, Otrexup is not recommended for females of childbearing potential unless there is clear medical evidence that the benefits can be expected to outweigh the considered risks. Otrexup is contraindicated in pregnant women with psoriasis or rheumatoid arthritis.

Females of childbearing potential should not be started on Otrexup until pregnancy is excluded and should be fully counseled on the serious risk to the fetus should they become pregnant while undergoing treatment. Appropriate steps should be taken to avoid conception during Otrexup therapy. Pregnancy should be avoided if either partner is receiving Otrexup; during and for a minimum of three months after therapy for male patients, and during and for at least one ovulatory cycle after therapy for female patients.

5.3 Effects on Reproduction

Methotrexate has been reported to cause impairment of fertility, oligospermia and menstrual dysfunction in humans, during and for a short period after cessation of therapy.

The risk of effects of reproduction should be discussed with both male and female patients taking Otrexup.

5.4 Laboratory Tests

Patients undergoing Otrexup therapy should be closely monitored so that toxic effects are detected promptly. Baseline assessment should include a complete blood count with differential and platelet counts, hepatic enzymes, renal function tests and a chest X-ray.

During therapy, monitoring of these parameters is recommended: hematology at least monthly, renal function and liver function every 1 to 2 months [*see Warnings and Precautions (5.1)]*.

During initial or changing doses, or during periods of increased risk of elevated methotrexate blood levels (e.g., dehydration), more frequent monitoring may also be indicated.

Liver Function Tests

Transient liver function test abnormalities are observed frequently after methotrexate administration and are usually not cause for modification of methotrexate therapy. Persistent liver function test abnormalities, and/or depression of serum albumin may be indicators of serious liver toxicity and require evaluation [*see Warnings and Precautions (5.1)]*.

A relationship between abnormal liver function tests and fibrosis or cirrhosis of the liver has not been established for patients with psoriasis. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid arthritis population.

Pulmonary Function Tests

Pulmonary function tests may be useful if methotrexate-induced lung disease is suspected, especially if baseline measurements are available *[see Warnings and Precautions (5.1)]*.

5.5 Risks from Improper Dosing

Both the physician and pharmacist should emphasize to the patient that Otrexup is administered weekly and that mistaken daily use has led to fatal toxicity *[see Dosage and Administration (2)]*.

5.6 Patients with Impaired Renal Function, Ascites, or Pleural Effusions

Methotrexate elimination is reduced in patients with impaired renal function, ascites, or pleural effusions. Such patients require especially careful monitoring for toxicity and require dose reduction or, in some cases, discontinuation of Otrexup administration.

5.7 Dizziness and Fatigue

Adverse reactions, such as dizziness and fatigue, may affect the ability to drive or operate machinery.

5.8 Malignant Lymphomas

Non-Hodgkin's lymphoma and other tumors have been reported in patients receiving low-dose oral methotrexate. However, there have been instances of malignant lymphoma arising during treatment with low-dose oral methotrexate, which have regressed completely following withdrawal of methotrexate, without requiring active anti-lymphoma treatment. Discontinue Otrexup first and, if the lymphoma does not regress, appropriate treatment should be instituted.

5.9 Tumor Lysis Syndrome

Like other cytotoxic drugs, methotrexate may induce "tumor lysis syndrome" in patients with rapidly growing tumors.

5.10 Concomitant Radiation Therapy

Methotrexate given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling.

- Organ System Toxicity *[see Warnings and Precautions (5.1)]*
- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.2)]*
- Effects on Reproduction *[see Warnings and Precautions (5.3)]*
- Malignant Lymphomas *[see Warnings and Precautions (5.8)]*

The most frequently reported adverse reactions include ulcerative stomatitis, leukopenia, nausea, and abdominal distress. Other frequently reported adverse reactions are malaise, undue fatigue, chills and fever, dizziness and decreased resistance to infection.

6.1 Clinical Trials Experience

This section provides a summary of adverse reactions reported in subjects in clinical studies conducted with Otrexup as well as with methotrexate injection and oral methotrexate.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug, and may not reflect the rates observed in practice.

Rheumatoid Arthritis

The approximate incidences of methotrexate-attributed (i.e. placebo rate subtracted) adverse reactions in 12 to 18 week double-blind studies of patients (n=128) with rheumatoid arthritis treated with low-dose oral (7.5 to 15 mg/week) pulse methotrexate, are listed below. Virtually all of these patients were on concomitant nonsteroidal anti-inflammatory drugs and some were also taking low dosages of corticosteroids. Hepatic histology was not examined in these short-term studies.

Incidence greater than 10%: Elevated liver function tests 15%, nausea/vomiting 10%.

Incidence 3% to 10%: Stomatitis, thrombocytopenia (platelet count less than 100,000/mm^3).

Incidence 1% to 3%: Rash/pruritis/dermatitis, diarrhea, alopecia, leukopenia (WBC less than 3000/mm^3), pancytopenia, dizziness.

Two other controlled trials of patients (n=680) with Rheumatoid Arthritis on 7.5 mg to 15 mg/wk oral doses showed an incidence of interstitial pneumonitis of 1%.

Other less common reactions included decreased hematocrit, headache, upper respiratory infection, anorexia, arthralgias, chest pain, coughing, dysuria, eye discomfort, epistaxis, fever, infection, sweating, tinnitus, and vaginal discharge.

Polyarticular Juvenile Idiopathic Arthritis

The approximate incidences of adverse reactions reported in pediatric patients with pJIA treated with oral, weekly doses of methotrexate (5 to 20 mg/m^2/wk or 0.1 to 0.65 mg/kg/wk) were as follows (virtually all patients were receiving concomitant nonsteroidal anti-inflammatory drugs, and some also were taking low doses of corticosteroids): elevated liver function tests, 14%; gastrointestinal reactions (e.g., nausea, vomiting, diarrhea), 11%; stomatitis, 2%; leukopenia, 2%; headache, 1.2%; alopecia, 0.5%; dizziness, 0.2%; and rash, 0.2%. Although there is experience with dosing up to 30 mg/m^2/wk in pJIA, the published data for doses above 20 mg/m^2/wk are too limited to provide reliable estimates of adverse reaction rates.

Psoriasis

There are two literature reports (Roenigk, 1969, and Nyfors, 1978) describing large series (n=204, 248) of psoriasis patients treated with methotrexate. Dosages ranged up to 25 mg per week and treatment was administered for up to four years. With the exception of alopecia, photosensitivity, and "burning of skin lesions" (each 3% to 10%), the adverse reaction rates in these reports were very similar to those in the rheumatoid arthritis studies. Rarely, painful plaque erosions may appear (Pearce, HP and Wilson, BB: Am Acad Dermatol 35: 835-838, 1996).

6.2 Other Adverse Reactions

Other adverse reactions that have been reported with methotrexate in oncology, RA, pJIA, and psoriasis patients are listed below by organ system.

Alimentary System: gingivitis, pharyngitis, stomatitis, anorexia, nausea, vomiting, diarrhea, hematemesis, melena, gastrointestinal ulceration and bleeding, enteritis, pancreatitis.

Blood and Lymphatic System Disorders: suppressed hematopoiesis, anemia, aplastic anemia, pancytopenia, leukopenia, neutropenia, thrombocytopenia, agranulocytosis, eosinophilia, lymphadenopathy and lymphoproliferative disorders (including reversible). Hypogammaglobulinemia has been reported rarely.

Cardiovascular: pericarditis, pericardial effusion, hypotension, and thromboembolic events (including arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, thrombophlebitis, and pulmonary embolus).

Central Nervous System: headaches, drowsiness, blurred vision, transient blindness, speech impairment including dysarthria and aphasia, hemiparesis, paresis and convulsions have also occurred following administration of methotrexate. Following low doses, there have been occasional reports of transient subtle cognitive dysfunction, mood alteration or unusual cranial sensations, leukoencephalopathy, or encephalopathy.

Hepatobiliary Disorders: hepatotoxicity, acute hepatitis, chronic fibrosis and cirrhosis, hepatic failure, decrease in serum albumin, liver enzyme elevations.

Infection: There have been case reports of sometimes fatal opportunistic infections in patients receiving methotrexate therapy for neoplastic and non-neoplastic diseases. *Pneumocystis jiroveci* pneumonia was the most common opportunistic infection. There have also been reports of infections, pneumonia, Cytomegalovirus infection, including cytomegaloviral pneumonia, sepsis, fatal sepsis, nocardiosis; histoplasmosis, cryptococcosis, *Herpes zoster*, *Herpes simplex* hepatitis, and disseminated *Herpes simplex*.

Musculoskeletal System: stress fracture.

Ophthalmic: conjunctivitis, serious visual changes of unknown etiology.

Pulmonary System: respiratory fibrosis, respiratory failure, alveolitis, interstitial pneumonitis deaths have been reported, and chronic interstitial obstructive pulmonary disease has occasionally occurred.

Skin: erythematous rashes, pruritus, urticaria, photosensitivity, pigmentary changes, alopecia, ecchymosis, telangiectasia, acne, furunculosis, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, skin necrosis, skin ulceration and exfoliative dermatitis.

Urogenital System: severe nephropathy or renal failure, azotemia, cystitis, hematuria, proteinuria; defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, vaginal discharge, and gynecomastia; infertility, abortion, fetal death, fetal defects.

Other rarer reactions related to or attributed to the use of methotrexate such as nodulosis, vasculitis, arthralgia/myalgia, loss of libido/ impotence, diabetes, osteoporosis, sudden death, lymphoma, including reversible lymphomas, tumor lysis syndrome, soft tissue necrosis and osteonecrosis. Anaphylactoid reactions have been reported.

7 DRUG INTERACTIONS

7.1 Aspirin, Nonsteroidal Anti-Inflammatory Drugs, and Steroids

Nonsteroidal anti-inflammatory drugs (NSAIDs) should not be administered prior to or concomitantly with the high doses of methotrexate, such as used in the treatment of osteosarcoma. Concomitant administration of some NSAIDs with high dose methotrexate therapy has been reported to elevate and prolong serum methotrexate levels, resulting in deaths from severe hematologic and gastrointestinal toxicity *[see Warnings and Precautions (5.1)]*.

Caution should be used when NSAIDs and salicylates are administered concomitantly with lower doses of methotrexate, including Otrexup. These drugs have been reported to reduce the tubular secretion of methotrexate in an animal model and may enhance its toxicity.

Despite the potential interactions, studies of methotrexate in patients with rheumatoid arthritis have usually included concurrent use of constant dosage regimens of NSAIDs, without apparent problems. It should be appreciated, however, that the doses used in rheumatoid arthritis (7.5 to 15 mg/week) are somewhat lower than those used in psoriasis and that larger doses could lead to unexpected toxicity. Aspirin, NSAIDs, and/or low dose steroids may be continued, although the possibility of increased toxicity with concomitant use of NSAIDs including salicylates has not been fully explored. Steroids may be reduced gradually in patients who respond to methotrexate.

7.2 Proton Pump Inhibitors (PPIs)

Use caution if high-dose methotrexate is administered to patients receiving proton pump inhibitor (PPI) therapy. Case reports and published population pharmacokinetic studies suggest that concomitant use of some PPIs, such as omeprazole, esomeprazole, and pantoprazole, with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate, possibly leading to methotrexate toxicities. In two of these cases, delayed methotrexate elimination was observed when high-dose methotrexate was co-administered with PPIs, but was not observed when methotrexate was co-administered with ranitidine. However, no formal drug interaction studies of methotrexate with ranitidine have been conducted.

7.3 Oral Antibiotics

Oral antibiotics such as tetracycline, chloramphenicol, and nonabsorbable broad spectrum antibiotics, may decrease intestinal absorption of methotrexate or interfere with the enterohepatic circulation by inhibiting bowel flora and suppressing metabolism of the drug by bacteria.

Penicillins may reduce the renal clearance of methotrexate; increased serum concentrations of methotrexate with concomitant hematologic and gastrointestinal toxicity have been observed with high and low dose methotrexate. Use of Otrexup with penicillins should be carefully monitored.

Trimethoprim/sulfamethoxazole has been reported rarely to increase bone marrow suppression in patients receiving methotrexate, probably by decreased tubular secretion and/or an additive antifolate effect.

7.4 Hepatotoxins

The potential for increased hepatotoxicity when methotrexate is administered with other hepatotoxic agents has not been evaluated. However, hepatotoxicity has been reported in such cases. Therefore, patients receiving concomitant therapy with Otrexup and other potential hepatotoxins (e.g., azathioprine, retinoids, and sulfasalazine) should be closely monitored for possible increased risk of hepatotoxicity.

7.5 Theophylline

Methotrexate may decrease the clearance of theophylline; theophylline levels should be monitored when used concurrently with Otrexup.

7.6 Folic Acid and Antifolates

Vitamin preparations containing folic acid or its derivatives may decrease responses to systemically administered methotrexate. Preliminary animal and human studies have shown that small quantities of intravenously administered leucovorin enter the CSF primarily as 5-methyltetrahydrofolate and, in humans, remain 1 to 3 orders of magnitude lower than the usual methotrexate concentrations following intrathecal administration. However, high doses of leucovorin may reduce the efficacy of intrathecally administered methotrexate. Folate deficiency states may increase methotrexate toxicity.

Trimethoprim/sulfamethoxazole has been reported rarely to increase bone marrow suppression in patients receiving methotrexate, probably by decreased tubular secretion and/or an additive antifolate effect.

7.7 Mercaptopurine

Methotrexate increases the plasma levels of mercaptopurine. The combination of Otrexup and mercaptopurine may therefore require dose adjustment.

7.8 Other Drugs

Methotrexate is partially bound to serum albumin, and toxicity may be increased because of displacement by certain drugs, such as salicylates, phenylbutazone, phenytoin, and sulfonamides.

Renal tubular transport is also diminished by probenecid; use of Otrexup with this drug should be carefully monitored.

Combined use of methotrexate with gold, penicillamine, hydroxychloroquine, sulfasalazine, or cytotoxic agents, has not been studied and may increase the incidence of adverse effects.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X *[see Contraindications (4)]*

Methotrexate has been reported to cause embryotoxicity, fetal death, congenital anomalies, and abortion in humans and is contraindicated in pregnant women.

8.3 Nursing Mothers

Because of the potential for serious adverse reactions from methotrexate in breast fed infants, methotrexate is contraindicated in nursing mothers. Therefore, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Methotrexate has been detected in human breast milk. The highest breast milk to plasma concentration ratio reached was 0.08:1.

8.4 Pediatric Use

The safety and effectiveness of methotrexate, including Otrexup, have not been established in pediatric patients with psoriasis.

The safety and effectiveness of Otrexup have not been established in pediatric patients with neoplastic diseases.

The safety and effectiveness of methotrexate have been established in pediatric patients with polyarticular juvenile idiopathic arthritis *[see Clinical Studies (14.2)]*.

Published clinical studies evaluating the use of methotrexate in children and adolescents (i.e., patients 2 to 16 years of age) with pJIA demonstrated safety comparable to that observed in adults with rheumatoid arthritis [*see Adverse Reactions (6.1)*].

Otrexup does not contain a preservative. However, methotrexate injectable formulations containing the preservative benzyl alcohol are not recommended for use in neonates. There have been reports of fatal ‘gasping syndrome’ in neonates (children less than one month of age) following the administrations of

intravenous solutions containing the preservative benzyl alcohol. Symptoms include a striking onset of gasping respiration, hypotension, bradycardia, and cardiovascular collapse.

Serious neurotoxicity, frequently manifested as generalized or focal seizures, has been reported with unexpectedly increased frequency among pediatric patients with acute lymphoblastic leukemia who were treated with intermediate-dose intravenous methotrexate (1 gm/m^2) *[see Warnings and Precautions (5.1)]*.

8.5 Geriatric Use

Clinical studies of methotrexate did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious reflecting the greater frequency of decreased hepatic and renal function, decreased folate stores, concomitant disease or other drug therapy (i.e., that interfere with renal function, methotrexate or folate metabolism) in this population *[see Warnings and Precautions (5.1) Drug Interactions (7.7) and Use in Specific Populations (8.7)*]. Since decline in renal function may be associated with increases in adverse reactions and serum creatinine measurements may over estimate renal function in the elderly, more accurate methods (i.e., creatinine clearance) should be considered. Serum methotrexate levels may also be helpful. Elderly patients should be closely monitored for early signs of hepatic, bone marrow and renal toxicity. In chronic use situations, certain toxicities may be reduced by folate supplementation. Post-marketing experience suggests that the occurrence of bone marrow suppression, thrombocytopenia, and pneumonitis may increase with age [*see Warnings and Precautions (5.1)]*.

8.6 Females and Males of Reproductive Potential

Otrexup is not recommended for females of childbearing potential unless there is clear medical evidence that the benefits can be expected to outweigh the considered risks. Females of childbearing potential should not be started on methotrexate until pregnancy is excluded and should be fully counseled on the serious risk to the fetus should they become pregnant while undergoing treatment [see Use in Specific Populations (8.1)].

Appropriate steps should be taken to avoid conception during Otrexup therapy. Pregnancy should be avoided if either partner is receiving methotrexate; during and for a minimum of three months after therapy for male patients, and during and for at least one ovulatory cycle after therapy for female patients.

Methotrexate has been reported to cause impairment of fertility, oligospermia and menstrual dysfunction in humans, during and for a short period after cessation of therapy.

8.7 Renal Impairment

Methotrexate elimination is reduced in patients with impaired renal function. Such patients require especially careful monitoring for toxicity and require dose reduction or, in some cases, discontinuation of Otrexup administration.

8.8 Hepatic Impairment

The effect of hepatic impairment on methotrexate pharmacokinetics has not been studied. Otrexup is contraindicated in patients with alcoholic liver disease or other chronic liver disease. Patients with obesity, diabetes, hepatic fibrosis or steatohepatitis are at increased risk for hepatic injury and fibrosis secondary to methotrexate, and should be monitored closely [*see Warnings and Precautions (5.1)*].

10 OVERDOSAGE

Leucovorin is indicated to diminish the toxicity and counteract the effect of inadvertently administered overdosages of methotrexate. Leucovorin administration should begin as promptly as possible. As the time interval between methotrexate administration and leucovorin initiation increases, the effectiveness of leucovorin in counteracting toxicity decreases. Monitoring of the serum methotrexate concentration is essential in determining the optimal dose and duration of treatment with leucovorin.

In cases of massive overdosage, hydration and urinary alkalinization may be necessary to prevent the precipitation of methotrexate and/or its metabolites in the renal tubules. Generally speaking, neither

hemodialysis nor peritoneal dialysis has been shown to improve methotrexate elimination. However, effective clearance of methotrexate has been reported with acute, intermittent hemodialysis using a high-flux dialyzer (Wall, SM et al: *Am J Kidney Dis* 28 (6): 846-854, 1996).

Accidental intrathecal overdosage may require intensive systemic support, high-dose systemic leucovorin, alkaline diuresis and rapid CSF drainage and ventriculolumbar perfusion.

In postmarketing experience, overdose with methotrexate has generally occurred with oral and intrathecal administration, although intravenous and intramuscular overdose have also been reported.

Reports of oral overdose often indicate accidental daily administration instead of weekly (single or divided doses). Symptoms commonly reported following oral overdose include those symptoms and signs reported at pharmacologic doses, particularly hematologic and gastrointestinal reaction. For example, leukopenia, thrombocytopenia, anemia, pancytopenia, bone marrow suppression, mucositis, stomatitis, oral ulceration, nausea, vomiting, gastrointestinal ulceration, gastrointestinal bleeding. In some cases, no symptoms were reported.

There have been reports of death following overdose. In these cases, events such as sepsis or septic shock, renal failure, and aplastic anemia were also reported.

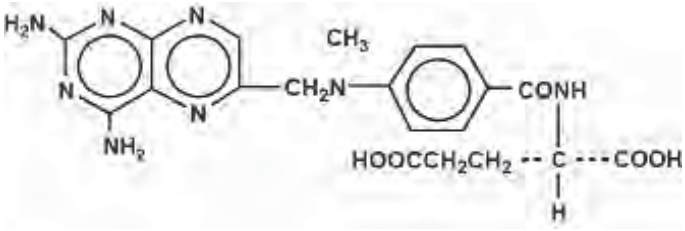
Symptoms of intrathecal overdose are generally central nervous system (CNS) symptoms, including headache, nausea and vomiting, seizure or convulsion, and acute toxic encephalopathy. In some cases, no symptoms were reported. There have been reports of death following intrathecal overdose. In these cases, cerebellar herniation associated with increased intracranial pressure, and acute toxic encephalopathy have also been reported.

There are published case reports of intravenous and intrathecal carboxypeptidase G2 treatment to hasten clearance of methotrexate in cases of overdose.

11 DESCRIPTION

Otrexup contains methotrexate, a folate analog metabolic inhibitor.

Chemically, methotrexate is [N-[4-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-Lglutamic acid. The structural formula is:



$C_{20}H_{22}N_8O_5$ M.W.= 454.45

Otrexup contains methotrexate in a sterile, preservative-free, unbuffered solution with a 27 gauge ½ inch needle for a single subcutaneous injection. Otrexup solution is yellow in color.

Inactive ingredients include sodium chloride and water for injection, USP. The amounts of sodium chloride vary with the amount of methotrexate.

Amount of methotrexate (mg) per 0.4 mL	7.5	10	15	20	25
Amount of sodium chloride (mg) per 0.4 mL	2.6	1.96	1.60	1.28	0.56

Hydrochloric acid and additional sodium hydroxide may have been added, if necessary, to adjust the pH to 8.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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.

The mechanism of action in rheumatoid arthritis is unknown; it may affect immune function.

12.2 Pharmacodynamics

Two reports describe *in vitro* methotrexate inhibition of DNA precursor uptake by stimulated mononuclear cells, and another describes in animal polyarthritis partial correction by methotrexate of spleen cell hyporesponsiveness and suppressed IL 2 production. Other laboratories, however, have been unable to demonstrate similar effects. Clarification of methotrexate's effect on immune activity and its relation to rheumatoid immunopathogenesis await further studies.

In psoriasis, the rate of production of epithelial cells in the skin is greatly increased over normal skin. This differential in proliferation rates is the basis for the use of methotrexate to control the psoriatic process.

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.

12.3 Pharmacokinetics

Absorption

In adults, oral absorption appears to be dose dependent. Peak serum levels are reached within one to two hours. At doses of 30 mg/m^2 or less, methotrexate is generally well absorbed with a mean bioavailability of about 60%. The absorption of doses greater than 80 mg/m^2 is significantly less, possibly due to a saturation effect.

In relative bioavailability studies in rheumatoid arthritis patients, systemic exposure of methotrexate was found to be similar between Otrexup and intramuscular or subcutaneous administration of methotrexate injection at the same doses, however systemic exposure of methotrexate was higher with Otrexup as compared to oral administration of methotrexate at the same dose. Bioavailability following oral dosing showed a plateau effect at doses of 15 mg and greater. The systemic exposure of methotrexate from Otrexup at doses of 10, 15, 20, and 25 mg was higher than that of oral methotrexate by 17, 13, 31, and 36%, respectively. Methotrexate systemic absorption from Otrexup was similar when administered into the abdomen or thigh.

In leukemic pediatric patients, oral absorption of methotrexate also appears to be dose dependent and has been reported to vary widely (23% to 95%). A twenty fold difference between highest and lowest peak levels (Cmax: 0.11 to 2.3 micromolar after a 20 mg/m^2 dose) has been reported.

Significant interindividual variability has also been noted in time to peak concentration (Tmax:

0.67 to 4 hrs after a 15 mg/m^2 dose) and fraction of dose absorbed. The absorption of doses greater than 40 mg/m^2 has been reported to be significantly less than that of lower doses. Food has been shown to delay absorption and reduce peak concentration. Methotrexate is generally completely absorbed from parenteral routes of injection. After intramuscular injection, peak serum concentrations occur in 30 to 60 minutes. As in leukemic pediatric patients, a wide interindividual variability in the plasma concentrations of methotrexate has been reported in pediatric patients with JIA. Following oral administration of methotrexate in doses of 6.4 to 11.2 mg/m^2/week in pediatric patients with JIA, mean serum concentrations were 0.59 micromolar (range, 0.03 to 1.40) at 1 hour, 0.44 micromolar (range, 0.01 to 1.00) at 2 hours, and 0.29 micromolar (range, 0.06 to 0.58) at 3 hours.

Distribution

After intravenous administration, the initial volume of distribution is approximately 0.18 L/kg (18% of body weight) and steady-state volume of distribution is approximately 0.4 to 0.8 L/kg (40 to 80% of body weight). Methotrexate competes with reduced folates for active transport across cell membranes by means of a single carrier-mediated active transport process. At serum concentrations greater than 100 micromolar, passive diffusion becomes a major pathway by which effective intracellular concentrations can be achieved. Methotrexate in serum is approximately 50% protein bound. Laboratory studies demonstrate that it may be displaced from plasma albumin by various compounds including sulfonamides, salicylates, tetracyclines, chloramphenicol, and phenytoin.

Methotrexate does not penetrate the blood-cerebrospinal fluid barrier in therapeutic amounts when given orally or parenterally. High CSF concentrations of the drug may be attained by intrathecal administration of other parenteral forms of methotrexate.

In dogs, synovial fluid concentrations after oral dosing were higher in inflamed than uninflamed joints. Although salicylates did not interfere with this penetration, prior prednisone treatment reduced penetration into inflamed joints to the level of normal joints.

Metabolism

After absorption, methotrexate undergoes hepatic and intracellular metabolism to polyglutamated forms which can be converted back to methotrexate by hydrolase enzymes. These polyglutamates act as inhibitors of dihydrofolate reductase and thymidylate synthetase. Small amounts of methotrexate polyglutamates may remain in tissues for extended periods. The retention and prolonged drug action of these active metabolites vary among different cells, tissues and tumors. A small amount of metabolism to 7-hydroxymethotrexate may occur at doses commonly prescribed. Accumulation of this metabolite may become significant at the high doses used in osteogenic sarcoma. The aqueous solubility of 7-hydroxymethotrexate is 3 to 5 fold lower than the parent compound. Methotrexate is partially metabolized by intestinal flora after oral administration.

Half-Life

The terminal half-life reported for methotrexate is approximately three to ten hours for patients receiving treatment for psoriasis, or rheumatoid arthritis or low dose antineoplastic therapy (less than 30 mg/m^2). For patients receiving high doses of methotrexate, the terminal half-life is eight to 15 hours.

In pediatric patients receiving methotrexate for acute lymphocytic leukemia (6.3 to 30 mg/m^2), or for JIA (3.75 to 26.2 mg/m^2), the terminal half-life has been reported to range from 0.7 to 5.8 hours or 0.9 to 2.3 hours, respectively.

Excretion

Renal excretion is the primary route of elimination and is dependent upon dosage and route of administration. With IV administration, 80% to 90% of the administered dose is excreted unchanged in the urine within 24 hours. There is limited biliary excretion amounting to 10% or less of the administered dose. Enterohepatic recirculation of methotrexate has been proposed.

Renal excretion occurs by glomerular filtration and active tubular secretion. Nonlinear elimination due to saturation of renal tubular reabsorption has been observed in psoriatic patients at doses between 7.5 and 30 mg. Impaired renal function, as well as concurrent use of drugs such as weak organic acids that also undergo tubular secretion, can markedly increase methotrexate serum levels.

Excellent correlation has been reported between methotrexate clearance and endogenous creatinine clearance.

Methotrexate clearance rates vary widely and are generally decreased at higher doses. Delayed drug clearance has been identified as one of the major factors responsible for methotrexate toxicity. It has been postulated that the toxicity of methotrexate for normal tissues is more dependent upon the duration of exposure to the drug rather than the peak level achieved. When a patient has delayed drug elimination due to compromised renal function, a third space effusion, or other causes, methotrexate serum concentrations may remain elevated for prolonged periods.

When other forms of parenteral methotrexate are administered during cancer chemotherapy, the potential for toxicity from high dose regimens or delayed excretion is reduced by the administration of leucovorin calcium during the final phase of methotrexate plasma elimination.

Pharmacokinetic monitoring of methotrexate serum concentrations may help identify those patients at high risk for methotrexate toxicity and aid in proper adjustments of leucovorin dosing.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Methotrexate has been evaluated in a number of animal studies for carcinogenic potential with inconclusive results. Although there is evidence that methotrexate causes chromosomal damage to animal somatic cells and human bone marrow cells, the clinical significance remains uncertain.

Data are available regarding the risks for pregnancy and for fertility in humans *[see Use in Specific Populations (8.1 and 8.6)]*.

14 CLINICAL STUDIES

14.1 Rheumatoid Arthritis

Clinical trials in patients with rheumatoid arthritis were performed using other formulations of methotrexate.

In patients with rheumatoid arthritis, effects of methotrexate on articular swelling and tenderness can be seen as early as 3 to 6 weeks.

Most studies of methotrexate in patients with rheumatoid arthritis are relatively short term (3 to 6 months). Limited data from long-term studies indicate that an initial clinical improvement is maintained for at least two years with continued therapy.

14.2 Polyarticular Juvenile Idiopathic Arthritis

Clinical trials in patients with polyarticular juvenile idiopathic arthritis were performed using other formulations of methotrexate.

In a 6-month double-blind, placebo-controlled trial of 127 pediatric patients with pJIA (mean

age, 10.1 years; age range, 2.5 to 18 years; mean duration of disease, 5.1 years) on background nonsteroidal anti-inflammatory drugs and/or prednisone, methotrexate given weekly at an oral

dose of 10 mg/m^2 provided significant clinical improvement compared to placebo as measured by either the physician's global assessment, or by a patient composite (25% reduction in the articular-severity score plus improvement in parent and physician global assessments of disease activity). Over two-thirds of the patients in this trial had polyarticular-course JIA, and the numerically greatest response was seen in this subgroup treated with 10 mg/m^2/wk methotrexate.

The overwhelming majority of the remaining patients had systemic-course JIA. All patients were unresponsive to NSAIDs; approximately one-third were using low dose corticosteroids.

Weekly methotrexate at a dose of 5 mg/m^2 was not significantly more effective than placebo in this trial.

15 REFERENCES

1. "Hazardous Drugs". *OSHA*. http://www.osha.gov/SLTC/hazardousdrugs/index.html

16 HOW SUPPLIED/STORAGE AND HANDLING

Otrexup contains methotrexate in a preservative-free sterile solution for a single subcutaneous injection. Otrexup is available in the following strengths and configurations.

Otrexup (methotrexate) injection **7.5 mg/0.4 mL**

- Carton of 1 NDC 54436-075-01
- Carton of 4 NDC 54436-075-04
  - Otrexup NDC 54436-075-02

Otrexup (methotrexate) injection **10 mg/0.4 mL**
- Carton of 1 NDC 54436-010-01
- Carton of 4 NDC 54436-010-04
  - Otrexup NDC 54436-010-02

Otrexup (methotrexate) injection **15 mg/0.4 mL**
- Carton of 1 NDC 54436-015-01
- Carton of 4 NDC 54436-015-04
  - Otrexup NDC 54436-015-02

Otrexup (methotrexate) injection **20 mg/0.4 mL**
- Carton of 1 NDC 54436-020-01
- Carton of 4 NDC 54436-020-04
  - Otrexup NDC 54436-020-02

Otrexup (methotrexate) injection **25 mg/0.4 mL**
- Carton of 1 NDC 54436-025-01
- Carton of 4 NDC 54436-025-04
  - Otrexup NDC 54436-025-02

Store at controlled room temperature, 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). PROTECT FROM LIGHT.

Handling and Disposal

Handle and dispose of Otrexup consistent with recommendations for handling and disposal of cytotoxic drugs.[1]

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information and Instructions for Use)

Risk of Organ Toxicity

Inform patients of the risks of organ toxicity, including gastrointestinal, hematologic, hepatic, infections, neurologic, pulmonary, renal and skin as well as possible signs and symptoms for which they should contact their healthcare provider. Advise patients of the need for close follow-up, including periodic laboratory tests to monitor toxicity [*see Warnings and Precautions (5.1 and 5.4)*].

Importance of Proper Dosing and Administration

Both the physician and pharmacist should emphasize to the patient that the recommended dose is taken weekly and that mistaken daily use of the recommended dose has led to fatal toxicity [*see Dosing and Administration (2)*].

Otrexup is intended for use under the guidance and supervision of a physician. Patients should not self-administer until they receive training from a healthcare professional. The patient's or caregiver's ability to administer Otrexup should be assessed. A trainer device is available for training purposes.

Patients should be instructed to use administration sites on the abdomen or the thigh. Administration should not be made within 2 inches of the navel. Instruct patients not to administer Otrexup to the arms or any other areas of the body, as delineated in the Otrexup Instructions for Use *[see Instructions for Use]*.

Risks of Pregnancy and Reproduction

Advise patients that Otrexup can cause fetal harm and is contraindicated in pregnancy. Advise women of childbearing potential that Otrexup should not be started until pregnancy is excluded. Women should be fully counseled on the serious risk to the fetus should they become pregnant while undergoing treatment. Inform patients to contact their physician if they suspect that they are pregnant.

Advise patients that pregnancy should be avoided if either partner is receiving Otrexup; during and for a minimum of three months after therapy for male patients, and during and for at least one ovulatory cycle after therapy for female patients *[see Warnings and Precautions (5.2)]*.

Discuss the risk of effects on reproduction with both male and female patients taking Otrexup.

Inform patients that methotrexate has been reported to cause impairment of fertility, oligospermia and menstrual dysfunction, during and for a short period after cessation of therapy *[see Use in Specific Populations (8.6)]*.

Nursing Mothers

Inform patients that Otrexup is contraindicated in nursing mothers [*see Use in Specific Populations (8.3)*].

Ability to Drive or Operate Machinery

Inform patients that adverse reactions such as dizziness and fatigue may affect their ability to drive or operate machinery.

Proper Storage and Disposal

Advise patients to store Otrexup at room temperature (68 to 77°F or 20 to 25°C). Inform patients and caregivers of the need for proper disposal after use, including the use of a sharps disposal container.

Address Medical Inquiries to:
Antares Pharma, Inc.
Medical Communications
100 Princeton South, Suite 300
Ewing, NJ 08628
1-855-Otrexup (1-855-687-3987)

Manufactured for:
Antares Pharma, Inc.
100 Princeton South, Suite 300
Ewing, NJ 08628 USA

PATIENT INFORMATION

Otrexup™ (oh-TREKS-up)
(methotrexate)
injection, for subcutaneous use

What is Otrexup?

Otrexup is a single-dose auto-injector containing a prescription medicine, methotrexate. Methotrexate is used to:

- treat certain adults with severe, active rheumatoid arthritis (RA), and children with active polyarticular juvenile idiopathic arthritis (pJIA), after treatment with other medicines including non-steroidal anti-inflammatory (NSAIDS) have been used and did not work well.
- control the symptoms of severe, resistant, disabling psoriasis in adults when other types of treatment have been used and did not work well.

Otrexup is only available in doses of 7.5, 10, 15, 20 and 25 mg. Your doctor will prescribe a different way to take methotrexate if you need to take methotrexate by mouth or in some other way. Your doctor may also change your prescription if your dose does not match the available Otrexup doses, such as doses of less than 7.5 mg, more than 25 mg, or doses in between the available Otrexup doses.

Otrexup should not be used for the treatment of cancer.

Otrexup should not be used for the treatment of children with psoriasis.

What is the most important information I should know about Otrexup?

Otrexup can cause serious side effects that can lead to death, including:

1. Organ system toxicity. People who use methotrexate for the treatment of cancer, psoriasis, or rheumatoid arthritis, have an increased risk of death from organ toxicity. Types of organ toxicity can include:

- gastrointestinal
- bone marrow
- liver
- immune system
- nerve
- lung
- kidneys
- skin

Your doctor will do blood tests and other types of tests before you take and while you are taking Otrexup to check for signs and symptoms of organ toxicity. Call your doctor right away if you have any of the following symptoms of organ toxicity:

- vomiting
- diarrhea
- mouth sores
- fever
- confusion
- weakness
- temporary blindness
- seizures
- headache
- back pain
- neck stiffness
- paralysis
- irritability
- sleepiness
- problems with coordination
- dry cough
- trouble breathing
- severe skin rash

2. Women who are pregnant are at increased risk for death of the baby and birth defects. Women who are pregnant or who plan to become pregnant **must not take Otrexup.** A pregnancy test should be performed before starting Otrexup.

Contraception should be used by both females and males while taking Otrexup. Pregnancy should be avoided if either partner is receiving Otrexup:

- for a minimum of 3 months after treatment with Otrexup for males.
- during and for at least 1 menstrual cycle after treatment with Otrexup for females.

Who should not take Otrexup?
Do not take Otrexup if you:

- are pregnant or planning to become pregnant. See **"What is the most important information I should know about Otrexup?"**
- are breastfeeding.
- Otrexup can pass into your breast milk and may harm your baby. **Do not** breastfeed while taking Otrexup. Talk to your doctor about the best way to feed your baby if you take Otrexup.
- have alcohol problems (alcoholism)
- have liver problems
- have problems fighting infection (immunodeficiency syndrome)
- have been told you have (or think you have) a blood disorder such as low levels of white blood cells, red blood cells (anemia), or platelets.
- have had an allergy to methotrexate or any of the ingredients in Otrexup. See the end of this leaflet for a complete list of ingredients in Otrexup.

Talk to your doctor before taking this medicine if you have any of these conditions.

What should I tell my doctor before taking Otrexup?
Before you take Otrexup, tell your doctor if you have any other medical conditions.

Tell your doctor about all of the medicines you take, including prescription, over-the-counter medicines, vitamins, and herbal supplements.

Otrexup may affect how other medicines work, and other medicines may affect how Otrexup works causing side effects.

Ask your doctor or pharmacist for a list of medicines if you are not sure.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take Otrexup?

- **Read the Instructions for Use that come with Otrexup.**
- Take Otrexup exactly as your doctor tells you to take it.
- Inject Otrexup **only 1 time each week**. **Do not** take Otrexup every day. Taking Otrexup every day may cause death from toxicity.
- Your doctor will show you or your caregiver how to inject Otrexup. You should not inject Otrexup until you have been trained on the right way to use it.

- Check Otrexup before you inject it. Otrexup should be yellow in color and should not have any lumps or particles in it.
- Otrexup should be injected in the stomach (abdomen) or thigh.
- **Do not** inject Otrexup within 2 inches of the belly button (navel).
- **Do not** inject Otrexup in the arms or any other areas of the body.
- **Do not** inject Otrexup in areas where the skin is tender, bruised, red, scaly, hard, or has scars or stretch marks.
- If you are not sure if Otrexup was injected, or if you have hard time giving the injection, **do not** inject another dose. Call your pharmacist or doctor right away.
- If you inject too much Otrexup, call your doctor or go to the nearest hospital emergency room right away.

What should I avoid while taking Otrexup?

- Do not drink alcohol while taking Otrexup. Drinking alcohol can increase your chances of getting serious side effects.
- Otrexup can cause dizziness and tiredness. Do not drive a car, operate machinery, or do anything that needs you to be alert until you know how Otrexup affects you.
- Certain vaccinations should be avoided while taking Otrexup. Talk to your doctor before you or members of your household receive any vaccines.

What are the possible side effects of Otrexup?
Otrexup may cause serious side effects, including:
See **"What is the most important information I should know about Otrexup?"**

- **fertility problems.** Methotrexate, the active ingredient in Otrexup, may affect your ability to have a baby. Males may have a decreased sperm count, and females may have changes to their menstrual cycle. This can happen while taking Otrexup and for a short period of time after you stop.
- **certain cancers.** Some people who have taken methotrexate have had a certain type of cancer called Non-Hodgkin's lymphoma and other tumors. Your doctor may tell you to stop taking Otrexup if this happens.
- **tissue and bone problems.** Taking Methotrexate while having radiation therapy may increase the risk of your tissue or bone not receiving enough blood. This may lead to death of the tissue or bone.

Common side effects of Otrexup include:

- nausea
- stomach pain
- indigestion (dyspepsia)
- mouth sores
- rash
- stuffy or runny nose and sore throat
- diarrhea
- abnormal liver function tests
- vomiting
- headache
- bronchitis
- low red, white, and platelet blood cell count
- hair loss
- dizziness
- sensitivity to light
- burning skin lesions
- lung problems

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of Otrexup. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I dispose of Otrexup?

- **Do not throw away in the household trash.** Put used Otrexup in a FDA-cleared sharps disposal container right away after use.
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  o made of a heavy-duty plastic
  o can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
  o upright stable during use
  o leak-resistant
  o properly labeled to warn of hazardous waste inside the container
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about the safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.
- Safely dispose of Otrexup that is out of date or is no longer needed.

How should I store Otrexup?

Store Otrexup at room temperature between 68°F to 77°F (20°C to 25°C)

- Do not freeze
- Keep Otrexup out of the light.

Keep Otrexup and all medicines out of the reach of children.

General information about the safe and effective use of Otrexup.

Methotrexate is sometimes prescribed for purposes other than those listed in Patient Information leaflet. Do not use Otrexup for a condition for which it was not prescribed. Do not give Otrexup to other people, even if they have the same symptoms that you have. It may harm them.

This Patient Information leaflet summarizes the most important information about Otrexup. If you would like more information, talk to your doctor. You can ask your doctor or pharmacist for information about Otrexup that is written for health professionals.

For more information, go to www.Otrexup.com or call 1-855-Otrexup (1-855-687-3987).

What are the ingredients in Otrexup?
Active ingredient: methotrexate
Inactive ingredients: hydrochloric acid, sodium chloride, sodium hydroxide and water for injection, USP.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Manufactured for:
Antares Pharma, Inc.
100 Princeton South, Suite 300
Ewing, NJ 08628 USA

antares pharma

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