HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use. RASUVOTM 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 (51).

· 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/m² once weekly (2.2)
 - Psoriasis: 10 to 25 mg once weekly of an oral, intramuscular, subcutaneous, or intravenous formulation (2.3)

FULL PRESCRIBING INFORMATION: CONTENTS* WARNING: SEVERE TOXIC REACTIONS, INCLUDING EMBRYO-FETAL TOXICITY AND DEATH

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 - 2.3 Psoriasis
 - 2.4 Administration and Handling

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 (71)
- 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.

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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 antiinflammatory 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 lowdose 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/m²/wk in children, there are too few published data to assess how doses over 20 mg/m²/wk might affect the risk of serious toxicity in children. Experience does suggest, however, that children receiving 20 to 30 mg/m²/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 drugs¹.

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:

• <u>Pregnancy</u>

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)].

<u>Nursing Mothers</u>

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)].

<u>Alcoholism or Liver Disease</u>

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)].

<u>Preexisting Blood Dyscrasias</u>

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

• <u>Hypersensitivity</u>

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/mm³) was seen in 2 patients, thrombocytopenia (platelets <100,000/mm³) 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/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, 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/mm³).

Incidence 1% to 3%: Rash/pruritis/dermatitis, diarrhea, alopecia, leukopenia (WBC less than 3000/mm³), 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 $20 \text{ mg/m}^2/\text{wk}$ 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/m²/wk in pJIA, the published data for doses above 20 mg/m²/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 H₂ 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.

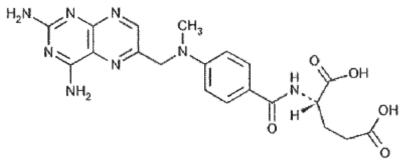
Symptoms of intrathecal overdose are generally central nervous system (CNS) symptoms, including headache, nausea and vomiting, seizure or convulsion, and acute toxic encephalopathy. In some cases, no symptoms were reported. There have been reports of death following intrathecal overdose. In these cases, 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/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 40 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 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/m²), 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/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 JIA, 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-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:
 - o gastrointestinal o nerve
 - o bone marrow o lung
 - o liver o kidneys
 - o immune system

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:

- o vomiting
- o diarrhea
- o mouth sores
- o fever
- o confusion
- o weakness

o neck stiffness

o skin

- o paralysis
- o irritability
- o sleepiness
- o problems with coordination
- o dry cough

- temporary blindness
 trouble breathing
- o seizures
- o headache
- o back pain

- 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:

- o nausea
- o stomach pain
- indigestion (dyspepsia)
- o mouth sores
- o rash
- stuffy or runny nose and sore throat
- o diarrhea
- abnormal liver function tests
- o vomiting

- o headache
- o bronchitis
- low red, white, and platelet blood cell count
- o hair loss
- o dizziness
- o sensitivity to light
- o burning skin lesions
- o 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 FDAcleared 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
 - o 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

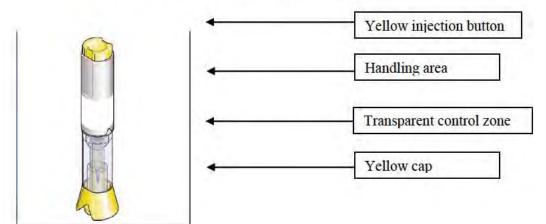
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Read this Instructions for Use before using

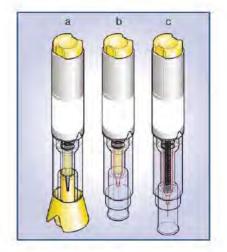
Rasuvo™ (ruh-SOO-voh) (methotrexate) injection, for subcutaneous use

Follow these instructions each time you use Rasuvo™.

Parts of your Rasuvo auto-injector



(Figure A)



(Figure B)

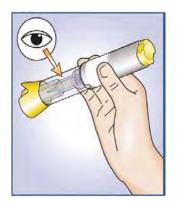
- a) Pre-filled auto-injector with cap before injection
- b) Pre-filled auto-injector after cap removal before injection
- c) Pre-filled auto-injector after injection

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



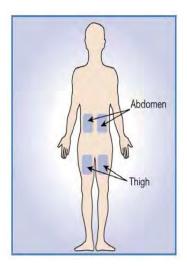
(Figure C)

- 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 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.



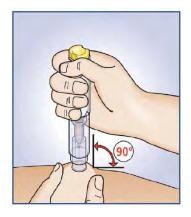
(Figure F)

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.

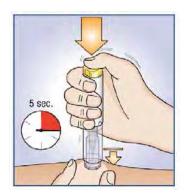


Figure H

- 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

Check 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 FDAcleared 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
 - o upright and stable during use
 - o 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

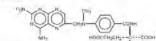
WARNINGS

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

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Tablets, USP Methotrexate

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The patiential for footistly from high door regiments or delayed econtless is induced by the administration of kucceyorin calcium doring the timal phase of interfoctments plasma silmination.

Pharmacekinetic monitoling of methotoxicals saratin concentrations may hep-salentity heats patients al high tab far methotic each locatidy and ally to proprior adjustment of heuropoint during Galdetines for monitoring section monitority data when, and for adjustment of locationet adjust to reduce the risk of methotoxical tradicity, are provided balance in DOSAGE AND ADMINISTRATION

Methodisexate has been detected in forman branch with. The bighest larence with in pleasan concentration value reacted war 0.0011.

INDICATIONS AND USAGE die Di

Methomstate is indicated in the freatment of gestational chooccarcinena, conco-ademina de and hydaitillerm mate

Methorizeda la orea in avaintenane thereacy in combination with other chemotherapeutic agents. Mamorezona in avait atoms or in commance wire other amonaper agents in the transmit of breast cancer, eligibility and the transmit of the start of network chemotherapeutic trapoles (custoresc) code prophenity, and lang varies; particularly agentees and and ented and and trapoles (custoresc) doe used in curve in cancel and the combined methods in the challment of custors and a custor and and and and and and and the custor of automat closes doe used in cancellation with other combineding-data grands in the challment of automat closes and out on the cancellation with other combineding-data grands in the challment closes and combined and the cancel access of the combined out of the cancellation of the challment closes and closes the combined out of the charge of closes and closes are combined out of the cancellation of the charge of closes and closes the closes of the cancel closes and the closes of the closes are closes and close the closes of the closes and close the closes of the closes of the closes and closes the closes and the closes of the close and the closes of the closes are closes and the closes of the closes and close are closes and close and close and close and close are closes and closes are closes and close and close are closes are c non-Hisiokin's tymphomas

Pranasis

Paramate Manameesian is indicated on the symptomatile control of severe, recalisizani, titaziong poortisics that is non anaquately responsive to other tomics of thrange para only even in the digmates has been indicatabilish, and you hange and the other contractinger constraints. It is important to annes that a spectralistic "taxes" is not due to an undiagnosed concornizer direate attracting immune responses.

Bisematoid Arthritis including Polyariloslas-Course Javenile Riaumstoid Arthritis Motorcourses in thotoste in the managements of selected sidute with seven, active, maintaida attribute (VAR course), or tailition attribute polyaritosito-course al yoend finalmatical attribute, while inter load an insufficient filmungimiti programs (or is an inholecant of , an adrepute Hail) at relative transport actional galaxies and an adversaria and an adversaria attribute. An adversaria attribute and an adversaria attribute and the adversaria attribute and adversaria attribute attribute and adversaria and adversaria attribute. Adversaria attribute attribute attribute and adversaria attribute and adversaria attribute.

constrainty inserting an over the second second

CONTRAINDICATIONS

CONTRADUCIDATIONS: Memoryland and featu death or terabgenic effects when administered to a prepriant woman. Mellioniveste is contactiviticated to pregnant women wills pointeds or rheamated witherful and wheat is sumd in the featurement of excepturely assesses anyly when the pointed barreling antwegter the rank to the history. Women of chaftering potential second not be dated or characterized and preprinter is excited and wheat hey to possible and the second and the feature of the PRERME TOSK) potentiate pocomes prepared with uncorrection presentement. Prepared motion be writted on a feature with the threat these motions are interesting as the second and the second advectional and the second and the second and the second and the second advection of the second and the second and the second advection of the second and the second advection of the second and the second and the second advection of the second and the second advection of the for male patients, and during and fel at least one contactory cycle after therapy for female patients. (See Boxol WARHINGS.)

JB

same of the potential for serious adverse (eaciliting from methodiecate in bread field infants, it is trail-scated in earling mollines.

Palienta with promote, or observatoid artitutiis with alcoholitan, alcoholita liver disease or office consult liver disease should not receive mathotrezate.

Patients with psonasis of rheumatolid attitutes who have meet of laboratory evidence of emission (a calency synthemes strends not receive meltinizeday.

Patients with poortisiss or resumations arthritin who have preexisting blood drustmann, such as oone matrow hypoplasia, leukoeeta, thromoscytopenik or significant animita, should not receive

Patients with a known hypersunativity to methotraxite should not receive the drug

WARNINGS - SEE DOXED WARNINGS,

and dilevole containing preservatives must set be used for infratileval or high dose melt revals therapy

PRECAUTIONS

should be carried out with caution, with edeouate consideration of further need for the drug and with receivered alerthesis as in possible mountained of faskelity

The clinical promecology of methorhoute has not been well intuitied in older individuals. One in diminished hepatic and renal tunction as well all decreated totals store in this population, retaining low doars should be considered, and these patients should be closely monitored for early again of toricity

Parients nousi of informed of the early signs and avmptoms of toochy, of the need to see their physican periodic 10 they occur, and the need for close following, including periodic luboraticy tests to moniter feelocity

The first of the objection and pharmacelal should weightacts to the patient that the recommend taken weaky in meantable attribute and postnatis, and that mistakin daily use of the set open key do the data landschip. Patients should be exposured to read the first initiation interference within the Doce Pack. Prescriptons should not be written or refined on a PRN basis. indians shadt

Pasiants nowald be informed of the potential benefit and this in the use of multiplicasis. The risk of effects on reproduction should be discussed with both male and tentals patients being methorwate. Laboratory Texts

Laboratory Tatis "Balands undergraving melliterinsian threapy standards to standards accomplete blood count with other without and platelet asserts, heplatic accounts at the standard technical accomplete blood count with other without and platelet asserts, heplatic accounts and accounts and accounts of the standard accounts and accounts, monotomy of the accounts and accounts, monotomy of the accounts and accounts, monotomy of the accounts in accounts and accounts and accounts and accounts and accounts and accounts, monotomy of the accounts and accounts accounts and accounts accounts account account account accounts account accoun may sloo be indicated

Instalent liver function test phonomalities are observed insquently after metholisasta administration and are auaary not cause for modification of metholoxeast brierage. Permitten fiver function test administration and or detection of access the indicators of second liver forcing and require evaluation. (See PRECAUTION), Organ System Taskinty Aparts)

A relationship between abnormal liver function heats and fibrasis or airritests of the liver fass not teles established for patients with patrents. Perticitient abnormalifies in liver function tests may procede appearance of fibricals or compasis in the mean-idoid arthritis population.

Polynomiary function losts may be useful if methodownike behaved long disease in suspir If baseline measurements are evaluate

Drug leteractions

ung transmission attrinistration of some NSAIDs with high bose methotiexale therapy has been repen-do viewals and prolong serum methotrexate lewis, resulting in deaths from severe ternatologic and gastrolisherthal hatchy.

Calculate should be used when NSAIDs and salisylikes are administered conconstantly with lower moves of methodowsite. These drugs have been imported to induce the future secretion of methodoxide in an animal model and may enhance its toxicity.

Displis for potential immediates, studies of methodsextel in patients with characteristic antivitia new usually resulted concurrent was of constant datager regenerate of RESIDE, without apparent prob-lemit. It striked be appreciated, however, that the dones used in meterinated artimity (7.5 to 20 mpl/wink) and in doministral how that more used in potential and that appreciate data strategy and approximate the constraint of how that more used in potential and that appreciate data strategy and appreciate the constraint of how that more used in potential and that appreciate data strate that data appreciate the constraint of the strategy appreciation of the strategy data strategy appreciation of the strategy data strategy data strategy appreciation of the strategy data stra stravpacted toolcity.

Methodesate is partially bound to service unknownin, and forciny may be increased bicause of displarement by certain drugs, such as satisfying, planytimizzone, planytipin, and subtainentiae. Term labeling transport is size dismission by proceeds, see of methodesate with this area shelid as acativity accented.

One anilliantics such as tetracycline, oblazamplement, and mendoarcable breate operity indics, may decrease intestinal absorption of methodyscate or interfere with the entero cocalation by invubiting boxet flors and suppressing instaorbism of the drug by bacteria

Penalities may reduce the renal charance of inelthetresale, increased server soosentrations. IN intellectrosate with concombinit hematicoopic and galationitisations folding have been observed with methodrosate. Use of methodrosate with genetilities should be sarehaly monitored.

Methatrivitie may decrease the clearance of liveopryline; theophyline levels should be increased when used concerning with methodiexide.

Certain side effects such as moulh sores may be renared by totale supplementation with notical Intellingenerstullig-involtionazote trass been reported carefy to increase been marrow suppression in dentify receiving methodreckle, probably by an additive entitionide effect.

Dereiningenetiste, Minlegenetiste, and Impairment of Farfülly No cardinale humon data wolf regariting the skin of energisest with mathematicals. Mithathematic Nan-bern invaluable for yourship of annual calculates for paramignative closeful with incollecturine rewails. Although there is weldened that uninformatic calculates thereare sensitive closeful with incollecturine rewails. Appropriate and other turners have been excluded in publication excluding the other wide methodowate. However, have have been instances of malphani herepoints article dating reactions with the other observation of methodowate. In methodowate, which have regression tomplicity hybridy with a strate of adding the same of the other regressing active and -hypothese treatment. Benefits should be weighter against the positive ratio rate rates and an adding active and -hypothese treatments.

4/28/09

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.

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

r builting clinical studies variating inclusion interformation and autorescens (e., patients 2 to 16 years of age) with JRA demonstrated safety comparable to that observed in adult with rheumatoid arthritis. (See CLINICAL PHARMACOLOGY, ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION.)

AND ADMINISTRATION.) **Clearise Law** Diamida Lawlee of metholwarea diaf not include sufficient numbers of subjects age 65 and over to distribute subjects of the second differently from younger subjects. In general, does selection for a distribute subject of the second differently from younger subjects. In general, does selection for and include, accessed folias stores, concommand tidease or other drug theory (in the interfere with renal function, increased folias stores, concommand tidease or other drug theory (in the interfere with renal function, methorized or foliate metabolism) in this population (See PRECAUTIONS, Drug **Interactions**). Since decline in renal function may be associated with increases in advecen events and astrum creatione measurements may over estimate renal function in the identify, more accurate methods (is; creating clearance) stored be considered. Summer methorized televity, more accurate methods, being the clearance) stored be considered. Summer methorized televity and accurate plental toxici). In chronic use shatlance, creatina toxicitism are be reduced by toxicRES executions. Destinguistication renaises with age. See Nood WARNINSS and ADVERSE ERECTIONS. **Summer Version**

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

Hematologi: Methotinoste can suppress hematopolesis and cases anemia, aplastic anemia, pancytopenia, leukopenia, mutropenia, andro thrombocytopenia, in patients with malignancy and preexisting hematopoleti impairment, the drug should be used with cancino. If at al. In controlled clinical trails in theuratopoleti impairment, the drug should be used with cancino. If at al. In controlled clinical trails in theuratopoleti impairment, the drug should be used with cancino. If at all, in controlled clinical trails in theuratopoleti impairment, the drug should be used with cancino. If at all, in controlled clinical trails in fluctures (1), the drug should be used with cancing and the drug should be used with cancing and gliabetes (1), doublets (1). The drug and participania in patients, thrombocytopenia gliabetes (1), doublet and apartopenia in 2 patients.

In psoriasis and rheumatoid arthritis, methotrexate should be stopped immediately if there is a In psychosts and metamation atomics, mentioreade source are specific diseases, method with the statement of neoplastic diseases, method trockards hour do continued only if the potential benefit warrants the risk of severe myelosuppression. Patients with profound granulocytopenia and ever should be evaluated immediately and usually require parente broad-spectrum antibiotic therapy.

undar-spectrum animotic trenzy. Hepatic: Whothevest has the potential for acute (elevated transaminases) and chronic (fibrosis and circhosis) hepatotociclic, Chronic toxicity is potentially fatal: It generally has occured after prolonged use (generally two years or more) and after a total dose of at least 1.5 grams. In studies in peortatic patients, hepatotoxicity, appeared to be a function of total curruntility 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.

indicated in the presence of prevexiting live damage or impared hepatic function. In parviasis, liver function tests, including serum allumin, should be performed periodically prior to dosing but are often normal in the face of developing fibrosis or circhosis. 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 botal cumulate does of 15 grams, and 3) after such additional 1.0 to 15 grams. Moderate throsis or any circhosis normally leads to discon-tinuation of the may (2 - 4) months), 2) a botal cumulate does of 15 grams, and 30 after such additional 1.0 to 15 grams. Moderate throsis or any circhosis normally leads to discon-tinuation of the may (2 - 4) months) and y suggests a repeat loops in 6 months. Mider histologic findings such as fatty change and low grade portal inflammation are relatively common pretherapy. Athough these mild changes are usually not a reason to avoid or discontinue methorbarate therapy, the drug should be used with caution.

In rheumatoid arthritis, age at first use of methotrexate and duration of therapy have been reported In rheumatoid arthrits, age at Inst use of methorecate and duration of therapy have been reported as risk factors for hepatoxicity), other risk factors, similar to those observed in porxisis, may be present in theumatoid arthritis but have not been confirmed to date. Persistent abnormalities in liver function tests may precede appearance of fibrosis or crimoss in this population. Three is a combined reported experience in 217 rheumatoid arthritis patients with liver biopsies both before and during treatment (after a cumulative does of at least 1.5) and in 714 patients with a biopsi only during treatment. There are 64 (7%) cases of throsis and 10, 1%) case of crimosis. Of the 64 cases of throsis, 60 were demend mild. The reticului rain is more ensitive for early florosis and its use may increase these figures. It is unknown whether even longer use will increase these

Trass. Liver function tests should be performed at baseline and at 4-8 week intervals in patients receiving methotexate for rheumatoid arthritis. Petreatment liver biopsy should be performed for patients with a history of excessive alcohol concumption, persistemity abnormal haseline liver function tasts values or chronic hepatitis B or C infection. During therapy, liver biopsy should be performed if there are persistent liver function tast banomalities or there is a decrease in serum albumin below the normal range (in the setting of well controlled rheumatoid arthritis).

In the second second

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

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

and an infiltrate on chest can occur at all dosages.

Renal: Methotrevate may cause renal damage that may lead to acute renal failure. Nephrotoxicity is due primarily to the precipitation of methotrevate and 7-hydroxymethotrevate in the renal hubules. Close attention to renal function including dequade hydration, urine alkalinistication and measurement of serum methotrevate and creatinine levels are essential for ade administration.

Skin: Severe, occasionale and occasion and examination or any summarization. Skin: Severe, occasionally fatal, dermatiski, skin occasional, including toxic epidemal netrolysis, Stevens-Johnson syndrome, a cololiaria dermatilis, skin oracis, and erythema multiforme, have seven-sponte in distanti and adults, whiti mass of oral, intramuscular, intravenous, or intrathee methotesets and multistation. Reactions were noted after single or multiple, low, intermediate or high doess of ambinistation. Reactions were noted after single or multiple, low, intermediate or losses.

One Precautions: Methotrexate should be used with extreme caution in the presence of del Methotrexate exits slowly from third space compartments (eg, pleural effusions or ascites), results in a prolonged terminian plasma that-life and unexpected toxicity. In patients with sign third space accumulations, it is advisable to evacuate the fluid before treatment and to moni plasma methotrexet levels. third space accur nlasma methotre

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 adominal distress. Other frequently reported adverse effects are malaise, undue fatigue, chills a fever, dizziness and decreased resistance to infection.

Other adverse reactions that have been reported with methorexate 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, stornatitis, anorexia, nausea, vomiting, diarrhea, hematemesis melena, gastrointestinal ulceration and bleeding, enteritis, pancreatitis.

Interna garoomeana uceano na orecong enternas, parceanas.
Blood and Lymphatic System Disorders: suppressed hematopolesis causing anemia, aplastic anemia, parchopenia, leukopenia, neuropenia and/or thrombocytopenia, hymphadenopathy and lymphopro-liferative 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, thrombosis, thrombosis phlebitis, and pulmonary embolus).

precurs, and parmonary encours). Central Nercous System: haddances, drowsiness, blurred vision, transient blindness, speech impairment including dysarthria and aphasia, hemiparesis, paresis and convusions have also courred following administration of methoreaute. Following for doess, there have been occa reports of transient subtle cognitive dysfunction, modo alteration, unusual cranial sensations, leukoncepshalogustry, or encephalogustry.

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

Interioria: The have been case reports of sometimes tatal opportunistic infections in patients receiving methotrexate therapy for neoplastic and non-neoplastic diseases. Pneumocystic carnii perumonia was te most common opportunistic infection. There have also been periods of interfaces pneumonia, sepsis, nocardiosi, histoplasmosis, cryptococcesis, herpes zoster, H simplex hepatific, 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 extoliative dermatitis.

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

Der varer reactions inder und vollen. Die vollen der vollen der

Adverse Reactions in Double-Blind Rheumatoid Arthritis Studies

Reverse relativismi in divergenzemente internazionale variente suores. In seguronamia indicativas di medinicata attitubili di patri di subarta 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/mm³).

Incidence 1% to 3%: Rash/pruritus/dermatitis, diarrhea, alopecia, leukopenia (WBC less than 3000/mm3), 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 infec anorexia, arthralgias, chest pain, coughing, dysuria, eye discomfort, epistaxis, fever, infection, sweating, tinnitus, and vaginal discharge.

swearing, immus, and vapine inscringe. Alverse Reactions in Portiasis There are no recent placebo-controlled trials in patients with psoriasis. There are two literature reports (Roemijk, 1968 and Myots, 1978) describing large series (n=204, 248) of psoriasis patients treated with methwater. Dosages ranged up to 25 m gper week and treatment was administie for up to four years. With the exception of alopecia, photosensitivity, and "burning of skin lesion (ed.a3 % to 10%), the adverse racefoul race is in these reports were very similar to those in the rheumatolid arthritis studies. Rarely, painful plaque erosions may appear.

rheumatoli arthritis studies. Rarely, painful plaque erosions may appear. Adverse Reactions in JAR Studies The approximate incidences of adverse reactions reported in pediatric patients with JRA treated with critic weekly doese of methotreaate (5 to 20 mp/m/wk or 0.1 to 0.05 mp/kg/wk) were as follows (virtual) all patients were receiving concomitant nonsterotoxid anti-infimitratory drugs, and some also were taking low doese of cortico-steroids): elevated liver function tests, 14%; gastrointestinal reactions (en, ausse, voniting, darfrah, 11%; signatting); Ky: leakopeni, 27%; adopecia, 05%; dizinese, 0.2%; and rs.ah, 0.2%. Although there is experience with dosing up to 30 mg/m/wk in JRA the publiched data for doese above 20 mg/m/wk are too limited to provide reliable estimates of adverse reaction rates.

OVERDOSAGE

OVENDEXAGE Leucovorni is indicated to diminish the toxicity and counteract the effect of inadvertently administered overdosages of methotreaate. Leucovorni administration should begin as promptly as possible. As the time intertual between methotreaate administration and leucovorni initiation increases. The effectiveness of leucovorni in counteracting toxicity decreases. Monitoring of the serum methotreade concentration is essential in determining the optimal doce and duration of treatment with leucovorti

Concentration is essentian to experiment use primaria use and using the concentration is essentian to experiment with recovering in cases of massive overforsage, hypothesis and using a value to the end to bubbles. Generally speaking, neither here and spaces in our period with a concentration and using a value to the end to bubbles. See the spectration of the end to bubbles of the end to bubbles of the end to bubbles of the end to bubbles. The end to bubbles of the end to bubbles. The end to bubbles of the end to bubbles of

In postmarketing experience, overdose with methotrexate has generally occurred with oral and intrathecal administration, although intravenous and intramuscular overdose have also been repo Reports of and overdose often indicate accidental daily administration insteaded over object divided doses). Symptoms commonly reported following and overdose include those symptoms and signs reported at pharmacologic doses, particularly hematologic and gastroinstestial relation. For example, leukopenia, thrombocytopenia, anemia, pancytopenia, hone marrow suppression. mucositis, stomatitis, onal uceration, nausea, vomiting, gastrointestinal ulceration, gastrointestinal bleding. 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

Negliastic 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 intra controctantinua and similar dopinotastic useases metrotexate is administerio drany or mud-muscularly 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 uma any maintessing toxe symptomis studiete. Ine retretiveness of therapy is ordinarily evaluated by 24 hour quantitive analysis of unitary chonoring oparatoropin (hCG), which should return to normal or less than 50 IU24 hr usually after the third or fourth course and usually be followed by a complete resolution or measurable lession in 1 6 or weeks. One to two courses of methortexate after normalization of hCG is usually recommended. Before each course of the drug careful clinical assessment is essential. Opelic 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 doese similar to those recommended for chorocarcinoma. *Lowenini*: Acube tymphotolasic lowakom in poduric patients and young addescents is the most responsive to present day chemotherapy. In young adults and older patients, clinical remission is more difficult to obtain and early relates is 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 nic drugs or in cyclic combinations with methotrexate included, has appeared to produce effective remissions. When used for induction, methotrexate in doses of 3.3 mg/m² in rapid and effective rem rapid and effects emissions. When used for induction, methofrexate in does of 3.3 mg/m² in combandion with 6% of patients and the second emissions in 50% of patients streamed, usually within a period to 4 to 6 weeks. Methofrexate in combination with other agents appears to be the drug of choice for seconding maintenance of general clinical improvement, maintenan emission is achieved and subordive care has produced period clinical improvement, maintenan therapy is initiated. Is clinics. When the appendix of a sub-intramunocular biology of the second second second second second second second intramenously with total weekly does of 30 mg/m². It has also being biolice on an again second seco 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.

Lymphonas: In Burkit'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 comonshy given concomstantly with other anti-lumor agents. Treatment in all stages usually consists of several courses of the drug interposed with 7 to 10 day rest periods. Lymphosarcoms as Isdage III any sepsond to combined from thetrovate given in thortowaster of the stage in the several courses of the drug interposed with 7 to 10 day rest periods. doses of 0.625 to 2.5 mg/kg daily.

Mycosis Fungoides (cutaneous T cell /ymphoma): Therapy with methotexate as a single agent appears to protoce clinical responses in up to 5% of patients treated. Dosage in early stages is usably 5 to 50 more weekly. Dose recipications or cessation is guided by patient response and hematologic monitoring. Methodexate has also been administered here weekly in does ranging tion 15 to 37.5 mg a patients with Dave responded poorly to weekly therapy.

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

2. Divided oral dosages of 2. and the events of a dosage of 2. and the events of a dosage of 2. and the events of a dosage of 2. and the events of the event of the even of the event of the event of the e

grant non-receive. 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 tooir cracions, especially how marrow suppression, at doses greater than 20 mg/wk, in adults. Athrough there is experience with doses up to 30 mg/m²/wk in children, there are too few published data to assess how doses over 20 mg/m²/wk implifaction this risk erisious tookily in children. Experience does suggest, however, that children receiving 20 to 30 mg/m²/wk (0.65 to 1.0 mg/kg/wk) mg/she better asseption and fewer gastoninestinal side effects if methotrexate is administered either intramuscularly or suboutaneously.

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.

uireajy, vinimi inelioiotekae is backnimulea, lue aunite takang vionensis winimi s to b weeks. The patient should be tilvij informand of the risks involved and should be under constant supervision of the physician (See Information for Patients under PRECAUTIONS). Assessment of hermatologic, hepatir, enal, and upuinoarja function should be made by bitory, physical examination, and labo-ratory tests before beginning, pariodically during and before reinstatuling 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.¹⁵ There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate

HOW SUPPLIED

Grat: 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

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 g occupational exposure to hazardous drugs (OSHA Work-Practice Guidelines). Am J

- Health Syst Pharm 1996: 53: 1669-1685
- Hatah Syst Pharm 1996: 53: 1669-1665.
 2. National Sudy Commission on Cytotoxic Exposure Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, Sc D. Chairman, National Study Commission on Cytotoxic Exposure. Massachuetts College of Pharmary and Alleid Health Sciences, 179 Longwood Avenue, Boston, Massachuetts 20115.
 3. Clinical Oncological Society of Australia: Guidelines and recommendations for safe handling of antimeoplastic agents. *Med J Australia* 1983; 1:426-428.
 4. Jones RH, et al. Sch handling of Charlon Langents: A roport from the Mount Sinai Medical Control. CA: A Canow Journal for Clinicains SeptVict 1983; 258-263.
 5. American Society of Hospital Pharmalists technical assistance buildin on handling cytotoxic and hazardous drugs. *Am J Hosp Pharm* 1990; 47:1033-1049.

Manufactured For: DAVA Pharmaceuticals, Inc. Fort Lee, NJ 07024 USA

EXCELLA GmbH

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.

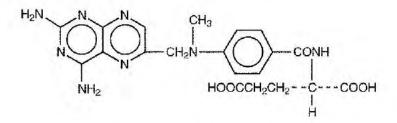
- 1. Methotrexate has been reported to cause fetal death and/or congenital anomalies. Therefore, it is not recommended for women of childbearing potential unless there is clear medical evidence that the benefits can be expected to outweigh the considered risks. Pregnant women with psoriasis or rheumatoid 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 C20H22N8O5

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/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-course 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.

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/m² dose) has been reported. Significant interindividual variability has also been noted in time to peak concentration $(T_{max}: 0.67 \text{ to } 4 \text{ hrs after a } 15 \text{ mg/m}^2 \text{ dose})$ and fraction of dose absorbed. The absorption of doses greater than 40 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 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/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 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/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 (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/m²). (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/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. 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/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 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/mm³).

Incidence 1% to 3%: Rash/pruritus/dermatitis, diarrhea, alopecia, leukopenia (WBC less than 3000/mm³), 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/m²/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/m²/wk in JRA, the published data for doses above 20 mg/m²/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/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/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/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	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†	$50 \text{ mg/m}^2 \text{ IV}$	20,23,33,36
Cisplatin†	$100 \text{ mg/m}^2 \text{ IV}$	20,23,33,36
Bleomycin†	15 units/m ² IV x 2 days	2,13,26,39,42
Cyclophosphamide†	$600 \text{ mg/m}^2 \text{ IV x}$ 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/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. 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.^{\dagger}
- 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/m² 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/m²/wk in children, there are too few published data to assess how doses over 20 mg/m²/wk might affect the risk of serious toxicity in children. Experience does suggest, however, that children receiving 20 to 30 mg/m²/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

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*, March 15, 1985.
- 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.

‡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.



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 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*).

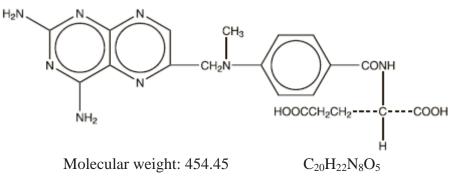
- 5. Methotrexate-induced lung disease, including acute or chronic interstitial pneumonitis, is a potentially dangerous lesion, which may occur acutely at any time during therapy and has been reported at low doses. It is not always fully reversible and fatalities have been reported. Pulmonary symptoms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



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/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-course 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.

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/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 40 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 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/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 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/m²). (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/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 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/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, 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/mm³).

Incidence 1% to 3%: Rash/pruritis/dermatitis, diarrhea, alopecia, leukopenia (WBC less than 3000/mm³), 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/m²/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/m²/wk in JRA, the published data for doses above 20 mg/m²/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/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/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/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	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	$30 \text{ mg/m}^2 \text{ day IV x 3 days}$	8,17
Doxorubicin [†]	$50 \text{ mg/m}^2 \text{ IV}$	20,23,33,36
Cisplatin [†]	$100 \text{ mg/m}^2 \text{ IV}$	20,23,33,36
Bleomycin [†]	$15 \text{ units/m}^2 \text{ IV x } 2 \text{ days}$	2,13,26,39,42
$Cyclophosphamide^{\dagger}$	$600 \text{ mg/m}^2 \text{ IV x 2 days}$	2,13,26,39,42
Dactinomycin [†]	$0.6 \text{ mg/m}^2 \text{ IV x } 2 \text{ days}$	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. 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.[†]
- 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/m² 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/m²/wk in children, there are too few published data to assess how doses over 20 mg/m²/wk might affect the risk of serious toxicity in children. Experience does suggest, however, that children receiving 20 to 30 mg/m²/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.^{\dagger}
- 2. Divided oral dose schedule 2.5 mg at 12 hour intervals for three doses.^{\dagger}

[†]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 VialNDC 61703-408-221 g, 40 mL VialNDC 61703-408-412.5 g, 100 mL VialNDC 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

- 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.

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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



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.

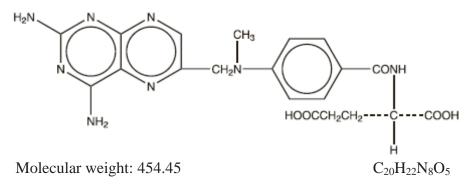
11. Methotrexate given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.

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:



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/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-course 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.

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/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 40 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 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/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 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/m²). (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/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 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/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, 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/mm³).

Incidence 1% to 3%: Rash/pruritis/dermatitis, diarrhea, alopecia, leukopenia (WBC less than 3000/mm³), 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/m²/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/m²/wk in JRA, the published data for doses above 20 mg/m²/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/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/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/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	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 [†]	$50 \text{ mg/m}^2 \text{ IV}$	20,23,33,36
$Cisplatin^{\dagger}$	$100 \text{ mg/m}^2 \text{ IV}$	20,23,33,36
Bleomycin [†]	15 units/m ² IV x 2 days	2,13,26,39,42
Cyclophosphamide [†]	$600 \text{ mg/m}^2 \text{ IV x 2 days}$	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/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. 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.^{\dagger}
- 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/m² 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 $30 \text{ mg/m}^2/\text{wk}$ in children, there are too few published data to assess how doses over $20 \text{ mg/m}^2/\text{wk}$ might affect the risk of serious toxicity in children. Experience does suggest, however, that children receiving 20 to 30 mg/m²/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.^{\dagger}
- 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 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).
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

CENTER FOR DRUG EVALUATION AND RESEARCH

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Application Number 40-233

Approval Letter

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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,

6/17/99 Douglas L. Sporn Director

Office of Generic Drugs Center for Drug Evaluation and Research

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> > - 6/11/ag

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cc: ANDA 40-233

Endorsements:

CENTER FOR DRUG EVALUATION AND RESEARCH

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Application Number 40-233

FINAL PRINTED LABELING

Page 00113

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-----Tablets, USP R only

WARRINGS

TABLETS, USP

METHOTREXATE

METHOTREXATE

TABLETS. USP

WARRINGS METHOTREKATE SHOULD BE USED ONLY BY PHYSICIANS WHOSE KNOWLEDGE AND EXPERIENCE INCLUDE THE USE OF ANTI-METABOLITE THERAPY BECAUSE OF THE POSSIBILITY OF SERIOUS TOXIC REACTIONS

WHICH CAN BE FATAL)

HILM LAW BE FAIALL METHLATERSATE SHOULD BE USED ONLY IN LIFE THREATENING NEOPLASTIC DISEASES OR IN PATIENTS WITH PSORIASIS OR RHEUMATOIBMATHRITIS WITH SEVERE RECALCITRANT DIS-AULING DISEASE WHICH IS NOT ADEQUATELY RESPONSIVE TO

OTHER FORMETOR THEORY DEATHS HAVE BEEN REPORTED WITH THE USE OF METHOTREXATE IN THE TREATMENT OF MALIGNANCY, PSORIASIS, AND RHEUMA-TOID ARTHRITUP

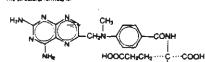
PATIENTS SHOULD BE CLOSELY MONITORED FOR BONE MAR-ROW LIVER, LUNG AND KIDNEY TOXICITIES (Son PRECAUTIONS) PATIENTS SHOULD BE INFORMED BY THEIR PHYSICIAN OF THE RISKS INVOLVED AND BE UNDER A PHYSICIAN'S CARE THROUGHOUT THERAPY

- Methotrexate has been reported to cause retai death and/or con-genifai anomalies. Therefore, it is not recommended for women of childbearing potential unless there is clear medical evidence that the benefits can be expected to outway the considered risks Pregnam women with psonasis or meumatoid artificities should not receive methotrekate. (See CONTRAINDICATIONS.) ed arthritis should not
- Methotrexate elimination is reduced in patients with imparted renal 2 function ascites, or pleural effusions. Such patients require esne cially careful monitoring for toxicity, and require dose reduction or in some cases, discontinuation of methotrexate administration.
- Unexpectedly severe isometimes fatall bone marrow suppression and gastrointestinal function have been reported with concompany administration of methotrexate (usually in high dosage) along with 3 some nonsteroidal anti-inflammatory drugs (NSAIDs), (See PRE-JØ INTERACTIONS.)
- state causes hepatotoxicity, fibrosis and cirmosis, but Mate generally only after prolonged use. Acutely, inverse argume eleva-is are frequently seen. These are usually transent and asymptomatic, and also do not appear predictive of subsequent he disease. Liver bloosy after sustained use often shows histo changes, and fibrosis and cirrhosis have been reported; these intter lesions may not be precaded by symptoms or abnormal liver function tests in the psonasis population. For the reason, periodic Iver biopsies are usually recommended for psorubic patients who are under long-term treatment. Persistent abnormalities in liver function tests may precede appearance of fibroses or currhosis in the rheumatoid arthritis population. (See PRECAUTIONS: Organ System Toxicity, Hepatic.)
- Methotrexate-induced lung disease is a potentially dangerous 5 lasion, which may occur acutely at any twise 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, honoroductive couch) may require interruption of tradment and careful investigation
- Diarrhea and ulcerative stomates require interruption of therapy; otherwise, hemorthagic ententis and death from intestinal perforation may occur
- Makonant hypothemas, which may moress following withdraway of melogram rynnownas, much may ngress rollowing withoread o methofreats. may occur in patients' receiving forw-doke methofreats and thus, may not require cytotoxic treatment. Discontinue methofreate first and, if the lymphome does not regress, approvate treatment blook do antictude. Like other cytotoxic drugs, methofreats may induce "tumor lysis
- 8 Syndrome" in patients with rapidly growing turnors. Appropriate Supportive and pharmacologic measures may prevent or alleviate this complication.
- Several occasionally fatal, slor reactions have been reported to 9 lowing single or multiple doses of methotrouste. Reaction have occurred within days of oral, intramuscular, intravenous. intrathecal methotrexate administration. Recovery has been reported with discontinuation of therapy. (See PRECAUTIONS. Organ System Tuzicity, Skm.)
- 10 Potentially fatal opportunistic infectione, especially Pneumocystes carinu pneumonia, may occur with methotraxate therapy.

RESCRIPTION

Methotrezate (formerly Amethoplerin) is an anometabolith used in the treatment of certain neoplastic diseases, severe peoplasis, and adult rheumatool arthmbs

Chemically methotrexate is #-[4-[[(2,4-diamino-6-ptendinyi)methyi)methyi amino (bilinzoyi)-L-glutamic acid The structural formula is:



Molecular weight: 454.45

C,,H_,H,O, Each tablet for oral administration contains methotropate sodium eq to 2.5 mg of methotrexere. In addition, each tablet contains the following ints: lactose monohydrate, magnesium steerale and prege Baized Starch

CLINICAL PHANMACOLOGY

Alethotrexate inhibits dihydrotokic acid reductase. Dihydrotolates must be reduced to tetrahydrotokates by this enzyme before they can be utilized as carriers of one-carbon groups in the synthesis of purne nucleotides and thymidytals. Therefore, methotrikate intelleres with DKA synthesis, repair. and calkias relations interaction interacting with Order systems in space and calkias relations interacting problems of Brases such as mailynant others. Done marrow letal cells, bucca, and intestinal muccas, and cells of the un-nary bladder are in general more sensitive to this effect of methodrivate. When cellular orbiteration in malignant status is granter than in most normail tissues, methotrakate may impair makignant growth without imversible damage to normal tissues

The mechanism of action in rheumatoid arthritis is unknown; it may affect immunal unction. Two reports discribe in vitro methotraxate inhibition of DNA precursor uptake by stimulated monutostate initiation ONA precursor uptake by stimulated monutostate energy describes in animal polyarithms partial correction by methodinate of spleen cell hyporesponsiveness and suppressed IL 2 production. Other laborationes, novever have been unable to demonstrate similar effects. Clarification of novever have been unable to demonstrate similar effects. Clarification of interchorestes effect on immune activity and its relation to rheumatoid immunopathogenesis awari further studies. In patients with rheumatoid arthritis, effects of methotrexate on articular

- > weeks -Athough herhoprexate treamy interporters symptoms of inflammation pain swelling stiffness; there is no evidence that it induces remission or theumation article is nor has a peneticial stiet been demonstrated on bone erosio ogic changes which result in impaired loth use. functional disability and deforming

Most studies of methotrexate in patients with meumatoid arthritis are relalivery short lerm (3 to 6 months). Limited data from one-term stores indi-cate that an initial clinical improvement is maintained for at least two vears with continued therapy

with controlled metabyling of production of epithekal cells in the skin is greatly increased over normal skin. This differential in proliferation rates is the basis for the use of methotrexate to comrol the psonatic process.

Pharmaselinetics

Thermademinister Absorbation - adults, oral absorption abpears to be dose dependent. Peak serum levels are reached within offe to two hours At doses of 30 mg/m or dess methorizents is generative well absorbed with a mean touraviablewy of about 60%. The absorption of doses greater than 80 mg/m is significantly ess possibly due to a saturation effect

iess possibly due to a spluration effect in leukemic pediatric patients, or is absorbed to the two water to be a spluration effect water water is a spluration of the splurat concentration

concentration Distribution- After intravenous administration, the initial volume of distribu-ion is approximately 0, 18 L/bg (18% of body weight) and steady-state vol-ume of distribution is approximately 0.4 to 0.8 L/bg (16%) to 80% of body weight). Methotrakate competes with reduced tolates for active transport across cell mempares by means 01 a single carrier-mediates drive transport process. Al serum concentrations greater than 100 micromolar, passive driftpouss, ni sarum concentrators greater inter i ou micromotal, passee diffu son becomes a macro pathway by which effective intracellusitic concentration can be achieved. Methodresste in serum is approximately 50% portein dound Laboratory studies demonstrate that it may be displaced from beama abu min by vanous compounds including suitonamudes, sakeylates, tetracyclines chloramphenicol and oherwin

Concerning memory and preservoir Methotrastic does not perfinite the olood-cerebr, invest fluid barwer in ther-abstric arryons when origin origin or perividensity, high CSE concentrations of the drug may be attained by intrathecal administration.

of the orug may be suppred by minimum extrimitivement. In dogs, synovial fluid concentrations after oral dosing were higher in inflamed than uninflamed (bask. Although saicylates dai not inflarfere with this genetration, prior oredinisone treatment reduced benetration into ed white to the level of normal lowes

Inflamed banks to the level of normal jooms. Metabolism-Netra absorption methodrexist undergoes hapsize and intracentu-lar metabolism to polyguitamated forms which can be converted back to methodrexiant by involutase enzymes. These polyguidamates acc as miniphores of divivorofolder adductase and thromolygital symitetase. Small amounts on methodrexite adductase and thromolygital symitetase. Small amounts on methodrexite polyguidamuties may remain in tissues for extended penode. The retention and prolonged drug action of these active metabolities vary among different cells, insues and fumors. A small amount of metabolism to 7-rydroxymethotsmate may occur at doses commonly operating docum-ation of this metabolitie may become significant at the high doses used in offeogenic sarcoma. Methotrasiate is narbally metabolized by interconal flora after oral administration

after orgal administrations. Maff Link - The terminian half-life reported for methydrexate as approximately threat to tern hours for patients receiving intertwent for peoness, or meume-tod artifrite or low togos antimepolastic threaty (less than 30 mg/m). For patients receiving high doese of methodrexate, the terminal half-life is 8 to 15 hours.

Accesson-Renal extration is the primary rouse of elemination and is dependent upon dosage and rours of administration. With IV accession, 80% to 90% of the administrated dose is excited enchanged in the universe within 24 hours. There is limited believy sucretion amounting to 10% or less of the administration.

There a limited bilary suscrition amounting to 10% or less of the administered dose, Enteronepade recrucitation of methodrawate has been proposed. Renal excretion occurs by glorenrular Mitrzbon and active tubular secretion. Nonlinear elementation due to saturation of renal bubuar reassorbion has been observed in peonitic patients at dolase between 7.5 and 2.5 mg, inseased renal function, as well as concurrent use of drugs such as watek organic acids that also undergo tubular secretion, can markedly increase methodrexate clearance and enogenous creationire clearance.

Methotrexate clearance rates vary widely and are generally decreased at higher coses. Delayed drug clearance has been identified as one of the major factors responsible for methotrexats toxicity. If has been postulated that the

Intergramma elevated for process and second and a second concernations may remain elevated for process and an annual breast milk. The highest breast milk to plasma concentration ratio reached was 0.08(1.

NOICATIONS AND USAGE islastit Öla

Methotruzzes is indicated in the insertence of gestational choracarcinoma, chorioadenome destruene and hysisticiform mole. In acute lymphocytic leukeme, methotisizate is indicated in maintenance.

Interacy in contensition with other chemotenagesuce approximate a also indicated in the treatment of meningue leukemis. Methotraxies is Methotraxies is used alone or in combination with other anti-cancer agents in

the treatment of breast cancer, ebidermoid cancers of the feed and neck advanced mycous fungoides, and tung cancer. Puriousiny squamous cell and small cell types. Methetraxis is also used in combination with other chemolinerapeutic agents in the treatment of advanced stage non-Hodgion's vinninga

Methotreate is indicated in the symptomatic control of severe, recalcitrant disabling psocases that is not adequately resonance to other forms of therapy but one y when the diagnosis has been established, as by bropey and/or afte bropic consultation. It is important to ensure their a peonesia "flare" i not due to an undergnosed concomitant disease affecting imm abit Arthritis

Methotrasate is indicated in the management of selected adults with seven active, classical or definite rhounation arthritis (ARA criteria) who have ha an insufficient therapeutic response to, or are intolerant of, an adequal

an instificient therapeutic response to to are indetermini of, an adequate there of first-iner benagy including hald does NSAUDs and usually a triat of all least one or more disease-modifying anticheumatic drugs. Aspinn, nonsteroidal anti-inflemmatory agents, and/or low does steroids may be computed, although the possibility of informatic tower does steroids may be computed, although the possibility of informatic tower does steroids may be computed, although the possibility of informatic tower does steroids may be computed, although the possibility of informatic tower does steroids and concomentations. Steroids may be indiced gradient with good, pen-whor respond to mathematications. Compared use of method proteinade with good, pen-Illiamine, hydroxytchioroquine, suffasalazine, or cytotoxic agents, has not even studied and may increase the incidence of adverse effects. Rest and invisionerapy as indicated should be continued. cilla

CONTRANIOICATIONS

Methotraxate can cause letal death or teratogenic effects when ad-Methorspate can cause (etail desit or iteratogene, effects when administratio to a pregnant woman. Methorspate is contraindicated in pregnant women with asonausis or insumation arthritis and should be used in the treatment of neousetic diseases only when the obtained banefit outweight the risk to the intel. Women of childbearing potenties should be fully counseled on the sensus until pregnancy is accluded and should be fully counseled on the sensus risk. To the Mus, isse PRECAUTIONS) should they become pregnant write under-going treatment. Pregnancy should be avoided in ether services in under-going treatment. Pregnancy should be avoided in ether services in under-going treatment. Pregnancy should be avoided in ether services is recovering methoetsuste: during and for a minimum of three months after therapy for whe cations used curring und or it east one overatory come arter meratry for emain patients. See Boxed WARNINGS

Because of the potential or serious squerse reactions from metho are in preast regiinfants. It is contraindicated in hursing mothers Patients with oportable or ineumatoid arthritis with alcoholism alco-holic liver disease or other chronic liver disease should not receive

Patients with psociasis or relevination arthres and have overt or abo TRODY EXIDENCE OF UTTIMUNODEFICIENCY SYNOLOTIES SHOULD NOT RECEIVE nethotresate

Patients with psonasis or ineumatoid arthritis who have preexisting blood dyscrasias, such as bone marrow hypopiasial eukopenial thrombocytopenia or significant ariemial should not receive hotrexate

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

WARNINGS - SEE BOXED WARNINGS. PRECAUTIONS

General

demotrexate has the potential for serious toxicity (See Boxed WARN-Methodistate has the overstate in seriods (buckly lose boxed warms INGS / row effects may be retained in requency and seventy to dose or frequency of administration but have been seen at sit doses Because they can occur at any time buring therapy, it is necessarily follow batients on methodirexalle closely. Most adverse reactions are "eversible if detected early when such reactions do occur the drug should be reduced in dosage of discontinued and appropriate correc-mentation." tive measures should be taken if necessary, this could include the use of leucovorin calcium, i see OVERDOSAGE L if methotrexate therapy is reinstituted, if should be carried out with caution, with adequate con sideration of further need for the drug and with increased alertness as

sideration of further relea for the drug and with increased alertness as to possible relurance of location of the drug and with increased alertness as to possible relurance of location of the drug and the second of the the linkage of the second of the second of the second of the well as declassed lobals stores in this population, reservely, we does should be considered, and these patients should be closely monitored for a dominance in termination. for early signs of toxicity.

motion for Patients

Parients should be inform of the early signs an, symptoms of write ity, of the-reed to see their physician promotivil they occur and the need for close follow-up, including periodic laboratory lesis to monitor 10xiCity

Both the physician and pharmacist should emphasize to the patient that the recommended dose is taken weekly in rheumatoid arthritis and osoriasis, and that mistake daily use of the recommended dose has led to tatal toxicity. Prescriptions should not be written or refileg

has led to tatal toxicity, integrations among the operation of the second of the second of the operated should be informed of the operated should be informed of the operated should be dis-of methodrexate. The nex of effects on reproduction should be dis-cussed with both male and temale papents taking methodrexate.

Patients undergoing methotrexate therapy should be closely moni-tored so that toxic effects are detected promptly, Baseline assessment should include a complete blood court with differential and plateat counts, hepatic enzymes, renal function test@rand a chest X-ray courses negatic enzymes, renal function testignered a crest A-ray buring therapy of refunction arbitritis and oscifiatiss, monitoring of these darameters is recommended: hemistology allases monthly, renal function and liver function every 1 to 2 months. More frequent mon-trong is usually indicated during anneoeusiant Twerty. Purning immail or changing doses, or during periods of incredised risk of elevated mathoticitate lood levels (eg. dehydration), more frequent monitoring may also be indicated.

Transiers liver function test abnormatities are observed frequently atter realiseen inter unicour aas abnumaans are ousaive requering are nettotocusta administration and are usually no cause for modication of methoreaste therapy. Persistent liter function test abnormatities, and/or depression of serum albumin may be indicators of serious liver functify and require evaluation. Isee PRECAUTIONS, Organ System Toxicity, Mediatic I

A relationably between abnormal Aver function tests and function or un-fronts of the finan not been established for justerits with psoriasis Persistent abnormalities in liver function tests may precede appearance. of fibrosis or cirrhosis in the rheumatoid arthritis population

nonary function tests may be useful if methotrexate-induced lung lase is suspected, aspecially if baseine masurements are exclable **Orne 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

methofisates levels, resulting in deaths from Severe nematologic and gastrointestinal lowcrity. Caution should be used when NSAIDs and sancylates are administered concomfantly with lower doses of methotrexitis. These drugs have been reported to reduce the tubular secration of methotrexite in ave animal model and may enhance its loxcrity. Despite the obtential interactors, studies of methotrexitis in patients with their sector entries have all concisions.

with rheumatoid arthritis have usually included concurrent use of con-stant dosage regiments of NSAIDs, without apparent problems, it start observer regiments of novicos, without apparant problems, it should be appricated, however, the the doses user in insuration artitritis (7.5 to 1.5 mg/week) are somewhat lower than iffose used in peoriesis and that larger doses could lead to unexpected toxicity.

Methomsteat is pertainly bound to serum albumin, and foxchy may be increased because of displacement by certain drugs, such as sericy-lates, phenylbutazone, phenytoin, and sufformandes, Renar tubular transport is also diminished by probehecid; usa of methotrexate with this drug should be carefully monitored.

this oring should be carefully monitored. Oral ambiports such as terrary monitored. Torial ambiports such as terrary encrease missional absorption of methodesate or interfars with the ensorbleague croutation by inhibiting bowel force and suppression, metabolism of the drug by Bactma. Pencelians may reduce the renal clearance of methorstate, increase surm concernizations of methorstate with concornarian themalologic and gastrointestinal loxicity have been observed with high and low may methorstate. Joss of methorstate with chancellings tabuild he

thotrexate. Use of methotrexate with periodilins carefully monitored.

Patients receiving concomitant therapy with methotrexate and etreti-nate or other retinoids should be monitored closely for possible increased raik of hepstotoxic/dy. Methodixiaat may decrease the clearance of theophylikne: theophylikne

levels should be monitored when used concurrently with methomsaite. Vitemin preparations containing toke and or its derivatives may decrease responses to systemically administered methotrexate. declasa trabonisa to systemicary administratio methotekae Preliminary amini and human studies have shown trat small quaht-hee of intravenously administered ielocoroni enter the CSF primarily as 5-methylettahydrotolais and, in humani, raman 1-3 profes of magnitude lower than the usual memotraxate concentrations following intrathecat administration. However, high doses of leucovorin may reduce the efficacy of intrathecally administered metholereate.

Folate detroiency states may increase methorrexate toxicity Trimethoprim/sultamethoxazole has been reported rarely to increase bone marrow suppression in patients receiving methotrexate probably by an additive antiholate effect.

openania. Mutopenasis, Imp at at Fartille

No controlled human data sirst regarding the risk of neoptasia with methomersaas. Jashhotersaate has been evaluated in a number of animar studies for carcinogenic potential with inconclusive results. Attriougn there is evidence that methomersaate cavies chromosoma comage to animal somatic cells and human bone marrow cells. The clinical signifi-cance remains uncertain across a cells and indiring and other tumors have been reported in patients receiving low-dose oral methorrexate

Juri & treamentality ownose oral metholicetale which have ingressed concerent voloeing whitesweet of methodosate whites requiring active arei-impoint insement. Benefits should be elegand agilunas the potential insis before using methorresate alone or in com-binetion, with other drugs asbecally in pediatric patients or young durits Methorizate dausse emoryoloxicity abornion and fetal detects in humans it has also been reported to cause impairment of fetality. oligospermia and menstrual dysfunction in humans, during and for a short period after cessation of therapy

PSORiasis and meumatoid arithmis. Methotrevate is in Pregnancy Category X Set CONTRAINDICATIONS.

See CONTRAINDICATION

Pediatric Use

Salaty and effectivenessin pediatric patients have not been estabished other than in cancer chemotherapy Organ System Texisity

organ appears tassaus it sometige, darmas, or stomatrics occur, which may esuit in debugsaban, methotrexate should be discontinued until recovery occurs. Methotrexate should be used with extreme caution in the presence of peptic uicer disease or ulcerative colitis.

Mematologic Methotrexate can suppress hematopoiesis and cause anema: isukopena; and/or thrombocytopena. In patients with maig-nancy and presisting hematopoietic impairment, the orug should be used with caughton. I at all in controlled himital trails in meumatord arthritis (n = 128), leukopania (WBC <3000/mm²) was seen in 2 patients, thrombocytopenia (plateets <100.000/mm²) in 6 patients and pancytopenia in 2 patients.

and perception in a percent. In portials and returnational arthrins, methotrexite should be stopped immediately if there is a significant grop in blood counts, in the treat-ment of neoplastic diseases, methotrexite should be continued only if the potential benefit warrants the risk of severa myelosuppression Patients with protound grasulocytopenia and lever should be mediately and usually require parenteral broad-spectrum ated in herapy

Hepatic: Methotrewate has the potential too acute (elevated transam Gass) and chronic librosis and cirrhosmi hepatotoxicity. Chronic tox-city is potentially fatal, it generally has occurred after protonged use (generally two years or more) and after a total dose of at least 1.5 grams. In studies in oscialic patients, hepstotoxicity appeared to be function of total cumulative dose and appeared to be enhanced by alcoholism, obeanly, diabetes, and advanced age. An accurate incr dence rate has not been determined; the rate of progression and reversibility of leasons in classific damage or impaired by optication and presence of preexisting liver damage or impaired hepitic function. In psonasis, liver function tests, including serum albumm, should be

In book as a liver initiation deal, including serum apprent, should be performed periodically prior to dosing but are often normal in the face of developing librosis or cimbosis. These lassions may be detectable only by oxopsy. The usual recommendation is to obtain a liver boopsy of 1) protherapy or shortly sate initiation of therapy (2 - 4 months), 2) a total cumulative dose of 1 5 grams, and 3) effer each additional 10 to

1.5 grams. Moderate librose or any cirrhosis normally leads to de-continuation of the drug; mild fibrosis normally suggests a repeat biopsy in 6 months. Milder histologic findings, such as fully charge and low grade portal inflammation are relatively common pretareag Although these mild changes are suusity not a reason to avoid or de continue methotrasate therapy, the drug should be used with caution

In rheumatoid arthmis, age at first use of methotrixizite and duration of therapy have been reported as risk factors for hepatotoxicity, other risk factors, similar to those observed in psonasis, may be present in meumatoid arthritis but have not been confirmed to date. Persisten anormative a lower to the set of before and during treatment (after a cumulative dose of at least 1.5 g) and H1719 patients with a bicenty only during treatment. There are 64 (7%) cases of fibrosis and 1 (0.1%) case of cirrhosis. Of the 64 cuses

of throase of word deemed mild. The reticule start is more sen for early fibrose and its use may increase these figures. It is union whether even longer use will increase these rates. Liver function tests should be performed at baseline and at 4 - 8 weak intervals in patients receiving metholrexate for relevand arthrostic.

mervars in patients receiving methodrexate for meruhation artitritis. Petritrastment lines bacips should be performed for patients, with a ha-tory of excessive alcohol consumption, persistently abnormal base-line liver function test values or chronic negative B or C inflection. Journg therapy, liver bloops hould be performed if them are pensis-tent liver function test abnormalities or them is a decrease in seruit albumin below the normal range (in the setting of well co neumatoid antimitis)

results of liver biopsy show mild changes (Roompk grades I, II, In the issues of liver opcays show mail changes (Hoening) grades 1, 10 (118), methodrivata may be continued and the petient monitorical as per recommendations issaed above. Methodrivates should be discontinued in any patient who displays persustently abnormal liver function tasks and refuses (new boopty or in any petient whose liver biopsy shows moderatis to severe changes (Roening) grade 110 or IV).²

Infection or immunologic States: Metholicisties should be used with extreme clution in the presence of active infection, and is usually con-Extrantic clusters in the presence of active infection, and is usually com-transferration, reading, with your or laboratory evidence of immunosati-ciancy syndromes. Immunosation may be institled with even given during instructions and therapy. Immunosation with the wina viscomes a generally not recommended. There have been reports of disseminipted vaccins intections after smelloor errorganization in patients receiving methodiscate generally. Hypotheration tables are pointed arready.

Potentially fatal opportunistic infections, supecially Pneumocystus cannii pneumoma, may occus with methotrausis therapy. When a

optient pressioners with outcomers should be considered. Meurologie: There have been reports of leukonecephalopethy following intravenous administration of methodrausa to patients who have had craniosoinal irradiation

cranospinal irradiston. Pulmonary: Pulmonary symptoms (especially a dry, nonproductive couph) or a nonspecific onsumoniss occurring during methodrexate therapy may be indicative of a potentially dangerous leason and require indiamuption of trastment and carrivil investigations. Although clinically variable, the typical passes with methodrexate indiced hing desases presents with fiver, couph, dyspane, hypotexet, and an infli-trate on chest X-ray; infaction needs to be excluded. This leason can incrus st all diseases. occur at all deeper

Renal: High doses of met otreate used 41 the treatme coma may cause renal damage teading to acute renal fature. Nephrotoxicity is due primarily to the precipitation of methodragia and 7-hydroxymethotraxate in the renal tubules. Close attaintion to renal function including adequate hydration, unive alkalinization and measurement of serum methotrauate and creationing levels are essential for safe administration

Skin: Severe, occasionally fatal, dermatologic reactions, including Toxic epidermal necrolysis. Stevens Johnson syndrome, activative dermatitis, skin necrosis and erythema multiforma, have beer reported in chiefere and adjues, within days of oral, immanuscular intravenous, or intrathecal methotranata administration. Reactions were noted after single or multiple, low, intermediate or high doese of methotrexate in patients with reoplastic and non-neoplastic disease. acautions: Methodracate should be used with extreme caution in the presence of deb

Methotrexate exits slowly from therd-space compartments (eg. pleural

NUMBER 1 chestre all'indian-AND A DECIDE CLACITY IN DEPENDENT MIT SOMMERANT THREE CONTRACTS OF ADDRESS * advisable to evaluate the fluid before treatment and to monitor plasma ethotresate levels

Lesions of psonasis may be appravaled by concomitant exposure to utiliavio-let rapiation. Radiation dermatitis and sunburn may be recalled, by the use

ADVERSE REACTIONS

INTERNAL THE INCIDENCE AND SEVERITY OF ACUTE BIOE EFFECTS ANE RELATED TO DOSE AND FREQUENCY OF ADMINISTRATION. THE MOST SERIDUS REACTIONS ARE DISCUSSED ABOVE UNDER ORGAN SYSTEM TOXICITY IN THE PRECAUTIONS SECTION. THAT SECTION SHOULD ALSO CONSULTED WHEN LODKING FOR INFORMATION ABOUT ADVERSE REACTIONS WITH METHOTRENATE.

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

Other adverse reactions into any other reported with methotrexate are listed below by organ system. In the oncorcy setting, concomtant treatment and the underiving disease make specific attribution of a reaction to methotrexate. Gifficuit

Alimentary System gingivitis, pharyngitis, stomatitis, anorexia, nausaa, s rling, diarrhéa, hematemesis, melena, gastrointestinal ulceration and bleed-ing, enteritis, pancreatris

Cardiovascular pericarditis, pericardial effusion, hypotension, and throm bembolic wents including arterial thrombosis, cereprat thrombosis, deep vent including arterial thrombosis, cereprat thrombosis, and pulmonary vent thrombosis, retinal vein thrombosis, thrombosis, and pulmonary embolus).

trai Nervous System: headaches, drowsiness, blutted vision. A hemiparesis, paresis, and convuisions have also occurred following admin stration of methotrexate. Following low doss, there have been occasional reports of transient subtle cognitive dysfunction, mood alteration, unusual cranial sensations, leukoencephajopathy, or encephajopathy

infection. There have been case reports of sometimes fatal opportunistic Infections in patients receiving methodrexite therapy for neoplastic and non-neoplastic disass², *Pheumocystic carri*, oneumonia was the most common infection. Other reported infections included nocardiosis: histoplasmosis, cryptococcosis, Herpes zoster, H. simplex hepatitis, and disseminated H. simplex

imic conjunctivitis, serious visual changes of unknown abology

Pulmonary System, interstitial pneumonitis deaths have been reported, and chronic interstitial obstructive pulmonary disease has occasion Skin: erythematous rashes, pruntus, uniceria, photosensitivity, pigmentary changes, alopacia, acchymosis, talangiectasu, acne, furunculosis, endhema muthforme, toxic apidermal necrolysis, Stevens-Johnson Syndrome, skin necrosis, and extoletive dermistles.

necross, ana antineure permateur. Uropendal System: severa nephropathy or renal failura, azotemal, cystitia, hemástura: distoctive oogenesis or spermatogenesis, transient oligosperma, menstrual dystunction, vagunal discharge, and gynecomastia: interality, aborent de

obn.real evenus. Other rater rations related to or-stimbuted to the use of methotrexate such as nodulosis, vasculins, arthragummysgis, loss of libido/impotence, da-beres, ostacoprosis, sudden death, and revenuble lymphomas. Anaphylactoid reactions have been reported.

Adverse Republican in Double-Allest Ris aid Arthritis 21

proximate incidences of methotreaste attributed (ie, piecebo rate sub-adverse reactions in 12 to 18 week double-blind studies of patients (n = 128) with meumatoid arthmis treated with low-dose oral (7.5 to 15 mg/week) pulse methomizade, are listed below. Virtually all of these petients were on concombant nonsteroidal anti-inflammatory drugs and some were were on concomitant nonsteroidal also taking low dosages of controls

incidence prester than 10%: Elevated liver function tests 15%, neuses/vomiting

nce 3% to 10%: Stomatitis, thrombocytope nun. (Diet of count less than 100.000/m

100.000/mm?). Incidence 1% to 3%: Rash/prumtus/sematitis, diarnhee, stopecia, leukopenia (WBC less than 3000/mm?), pancytopenia, dizziness. No pulmonsy? toxicny was seen in these their trais. The incidence is probably less than 2.5% (95% C.L.). Hegetic histology was not examined in these short-term studies. (See PRECAUTIONS.)

less common reactions included decreased hemalocrit, headache. upper respiratory infection, anorexia, arthraigias, chest pain, coughing, dysura, eye discomfort, epistaxis, fever, infaction, sweating, tinnitus, and vaginal discharge. Advarus Reastler

. In in Paari

There are no recent placebo-controlled trials in camerits with pa are two Herature reports (Roenige, 1969 and Nytors, 1978) describing large series (n = 204, 248) of psoriasis patients traated with methotresate. Dosages ranged up to 25 mg per week and treatment was administration for up to four years. With the exception of alopeca, photosenstwhy, and "burn-ing of sans featoms" (sech 3% to 10%), the adverse reaction rates in these reports were very similar to those in the meunistoid aritimts studies.

Distance and

diversionsace Leuconom is indicated to diminish the busicity and counteract the effect of indevertently administened evendosages of methodrescate. Leuconom admin-stration should begin as promoty as possible. As the time interve between methodrescate doministration and becomen instation increases. It effective ness of leuconom in counteracting busicity decreases. Monitoring of the serum methotraxate concentration is essential in determining the optimal dose and duration of treatment with inscremen

In cases of massive overdoage, hyereton and unnary alkalinization may be necessary to prevent the precipitation of methotrisate and/or its metabolities in the renal lubules. Nether hemodallysis nor pertonesi dialysis have been shown to motive methotrisate elimination.

DOGAGE AND ADDRESTRATION

in Diese

Orai admir stration in tablet form is often preferred when low doess are beadministered since absorption is rapid and effective serum levels are obtained. Methodizate social invictors and for injection may be given by the inframuscular, infravenue, intra-artistic or investiceal route. However, the preserved formulation contains Berzyl Alcohol and must not be used for mirathecal or Noh dose therapy.

Intramocal of migh dose therapy. Chonocacronoma and similar trophoblestic diseases: Methothexate is admin-istered oraby or intramusculery in doses of 15 to 30 mg daily for a this-day course. Such courses and susually repeated for 3 to 5 times as negarid, with risit pendid 0 field or more weeks interproced between courses. Until any manifesting flotdic symptoms subside. The effectiveness of therapy is ordinar-tly availated by 24 hour quantitative analysis of unrary choronicu-gonadoropen INGS), which should return to normal or less than 50 litizet he usually after the third or fourth course and usually be followed by a com resolution of measurable lessons in 4 to 6 weeks. One to two course methotrexate after normalization of hCG is usually recommended. Be each course of the drug careful clinical assessment is essential. Cyclic combi nation therapy of methotraxate with other antitumor drugs has been reng useful -

Since hydalidiform mole may precede choriocarcinoma, prophylactic motherapy with methotricule has been recommended.

solenoma destruens is considered to be an invesive form of hy noie. Methotnexite is administered in these disease states in ar to those recommended for chonocarcinoma. e disease states in do

Leukerne: Acula tymohobiastic leukerne in pediatric patients and young adoissounts is the most responsive to present day chemotherapy. In young adults and older patients, clinical remission is more difficult to obtain and

Wethotrexate Jione in a compination with steroids was used initially for induction mamossion in source withologiastic estamatic More recently com-Solution the state of the stat 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 e for securing maintenance of drug-induced remissions. When remis-is for securing maintenance of drug-induced remissions. When remis-is achieved and supportive care has produced general clinical more-maintenance therapy is initiated, as tonows. Methotrexate is adminisment. tered 2 times weekly either by mouth or intramuscularity in total weekly 305es of 30 mg/mr it has also been given in goses 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 retimen-A variety of combination chemotherapy regimens have been used for both induction and maintenance therapy in acute lymphoplastic leukemia. The

physician should be familiar with the new advances in antileukemic theraby Lymphomas: In Burktti's tumor. Stages I-II, methotreata has produced pro-longed remissions in some cases. Recommended dosage is 10 to 25 mg day onget remissions in some cases inecommenced gospage's fullo 2 mg day orally for 4 to 8 ays in Stage III. methoresate is commonly gree concom-tantly with other anni-umor agents. Teatment in all stages usually consists of several courses of the drug interposed with 7 to 10 day rest bet-ods Lymphosarcomas in Stage III may respond to combined drug therapy with metholeraate given in doass of 0.625 to 2.5 mg/kg daily

Mycosis Europaides. 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 Inframuscularly in doses of 50 mg once weekly or 25 mg 2 times wee Pseriesis and Rhoumatold Arthritis

The patient should be lully informed of the risks involved and should be under constant supervision of the physician. (See information for Patients under PRECAUTIONS) "Assessment of hematologic, nepatic, renal and pulmonary function should be made by history, physical examination, and labo-Torona y functions statute de mass by maxiny prystata examinatori, ano adou-rationy less before beginning, periodically during, and before institutions methotreate therapy isse PRECAUTIONS i Appropriate steps should be taken todavold conception during methotreater arapy (see PRECAUTIONS AND CONTRAINDICATIONS).

All schedules should be continually tailored to the individual patient. An initial extreme sensitivity to adverse effects. See ADVERSE REACTIONS) Maximal TVNOSUDORESSION IISUARY OCCUTS IN Seven In ten davis

Psonasis: Recommended Starting Dose Schedules

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

Oivided oral dose schedule: 2.5 mg at 12-hour intervals for three doses

Conversion of an Ocean environment, a const and a manufacture data for three dovers Docades in each schedule may be gradually adjuste to 'achieve optimal cincil response. 30 mexes should not ormarnly be succeeded. Once optimal cincil response has been achieved. Tach dosage schedule should be reduced to the lowest possible amount of engl and to the longest possible rest period. The use of methodrastic may permit the return to con-ventional topical therapy, which should be encouraged. possible rest period, the use of metrovake may period, one period and the second the second the second states of t

Single oral doses of 7.5 mg once weeks

Consider on a basis of 7.5 mg at 12 hour intervals las 3 doses given as a Consider once weekly.
 Dosages in each schedule may be adjusted gradually to achieve an ophmal

response, but not ordenanly to exceed a total weekly dose of 20 mg. Limited experience shows a significant increase in the incidence and severity of senous toxic reactions, especially bone marrow suppression, at doses greater than 20 mg/wk.

Since response has been achieved, each schequie should be reduced, if pos-sible, to the lowest possible effective dose.

sible, to the lowest possive energies cose. Therapeutic response sussible begins within 3 to 5 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 india chinical improvement is maintained for at least two years with continued therapy. When methotreate is discontinued.

HANDING AND DISPOSAL

the arthritis usually worsens within 3 to 6 weeks

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.²⁴ There is no general agreement that all of the procedures recommended in the guide-

lines are necessary or appropriate. Paremeral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and contained oermet

HOW SUPPLIED

Anthoresate tablets. USP, 2.5 mg, are yellow, oval and debossed on the scored side with "4" and "509" in bottles of 38 (NDC 51285-509-36) and 100 (NDC 51285-509-32).

Store at 25°C (77°F), excursions permitted to 15°-30°C (59°-86°Ff (see USP Controlled Room Temperature) Protect From Light.

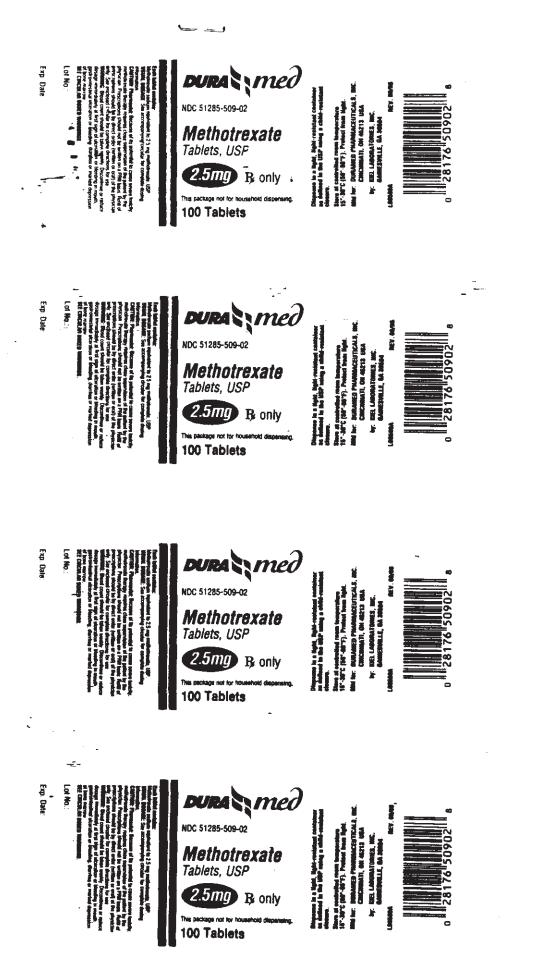
Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure

Wid. for:	DURAMED PHARMACEUTICALS, INC.		
	Cincinnati, OH 45213 USA		
Dy:	KIEL LABORATORIES. INC.		
	Gainesville GA 30504 USA		
		REV.	34/89

100324 STREET, SHOT

Ronnigk HH, Auerbach R, Maibach HI, et al. Methotrexate in Psonasis Revised Guidelines. J Am Acad Dematol 1988; 19:145-155.

- Revised Guidelmes, J. Am Acad Dematol 1968, 19:145-156. Kremer J.M. et al. Mehlotrasti for Rheumatoid Arthotis: Suggested Guidelines for Montoring Liver Toucity. Arth Rheum 1994; 37:316-328. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 35:2627. For safe by the Superintendent of Documents, U.S. Government Printig Othics, Washington, DC 20402. 2
- AMA Council Report. Guidelines for Handling Parenteral Antineoglastics. JAMA March 15 1985.
- National Study Commission on Cytotoxic Exposure—Recommendations for Handling Cytotoxic Agenta, Available from Louis P. Jeffrey, ScD., Chairman, National Study Commission on Cytotoxic Exposure 5 Chainman, National Study Commission on Cytobart Esposite Massachusetta College of Pharmacy and Alled Maith Sciences. 179 Longwood Avence, Boston, Massachusetta (2115, Clinical Oncological Society of Australia: Guidelines And Recommendations for Safe Handling of Antineoplastic Agents. Med J
- Australia 1983: 1 426-428
- Iones R8, et al. Sale handling of chemotherapeutic agents. A report from the Mount Sinai Medical Center. Ca A Cancer Journal for Clinicians. 1983: (Sant/Oct) 258-263
- American Society of Hospital Pharmacists. Technical Assistance Bulletin on Handing Cytotoxic and Hazardous Drugs. Am J Hosp Pharm 1990. 47:1033-1049.



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NDC 51285-509-36 Methotrexate Tablets, USP 2.51119 B only The manual of the function of the manual 36 Tablets An one of the second se 014 W 25 M ł

Exp. Date: Lot No.: 20.0

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Mile 25 mg

36 Tablets

Exp. Date: Lot No.:

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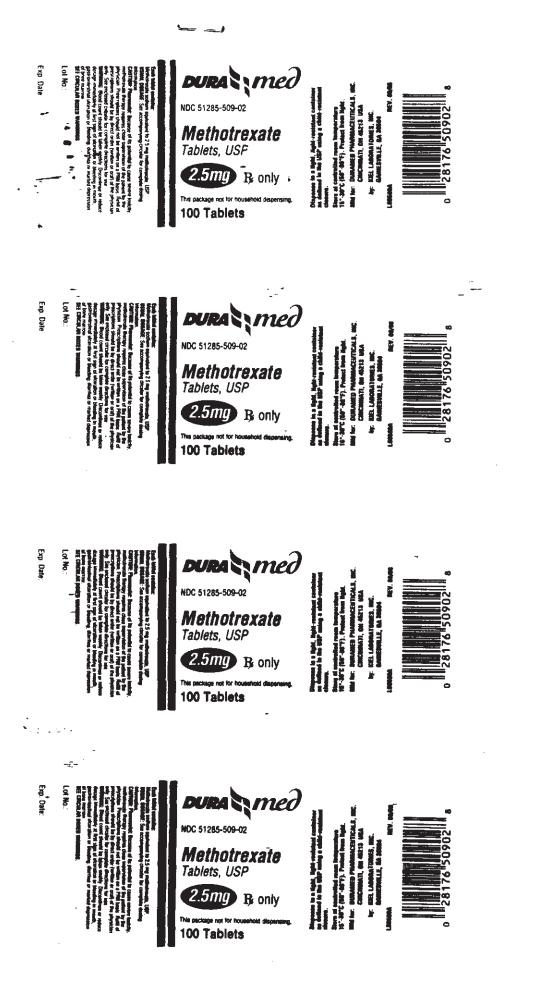
and med

NOC 51285-509-38 Methotrexate Tablets, USP 2.51119 B only 36 Tablets

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BURA med NGC 51205-509-30 Methotrexate Tablets, USP States of the second 2817675 Ï

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CENTER FOR DRUG EVALUATION AND RESEARCH

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Application Number 40-233

CHEMISTRY REVIEW(S)

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- 1. CHEMISTRY REVIEW NO. 3
- 2. ANDA # 40-233
- NAME AND ADDRESS OF APPLICANT Duramed Pharmaceuticals, Inc. 5040 Lester Road Cincinnati, OH 45213
- 4. <u>LEGAL BASIS FOR SUBMISSION</u> 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. <u>SUPPLEMENT(s)</u> N/A
- 6. PROPRIETARY NAME None used.
- 7. NONPROPRIETARY NAME Methotrexate Tablets USP, 2.5 mg
- 8. <u>SUPPLEMENT(s) PROVIDE(s) FOR:</u> N/A
- 9. <u>AMENDMENTS AND OTHER DATES:</u> 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. <u>Rx or OTC</u> Rx
- 12. <u>RELATED IND/NDA/DMF(s)</u> 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. <u>CHEMICAL-NAME AND STRUCTURE</u> SEE CR # 1.
- 16. <u>RECORDS AND REPORTS</u> N/A
- 17. COMMENTS

 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.

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- 18. CONCLUSIONS AND RECOMMENDATIONS Approved pending acceptable EER status.
- 19.REVIEWER:
Mujahid L. ShaikhDATE COMPLETED:
5-27-99

Endorsements:

Page(s) Contain Trade Secret, Commercial/Confidential Information and are not releasable.

ist Review # 3

MPR 2 7 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:

llie.

- Your proposed blend uniformity specification as a routine inprocess 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:
 - 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.
 - You must also address the labeling deficiencies in your response.

Sincerely yours,

K, Rashmikand M. Patel, Ph.D. Director Division of Chemistry I Office of Generic Drugs Center for Drug Evaluation and Research

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Duramed Pharmaceuticals, Inc.

ANDA # 40-233 Methotrexate Tablets, USP, 2.5 mg

October 9, 1998 Amendment

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Side-by-Side Comparison - Insert		086	

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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) Contain Trade Secret, Commercial/Confidential Information and are not

178/97

releasable.

5. Your bioequivalence data is pending review.

4.

 You must also address the labeling deficiencies in your response.

Sincerely yours,

Rashmikant W. Patel, Ph.D. Director Division of Chemistry I Office of Generic Drugs

Center for Drug Evaluation and Research

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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,

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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

lethotrexate 7	Tablets	Duramed				
2.5 mg Tablets	- ۲	- Ciņcinnati, OH				
ANDA #40-233		Submission Date: 12/20/96				
Reviewer: Moo	Park					
REF PRODUCT	Methotrexate Sodium Tablets, 2.5 mg, manufactured by L Laboratories					
BE STUDY DESIGN	Open-label, balanced, crossover study	randomized, two period, single dose,				
STUDY SITE	1	A				
	I	· · · · · · · · · · · ·				
STUDY SUMMARY	healthy male sub crossover study.	Peak mean plasma levels for the test				
STUDY SUMMARY	healthy male sub crossover study. and reference pre- and 131.6 ng/mL LSMEANS are compa- products. The The 90% confident AUCT, AUCI and CH 80-125%. 2. Drug products: Th for the test and The batch size of	jects enrolled and all 26 completed the Peak mean plasma levels for the test oducts were 128.9 ng/mL at 0.67 hour at 0.83 hour, respectively. The arable for the test and reference Test/Reference ratios range 0.97-1.02. ce intervals for the log-transformed MAX are within the acceptable range of he assay and content uniformity data reference products are acceptable. f the test product was tablets. No serious medical events were reported				
BIOASSAY VALIDATION	 healthy male subject of the study. and reference present and 131.6 ng/mL LSMEANS are compared products. The 90% confidence AUCT, AUCI and CH 80-125%. 2. Drug products: The study of the study 3. Medical events: Auring the study 	jects enrolled and all 26 completed the Peak mean plasma levels for the test oducts were 128.9 ng/mL at 0.67 hour at 0.83 hour, respectively. The arable for the test and reference Test/Reference ratios range 0.97-1.02. ce intervals for the log-transformed MAX are within the acceptable range of he assay and content uniformity data reference products are acceptable. f the test product was tablets. No serious medical events were reported				
BIOASSAY	healthy male sub crossover study. and reference pre- and 131.6 ng/mL LSMEANS are compa- products. The ' The 90% confidence AUCT, AUCI and CL 80-125%. 2. Drug products: The for the test and The batch size of 3. Medical events: for during the study	jects enrolled and all 26 completed the Peak mean plasma levels for the test oducts were 128.9 ng/mL at 0.67 hour at 0.83 hour, respectively. The arable for the test and reference Test/Reference ratios range 0.97-1.02. ce intervals for the log-transformed MAX are within the acceptable range of he assay and content uniformity data reference products are acceptable. f the test product was tablets. No serious medical events were reported				

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NITIAL:	DATE: 7/8/91	2
EVIEWER: Moo Park, Ph.D.		
RANCH: III		
EAM LEADER: Ramakant M. Mhatre, Pl	DATE: 7/5/97	
RANCH: III		
NITIAL: /C/	DATE: 1/16/98	
IRECTOR: Mainlas Fleischer, Ph.D		0
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OFFICE OF GENERIC DRUGS DIVISION OF BIOEQUIVALENCE

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Methotrexate T	ablets	Duramed		
2.5 mg Tablets	هاد مع بر المع مراجع المعالي المحالي ا	Cincinnati, OH		
ANDA #40-233		Submission Date: 12/20/96		
Reviewer: Moo Park				
REF PRODUCT	Methotrexate Sodium Ta Laboratories	blets, 2.5 mg, manufactured by Lederle		
BE STUDY DESIGN	Open-label, balanced, crossover study	randomized, two period, single dose,		
STUDY SITE		-		
		· · · · · · · · · · · · · · · · · · ·		
	healthy male subj crossover study. and reference pro and 131.6 ng/mL a LSMEANS are compa products. The T The 90% confidenc	nd statistical evaluation: Twenty-six ects enrolled and all 26 completed the Peak mean plasma levels for the test ducts were 128.9 ng/mL at 0.67 hour t 0.83 hour, respectively. The rable for the test and reference est/Reference ratios range e intervals for the log-transformed AX are within the acceptable range of		
_ •	for the test and	e assay and content uniformity data reference products are acceptable. the test product was		
	3. <u>Medical events:</u> N during the study.	o serious medical events were reported		
BIOASSAY VALIDATION	Pre-study and within-s	tudy validation data are acceptable.		
DISSOLUTION	The test product, lot specifications.	#GA194, met the USP dissolution		
WAIVER	n/a			

INITIAL: REVIEWER: Moo Park, Ph.D.	DATE: 7/4/97
BRANCH: III INITIAL: TEAM LEADER: Ramakant M. Mnatre, Fu.D. BRANCH: III	DATE: 7/9/97
INITIAL: DIRECTOR: Nicholas Fleischer, Ph.D. DIVISION OF BIOEQUIVALENCE	DATE: 1/16/98
INITIAL: DIRECTOR OFFICE OF GENERIC DRUGS	

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BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

11

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,

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Rabindra N. Patnaik, Ph.D. Acting Director Division of Bioequivalence Office of Generic Drugs Center for Drug Evaluation and Research NOV 1 3 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/m² 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 2-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

Investigator

Study sites

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.

Twenty-six healthy male subjects were recruited Subjects -- 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 Test product: Methotrexate Tablets, USP, 2.5 Drug products 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. In this study, subjects are dosed with 2 x 2.5 Dosing mg tablets twice, once for each period. Prior to each period there was an overnight Food and fast of at least 10 hours. Water was consumed fluid 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 sport 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.

Subject Consent Form was signed by each subject Informed who participated in the study. consent

Assay method for blood samples

Methotrexate Analytes

AUCT, AUCI, CMAX, TMAX, KE, and THALF were PK analysis calculated.

90% confidence intervals were calculated for Statistical log-transformed AUCT, AUCI and CMAX. analysis

IV. Bioanalytical Method Validation

Plasma methotrexate was analyzed using ng/mL. detection over a concentration range of

Pre-study Validation Α.

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 mathod:	' 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.
441 1 -	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.
-2+	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

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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		1	Í	1	1	
0	- i	0.001	0.001	0.001	0.001	C
0.25	1	18.151	15.341	13.681	15.091	1.33
0.5	- 1	97.041	39.821	82.551	40.271	1.18
0.67	- 1	128.891	40.531	124.131	44.971	1.04
0.83	1	128.721	33.991	131.591	39.061	0.98
1	1	122.931	32.431	126.141	32.961	0.97
1.25	1	110.18	33.271	115.811	27.401	0.95
1.5	1	95.371	24.851	100.71	24.891	0.95
2	1	75.371	18.851	78.421	15.021	0.96
2.5	Ĩ	62.391	15.011	63.051	11.391	0.99
3	Ĩ	51.601	14.271	52.51	10.601	0.98
4	1	35.981	9.721	36.201	8.61	0.99
5	- E	30.151	9.191	30.771	8.471	0.98
6	ſ	21.941	7.511	21.101	6.971	1.04
8	1	10.93	5.541	11.621	5.071	0.94
10	i i	5.151	4.471	5.464	4.961	0.94
12	1	1.86	3.751	1.61	3.551	1.15
16	Ì	0.461	1.611	0.451	1.591	1.02
24		0.001	0.001	0.001	0.001	

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

F LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG MEAN1=TEST; MEAN2=REFERENCE; RMEAN12=MEAN1/MEAN2 RATIO SD=STANDARD DEVIATION

		1	MEAN1	SD1 I	MEAN2	SD2	RMEAN12
PARAMETER		1		1	1	1	
AUCI		10	433.581	95.141	428.751	95.081	1.01
AUCT		- 11	393.851	99.991	396.621	93.091	0.99
CMAX	10.1	- Ì.	144.291	34.61	146.831	29.381	0.98
KE	2.	1	0.301	0.051	0.311	0.061	0.99
LAUCI		1	424.531	0.21)	420.041	0.201	1.01
LAUCT		лĴ.	382.651	0.241	387.591	0.211	0.99
LCMAX		1	140.101	0.251	143.691	0.221	0.97
THALF		1	2.351	0.451	2.361	0.561	1.00
TMAX		Ť.	0.881	0.321	0.971	0.401	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; UPPC112=UPPER 90% CI

t		1	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
						+	
PARAMETER		- 1					
AUCI		1	435.751	427.541	1.021	97.971	105.87
AUCT		- I.	393.851	396.621	0.991	94.831	103.77
CMAX		1	144.291	146.831	0.981	92.711	103.83
LAUCI		1	425.131	418.781	1.021	97.581	105.61
LAUCT	1.00	1	382,651	387.591	0.991	94.261	103.40
LCMAX		_î.	140.101	143.691	0.971	91.46	103.94

VI. Formulation and Dissolution Data

1. Formulation

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The test formulation is shown in Table VI-1.

Table V-1. Test Formulation

Ingredient.	- Amount	per tablet, mg
Methotrexate,	2.5	
Lactose Monohydrate,	1	
Pregelatinized Starch,		
£	· *	
Magnesium Stearate,		
Total weight		

2. Assay and content uniformity data

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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: cablets		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. <u>Bioanalytical method validation:</u> Pre-study and within-study validation data are acceptable.
- 3. **Dissolution testing:** The test product, lot #GA194, met the USP dissolution specifications.
- 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.
- 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

- The in vivo bioequivalence study conducted under fasting 1. 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.
- The USP dissolution testing should be incorporated into the 3. 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.

Moo Park, Ph.D. Chemist, Review Branch III Division of Bioequivalence

RD INITIALED RMHATRE FT INITIALED RMHATRE Ramakant M. Mhatre, Ph.D. Team Leader, Review Branch III Division of Bigequivalence

Date:

Nicholas Fleischer, Ph.D. Director

Concur: .

Division of Bioequivalence

	Tab	le-IV-	3. In Vi	tro Disso	olution Te	sting Data	
	1.5	•	I. Ger	neral Inf	ormation		
Drug Name)	Product	(Gener:	ic Met	Methotrexate Tablets			
Stren	gth		2.5	mg			
ANDA	Number	÷.	40-	233			-
Appli	cant			amed			
Refer Produ	ence Dr ct	ug		Lederle's Methotrexate Sodium Tablets, 2.5 mg			
		II. US	P Method	i for Dis	solution ?	festing	
Mediu	m and V	olume	0.1 N	N HCl; 900 mL			
Appar	atus and	d rpm	2 (pad	(paddle); 50 rpm			
Time 45 m.			45 min	min			
Tolerances NL			NLT 75	JT 75% (Q)			
Assay	Method	ų		141	atom.		
			III. Di	ssolutior	n Data (%)		
Time - Test Product Lot No: GA194 Strength: 2.5 mg No of Units: 12		Lot No:	: 2.5 mg	luct			
Min	Mean		Rande	%CV	Mean	Range	%CV
5	83	7-		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
						1112	
					1220 171	1.	

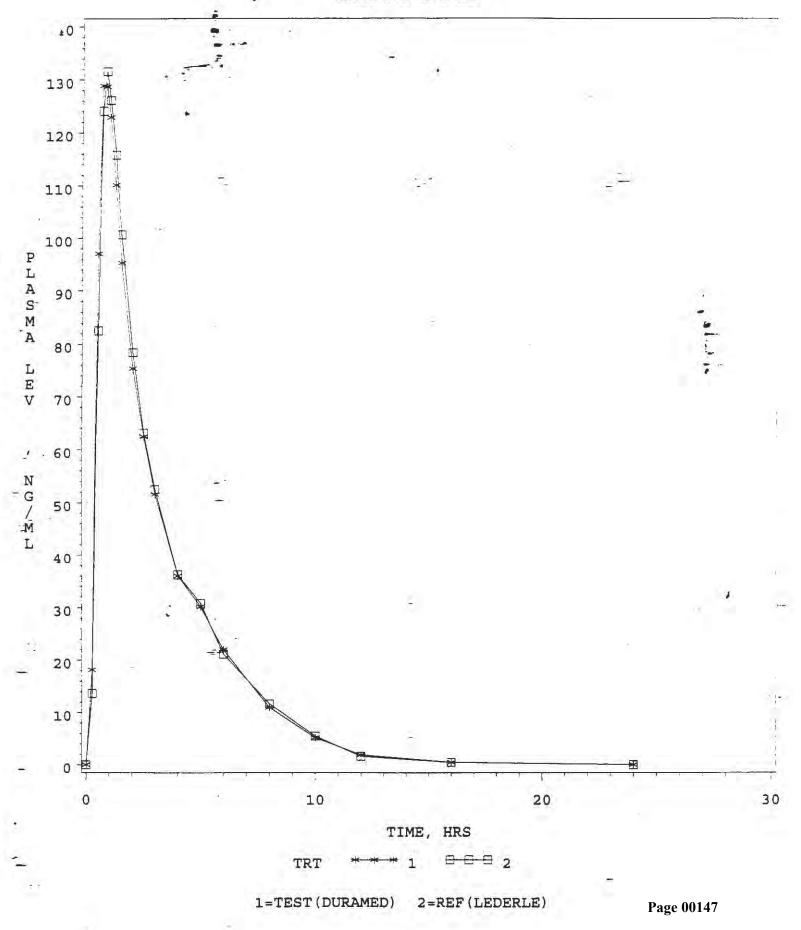
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FIG P- . PLASMA METHOTREXATE LEVELS

METHOTREXATE TABLETS, 2.5 MG, ANDA #40-233 UNDER FASTING CONDITIONS DOSE=2 X 2.5 MG



	EQUIVALENCY - Acceptable	
ANDA	A/AADA: 40 233 APPLI	CANT: Duramich
DRUG	A/AADA: 40 233 APPLI G PRODUCT: = Mothotrexate	2.5my tabs
$\left(1\right)$	FASTING STUDY (STF)	Strengths: 2.5 mg Acceptable
<u> </u>	Clinical: Analytical:	Outcome AC IC UN NC
2.	FOOD STUDY (STP)	Strengths:
·	Clinical: Analytical:	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:
6.	WAIVER (WAI)	Strengths:
		Outcome: AC IC UN NC
7.	DISSOLUTION WAIVER (DIW)	Strengths:
	-	Outcome: AC IC UN NC
8.	OTHER (OTH)	Strengths:
0		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
OUTC	OME DECISIONS:	

AC - Acceptable NC - No Action UN - Unacceptable (fatal flaw) IC - Incomplete

CENTER FOR DRUG EVALUATION AND RESEARCH

4

Application Number 40-233

ADMINISTRATIVE DOCUMENTS

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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

<u>SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?):</u> Methotrexate Tablets 2.5 mg (used for in-vivo bio studies and invitro dissolution studies): Lot # GA 194 (Size: Tablets).

Present status of Referenced DMF:

Referenced lor 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).

Manufacturing process for intended production size batch is same as used for the bio/stability br"ches.

Mujahid L. Shaikh Review Chemist Division of Chemistry I OGD/CDER 5-28-99 Steve Sherken for Mike Smela/5/28/99

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REVIEW OF PROFESSIONAL LABELING DIVISION OF LABELING AND PROGRAM SUPPORT LABELING REVIEW BRANCE

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 L 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.)
- 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 7hydroxymethotrexate 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

.. 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.

A. 115

Jerry Phillips Director

Division of Labeling and Program Support Office of Generic Drugs Center for Drug Evaluation and Research

13-APK-1777

FDA UDEK EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Stamp: 23-DE Applicant:	M. SMELA JR (HFD-625)	Generic Name: Dosage Form: Strength:	Org Code: 600 District Goal: 23-FEB-1998 c: METHOTREXATE TAB (TABLET) 2.5 MG Project Manager Team Leader
	OLD on 30-JUN-1998 by J. D Al OLD on 08-MAY-1998 by R. W(
Establishment:		DMF No: - AADA No:	
	OAI Status: NONE OC RECOMMENDATION 06-APR-1999 ACCEPTABLE BASED ON PROFILE	Responsibilities:	DRUG SUBSTANCE OTHER
Establishment:		DMF No: AADA No:	
	/)504		
Profile: TCM Last Milestone: Milestone Date:	OAI Status: NONE ASSIGNED INSPECTION TO IB 12-APR-1999	Responsibilities:	FINISHED DOSAGE MANUFACTURER FINISHED DOSAGE OTHER TESTER FINISHED DOSAGE PACKAGER
Establishment:		DMF No: AADA No:	
Profile: CSN Last Milestone: Milestone Date: Decision:	OC RECOMMENDATION 07-APR-1999	_ Responsibilities:	DRUG SUBSTANCE MANUFACTURER

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10-AFK-1777

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FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Reason:	BASED ON PROFILE	-	
Establishment:		DMF No: AADA No:	
Profile: CTL Last Milestone: Milestone Date: Decision: Reason:	- OAI Status: NONE OC RECOMMENDATION 06-APR-1999 ACCEPTABLE BASED ON PROFILE	- Responsibilities:	DRUG SUBSTANCE OTHER TESTER FINISHED DOSAGE OTHER TESTER

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 40-233

CORRESPONDENCE

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The Art of Leadership ... The Science of Change Duramed Pharmaceuticals, Inc. 5040 Duramed Drive Cincinnati, Ohio 45213

(513) 731-9900

NC to Fax

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

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

John R. Rapoza, M.S., K.Ph. Vice President, Regulatory Affairs

Enclosures:

completed Form FDA 356h





ORIG AMENDMENT

Duramed Pharmaceuticals, Inc. 5040 Lester Road Cincinnati, Ohio 45215 (513) 751-9900

(800) 543-8338

The Art of Leadersbip ... 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,

Janette artingham / yest

John R. Rapoza, M.S., R.Ph. Vice President, Regulatory Affairs

Enclosures:

completed Form FDA 356h



The Art of Leadership ... The Science of Change

April 16, 1997

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

Duramed Pharmaceuticals, Inc. 5040 Lester Road Cincinnati, Ohio 45213 (513) 731-9900

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 7 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 ohn B. Rapoza, N

Vice President, Regulatory Affairs

Enclosures:

completed FDA 356h stability tables



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GENERIC DRUGS



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Alline form

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 Duramed Pharmaceuticals, Inc. 5040 Lester Road Cincinnati, Ohio 45213 (513) 731-9900

NEA CEIO

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. ohn R. Rapoza, M.S. R.Ph.

Vice President, Regulatory Affairs

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MAR 1 4 1997 GENERIC DRUGS

ANDA 40-233

Duramed Pharmaceuticals, Inc. Attention: John Repoza 5040 Lester Read 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

Jerry Phillips An 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 2 8 .397

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 90day 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,

Jerry Phillips / 2/25/57 Director Division of Labeling and Program Support Office of Generic Drugs

Center for Drug Evaluation and Research



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Duramed Pharmaceuticals, Inc. 5040 Lester Road Cincinnati, Ohio 45213 (513) 731-9900 (800) 543-8338

December 20, 4996

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 Centennial Drive in Gainesville, Georgia. located at 2225

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 (ted 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 acomputer disk, in 3.5" format, containing ASCII files of the measured concentrations of the drug substance and the kinetic parameters for the bioequivalence study.

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GENERIC DRUGS

Page 00167

Page 2 To: Mr. Douglas L. Sporn Subject: ANDA for Methotrexate Tablets, USP, 2.5 mg

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



METHOTREXATE INJECTION USP (Contains Preservative)

WARNINGS

METHOTREXATE SHOULD BE USED ONLY BY PHYSI-CIANS WHOSE KNOWLEDGE AND EXPERIENCE INCLUDE THE USE OF ANTIMETABOLITE THERAPY

BECAUSE OF THE POSSIBILITY OF SERIOUS TOXIC RE-ACTIONS (WHICH CAN BE FATAL):

METHOTREXATE SHOULD BE USED ONLY IN LIFE THREATENING NEOPLASTIC DISEASES, OR IN PATIENTS WITH PSORIASIS WITH SEVERE, RECALCITRANT, DIS-ABLING DISEASE WHICH IS NOT ADEOUATELY 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 ME-TIC/LOUIS CARE: (SAN OBCAGE AND ADMINISTRATION) HIGH DOSE REJIMENS FOR OTHER NEOPLASTIC DIS-BASES 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 METHOTREX-ATE THERAPT.

Methotrexals has been reported to cause fetal death and/ or congenital anomalies. Therefore, it is not recommended for women of chickearing potential unless there is clear medical anderice that the benefits can be expected to cultweigh the considered mais. Pregnam women with pocasis should not receive methotrexate. (See CONTRAINDICATIONS).

Methotrexate elimination is reduced in patients with im-pared renail functions, ascillar, or pleural efflusions, Such patients require dose reduction or, in some cases, discontinu-ation of methotizesta administration.

3. Unexpectedly severe (softelimes fatal) bere marrow suppression and gastrointestinal toworky have been reported with tomoundant administration of methotexate (usually in high discage) along with some nonseroid an ex-attention discharmatory drugs (NSAIDs). (See PRECAUTIONS, Drug interactions).

(INSAUS). (See PHECAUTIONS: Drug interactions).
4. Methotrexate causes hepatoloxicity, Ilbrosis and cirrho-sis, but generally only after protonged use. Acutery, liver enzymentexations arrowspringly seen; These are usually active of subsequant hepatolic divease. Liver body after sustained use often stores histologic changes, and bbo-sis and cirrhosis have been reported, these latter lesion-may not be preceded by symptoms or abnormal liver func-tion tests in the psortaist population. For this reason, periodic liver biopies are usually recommended for pso-nalic patients who are under long-isem treatment. (See PRECAUTIONS, Organ System Toxicity, Hepatic.)

5 Methotrerate indiced king disease is a potentially dangerous lesion, which may occur acutely at any time during therapy and which has been tiported at doses as low as 7.5 mg/week. It is not always tully eventible Putmonary symptoms (espective) and which has been tiported at doses as low as 7.5 mg/week. It is not always tully eventible Putmonary symptoms (espective) and the putmonary symptoms (espective) as a putmonary symptom (espective) and the putmonary symptoms (espective) and the putmonary symptoms (espective) and the putmonary symptoms (espective) as a putmonary symptom (espective) and the putmonary symptoms (espective) and the putmonary symptoms (espective) and the putmonary symptoms (espective) as a putmonary symptom (espective) and the putmonary symptoms (espective) as a putmonary symptoms (espective) and the putmonary symptoms (espective) as a putmonary symptom (espective) as a putmo

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nhea and utorralive stomabls require interruption of y otherwise, henomagic ententis and death from in-1 perforation may occur. therapy. Instinal

Malignant lymphomas, which may regress following withdraw/ofmetholinuate, may occur in patients receiving low-dosr methoriseste and, thus, may not require cylolauic treatment. Discontrave methodrestate listi and. If the tymphome does not regress, appropriate leatment should be instituted.

8. Like other cytotosic drugs, methotrssale may induce Tu-mor here syndrome in patients with rapidly growing lumors. Appropriate supportive such pharmacologic measures may prevent or alleviate this complication.

9 Sweet, occasionally fatal, skin macricons have been reported following ungle or multiple doase of methotrecate. Reactions have occurred within days of onal, instantuscias, infrarefronz, or intrafancial methodnesiae administration. Reaction has been reported with discontinuation of Benary (See PRECAUTIONS, Organ System Toxicity, skin.)

 Potentially latal apportunistic infections, especially Pneumocystis carinii pneumonia, may occur with methoti-exate therapy. 666

DESCRIPTION Methotrezate (formerly Amethoptenn) is an antimetabolite used in the heatment of centain neoplastic diseases and severe peonasis.

Chemically methotrexate is N-(4-(((2.4-diamino-6-pteridinyi)))

The structural formula is. -01,4-0 ------

The molecular formula is: CaH,N,O,

The molecular weight is: 454.45

Methotrevate injection USP is starile and non-pyrogenic and may be given by the intramacular, altravenous or intra-artienal route. (See DOSAGE AND ADMINISTRATION). However, this preser-vative formation contains Benzyl Accord and must not be used for intrathecul or high dose therapy.

Each mL contains methotrexits sodium equivalent to 25 mg meth-cirrexite, Presentative Benryl Alcohol 9.0% w/, and the following nactive angrediants: Sodium Hydraxide and/or Hydrachions Aod may be added to adjust the yff alung manufacture to 16 - 6.7.

may be added to aqual the pri during manufacture to to > 8.7. CLINICAL PHARMACOLOGY Methomsale inhibits oflystroloic acid reductase Dihydroloiates must be reduced to tetrihydroloiates by this enzyme before they can be united as another to rote the optione methodynalisation and a sub-side tetrihydroloiates by this enzyme before they can be united as another to rote the optione methodynalisation heres with DNA synthesis, repair, and cells of the unitary black cells. Nuccal and intestinal microsa, and cells of the unitary black er ave in general more tensitive to this altect of methodynalisation. When cells of collecter altower the option of the tensities of the unitary black when cells of collecter and intestinal microsal grawth without i investrable damage to normal hissies.

In psonasis, the rate of production of epithelial cells in the skin is greatly increased over normal skin. This differential in prolif-eration rates is the basis for the use of methotraxate to control the source process.

Methotyszate in high dostes, tolkowed by leucovorin rescue, is used as a part of the treatment of patients with non-metastitic outorsa-rooma. The original rationals for high dose methotrexate therapy was based on the chnologi of selective rescue of normal issues by leucovorin Move moent evidences suggests that high dose meth-oferate may also evincome methotrexate metatance caused by majaing adapts transport, decreased affinity of dihydroblok and reductises moulting from gene amplification, or decreased affinities. The exclusion of methotrexate the character of action is uphonemic of methotragets. The actual mechanism of action is uphonemic.

Two Padatine Discology Group studies (one randomized and one non-randomized) dimonstrated a significant improvement in re-lapse free survival in patients with non-metastatic obtestacoma, when hay do so methodivause with succorom rescue was used in combination with offer chemotherapeutic agents following sur-al resocion of the primary lumor. These studies were not designed to demonstrate the specific contribution of high dose methodres.

ate/succession rescue therapy to the efficacy of the combination. However, a coardination can be inferred from the reports of objec-tive responses to this therapy in patients with metastatic costosar-coma, and from reports of extensive tumor necrosis following pre-operative administration of this therapy to patients with non-meta-static celesearcoma.

Pharmacokinetics

Pramacourepce Methotraxate is generally completely absorbed from parenteral noutes of injection. After intramuscular injection, peak serum com-centrations occur in 30 to 60 minutes.

Destruction - National Science and Science

Methotrexate does not penetrale the blood-cereorospinal fluid bar-ner in therapeutic amounts when given panenterally

one in therapence annuality when given patienteeday Matabolism - Mitarabooption, methods said undergoest hapatic and encode/dar metaorism to polygitalizatal of gene shorts can be com-vertised back to methorizenate by hydrologital soldsmass. These polygitalizaties act as ierbibors of dimpicitivities (robusties and thymidylate synthesis. Small amplitist of colleging and polygitalizaties may menan in tissues for isoterised by the polygitalizaties may menan in tissues for isoterise obvide the bibly of 7-hydrolyginethores is a 15 to 516 for the biblies vary among different cells, issues and humon. The aqueous solu-tivity of 7-hydrolyginethores is a 15 to 516 for the the same compound. A small amount of metipolem to 7-hydrolyginethoresaie may occur at doess commonly prescribed. Mitarofittaties is partially metabolized by intestinal flora after oral administration.

Half Life - The terminal half life reported for memotrecate is approximately three to ten hours for patients receiving Insament for geonass or low does anismedistic threapy (less than 30 mpm²). For patients receiving ingli doese of metholizatie, the terminal half the is right to 15 hours.

BE Bingen to Concept Extension - Revail economics is the permany notes of elemenation and is dependent upon descipe and fourier administration. Whit is de-mentation of the loss is been permanent administrated does is extended unchanged in the unner administrated does in extended oreions amounting to 10% opties of the administrated does Enterohepatic recirculation of methodrexule has been proposed.

Renal excernion occurs by glomenular filtration and active tubular secretion. Nonlinear elemination due to saturation of renal tubular realisorption has been observed in psonatic publiers at doces be-liveen 7.5 and 30 mg impaired renaf function, as well as concurrent use of drugs source as weak organic actists that also undergo tubular secretion, can markedly increase methotrexate serum levels. Ex-cellent correlation has been reported between methotrexate clearance and endogenous creatione clearance.

Amborevale observance rates very widely and are generally at higher doses. Delayed drug dearance has been identified as one of the major lactors responsible for mathotismate toxicity. If has been pub-uitated that the locaticy of methoticmeate to normal issues is more oppendent upon the duration of exposure to the drug rather than the peak level achieved. When a patient has delayed drug alimna-tion due to compromised renal function, a third space effusion, or driver aussiss, methotismate serving constraintions may remain el-evated for prolonged penods.

The polninial for toxicity from high dese regiments of delayed accretion is reduced by the administration of excession can be accretion in reduced by the administration of excession can be accretion in the second second second second second second accretion and the indentity those patients at high risk tor metholicitate toxicity and ad in proper adjustments of texcess orin dosm, Caudalines for monitoring serum metholiceate levels, and for adjustment of texceson dosing to reduce the ask of metholicitation second second below in DOSAGE ANO ADMINISTRATION

Methotrexate has been detected in human breast milk. The highest breast milk to plasma concentration ratio reliched was 0.08.1

INDICATIONS AND USAGE Neoplastic Disases Mediformatic endicated in the instiment of gestational chonocat-cinoma, choricadenoma destruens and hydetrofform mote.

In acute hymphocytic leukernia, methotrexate is indicated in the pro-

phylaxis of meningeal leukemia and is used in maintenance therapy in combination with other chemotherapeutic agents.

Methotrexale is used alone or in combination with other anticancer agents in the treatment of breast cancer, epidermoid cancers of the head and next, evanced mycosis fungoides, and lung cancer, par-ticularly squamous cell and small call types. Methotrexate is also used in combination with offer demotiverage actic agents in the treat-ment of advanced stage non-Hodgian's hymphomas.

Methotrexate in high doses followed by leucovonn rescue in combination with other chemotherapeutic agents is affective a profonging retaines-ines survival in patients with non-metastatic osteosarcoma who have undergone surgical resection or am-putation for the primary fumor.

Pootests Methomication andicated in the symptomatic control of severe, re-calcitrari, distabiling pisonasis that is not adequately mesonave to other forms of Memary, but only when the daynosis has been es-tablished, as by boppy und/or after domatologic consultation. It is important to exourb that a psomiasis Thare's not due to an undiag-nosed concomtant datease affecting immune responses.

CONTRAINDICATIONS

Methotrazale can cause letal death or leratogenic effects when ad-mixistatered to a pregnant woman. Methotrexate is contraindicated in pregnant patients with psonasis and should be used in the treatin program patients with peoplasis and should be used in the treat-ment of resplicatic diseases only when the potential benefit outweight the risk to the fetus. Women of childbearing potential should not be atlande on methotexate unit programoy is excluded and chould be fully counseled on the sentous risk to the fetus (see PRECAUTIONS) should they become programi while undergoing theatimet. Pregnancy should be involved if eliter partners is neceiv-ing metholizerate, during and for a minimum of three months after hereps/for make patients, and during and for all least one ovulgatory cycle after therapy for female patients. (See Boxed WARNINGS).

Because of the potential for serious adverse reactions from metho-trevate 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 psonasis who have overt or laboratory evidence of immunodeficiency syndromes should not receive methotrexate

Patients with psonasis who have preexisting blood dyscrasilas, such as bone martow hypoplasia, leukopena, thrumbocytopena, or sig-nificant anema, should not receive methotrexate.

Patients with a known hypersensitivity to methol/exate should not receive the drug.

WARNINGS -SEE BOXED WARNINGS.

PRECAUTIONS

Precision interest General Metholinistate has the potential for serious toxicity (See Board Metholinistate has the potential for serious toxicity (See Board Metholinistate has the potential for serious toxicity (See Board Metholinistate) of administration but have been seen at all looses. Boccure of the series of a diministration but have been seen at all doses. Boccure of the series of the series of the series of the reactions are reversible if deleticate early Methol appropriate corrective measures should be taken. If necessar, this could include the use of Inucceon calcium (see OVERDOSAGE) Imetholariset literapy is remensitiend, at should be carried out with caution, with adequate correctiventiated. Series of the truty and instrusted electrons of further recerd for the drug and instrusted electrons as to possible recurrence of loopty.

The clinical pharmacology of methorexate has not been well stud-ied in older individuals. One to diminished hispatic and remail functions as well as decreased fokate subces in this population i relatively low does a should be considered, and these patients should be closely monitored for leady signs of luxcity.

Information for Patients Patients aboutd 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 fabo-ratory tests to monitor toxicity.

Both the physician and pharmacist should emphasize to the patient that the recommended dose is taken weekly in psona-sis, and that mistaken daily use of the recommended dose has led to tatal toricity Prescriptions should not be written or re-filed on a PRN basis.

Patients should be informed of the potential benefit and nsk in the use of methodnistale. The risk of effects on reproduction should be discussed with both male and temale patients faking metholresate

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Laboratory Tests Patientis undergoing methodnexate thorapy should be closely mon-iored so that toxic affects are detected promptly. Baseline assessment should include a complete blood count with differential and patieted courts, hepatic ancyrons, meni kunction tests and a chest X-ray. During therapy of portiasis, monitoring of these pa-immeters is precommended hematology at 16 asst monthly, renal lunction and lever function every 1 to 2 months. More frequent mon-trong is usually indicated during antisopolasic therapy. During testad or changing doses, or during periods of increased risk of elevated methodicase blood levels (eg. dehydration), more frequent mon-toring may also be indicated.

Transient liver function test abnormalities are observed frequently after methotexate administration and are usually not cause for mod-fication of methorexate therapy. Persistent liver function test abnormalities, and/or depression of sarum allumin may be indica-tors of servous liver forxicity and require evaluation. (See PRECAUTIONS, Organ System Toxicity, Hepatik).

A relationship between abnormal liver function tests and fibrosis or orritosis of the liver has not been established for patients with psoriasis.

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

Drug Interactions Nonsteroidal anti-inflammatory drugs should not be admenistered prior to or concentranity with the high doses of metholrexate used in the treatment of osteosarooma. Concomitant administration of some NSAIDs with high dose metholrexate breatly has been the portiad to elevise and prolong servin metholized evelo, resulting in deeths from severe hematologic and gastroniteshall loady

Caution should be used when NSAIDs and salicylates are adminis-tered conconvlantly with lower doase of methorissate. These drugs have been reported to reduce the tubular secration of methotrex-ate in an animal model and may enhance its losicity.

Methotrexate is parially bound to serum abumni, and loxicity may be increased because of displacement by certain drugs, such as salicipates, phenyfolut_acros, phenyfoin, and subforumdes. Renal lubular transport is also diminished by problemicid, use of methodi-scale with this drug should be carefully monitored.

In the treatment of patients with categosrcoma, caution must be exercised if high-close methodresate is administered in com-instation with a potentially nephrotoxic chemotherapeutic agent (eg. claptatin).

Oral antibiotics such as tetracycline, chloramphenicol, and nonab-sorbable broad spectrum antibiotics, may decrease intestinal absorption of methodravate or interfere with the enterophopatic cir-culation by inhibiting bowel flora and suppressing metabolism of the drug by bacteria.

Penicillins may reduce the renai clearance of methotrexate; increased setum concentrations of methodreate with concom-lant hematologic and gastronitasting! toxicity have been observed with low dose methodreate. Use of methotrexale with penicilians should be carefully monitored

Patients receiving conconvitant therapy with metholrexate and erreinate or other relinoids should be monitored closely for pos-sible higher risk of hepatotoxicity.

Methotresate may decrease the clearance of theophylline, theophylline levels should be monitored when used concurrently with methobsxate.

Vitamin preparations containing folic acid or its derivatives may decrease responses to systemically administered metholres-ate. Preliminary animal and human studies have shown that small quantities of miratvenously administered leucovoin eo-ter the CSF primarity as S-methylistrahydrofolate and, in humans, remain 1-3 orders of magnitude of wer than the usual metholiserate concentrations following intrathecal administra-tion. However, high doeso of bloccovin may reduce the efficacy of intrathecally administered metholiserate.

Folate deficiency states may increase methotrexate toxicity. Trimethoprim/sullamethoxazole has been reported rarely to increase bone martow suppression in patients receiving methotrexate, prob-sby by an additive anticidate effect.

Carchogeneels, Mutagenesis, Impairment of Fartility No controlled human data sust regarding the risk of recolasis with matriormasks. Mathematic has been reveluted in a number of animal studies for carchogenic potential with inconclusive results. Although there is evidence that methodresate caused concreasional damage to arismal scanatic cells and human bone marrow cells. Re-

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clinical significance remains uncertain. Benefits should be weighed against the potential risk before using methotesate alone or in combination with other drugs, aspecially in pediat-ric patients or young adults. Wethotrevate causes embryotoxicity, abortion, and fetal defects in humans. It has also been reported to cause impairment of ferlikty, oligosper-mis and mentamical dysfunction in humans, during and for a short period after cessation of therapy.

Pregnancy : Teratogenic Effects, Pregnancy Calegory X. Numling Mothers See CONTRAINDICATIONS.

Pediatric Use Safety and effectiveness in pediatric patients have not been estab-lished, other than in cancer chemotherapy

Organ System Taxlofty Gastoneliesing II vomening, diarrhea, or stomatris occur: which may reach in diarphatom, methotersate should be discontinued until re-covery occurs. Methotersate should be used with extreme caution in the presence of paperic uber disease or uberative cauties

Hemaiologic: Methotrixate can suppress hemaiopoiesis and cause anemia, loukopenia, and/or thromocoy/topenia. In patients with ma-lignancy and preexisting hematopoietic impairment, the drug should be used with causton, if all all

In psoriasis, methotraxate should be stopped immediately il there is a significant drop in blood counts. In the treatment of neoplastic diseases, methotrexate should be continued only if the polential benefit warrants the trick of severe myelocuppression. Patients with profound granulocytopenia and fever should be evaluated immediately and usually require parenteral broad-spectrum antibiolic therapy.

Hepatic Monacapeous an announce series y. Hepatic Metholisexate has the polential for acute (elevated tran-saminasea) and chromic (Bross and cirrhoss) hepatotoxicity. Chronic toxicity is potentially tatal, if generally has occurred after protorged use (generally two years or more) and after a load dose of at least 1.5 grants. In studies in possible patients, hepatotoxicity appeared load a lunction of total curuulative dose and appeared to be enhimiced by alcoholom, obsety, diabetes and advanced age an accurate incidence rate has not been determined, the rate of progression and reversibility of lesions is not known. Special cau-tion is indicated in the presence of preserving liver damage or impared hepatic function.

In paoriasis, liver function tests, including servim albumin, should be performed penedically prior to dosing but are often normal in the face of developing fibrosis or cirrhosis. These lesions may be detectable only by biogsy. The usual recom-mendation is to obtain a liver biogs at 1) pretherapy ur shortly dater initiation of theraps (24 months). 21 a total cumulative dose of 1.5 grams, and 3) after each additional 10 to 1.5 grams. Moderate fibrosis or any cirrhosis ormally leads to discon-tinuation 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 com-mon preherapy. Although these mild changes are usually not a reason to world or discontinue methofinesale herapy, the drug should be used with caution.

Infection or Immunologic States. Methotrexate should be used with extreme calation in the presence of active infection; and is usually contraindicated in patients with overt or laboratory evidence of im-munodeficiency syndromes. Immunization may be ineffective when given during methotrexate therapy. Immunization with ive virus vac-rines is generally not recommended. There have been reports of disseminated vacoma infections after smaltpox immunizations in patients recovery methotrexate therapy. Hypogarimag/obulinemia has been reported rarely.

Potentially latal opportunistic intections, especially Pneumocystis canni pneumona, may occur with methotherate therapy When a pallent presents with pulmonary symptoms, the possibility of Pneumocystis canni pneumonia should be considered.

Preumocyclis came preumone should be considered. Neurologic. There have been reports of leukoencephalopathy following intravenous administration of methotexate to patients who have had craniospinal irradiation. Serious neurotoxicity, requently maintisted as generalized or local seruros, has been reported with unexpectedly increased irrequency among pediatic patients with accide imphobastic feakemia who were treated with intermediate-dose intravenous methotizate (1 gm/ 1). Symptomatic patients were commonly noted to have leu-koencephalopathy and/or microangropathic caloritications on diagnostic maging studies. Choraic leukoencephalopathy has also been reported in patients who received repeated doses of high dose methodirectate with leucovini rescue even without camel irradiation. Discodiation, bit excellance always result in complete recovery

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

After the intraihecal use of methotrexate, the central nervous system foxicity which may occur can be classified as follows sould chemical actionodius mandlested by such symptoms as headache. Back pain, nuchat rigidity, and lever, such acute my slopathy characterized by paraparessiparaplegia associated with involvement with one or more spinal herve roots; chronic leukencephalopathy manifested by confusion, imtability, som nolence, ataxia, dementia, sourcies and coma. This condition can be progressive and even falal.

Pulmonary: Pulmonary symptoms (especially a diry nonproductive cough) of a non-specific pneumonitis occurring during methotes-ate benergy may be indicative of a potentially duringenous lisson and require interruption of treatment and careful investigation. Although chically vimable, the typical pushes with methoticreate induced larg disease presents with (ever. cough, dyspnea, hypoterma, and an initiarias on check is k-ray, infection needs to be excluded. This lesion can occur at all dosages.

Renal: High doses of methotrexate used in the treatment of op-teosarcona may cause renal damage leading to acute renal takino. Nephrotecast, is due primarily to the precipitation of methotrexate and 7-hydroxymethotrexate in the renal tubules. Close attention to renal hunclion including adequate hydration, unne alkaimization and measurement of servin methotrexate and creatinine levals are asneasurement of serum mecho sential for safe administration

Skin: Severe, occasionally latal, dermatologic reactions, includ-ing toxic epidermal necrolysis, Stevens-Johnson syndrome, eclositive dematistis, skin necrosis, and enythema multilorine, have been reported in children and adults, within days ol oral, naramacculer, intravenous, or initialnecal methotexate admin-iatation. Reactions were noted after single or multiple low-informódiate or high dorse of methotexate in patients with neoplastic and non-neoplastic diseases.

Other precautions: Methotraxate should be used with e dreme cau-tion in the presence of debility

Methotrexaile exits slowly from third space compartments (eg. plaural effusions or ascrites). This results in a prolonged terminal plasma half-life and unrespected stocory in patients with significant ittrict space accumulations, it is advisable to evacuate the final before treatment and to monitor plasma methoticecasie levels.

Lesions of psonasis may be aggravated by concomitant exposure to ultraviolet radiation. Radiation dematitis and surburn may be "inscalled" by the use of mathotrexate

ADVERSE REACTIONS

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

The most frequently reported adverse reactions include liberative stomatifs, leukopenia, nausea, and abdominal distress. Other fre-quently reported adverse effects are mailines, undve lappine, chills and fever. dtz/iness and decreased resistance to influction.

Other advetse reactions that have been reported with methodos: ate are listed below by organ system. In the procedays setting, con-bentiant leartherert and the underlying desease make specific attr-bution of a reaction to methotrexate difficult

Almentary System gingvitts, pharyngilis, stomatuis, ancrexa, nau-sea, vomiting, diarrhea, hematomissis, mellena, gastrointestinal ur ceration and bleeding, entertiis, pancreatitis.

Cardioviscular, pericarditis, pericardial effusion, hypotension, and thromboemboke events (including arterial thrombosis, cerebral Prombosis, deep ven thrombosis, retrivial vain thrombosis, thrombopheblits, and pulmonary embolus)

Central Nervous System headaches, drowsiness, blurred vi son Aphasia, hemparesis, paresis and convulsions have also occurred following administration of methotiexate. Following, low doses, here have been occasional reports of transient subtle cognitive dysfunction, mood alteration or unusual cra-mal sensations.

Inflection: There have been case reports of sometimes tatal oppor-lunstic inflections in patients receiving methodrexale therapy the negliater and non-neopisatic diseases. Prevancing preu-monia was the most common infection. Other reported infections

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included nocardiosis, histoplasmosis, cryptococcosis, Herpes zoster, H. simplex hepatitis, and disseminiated H simplex.

Ophthalmic conjunctivitis, serious visual changes of unknown etiology

Putnonary System intersitial pneumonitis deaths have been re-ported, and chronic intersitital obstructive pulmonary disease has occasionally occurred.

Skin: srythematous rashes, pruntus, urticana, photosensilivity, pigmentary changes, alopecia, ecchymosis, telanijectasia, acre, furuoculosis, erythema multiforme, foric epidermai necrolysis, Stevens-Johnson syndrome, skin necrosis, and exolitative dermatitis.

Urogenital System: severe naphropathy or renal laikire, azotemia, cystis, hematuria; defective organesis or spermalogenesis, tran-sent algospermia, menstrual dystunction, vagnal discharge, and gynecomastila; intertility, abortion, tetal detects.

Other rarer reactions to or attributed to the use of methorinate such as nodulosis, vasculitis, arthnalgu/imyalgia, loss of libido/im-potence, diabetes, osteoporosis, sudden death, revensible verprioritis and unior visis syndhome. Anaphylactoid reactions have been veported.

Advense Reactions in Paortaalis: There are no moont placebo-controlled thats in patients with pso-nasis. There are two literature reports (Roenigk, 1969, and Nyton, 1978) describing layes areise (n=240, 248) or psonasis patients treated with methotmistile. Dosages ranged up to 25 mg per week and thetament was administered for up to low years. With the ex-pach 3% to 10%, the advense metadow rates mesor moorts were very similar to those in the rheumatoid arthrits studies.

OVERDOSAGE

OVERDOSAGE Loucovoni is indicated to diminish the toxicity and counteract the affect of inadvertently administered overdosages of methomsate loucovoni administration at should begin as promptly as possible As the time interval between methoresate administration and leu-covorini inistiation increases. It he effectiveness of leucovorin in counteracting toxicity decreases. Monicoring of the serum method-satile concertification is essential in determining the optimal dose and duration of treatment with leucovorin.

In cases of massive overdosage, hydration and urnary alkaliniza-tion may be necessary to prevent the precipitation of methotresate and/or its metabolities in the renal lubules. Neither homodallysis nor peritoread dalysis has been shown to improve methotresate elimination

Accidental intrathecal overdosage may require intensive systemic support, high-dose systemic leucovorin, alkaline diuresis and rapid CSF drainage and ventriculoiumbar pertusion

DOSAGE AND ADMINISTRATION Neoplastic Diseases are being administered since absorption is rapid and effective sa-mi levels are obtained. Methors alse rejection may be given by the intranuscular, intravenous, or the intra-antenal route Horever, ins preserved tormulation contains Benzy Alcohol and <u>music not</u> be used for intrathecal or high dose therapy

De used of inframesia of migricolad tempy Chonecarcinoma and similar (cophoblastic diseases). Methorizukate is administered oraby or inframuscularly in dises of 15 to 30 mg table for a five-dis occurs 3 are usually repetited for 3 to 5 times as required, with rist periods of one or more weeks interposed between courses, until any manifesting foxic symptoms subside. The effectiveness of therapy is ordinarily available by 24 hour quantifastive analysis of unany chones or genzálarizopin (hCG), which about orlium to normal or less than 50 fU/24 hr usually after resolution of measurable lesions in 4 to 5 weeks. One to two courses of metholexasta dier romaiscano fluction tomesration dischersate with other testerilite course and therapy of methorexasta with other testerilite. essential. Cyclic combination therapy of methotrexate with other antitumor drugs has been reported as being useful

Since hydatdform mole may precede chorocarcinoma, prophy lactic chemotherapy with metholrexate has been recommended

Chorioedenioma destruens is considered to be an invasive form of hydabdform mole. Methotrevate is administered in these cisease states in doses similar to those recommended for choriocarcinoma.

Leukensa. Acute lymphoblastic leukernia in pediatric patients young adolescents is the most responsive to present day che therapy. In young adults and older patients, clinical remissio more difficult to obtain and early relapse is more common. and is

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Methotrevate alone or in combination with steroids was used initially for induction of remission in acute lymphoblastic leuka-mas. More recently corticosteroid therapy, in combination with other aniselumenic drugs or in cyclic combinations with meth-oresate induced, has appeared to produce rapid and effective emissions. When used for induction, methotrexate in does of 3.3 mg/m² in combination with 50 mg/m² of predisione, given adly, produced remissions in 50% of patients treated, usually within a period of 4 to 6 weeks. Methotrexate in combination with other agreent appears to be the drug of choice for securing maintenance of drug-induced remissions. When remission acute achieved and supportive care has produced general dinical im-provement, maintenance therapy is initiated, as follows: wethorecare is doministered 2 tems weekly either by mouth or intramuscularly in total weekly doese of 30 mg/m². It has also been when relapse does occur, reinduction of remission regimen ally 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 tymphoblastic leukemis. The physician should be familiar with the new advances in anbieuxemic therapy.

Meningeal Leukema: In the treatment of prophylaxis of meningeal leukemia, methotrexate must be administered intrathically

Preservative free methotrexate is diuted to a concentration of 1 mg/mL in an appropriate stante, preservative free medium such as 0.9% Socium Chloride Injection, USP.

The censorspinal 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 methodnexale administration at a dose of 12 mg/m² (max-mum 15 mg) has been reported to result in how CSF methodnexate concentrations and reduced efficacy in pediatric patients and heyb concentrations and neurotoxyr in adults. The lolkowing dosage regimen is based on age instead of body surface area



In one study in palients under the age of 40, this dosage reg-men Appeared to result in more consistent CSF methotreate concentrations and less neurotoxicily. Another study in pedia-ric patients with acute lymphocytic leukemia compared the regiment as dose of 2 rown (maximum 15 mg), a significant reduction the rate of CNS relapse was observed in the group whose dose was based on ago.

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

For the Irreatment of meriminate libularma, intratilitical methorineate-may be given at intervals of 2 to 5 days. However, administration at intervals of loss than I week may result in increased subscule low city. Methotrate is a diministred with the cell count of the cerebrospinal fluid returns to normal At this point one additional does in advisable. For prophysical against meningeal Lexikema, the dosage is the same as for treatmont except for the intervals of administration. On this subject, it is advisable for the physician to consult the medical iterature.

Unioward side effects may occur with any given initialhead injec-lion and are commonly neurological in character. Large doses may cause convulsations. Methoticale given by the initialhead toxic appears significantly in the systemic circulation and may cause systemic methoticate toxicity. Therefore, systemic antileukemic interapy with leding should be appropriately disulsid, reduced or discontinued. Focal isokemic anotherment of the central nervous system may not respond to mitathecal chemotherapy and is best treated with adjotherapy.

Unified and understanding of the set of the

Mycosis lungoides. Therapy with methotrexate appears to produce clinical remissions in one-half of the cases triated. Dosage is usu-

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ally 2.5 to 10 mg daily by mouth for weeks or months. Dose levels of drug adjustment of dose regimen by induction or cessation of drug are guided by patient response and hematologic monitoring Mechaneste has been given intramuscularly in doses of 50 mg once weekly or 25 mg 2 times weekly.

Dsteosarooma: An affective adjuvanit chemotiverapy regimen re-quires the administration of serviral cytotoxic chemotiverapeutic agents. In addition to high dose methotreaats with leucohom res-cue, these agents may noclude dosorubion cisplatin, and the combination of bisomycin, cyclophospharmide and dischomycin (GCD) in the doses and schedule shown in the table below. The starting dose for high-dose methotrexate tratament is 12 grand "I tiltis, dose is not sufficient to protica a peak serum methotrex-ale concentration of 1,000 micromolar (10² mol1) at the end of the embilicities in this sufficient to protica a peak serum methotrex-ale concentration of 1,000 micromolar (10² mol1) at the end of the embilicities and sufficient to protice a peak serum methotrex-ale concentration of 1,000 micromolar (10² mol1) at the end of the embilicities and medication, leucovorin is given IV or IM at the same dose and schedule.

	Drug*	Dose*	Treatment Week' After Surgery	
	Methotrexate	12g/m ² IV as 4 hour infusion (starting dose)	4.5.6,7,11,12,15 16,29,30,44,45	
	Leucovonn	15 mg orally every six hours for 10 doses starting at 24 hours after start of methotrexate infusion.		
	Doxorubicin 1 as a single drug	30 mg/m² day IV x 3 days	8,17	
	Dexenubican 1 Gisplatin 1	50 mg/m ² IV 100 mg/m ² 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	

* Lnk, MP. Goonn AM, Miser AW, et al. The effect of adjuvant che-motherapy on relapse-free survival in patients with osteosarcoma of the autremity. N Engl. J of Med 1985; 314(No 25) 1500-1505.

See each respective package most for full prescribing infor-mation. Dosage modifications may be necessary because of drug-induced loxicity.

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

Administration of methotrexate should be delayed until recovery

- the WBC count is less than 1500/microliter

- the revolution is easy than 1500/microliter, the revolution count is less than 1500/microliter, the platetel count is less than 15,000/microliter, the secure thickone level is greater than 150 U the sCIPT level is greater than 150 U microliter is present, und level is evidence of healing emprositient pleated efficient is present; this should be drained dry pont to influence.

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- 2 Adequate renal function must be documented. a. Serum creatinese must be normal, and creatinue clearance must be greater than 60 mL/mm, below initiation of therapy b. Serum creatinine must be measured prior to each subsequent course of therapy. If serum creatine thas increased by 50 % or more compared to a prior value, the creatione clearance must be measured and occumented to be greater than 60 mU min (even if the serum creatinne is still within the normal range).

- 2 Patients must be well hydrated, and must be treated with sodium beatbonails for unnay abalenzation. a Administer ID 000 mUm of untravenous fluid over 6 hours prior to initiation of the methotreate infusion. Continue hydration at 125 mUm/fc 13 letrasmic/data) during the methotreate infusion has been completed a Alaxianze unte to martine the tables. During methotreate infusion and leuconomic calcium therapy. This can be account on a prior to a separate infravenous solution.

1.00 Repeal serum creatinine and serum methotrexate 24 hours after starting methotrexate and at least once daily unlil the methotrex-ate level is below 5 x 10* mol/L (0.05 micromolar).

The table below provides guidelines for leucovorin calcium dos-age based upon serum methotrexate levels. (Sne table below ')

Patients who experience delayed early methotrerate elimination are likely to develop nonrevenable objuric renal takine. In addition to appropriate locovorit metangi, these patients require contrau-ing hydration and unany alialanization, and close monitoring of had and electorylet status, unrel the service motorionization failers to below 0.05 micromolar and the renal failure has resolved.

5. Some patients will have abnormative and regal regul regult faits resolved.
6. Some patients will have abnormatives in methodrexate elemena-tion, or abnormatities in methodrexate elemena-tion, and horn and function following methodrexate elemena-tis and the second second second second second second second annomatives described in the table below. These abnormatities may or may not be associated with significant diviced loxicity it significant toxicity is observed. Iseconom rescue should be ex-tended for an additional 24 hours (total 14 does over 64 hours) in subsequent caurase of therapy. The possibility that the patient is laking other medications which interact with meth-ortrexate is incling to serum abumen, or elimination) should always be reconsidered when laboratory abnormalities or clinical loxotices are observed.

CAUTION: DO NOT ADMINISTER LEUCOVORIN INTRATHECALLY

Psoriasis: The patient should be fully informed of the nsks involved and should be under constant supervision of the physician. [See Information for Patients Under PRECAUTIONS]. Assessment of hematologo, nepatic, rankal, and pubmonary function should be made by history, physical axamination, and laboratory tests before beginning, painotically during, and before remaintung methotexate therapy, (See PRECAUTIONS). Appropriate steps should be taken Io avoid conception during methotexate Userapy (See PRECAUTIONS and CONTRAINDICATIONS).

All schedules should be continually tailored to the individual pa-tions: An initial test doze may be given prior to the regular dowing schedule to doked any attemes sensitivity to adverse effects (See ADVERSE REACTIONS). Maximal myslosuppression usually oc-curs in seven to tan dave.

Psonasis Recommended Starting Dose Schedule:

Weekly single IM or IV dosage schedule: 10 to 25 mg per week unbi adequate response is achieved.

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

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

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

HANDLING AND DISPOSAL Procedures for proper handling and disposal of anforancer drugs should be considered. Sinversit guidelines on this subject have been published ²⁴ There is no general agreement that all of the proce-ures incommended in the guidelines are necessary or appropriate

Parenteral drag products should be inspected visually for partic-late matter and discoloration prior to administration, whenev solution and container permit.

DILUTION INSTRUCTIONS FOR LIQUID METHOTREX-ATE INJECTION PRODUCT: revale Injection USP Isolonic Liquid, Contains Preservative

If desired, the solution may be further dituled with a compat-ible medium such as Sodium Chlonde Injection. Storage for 24 hours at lemperature of 21 to 25°C results in a product which is within 90% of label potency.

HOW SUPPLIED

otrexate Injection USP Isotonic Liquid, Contains Preservative

Each mL contains methotrevate sodium equivalent to 25 mg methotrexate

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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 CON TENTS ARE USED

Manufactured by: Bigmar Pharmaceutica Barbengo, Switzerland ticals SA

Manufactured for:

Bigmar, Inc. Johnstown, OH 43031

Rev 05, November 1998

REFERENCES Roenigk HH, Auerbach R, Malbach HI, et al. Methodrexate in Pso-riasia: Revised Guidelines. J Am Acad Dermatol 1988 19.145-156

Kremer JM, et al. Methotraxate for Rheumstoid Arthritis: Sug-gested Guidelines for Monitoring Liver Toxicity. Arth Rheum 1994; 37:316-328.

Recommendations for the Safe Handling of Parenteral Antine-oplastic Orugs. NH Publication No: 83-2821. For sale by the Superivalent of Documents, U.S. Government Printing Office, Washington, DC 20402.

AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. JAMA, 1985; 253(11) 1590-1592.

National Study Commission on Cytoloxic Exposure-Recommen-dations for Handling Cytoloxic Agenta. Available from Lous P. Jeffrey, SCO, Datiman, National Study Commission on Cyto-toxic Exposure, Massachusetis College of Pharmacy and Alfed Health Sciences. 179 Longwood Avenue. Boston, Massachusetts 02115.

- Clinical Oncological Society of Australia: Guidelines and Recommendations for Sale Handling of Antineoplastic Agents. Med. J Australia 1983; 1:425-428.
- 7 Jones RB, et al. Sale Handling of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center, Ca-A Cancer Jour-nal for Clinicians Sept/Oct 1963; 258-263.
- American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. Am J Hosp Pharm 1990; 47.1033-1049

OSHA Work-Practice Guidelines for Personal Dealing with Cy-toloxic (Antineoplastic) Drugs. Am J Hosp. 1986; 43:1193-1204.

LEUCOVORIN RESCUE SCHEDULES FOLLOWING TREATMENT WITH HIGHER DOSES OF METHOTREXATE

Clinical Situation: Normal Moltotrexate Elemention Laboratory Findings: Serum methotrexate lavel approximately 10 micromotar at 24 hours after administration, 1 micromotar at 48 hours, and less than 0.2 micromotar at 72 hours Laucovorin Dosege and Duration: 15 mg PO, 1M, or IV q ti hours for 60 hours (10 doses starting at 24 hours after start of methotrexate infusion)

Clinical Situation: Delayed Late Methotiexate Elimination Laboratory Findings: Serum methotnecate level remaining above 0.2 micromolar al 72 hours, and more than 0.05 micromolar at 96 hours after administration. Leucovorin Docage and Duration: Continue 15 mg PO, 1M, or IV g six hours, until methotrexate level is less than 0.05 micromolar

qua hous, uni methoritean reachand contraction and contract Evidence of Acute Rend Inpury Evidence of Acute Rend Inpury Laboratory Frankings: Serum methotewale level of 50 micromotar or more at 24 hours, or 5 micromotar or more at 48 hours after administration O.R.a. 100% or genater increases in serum creatine level at 24 hours, after methotricale administration (eg. an increase from 0.5 migot, to a tevel of 1 migdt, or more). Leucoverin Doesge and Duration: 150 mg M q three hours, until methotricatele evide is less fram 1 micromotar. When 15 mg M q three hours until methoditectate level is less fram 0.05 micromotar

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Rx only



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 40265

DRAFT FINAL PRINTED LABELING



METHOTREXATE. INJECTION USP (Preservative Free) Rx only

WARNINGS

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

BECAUSE OF THE POSSIBILITY OF SERIOUS TOXIC RE-

METHIDTREKATE SHOULD BE USED DNLY IN LIFE THREATENING NEOPLASTIC DISEASES, OR IN PATIENTS WITH PSDRIASIS WITH SEVERE RECALCITRANT, DIS-ABLING, 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 TOXICI TIES. (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 METHOTHEXATE HIGH DOSE REGIMENS REC. OMMENDED FOR OSTEOSARCOMA REQUIRES METICULOUS CARE (Se ODSAGE AND ADMINISTRA-TION) HIGH DOSE RECIMENS 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 METHOTREX-ATE THERAPY

I Methotresate has been reported to cause fetal death and/or congental incomales. Therefore, it is not recommended to women of altibibaring potential unless there is doer metical evidence that the benefits can be expected to outweigh the considered reas. Program women with poonises should not receive methotmatia. (See CONTRAMCICATIONS)

2 Methotresate elimination is reduced in patients with im-paired renal function, ascitas, or pleural effusions. Such pallents require especially careful monitoring for taxicity and require dose reduction or, in some cases, discontinu-ation of methotresate administration.

3 Unexpectedly severe (sometimes latili) bore manow suppression and gasconiestina toxicity have been reported with opcontrivity definision of methodexate (sound) in high does age) along with some nonstanoidal anti-inflammatory drugs (ISADS). (See PRECAUTIONS, Drug printeractorys)

(Hondo); [See Precision (IRMS; Ling presidence); (IRMS); [See Precision (IRMS; Ling presidence); (IRMS); [See Precision (IRMS); [See State and critico is); but generally only after polongial das Acutely; [Ires innyme devolutions are frequently seen; They are provide (IRMS); [IRMS]; [IRMS];

5. Metholinexate-induced lung disease is a potentially danger-ous lesson, which may occur accely at any time during therapy and which has them reported at doses as low as 7.5 mg/ware list not alware fully inversible. Potencians somotions lesses.

cality a dry, nonproductive colign) may require interruption or irrediment and careful investigation

5 Diambea and ulcerative stomatitis require interruption of therapy, otherwise, heroorhagic ententits and death from in testinal perioration may occur.

7 Malignant lymphomas, which may regress totlowing web-orawal of methodresiate, may occur in patients receiving low does methodresiate and, thus may not require cytotoxic intentimet. Discrimitive methodresia first and, if the hymphoma does not hegress, appropriate treatment should be instituted.

8. Like other cytototic drugs, methotrésale may induce "tumor here syndrome" in patients with rapidly growing lumors. Ap-propriete supportive and plasmacologic measures may prevent or alleviate this complication.

9. Severe, occasionally falal, skin reactions have been reported following single or multiple doses of methodroxate. Reaction have occurred within days of charal, witninspectual, witninspectua or withflincal methodroxate administration. Recovery has been reported with discontinuation of therapy (See PRECAUTIONS, Organ System Toxicity, Skin.)

Potentially latal opportuniatic infections, especially Preumocystis canno pneumonia, may occur with methotr-exate therapy

DESCRIPTION Methotreasle (formerly Amethopiem) is an antimetaboate used in the treatment of certain neoplastic diseases and service psoriitsis

 $\label{eq:chemically} \begin{array}{l} Chemically methological is $N[4][(2,4)diamiss 6 pteridiny])$ mathyleathylaminological is glubamic acid. \end{array}$

The siructural formula is -----The molecular formula is C_H_N,O,

The molecular weight is 454.45

Methotrecals Injection USP is stanle and non-pyrogenic and may be given by the intramuscular, intravenous, intra-artenation intraffi received (See DOSAGE AND ADMINISTRATION)

Each mL contains methorizenate sodium equivalent to 25 mg metholizerate and the following inscriber ingredients: Sodium Christol & J305 why and Watter for Injection equivalent of the Sodium Mytholizer and 10 methods and/or Hydrochloiric And may be added to adjust the pH during manufacture to 5.5 d.1. The 2 mL 4 mL 8 mL and 10 mL solitons contain approximately 0.4. mEq. 0.06 mEq. 172 mEq. and 2.1.5 mEq. d1 Sodium per wall respectively, and are isotonic solitons.

CLINICAL PHARMACOLOGY

CLINICAL PHARMACOLOGY Methodisation inhibits dirytoloolica acid reductase. Dihydiorlolanes must be indiuced to tertanyckoloblass by this anzyms before they can be utilized as carriers of une-carbon groups in the synthesis of panne nucleotides and thymidylate. Therefore, methodinate effec-tines with DNA's synthesis: regulate and cellular replication. Activity positivities that synthesis regulate and cellular replication. Activity positivities that any analysis of the synthesis of the univary bladder and in genoral model. methods, and used a difference of the stand in most normal tissues: methodisense may impair making nant growth without interversible damage to normal tissues.

In psonasis, the rate of production of optitudial cells in the skin is greatly increased over normal skin. This differential in prolif exation rates is the basis for the use of methotrexate to control the psonatic process.

The periodic product is high doces, followed by levaryown rescue, is used as a part of the treatment of patients with non-metastatic orderosa-roma. The organa rationale for high doce methodrace therapy was based on the concept of steechive rescue of normal issues by houcevorn. Near more revenie volunces suggests that high dose meth-oferaste may also evenisome methodraste resolance caused by repaired advise transform forecasted alliney of drivytwicks and reductave resoling from gene amplification or decreased polyphamadon of methodresste. The actual mechanism of action is urbinary and the transform forecasted alliney is an order advictave resoling from gene amplification. or decreased polyphamadon of methodresste. The actual mechanism of action is urbinary.

Two Pediatric Oncology Group studies (one randomized and one non-randomized) demonstrated a significant improvement

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In relactse-free survival in patients with non-metastatic osteosa-rooms, when high dose methodevate with leucovoin rescue, was used in combination with other chemotherapeubc agents billowing surgical resection of the primary tumor. These stud-ies ever not designed to demostrate the specific contribution of high dose methodevate/electronic nestrue therapy to the efficiency of the combination. Weevers, a contribution can be unplatents with metastate/becovoin restrue therapy to the entropy to the other therapy of the administration of the replatents with metastate/becovoin restrue therapy to the entropy tumor necross following prospective administration of this therapy to patients with non-metastatic osteostaroma.

Pharmacoldnetics

acoxumesca hon-Methotristate is generally completely absorbed from val notes of injection. After inframuscular injection, peak concentrations occur in 30 to 60 minutes.

rðuðon- Aller infravenous aðrinnistration, tha instal volume of flution is apprusimstely 0.18 L/bg (18% of body vergigt) and dy-stale volume of distribution is approximately 0.4 to 0.8 L/bg is 6.80% of body vergigt). Nethods sale competers with reduced cross cell membranes by means of a l fransport process. Al serum concern romolar, passive diffusion becomes a crive intracellular concentrations can ed active trans - parameter of mich enterther intracesular concernations of theired. Methodizasate in parameter as approximately 50% protein d. Laboratory studies demonstrate that it may be displace liparame albumin by vincous compounds including sufficient plasma elbumin by vincous compounds including sufficient states, tetracyclines, chloramphenicol, and phenyton

Mathotrexate does not penetrate the blood-cerebrospinal lived barrier in therapoulic amounts when given parenter-ally High CSF concentrations of the drug may be attained by intrathecal administration.

by intrahecal administration. Metabolism - Aher absorption, metholinexale undergoes hopalic and intracellular metabolism to polygiulariated forms which can be converted back to matholinexale by hydrolase enzymes. These polygiulariates arguing the transmission of divisional and administrate to polygiulariates may remain in itsues for ar-tended periods. The meteholon and protonged drug action of these active metabolites vary among different cells; fasures and tumors. A small amount of metabolism in 0-7-hydroxymetholicitaal may occur at does commonly prescribed. Accumulation of this metabolism may become significant at the hydroxymetholicitaal may occur at does commonly prescribed. Accumulation of this metabolism tag become significant at the hydroxymetholicitesate in a docur actional the parent compound Methoritesate is partially metabolism to y intestinal fore after oral administration.

Hah-Life - The terminal half-life reported for methodresale is app prosmately three to ten hours for patients receiving imaginemit for psoriasis or tow dose anthresplasis: therapy (tess than 30 mg/m) for patients meaving high doces of methodresale, the terminal half vie is eight to 15 hours.

Excretion - Renal encretion is the primary mule of elimination, and is dependent upon decage and mule of administration. With IV ad-monstration, 1955, to 1956, of the administement done is excreted unchanged in the uses within 24 hours. There is initial billing excretion amounting to 175 to ever less of the administered doals Enterotepatic reconstation of metholmaste has been proposed.

Ensuring experience occurs by glomenufar literation and active tubular secretor. Nontrease elemenufar literation and active tubular enabliships to the sole of bound of the possible public reterm 7.5 and 20 mg. Imgained renal function, as well as concurrent use of drugs such as weak organize nodes that also undergo tubular societion. Can markedly increase methodisate serum levies. Ex-cellent Contrelation has been regioned between methodiseate organizes and endogemous creative clearance.

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Incrementer oferenance nates una vederal and are generally de-ante al inciper losses. Delayed dong desances hes toen dentified mu ol il en mageri lactos ne generalle los rechti been posituated has the losses of methological for normal sei is mote dependent upon the duration of execution and pathere. Las semi possibilitaria en la cara contago o menomenar na manta Insues is more dependent upon the duration of exposure to the drug rather than the peak lanet achieved. Where a patient has de-layed drug emission due to compromeder thank lanction, a third space difusion, or ether causes, methodustate serun concentra-horst may remain elevated to prolonged pendets.

The potential lor textory from high dose regiments or delayed ex-orition is reduced by the administration of lexconomic aslound during the final phase of interforkasite plasmins shrinkation. Pharmacodu-netic monitoring of methodesate serum concentrations: mary help identify threa gradentis at high mick low methodement lexcity and au in gradent antideplasming the low methodement lexcity and any gradent advantation and low down and lexcit and gradent advantation and and a down and and advantation of delay to reduce the risk of methodement toxicity, are provided be-low in DOSANCE AND ADMINISTRATION.

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Methotrasale has been detected in human broast nulk. The highest broast nulk to plasma concentration ratio reached was 0.08.1

INDICATIONS AND USAGE Neoplastic Diseases Methotrecale is indicated in the Insumment of gestational chonocar-cinoma, choroadenome destruisms and hydaboliom mole

In acute tymphocytic leukerna, metholitekate is indicated in the pro-phylaxis of moningpal leukerna and is used in muntenarice therapy in combination with other elementerapeutic agents. Methotickate is also indicated in the treatment of meningpal leukerna

Metholesials is used alone or in combination with other anticancer agents in the treatment of brassi cancer, replerenced cancers of the head and nack, advenced myccoss huppedes and turg cancer, par-lealaidy squareous onli and small oel types. Methotinistie is also used in combination with offer chronoldwarpeus caparis in the treat ment of advenced stage non-Hodglium's hymphomas

Methibizesale in high doses tollowed by leucovonn rescue in combination with other chemotherapeutic agents is effective in protonging matipus free survival in patients with non-metastatic satiosarcoma who have undergone surgical resection or am-polation for the primary tumor.

Porticular Methodraxule is indicated in the symptomatic control of severe, re-calchard, disabling portical that is not adequality response to able forms of therapy, but only men the diagnosis has been es-tablished, as by budgay and/or altw dematabage consultation it is important to ensure that a porcess Tarter is not due to an undiag-nosed concomitant disease allevating immune responses.

CONTRAINDICATIONS

CONTRAINDICATIONS Methotoxials can base feal death or teratogenic effects when ad-ministered to a pregnant woman. Methotixuate is contraindicated in program women with postase and should be used in the mail-adverse of the state of the second state of the mail-should not be stand on methotixuate of programs y a excluded ad should be tails out when with the energy formation at should not be stand on methotixuate of programs y a excluded and should be taily counseled on the second method pregnant when we availed in the two parts in the letter second the pregnancy should be availed in other states after therapy for mails patients, in during and for a minimum of theire months after therapy for mails patients, and using a state one ownatory cycle after thanks provided in the second method. See Boxed MANNINGS1. Because of the method is

Because of the polential for senous adverse reactions from metho-tresate in breast fed intants, it is contraindicated in nursing mothers

nts with psonasia with alcoholism, alcoholic liver disease or chronic liver disease should not receive methomerate

is with psoniasis who have overt or laboratory evidence of nodeficiency syndromes should not receive metholitexate.

Patients with psonasis who have previsiong blood dyscrasias, such as bone marraw hypoplasia, laukopenia, theimbocytopenia, or sig-nificant anemia, should not receive methotresate

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

WARNINGS -SEE BOXED WARNINGS.

PRECAUTIONS

PRECAUTIONS General Methodines has the polential for services nonchi, (See Boated Methodines), food effects were related in hopping and even-ity is done of requency of administration bat have been seen at at obset. Because they can accur at any time during therapy it is reconstant increased in the cancel and the during therapy it is reconstant to end should be reduced in donage or discontinued and occur the drug should be reduced in donage or discontinued and appropriate consolution and the source of the drug should be reduced and the drug should be reduced in donage or discontinued and occur the drug should be reduced in donage or discontinued and in methorersate therapy or ministratule, it haves the the drug of the caulding were discontinued and be carried and with cauldon, with adequate consolaration of lumber need to the drug and with moves and alterties as to possible meanment and the during the the set of the drug of the drug the technic means distributes at to possible meanment of the drug and with moves and alterties as to possible meanment before.

The clinical pharmacology of methotiescale has not been well stud-aed in older individuals. Due to diminisched hepatis and remain function as well as dischassel folder autores in this population, installingly low does a thruld be considered, and these patients should be closely monitored for early signs of housing.

Information for Parlenta 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 labo-rationy tests to monitor toxicity.

Both the physicial and pharmacist should emphasize to the patient that the recommended dote is taken weakly in pacina-sk, and that mititatian daily use of the recommended dose has led to fatal toocity. Prescriptions should not be written or re-field on a PHP basis.

Patents 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.

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bacabase with ocurrings and immate patients boring immatersele Laboratory Tests Patents undergoing methodesiate therapy alroads be closely mon-tioned to chart torike effects and elencided promptly Baseline assess-ment should include a complete blood count with differential and patient ocurring therapy of psonasis, monitoring of these parameters X-ray During therapy of psonasis, monitoring of these parameters as recommended hematology at least monitoring of these parameters y indicated hematology at least monitoring in the or chang-ing doese, or during periods of increased risk of elevated methoding aster torike (leg, dehydration), more frequent monitoring may also be indicated.

Transent liver function test abnormalities are observed imputently after methodmatte admirastration and are usually not cause for mod-hoaten or methodmatte admirastration and are usually not cause to import admirastratives, and/or depression of serum albumm may be indica-tors all services liver flasticity and flaguice availabilition. (See PRECAUTIONS, Organ System Toxicity, Hopenc.)

A relationship between abnormal liver function tests and forosis 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 Nensterolds are instantiative drugs should not be administered procision concommanity with the high doses of methotrexate used in the traditional objectations. Concurration administration of same NSARS with high dose multiciterate therapy has been pained to interact and protopy enum methotrexate levels, resulting in deaths from service hematologic and gastmoniestnal loxoity.

Caution should be used when NSAUs and salicylates are edminis-liered concomfantly with lower doess of mathotresale. These drugs have been reported to reduce the fubbale secretion of methotres-ate in an animal model and may enhance its lowohy.

Methobezate is pathally bound to serum albumin, and toxicity may be increased because of asplacement by certain drags, such as salkcrittes, phenyfloatazone, phinnyrion, and sulforamides. Benal bouer transport is also demonshed by probeneoid, use of methode easte with this drug should be carefully morefrond.

In the irealment of patients with osteosarcoma, caution musi be exercised it high-dose methotrexate is administated in com-braction with a obtentiality nephrotosic chemotherapeutic agent (eg. cspilation)

Oral antibolics such as tetracycline, chloramphenicol, and nonab-softable broad succirum antibiotics, may decrease intestina absorption of rethoritients or underfer with the enterolepade or subtor by inhering bowet hora and suppressing metabolism of the drog by bacteria.

Percellins may reduce the renal clearance of metholrexate; in-preased serum concentrations of methol/texates with concombant hermatilogic and galariontes/truta loadly have been observed with herp and low doce metholrexate. Use of methoderate with period-ling should be callered in motored.

Platents receiving concorrelant therapy with methotrexate and elitetinate or other rationads should be monitored closely for pos-sable increased risk of hepatotoxicity.

Methobrakale may decrease the clearance of theophylline theophylline levels should be monitored when used con-currently with methotresate

Villamin proparations containing folic acid or its derivatives may decrease responses to systemically administered methodra-ate. Preliminary annai and human studies have shown hat small quanties of antarvinously administered fauctoom en-ter the CSF primarily as 5-methyliotrans/dotolate and, in humans, remain 1-3 orders of magnitude shower than the usual methoticitate concentrations following intrathical administra-tion. However, high doss of luncovinin mgy reture the efficacy of intrathically administered methotnesate.

Folate deliciency states may increase metholrexate foxicity.

Trimethoprim/sultanethoxazole has been reported ramly to increase bone marrow suppression in patients receiving methotrezale, prob-ably by an additive antifotate effect.

any ty an accurve annotate entrol. Carcinoganesis, likutaganesis, impairment of Fartfitty Na controller huma: Satia accurs and paradrag the risk of neoplasis with methodmante. Methodravate has been envisualed in a number of animal shudes to carcongane collimal with inconduction hybrid. Although there evidence that methodescale causes chromosomal damage to animal shudes bed without both the evidence against the polential risks before using methodravate akon to combination with other dugs, sepecially in polating patients or young addits. Methodravate thas also been reported to cause impair-ment of kently (copperma and network) and to cause impairs during and for a short period efficiences also of hereigy.

Pregnancy: Taratogentic Effects, Pregnancy Category X See CONTRAINDICATIONS

Nursing Mothers See CONTRAINDICATIONS

idiatric Use dety and effectiveness in pediatric patients have not been estab-hed, other than in cancer chemotherapy

Drgan System Toxicity Gasizeniteshali Hvorrjäng, Glamilia, or storraitis occur, which may result in delitystaton, methodiste should be discontinued and en-covery occurs. Methodexista should be used with extreme causion in the presence of pagice user disease or discative collex.

Nomatokigic: Methodrasate can suppress hemistopolesis and cause anersis, leukopenia, and/or thrombocytopenia. In patients with ma-lignancy and preasisting hemislopolithic impairment the drug should be used with causion, if at all.

In psonasis, methorexals should be slopped immediately if there is a significant drop in blood counts. In the treatment of neoplastic diseases, methodesals should be continued only if this potential benefit werrants the risk of severe myelsuppression. Palaenis with protound granuloofpopena and lever should be availated nimesidately and usually require parenteral broad-spectrum antibiotic thetapy.

partnerma distance spectral memory contrary, Happetic Metrocrassi he site the potential for acrite (elevated tran-sammases) and chronic (Barress and cirritosa) hepstrotoschy. Chronic tostofs is poleradally tatki. It generally base soccurred after protorgod use (generally hev yeans or more) and after a kital does of at wast 15 generally hev yeans or more) and after a kital does apparent to be a lunction of load cumulative does and appaared to be induced by accordem, doesdy, datelets and advanced age. An accurate incidence date has not been determined. The rest of mis induction in the presence of pressioning lever damage or unparted hepatic function.

impared heblic bindion. In psortiasis, liver function feats, including settum albumin, should be performed periodically prior to dosing but are often normal in the face of developing factors or criticism. These learns may be detectable code by biopsy. The businal recom-ment instants to often a high corresp at 10 psychiatary or shortly ment instants to often a high corresp at 10 psychiatary or shortly dose of 15 gramma, and 31 after each additional to 16 15 gramm. Moderate forms or any circlosis normally leads to discon-tionation of the drug meld filterios in commaly leads to discon-tionation of the drug meld filterios in commaly leads to discon-tionation of the grade portari syndem method segrets a repeat bopsy in 6 months. Milder histologic findings such as faity change and to grade portari syndem method seats in the rapy. The drug should be used with Caution.

Infection or Immunologic States Methodneside should be used with externer caulion is the presence of active infection, and is usually contrainfocated in patients with or which or luboratory evidence of im-munofibilicency syndromes. Timmication may be influence when given during mathodresate therapy immunazation with live may vac-cines is generally not recommoded. There have been reports of disseminated vaccoma infections after smalpce immunazations in patients recomming methodresate filterapy Hypogammarglobulinemia hes been reported rarely.

Potentially label opportunistic infections, especially Pneumocystis carrill preumonia, may occur with metholisisale therapy. When a patient presents with putmonary symploms, the possibility of Pneumocystis carrill pneumonia should be considered.

Neurologic: There have been reports of feukoencephalopathy following intrivenous administration of metholiterate to petientla wind have had connoispinal intradition. Senous neurolitopoity, fre quently manifested as generalized or focal secures. has been

reported with unexpectedly increased frequency among pedi-attic patients with soule lymphoblastic feutemia who ware freated with informatications in the methoresate (1) gm/ m³). Symptomatic patients were commonly noted to have (su-koencephalopathy and/ar microangropathic calcifications on diagnostic imaging studies. Chronic leuker cephated doses of high-dose methotesate with feucoron rescue area without creati information. Discontinuation of methotravate dose not always fesult in complete recovery.

A transient acute neurologic syndrome has been observed in pa-tients treated with high dose regimens. Manilestations of this stroke hile excloplatopathy may include confusion, hemipatesis, seizures and coma. The skact cause is unknown.

After the intrathocal use of methotraviale, the central nervous system louicity which may occur can be classified as follows, acute chemical arachmoditis manifested by such symptoms as headsche, back pain, muchal rigidity, and fewr, sub acute mystopathy characterized by paragatesio/paraplege associated with involvement with one or more spiral nerve mois, chronic leukoencephalopathy menifested by contration, imballely, com-nicience, elasi, demente, solicures and coma This condition can be progressive and even latal.

Pulmonary: Pulmonary symptoms (especially a dry nonproductive cough) or a non-specific pneumonitis occurring during metholies-tel ferracy may be indicative of a potentially dragenous lesion and require interruption of treatment and cambul investigation. Atthough indicasily variable, the hybrid patient with metholisate induced ung disease presents with Hever, cough, dyspream, hypotentia, and en infitratio on ches k-ray, indication needs to be excluded. This lesion can occur at all dosages.

Renal: High closes of methotresists used in the treatment of os-teosarooma may cause minit damage leading to exite meal failure. High-indicating is due primarily to the precipition of methotresiste and 7-hydroxymethotresists in the renal lubules. Close attention to meth function rounding adequate hydration; unre alkalinization and measurement of serum methotresista and creationic loves are es-used to a value updoptidention. measurement of serum metho semial for sale administration

Skin. Severe, occasionally [ata], dermatologic reactions, includ-ing tosic epidermal neorolysis. Stevens Johnson syndrome, soliciative demailist, sitio neorosis and eryrithema multiforme, nave been reported in children and adults, within days ol oral, nave been reported in children and adults, within days ol oral, nave been reported in children and adults, within days ol oral, nave been reported and the single or multiple tow, intermodate or high doese of motholie rate admin-neeplastic and non-neoplastic diseases.

Other precautions: Metholicexate should be used with extreme cau-tion in the presence of debility.

Methotresate exits slowly from third space compartments (eg, pleural effusions or excrites). This results in a prolonged terminal plasma half-life and unexpected touchry in patients with significant third space accumulations, it is advisable to evacuate the fluid before freatment and to monitor plasma methodiversal levels.

Lesions of psonasis may be aggravated by concomitant exposure to ultraviolet radiation. Radiation demotifits and surburn may be 'recalled' by the use of methotrexate

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

The most imquently reported adverse reactions include ulcerative stomality, leukopena, nausea, and lebdominal distress. Other the-quently reported adverse telests are malaese, undue facue, chills and fever, discrimes and decreased resistance to infection.

Other adverse reactions that have been reported with methodres-ate are lated below by organ system. In the encodogs setting, concorreant treatment and the underlying disease make specific attribution of a reaching to methoresize difficult

Almentary System ginguros, pharyngios, stomalios, anorexia, nau-wa, vomiting, diarrhea, hematemesis, melena, gastroinlasteral alceration and bleeding, enlaritis, pancreatitis

Cardiovascular percentilits, percential effusion, hypotension, and microbioambole events (including attenui thrombosis, cerebral thrombosis, deep verin thrombosis, refinal verin thrombosis, throm-tophickis, and pulmonary ambolics)

Central Nervous System headaches, drowsiness, blurned vision Aphasia, hemparese, pareis and convisions have also occured lokwing administration of methomerapts. Foldwing tow doses, there have been occasional reports of transient suble cognitive dystunction, mode alteration, unusual cranial sensations, leukoencephalopathy or encephalopathy.

Inflection Thare have been case reports of sometimes fatal oppor-ances unlections in pasterts incerving methodiesase therapy lice inceptastic and non-neoplastic disastes. Phaemocyths carini pneumosa was the most common inflection. Other reported infle-tions included incoractious. Heriplasmostic, strupticocoms, Heripes zoster, H. simplex hepatistic, and disseminated H. simplex

Ophthalmic: conjunctivitis, serious visual changes of un-known etiology.

Pulmonary System interstitial pneumonitis deaths have been re-ported, and chronic intersitial obstructive pulmonary disease has occasionally occurred.

Skin erythematous risches, pruntus, urticaria, photosensilwity, promentary changes, alopecia, ecchymosis, ielangectsia, acne, luturoutosis, erythema multiforme, lović epiderimat necrolysis, Stevens Johnson syndrome, skin neciosis, and etokative domitalis.

Urogenital System servore nephropathy or recal failure, accientia, cysite, hematuna, defective togenuss or spermalogenesis, tran-siem aligosperma, mersihual dystanction, vagnual discharge and gynecomastia; infertility, abortion, total defects.

Other rater reactions related to or attributed to the use of meth-otraxate such as noclulosis, vasculitis, anthraigaulmystiga, loss of bioidorimpotence, dabetes, osteoporosis, sudden desth and reversible tymphomas. Anaphylactoid reactions have been re-ported

Advance Reactions in Peoriasis: These are no nocem placebo-controlled trais in patients with pso-raist. There are two iterature reports (Roemds, 1969), and Nytos, 1978) describing large series (na204, 248) of psortasis päheris timated with methoresaite. Dosages ranged up to 25 mg per week and treatment was administered for up to loar years

OVERDOSAGE

OVERUOSAGE Leacovanis is indicated to diminish the foxicity and counterand the effect of nactivenently administered overhologges of methotizate Leucovanis additional topics as group to a possible As the time interval between methodrease administration and keu-covorm initiation increases. It we affectiveness of leucovani in counteracting loaciely decreases. Monitoring of the serum methodr-easte concentration is essential in determining the optimal dose and dynation of insatment with leucovania.

In cases of massive overdosage, hydralion and urinary elka kinzation may be necessary to prevent the preceptation of memotraxitie under its metabolies in the reral tubules. Nei they hemodulysis nor peritorieal datyes has been shown to improve metotesate alimination. of ma

Accidental intrathecal overdosage may require intensive systemic support, high-dose systemic leucovonn, alkalime duresis and rapid CSP drainage and ventriculolumbar perfusion

DOSAGE AND ADMINISTRATION Neoplastic Disease Oral administration in tablet form is often preferred when low does are being administrated since absorption is rapid and effective serum levels are obtained Methotresale injection may be given by the intramuscular, intravenous, intra-artienal, or in trathecal toute

Interneutations and sensitir trigghobiastic diseases. Methemistate is administered only or intramuscularly in dosis of 15 to 30 mg day for a fine-dia youns Such counses are usually reparated for 3 to 5 times as required, with rest periods of one or more weeks intriposed between counses, und any marketisting (loss symptoms subside. The effectiveness of therapy is ordinarily exclusited by 24 hour guarantative analysis of unmary chorene grandstrope (MGG), which should return to rormal acies span 50 kU24 hi to subject the the thur of north course and usually be followed by a competer resolution of massumble issons in 4 to 6 weeks. Che to the course of immerities after combination the restay of methotre-aster with other antilumen drugs has been reported as being useful

Since hydalidiform mole may precise choriccarcinoma, prophy lactic chemotherapy with methol(evale has been recommended

Changadenoma destruens is considered to be an invasive form of hydabdiform mole. Methotrexate is administered in these disease

states in doses similar to those recommended for chorocarcinoma.

Leukemia: Acute lymphoblastic leukemia in pediatric patients and young adolescents is the most responsive to present day chemo-terapy. In young adults and jdder patients, clinical remession is more difficult to obtain and early relapse is more common.

more detaut to option and early reliable is more common. Methodresatis alone or in combination with steroids wills used initially for induction of remission in acuts tymphoblestic leuke-miss. More recently contracteroid therapy, in combination with other antieutemic drugs or in cyclic combinations with meth-otractile included, has appeared to produce rapid and effective remissions. When used for induction, methoticsate in doces of 3.3 mg/m² in combination with 60 mg/m² of predinisone, given daily, produced remissions in 50% of pairtients treated, usually within a period of 4 to 5 weeks. Methotracte in combination with other agents appears to be the drug of chacle for securing maintenance of drug-miduced remissions. When remission as acheved and all supportive cam has produced general chinical im-provement, maintenance, therapy is initiated, as follows: effortenate adamsisted of 25 mg/m ethore 190 mouth or entramacularly in tratavenely doese of 30 mg/m². Thas also been when in does of 25 mg/m tratevenely every 14 days. II and when relapte does occur, reinduction of remission regimen. Available to combinate metaling the initial induction regimen.

A variety of combination chemotherapy regiments have been used for both induction and maintenance therapy in acula lymphoblastic leukerna. The physician should be lamiliar with the new advances in antileukernic therapy

Meningeal Leskomis, in the treatment of prophylasis of meningeal leskense, methodissule must be administered intrathecally. Pro-synather free methodissuls is disked to a concentration of 1 mg/ mL na napopopala strike, preservative free medium such as 0.9% Sodium Chivines hypection. 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 maches the edult volume in several years.

Intrathecal methotrexate administration at a dose of 12 mg/ m¹ (maximum 15 mg) has been reported to result in low CSF methotreate concentrations and reduced ellicacy in pediatric patients and high concentrations and neurotoxic-ig in adults. The knowing dosage regimen is based on age instead of body surface area:

	AGE (years)	DOSE (mg)	
-	<1	6	_
	1	8	
	2	10	
	3 of older	12	

In one study in patients under the age of 40, this dosage regi-men appeared to result in more consistent CSF methoreaale concentrations and less neuroloxicity. Another study in podiat-tic 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 elderty patients.

For the itsakment of menorgeal levikemia, intrathecal methotrexate may be given al intervals of 2 to 5 days. However, administration al intervals of least than 1 week may result in uncreased subsorte toor, which texate is a daministered until this cell count of the cerebrospinal fluid returns to normal. At this point one additional does a advesable. For prophysical sogaramengeal levikema, the doesage st the same as for treatment except for the intervals of ad-ministration. On this subject, if a advesable for the physician to consult the medical hierature.

Unloward side effects may occut with any given initiathecal injec-tion and an commonly neurological is character. Large doses may cause convulsions. Metholexatal given by the initiathecal route appears significantly in the systemic circulation and may cause sys-temic methotrexate louicity. Therefore, systemic antileukemic therapy with the drug should be appropriately adjusted, reduced or discontinued. Focal leukemic involvement of the central ner-vous system may not respond to unrathecal chemotherapy and iss best freated with radiotherapy.

Lymphomas: In Burkin's tumor, Stages I-II, methotrecale has pro-duced proxinged remains in some class. Recommended docage is 10 to 25 mg/day orally for 4 to 8 days. Stage III, methotrecale is commonly given concontantly with other antitumor agents. Treat-ment in all stages usually consists of several courses of the drug interposed with 7 to 10 day restpends. Lymphosarcomas in Stage III may respond to combined drug therapy with methotrecale given

in doses of 0.625 to 2.5 mg/kg daily.

Mycosis Fungoides: Therapy with methotrezale appears to produce clinical remissions in one hait of the cases treated. Dosage is usu-ally 2.5 to 10 mg daily by mouth for weeks or months. Dose levels of isrug and adjustment of dose regiment by reduction or essation of drug are quided by patient response and hematologic monito-ing, Methotrezale has been griven intranucularity in doses of 50 mg once weekly or 25 mg 2 times weekly.

Osteosarzona, An effective adjuvant chemotherapy regimen re-quiras the administration of several cycloxic chemotheraputic agents. In addition to high-dose methodre value with lexcovorn res-out, these agents may include docurbicing, cisplatin, and the combination of bleorrycin, cyclophosphamide and dastinomycin (BCD) in the doses and schedule shown in the lable bleow. The starting dose for high-dose metholizerate treatment is 12 grand/ "/ this dose in distribution to produce a paus serum metholize-ate concentration of 1,000 micromodar (10⁴ mol/L) at the end of the methodrexate indication, the dose may be escatated to 15 grand/m² in subsequent treatment; If the patient is vorning or is unable (0 blerate cent medication, leucovonn is given IV or IM at the same dose and schedule.

Druce, guid beruezense.		
Drug" Week"	Dose"	Treslmen After Sur
Methol/exale 15, 16, 29,30,44,45	12g/m ¹ 1V as	4,5,6,7,11,12 4 hour infusion (starting dose)
Leucovonin	15 mg oxally every six hours for 10 doses starbing at 24 bours after start of memotrexate infusion.	
Doxorubicin' as a single drug	30 mg/m² day IV x 3 days	6,17
Dexorubicin' Cisplatin'	50 mg/m² 1V 100 mg/m² IV	20.23.33.36 20.23,33,36
Bleomycon	15 units/m² IV	2,13,26,39,42
Cyclophosphamider	x 2 days 600 mg/m² IV x 2 days	2,13,26,39,42
Dactinomycin	0.6 mg/m ^a IV x 2 days	2.13,26.39.42

* Link MP, Goonn AM, Miser AW, et al. The effect of adjuvant che-motherapy on relapsu-free survival in patients with osteosarcoma of the extremity. N Engl J of Med 1986; 314(No.25): 1600-1806

See each respective package insert for full prescribing infor-mation. Obsage modifications may be necessary because of drug-induced toxicity.

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

GUIDELINES FOR METHOTREXATE THERAPY WITH LEUCOVORIN RESCUE

enistration of methotrexate should be delayed until recovery

- the WBC count is tess than 1500/mcrolifer the neutrophil count is less than 2007/mcrolifer the platelist count is less than 7.5 000/mcrolifer the same plandin count is less than 7.5 000/mcrolifer the SQPT level is greater than 1.2 mg/dk the SQPT level is greater than 456.0 muccosts is present, until there is evidence of healing persistent plevail effusion is present. the should be dramed dry prior to infusion.

2. Adequate renal function must be documented

Adequate renal function must be documented a. Senum creatinine must be normal, and creatinine clearancel must be greater than 60 mU/min, bebre initiation of thorapy b. Senum creatinine must be measured pnor to each subsequent, course of therapy II senum creatinine has increased by 50 % or more compared to a prior value, the creatine dearance must be measured and documented to be greater than 50 mU/ min (even if the senum creatinine is still within the normal range)

3. Patients must be well hydrated, and must be treated with sodium

Patentis must be well hydrated, and must be treated with socium bochonate to univera yakinicization. a Administer 1,000 mL/m² of intravenous fluid over 6 hours pror to initiation of the methoexazie infusion. Continue hydraten at 185 mL/m²/m² (3 liters/m²/day) during the methotreate infu-sion, and to 2 days after the indision has been completed. b Alkalinure urine to maintain pH above 7.0 during methotreater

milusion and isocoronic calcium thirspy. This can be accom-plished by the administration of sodium bicarbonate orally or by incorporation into a separate intravenous solution.

4 Receat serum creatining and serum methotrexate 24 hours after starting methotrexate and at least once daily until the methotres-ate level is below 5 x 10* moVL (0.05 micromolar)

The table below provides guidelines for leucovorin calcium dos-age based upon serum methotrezale levels, (See table below.*)

Patents who expenence delayed early methotrexate elimination are lately to develop non-memoio eligunc meal failure. In addition to appropriate leucoroom hearing, these patients require contra-ing hydration and urinary altalinisation, and close memoinoring of flord and electrolyte status, until the sentim methorizotale level has failen to below 0.05 micromolar and the renal failure has resolved.

- 5. Some patients will have abnormatities in methotrasate elimination or abnormalities in renal function totowing methotrasate eliminarisation, which are septicant but less server than the abnormatities described in the table balow. These abnormalities may or may not be associated with significant dividence to the server than the abnormatities described in the table balow. These abnormalities may or may not be associated with significant divides the server than the abnormatives and the server than the server than the abnormatives are server to an additional 24 hours total 14 does over 8 hours, in subsequent counses of therapy. The possibility that the patient is testing other medications which near which reflect aways be reconsidered when laboration; an almostand is should abays be reconsidered when laboration; and medical insurial server than observed.

CAUTION DO NOT ADMINISTER LEUCOVORIN

Psotiasis: 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, hepsatic, enandi, and pulmoning function should be made by history physical examistion, and laboratory tests before beginning, periodically during, and before reinstituting methotrevale therapy (See PRECAUTIONS). Appropriate stops shuid be taken to avaid conception during methotrevate therapy. (See PRECAUTIONS AND CONTRAINDICATIONS).

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

Psonasis, Recommended Starting Dose Schedule

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

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 dos-age schedule should be roduced to the lowest possible amount of drug and to the longest possible rest period. The use of math-orrerale 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.³⁴ There is no guineral agreement that all of the proce-dures recommended in the guidelines are nocessary or appropriate

Paranteral drug products should be inspected visually for par-ticulate matter and discoloration prior to administration, whenever solution and container permit.

DILUTION INSTRUCTIONS FOR LIQUID METHOTREX-ATE INJECTION PRODUCT:

Methotrerate Injection USP, Isotonic Liquid, Proservative 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

Methotraxale Injection USP Isotonic Liquid, Preservative Free, for Single Use Only Each mL contains methotrexate sodium equivalent to 25

mg metholresale.

2 mL viai 50 mg 4 mL viai 100 mg 8 mL viai 200 mg 10 mL viai 250 mg

See package Insert for routes of administration.

Reonly

Store at controlled room lemperature 15-30°C (59'-86'F) Re in carton until time of use. Protect from light

Manufectured by: Shamaceuticals SA Bigmar Pharmaceutical Barbengo, Switzerland

nutactured for:

Bigmar, Inc. Johnstown, OH 43031

Rev 05- November 1998

REFERENCES

- Roenigk HH, Auerbach R. Maibach HI, et al. Metholrexale in P nasis: Revised Guidelines. J Am Acad Dermatol 1968, 19:145-145.
- 2 Kremer JM, et al. Methotrexate for Rheumatoid Artholis S gested Guidelines for Monitoring Liver Torcicity. Arth Rhe 1994, 37:316-328

Recommendations for the Safe Handling of Parantetal Anu-optastic Drugs, NH Publication No. 83-2621. For sale by Sugemendent of Documents, U.S. Governmont Printing Oft Washington. DC 20402.

- AMA Council Report. Guidelines for Handling Parente Anthreoplastics JAMA 1985, 253(11) 1590-1592.
- National Study Commission on Cytotoxic Exposure-Recommin dations for Handling Cytotoxic Agents Available from Loui Jeffrey, SC, Chairman, National Study Commission on C toxic Exposures, Massachusetts College of Pharmacy and Al Health Sciences, 179 Longword Ammune, Boston, Massachus 02115
- 6 Clinical Oncological Society of Australia Guidelines and F primendations for Safe Handling of Antineoplastic Agents / J Australia 1983, 1 426-428
- Jones RB, et al. Sale Handling of Chemotherapeutic Agent Report From the Mount Sina: Medical Center Ca: A Cancer Ji nal for Clinicians Sept/Oct 1983, 258-263
- American Society of Hospital Pharmaosts Technical Asseta Bulletin on Handling Cytotoxic and Hazardous Drugs Am./H Pharm 1990; 47:1033-1049
- OSHA Work-Practice Guidelines for Personnel Dealing with (otoxic (Antineoplastic) Drugs Am J Hosp Pharm, 19 43,1193-1204

LEUCOVORIN RESCUE SCHEDULES FOLLOWI TREATMENT WITH HIGHER DOSES OF METHOTREX

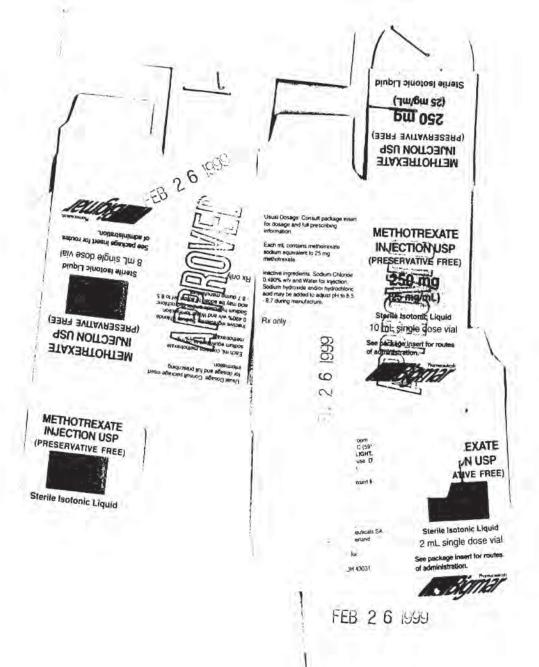
Clinical Situation: Normal Methotrexate Elimination Laboratory Findings: Serum methoticitate level approximately incorported at 24 hours after administration, 1 micromolar at Nours, and less films 02 micromolar at 22 hours Leucovorin Desage and Duration: 15 mg PO. IM, or IV hours lori 66 hours (10 doses starting at 24 hours after star methoticicate influsion)

Clinical Situation: Delayed Late Metholresiate Elimination Laboratory Findings: Serum methotresale level remaining ab 0.2 micromolar at 72 hours, and more than 0.05 micromolar a rs after adn Instration

Leucovorin Dosage and Duration: Continue 15 mg PO_1M, c g 5 hours, until methotrexate level is than 0.05 micromolar

Clinical Situation: Delayed Early Methotresate Elimination an Evidence of Acute Renal Inputy Laboratory Findings: Security methotresate level of 50 microm or more al 24 hours, or 5 micromotar or more al 46 hours -diministration, OB a 100% co gnator ancessae in serum treati-level at 24 hours, or 5 micromotar of administration (eg. an exce from 0.5 mg/d). To a level of 1 mg/d, or more) Leucovortin Dosage and Duration: 150 mg/V of 3 hours, or methotresate level is less than 1 micromotar. then 15 mg iV hours until methotresate level is less than 0.05 micromotar





Lot # Exp. Date

APPLICATION NUMBER: 40266

DRAFT FINAL PRINTED LABELING



METHOTREXATE FOR INJECTION USP

WARNINGS

METHOTREX.45E SHOULD BE USED ONLY BY PHYSI CIANS WHOSE KNOWLEDGE AND EXPERIENCE INCLUDE THE USE OF ANTIMETABOLITE THERAPY.

BECAUSE OF THE POSSIBILITY OF SERIOUS TOXIC RE-ACTIONS (WHICH CAN BE FATAL)

METHOTREXATE SHOULD BE USED ONLY IN LIFE THREATENING "COPLASTIC DISEASES OF IN NATIENTS WITH PSORIAGIS WITH SEVERE RECALCITRANT, DIS-ABLING, 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 RECCOMMENDED FOR OSTEOSARCOMA REQUIRES ME-TOLLOUS CARE, USAN DOSAGE AND ADMINISTRATION I NGCH DOSE REGIMENS FOR OTHER NEOPLASTIC DIS-EASES ARE INVESTIGATIONAL AND A THERAPEUTIC ADVINITIGE MAS NOT BEEN ESTABLISHED.

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

Methotizxate has been reported to cause testi death and/or contential aromales. Therefore, it is not recommended to women of childbaering pointial unless there is char medical endence that the benefits can be expected to cutweigh the considered disk. Preparit women with postass should not receive methotrexate. [See CONTRAINDICATIONS].

Mothotizkate elimination is reduced in pallents with im-paired renal function, ascress, or pleural effusions. Such patients require especially careful monitoring for toxicity, and require dose reduction or, in some cases, discontinua-tion of methotrasate administration.

Unexpectadly severa (sometimes fallal) bone manow suppression and gas/reintestinal busch/ have been reported with concombant administration of methodrexate (usually in high dotage) along with some nonservoid and reinfammatiny druge (NSAIDs) (See PRECAUTIONS: Drug Interactions).

A Methotroxate causes hepatotoxicity, fibrosis and c 4 Methotrexate causes hepatotonicity, forosis and cirrho-sis, but generally only after prolonged use. Acutally, liver enzyme elevations are frequently seen. These are usually transient and asymptomatic, usease Liver bropsy after sustained use often shows historlogic changes, and libor-sis and cirrhosis have been reported, these latter lessons may not be pricaded by symptoms or abnormal liver func-tion tests in the psortasis population. For this reason, periodic liver buopses are usually resommended for paoi-aic pa-itents who are under long-term trainmit. (See PRECAUTIONS, Organ System Tosicity, Hepatic.)

5 Methotresate-induced lung disease is a potentially danger-ous reskin, which may occur acutely alway time during througy and which has been insported al dostes as low at 75 m givenels. If a hot always hitly reveable. Pulmonary symptoms (espe-cally a dry, nonproductive cough) may require interruption of treatment and - who weeshapation.

Diarrhea and ulcerative stomatitis require interruption of therapy, otherwise, hemorrhapic ententis and dealth from in

1.1

ing the

testinal perioration may occur

Malignant lymphomas, which may regress following with-drawal of methoresate, may occur in patients receiving low-doce methoresate and. Brus may not require cytolosic treatment. Discontinue methodesate first and, if the lymphoma does not regress, appropriate instement should be instituted.

Like other cytotoxic drugs, methotrexate may induce "u-mor lysis syndrome" in patients with tapidly 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 methodresate. Reactions have occurred within days of olal, intramuscular, intravency, or intraheat methodresate administration. Re-covery has been reported with discontinuation of therapy. (See PRECAUTIONS, Organ System Toxicity, skin.)

Potentially fatal opportunistic inflections, especially Pneumocystis canni pneumonia may occur with metholes alle therapy.

DESCRIPTION

Methotraster (formerly Amethopterin) is an antimetabolite used in the treatment of certain neoplastic diseases and severe psonasis.

Chemically methotrexate is N-(4-(((2,4-diamino-6-pteridinyl) methylynethylaminojbenzoyl)-L-gkutamic acid The structural formula is



The molecular formula is C. H. N.O. The molecular weight is: 454 45

Methotraxate for Injection is stenie and non-pyrogenic and may be given by the intramiscular, intravenous, intra-anerical, or initathe-cal route (See DOSAGE AND ADMINISTRATION)

Each vial conjains metholrexate sodium equivalent to 1 g methot/ exate. Contains no preservative. Sodium hydroxide and/or hydrochlone acid may be added to adjust the jet during marufac-ture to 8.5-8.7. The 1 g val contains approximately 7mEq of sodium.

CLINICAL PHARMACOLOGY

CLINICAL PHARMACOLOGY Methotenais inhibits dihydrolox acid reductase, Dhydrololalis, mast be induced to lethatydroloxiaes by this enzyme before they can be utkiced as carriers of one-cartion groups in the synthesis of punne nucleocides and trymydylati. Therefore, methotestaals inter-keres with DNA synthesis, ropar, and cellular repication. Actively poliferating basives such as malignant cells, bone marrow, letal cells, buccal and intestinal muccaa, and cetts of the unitary blac-der are in general more sensitive to this affect of methotexatte When cellular proliferation in malignant tissues is greater than in most normal tissues, methotexate may impair malignant growth without irreversible damage to normal tissues.

In psonase, the rate of production of epithetial cells in the skin is greatly increased over normal skin. This differential in polifiera-bon rates at the basis for the use of methodrevate to control the psonabic process.

Methodresate in high doses, tailowet by lexcovorn rescue, is visid as a pair of the frastment of patients with non-metastatic optexts-coma. The organical rescovale for high dose methodresate therapy was based on the concept of selective rescue of normal bases by leucovorn. More recent avathere suggests that high dose meth-oterate may also overcome methotresate resistance caused by majoried active transport, decreased altimy of dirydrolokic acti of ductase for methotresate, increased levels of dirydrolokic action ductase for methotresate, increased levels of dirydrolokic action polygistramation of methotresate. The actual mechanism of action is unbrown.

Two Padiatric Oncology Group studies (one randomized and one non-randomized) demonstrated a significant improvement in relayse free sourvai in padients with nei-metastatic opteosa-rcoma, when high dose methoterate with leucoron rescue was used in combination with other chemotherapeutic agents following surgical resection of the primary tumor. These stud-ies were not designed to demonstrate the specific contribution of high dose methoteratelleucoronin rescue therapy. In the efficacy of the combination - Nowwer, a contribution can be inferred from the reports of objective responses to this therapy

.

SSI 97 TE in patients with metastatic osteosarcona, and from reports of extensive tumor necrose following proceedance administration of this therapy to patients with non-metastatic osteosarcoma

Pharmacokinetics Assorption-Methotrivate is generally completely absorbed from perentrieal routes of injection. After intramuscular injection, peak serum concentrations occur in 30 to 60 minutes.

Distribution: Alter Intervences administration. The initial victoms of distribution is approximately 0.18 July (11%) of body weight) and (11%) of body weight) and (11%) of body weight) and (40% to body weight). Methodensite competites with refuced schaes for active transport across call methodenines by means of a single currer-mediated active transport process. All secun concern traitsoing granter than 100 merconicul, passive diffusion becomes a major pattway by which effective intracelular concentrations can be activeved. Methodenias that a may be deplaced tiom plasma alterning by assive serum is approximately 50% protein bound. Laboratory studies demonstratis that it may be deplaced tiom plasma alterning by assive compounds activity sufficient

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

by minimetal submission of the second second

Half-Life - The terminal half-life reported for methotrexate is ap-proximately three to ten hours for patients noceiving (instance) for pocasis or low does antiinocolastic therapy (less than 30 mg/m) for patients neceriving high doess of methotrexate, the terminal half-life is eight to 15 hours.

Eccentron - Renal extension is the permary route of elimination, and is dependent upon desage and route of administration. With N ac-ministration, 80% to 90% of the administered does is becartled unchanged in the unive within 24 hours. There is limited bains, excetion amounting to 10% or lass of the administered does. Enterohepatic recrutation of metholtricate has been proposed.

Renal excretion occurs by glomenular fittration and active lubular secretion. Nonlinear elimination due lo saturation of renal hubular rabiospiton has been observed in sponsite, patients at doues to treasen 75 and 30 mg. Impaired renal function, as well as concurrent use of drugs such as weak organic acids that allo undergo tubular secretion, can markedly increase methortexate serum lavels. Ex-registent correlation has, been reported between methotrexate relation and endogenous crestinene clearances.

Methotrexate clearance rates vary wodely and are generally de-created at higher doese. Delayed drug desanace has been identified as one of the major factors responsible for methotrexate locacity it has been possibilitied that the toxicity of methotrexate is no normal basises as more dependent upon the duration of exposure to the drug rather than the paek level achieved. When a pakent has de-ayed drug elimination due to compromised renai function, a third space effusion, or other causes, methotrexate serum concentra-tions may remain elevated for prolonged penods.

The potential for taxicity from here gao generative areas a reduced by the administration of lecororim calcour during the final phase of methotrisate plasma elemention. Pharmacolu-natic monotonig of methotrisate service noncentrations may help identify those patients at high risk for methotresate toxory and all in progra adjustment of leucostrom dosing (calcience) for monitor-ing service tile ratio demotional electronic discoversion dosing to reduce the ratio of methotresate toxicity are provided the low in DOSAGE AND ADMINISTRATION

Methotrexate has been detected in fluman breast milk. The highest breast milk to plasma concentration rabo reached was 0.08 T

INDICATIONS AND USAGE

Neoplestic Diseases Methotrecate is indicated in the treatment of gestational choriocar onoma, chorioaderioma destruens and hydatoliform mole

In acute lymphocytic leukernia, methotrexate is indicated in the pro-phylasis of maningeal leukerna and is used in maintenance theragy in combination with other chernofterapeutic agents. Methotrexate is also indicated in the treatment of meningeal leukernia.

Methotrexate is used alone or in combination with other anticancer agains in the treatment of breast cancer, epidermood cancers of the head and neck schenced mycoses luppides, and lung cancer, par-ticularly squamous cells and small cell types. Methotrexate is also used in combination with other chemothreagewaite agents in the treat-ment of advanced stage non-Hodgkin % lymphomas.

Methotrestate in high doses followed by leucovorin rescue in com-bination with other chemotherapeutic agents is effective in prolonging reliajas-fee survai in palients with non-meta-static ostaosarcoma who have undergoine Surgical resection or angou-tation for the primary tumor.

Paoriasia Majholiceate is indicated in the symptomatic control of severe, re-calcriant, disabiling postasis that us not adequately responsive to other terms of thready, but only when the degress has been es-tablished as by blogdy and/or after dematlobage consultation. It is important to ensure that a pixoliasis Ttare' is not due to an undiag-noaed concomitant disease atticting immune responses.

CONTRAINDICATIONS

CONTRAINDICATIONS Methoreralic can cause kits death or teratogenic effects when ad-mentionered to a pregnant woman. Methoterate is containdicated o pregnant women with gostnass and should be used in the trans-ment of neoplistic diseases only when the potential benefit advestigh merics to the feature. When in dividebarring potential should not be started on methotrexate until pregnancy is excluded and should be fully counseled on the serious ratio to the feature PRECAUTIONS) should they become pregnant while undergoing treatment Pregnancy should be surinded if attemp factore is zecon-ing methotrexate, during and for a minimum of their months after herapy for measure patients. [See Bored WARNINGS]

Because of the potential for serious adverse machines from metho-trexate in breast ted infants, it is contraindicated in nursing mothers

Patients with psonasis with alcoholism, alcoholic liver disease or other chronic liver disease should not receive methotrexate

Patients with psonasis who have overt or laboratory evidence of immunodeticiency syndromes should hol receive metholrexate

Patients with psonasis who have presidently blood dyscrablas, such as bone merrow hypoplasta, leukopenia, thrombocytopenia, or sig-niticant anemia, should not receive metholizeate

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

WARNINGS -SEE BOXED WARNINGS.

PRECAUTIONS

PRECADUTORS Conversal Methycitricate has the potential for serious toxicity (See Boxel MARNINGS) Toxic effects may be related in frequency and sever ny to dose of treguency of admensization but have been seen at a doses. Because they can account a nay time during therapy, it necessary to tokew patients on methytherate closely Most adverse relacions are reventible if detected and/When such reactions of occou, the drug should be reduced in dosage or descontinued an appropriate corrective measures should be taken. It necessary, the could include the use of Huccoron calcium (See OVERDOSAGE immenoissant beregan a meestilued in strouble the carried out wit caution, with adequate consideration of birther need for the dur-and with increased alertness is to possible recurrence of lowers.

The princial pharmacology of methotreviate has not been well stur-red in oblist individuals. Our to diministrated hepatic and remail function as well as decreased totate stores in this population, relatively to dockes should be considered, and these patients should be dose monitored for early signs of toxicity.

220

Information for Patients Patients should be informed of the early signs and symptom of toxorby of the need to see their physician promptly if this occur, and the need for close follow-up; including periodic lab-rationy tests to monitor toxorby.

Both the physician and pharmacris should emphasize to the p text that the recommended dose is taken weekly in psonasis, at that mistaken daily use of the recommended dose has led to tak locicity. Prescriptions should not be written or refilled on a PP basis

Patients should be informed of the potential benefit and risk in t use of methotrexate. The risk of effects on reproduction should

discussed with both male and lemale patients taking metholre cale.

Laboratory Testa

1.0

1.1

1.04

110

Laboratory Tesis Patientis undergoing methodmicale literapy should be closely mon-fored as that loads effects are detected promptly. Baseline assessment should include a complete blood oount with differential and patieties counts, heightic encymes, renal hunchon iests, and a chest X-ray. During therapy of peofasis, monitoring of these pa-rameters is recommended, hematology at least monthly, renal function and love function every 1 to Zinostis. Note trequest mor-tioning is usually indicial during attreceptests therapy. During initial or cherging doese, or during periods of increased risk of elevated method tests and blood levels (og dehydation), more frequent mor-turing as also be indicided.

Transient liver function tost abnormabilies are observed frequently after methomsale administration and are usually not cause for mod-lication of intertoreaute therapy. Persistent liver function test abnormabilies, and/or depression of serum affaurnin may be indica-tors of a serious liver foreicity and require revaluation. (See PRECAUTIONS, Organ System Toxicity, Hepatic.)

A relationship between abnormal liver function tests and lib-rosis or circhosis of the liver has not been established for patients with psoriasis.

Pulmonary function tests may be useful if methotre cate-induced long disease is suspected, especially if baseline measurements are available

Drug Interactions Nonstroadal anti-inflammatory drugs should not be administered prior to or conconstantly with the high does of methodimizate used in the insetment of ostepasecona. Conconstant administration of some ISAIDs with high does methodizerate therapy has been re-pond to leavest and prolong serum methodizate leaves in subtra-in deaths from severe hematologic and gastrointestinal fourcity.

Causon should be used when NSAIDs and sakcyfates are adminis-tered concornantly with lower doales of methorizate. These drugs have been reported to reduce the tubular secretion of metholizer-ate in an annual model and may enhance its toxicity.

Methotrexale is partially bound to serum albumin, and toxicity may be increased bocause of displacement by certain drugs, such as sinclates, phenythotazone, phenytoin, and autonamides. Renal labular transport is also diminished by probeneod; use of methodr-eate with first drug should be caterbidy monitored.

In the treatment of patients with obleosarcome, caution must be exercised if high-dose methotresate is administered in com-bination with a potentially rephrotoxic chemotherapautic egent (eg, cisplatin).

Drai ambiotics such as tetracycline, chteramphenicol, and norab-softable broad spectrum antibiotics, may decrease infestinal absorption of methodinastic or enfance with the enterchepatic cir-culation by nihibing bowell fora and suppressing metabolism of the drug or bacteria.

Pencilins may reduce the renal clearance of methofrexate, in-creased serum concentrations of methofrexate with concontraint hephatologic and gastionsteptical locality have been observed with high and fow does methofrexate. Use of methodizexate with period-lins should be carefully momonited.

Paterils receiving concomiant therapy with methorrevate and etremate or other retinoids should be monitored closely for pos-sole increased risk of hepatotoxicity.

Methotrexate may decrease the clearance of theophylline, theophylline levels should be monitored when used con-currently with methotrexate

Vitamin preparations containing folic scid or its derivatives may decrease responses to systemically administered methotrec-ate. Preliminary animat and human studies have shown that small quantities of initizienously administered feucoroni en-ter the CSF primarity as S-methytietrahytorfoldate and, in humans, remain 1: 3 orders of magnitude lower than the usual methotrexate concentrations following intrathecial administra-tion. However, high doss of telecolowin may reduce the elificacy of infrathecally administered methotrexate.

Folate deficiency states may increase methotrexate toxicity frametworm/sutamethoxuzole has been reported rarely to monase boom marrow suppression in patients receiving methotrexate, prob-ativy by an addeive antibilate effect

1.1

Carcinogenesia, Mutagenesia, Impairment of Fertility No controlled human data exist regurating the risk of neoptasia with methodresate. Methotresate has been envaluated in a number of animal studies for carcinogenic potential with incoholusive results.

1.1

Although there is evidence that methotre sate causes chronicsonial damage to animal somalic cells and human bone marrow cells, the clinical significance remains unortain. Benefits should be weighed against the potential risks before using methotrexaile alone or in combination with other drugs, especially in pediatic patients or young adults. Methotrematic causes emphyticative, along the field effects in humans. It has also been reported to cause impair-ment of fortify ologosperma and mensional dytalcindon in humans, during and for a short period after cessation of therapy.

Pregnancy: Teratogentic Effects, Pregnancy Category X See CONTRAINDICATIONS

Nursing Mothers See CONTRAINDICATIONS.

Pediatric Use Safety and effectiveness in pediatinc patients have not been estab-lished, other than in cancer chemotherapy

Organ System Toxicity Castroninstituti If vominity, diarrhia, or stomaitis occur, which may result in dehysication, methorizotale should be discontinued until re-covery occurs. Methoresate should be used with extreme califor-in the presence of peptic ulser disease or ulcentive collis.

Hematologic: Methothexate can suppress hemitopolisis and cause anema, teukopolia, and/or thrambocytopolia. In patients with me-lignancy and presisting hemistopoletic impairment the drug should be used with caution, if all all

In psonasis, methotrenate should be stopped immediately if there is a significant drop in blood counts. In the insetment of neoplastic diseases, methotresate should be continued any if the potential benefit warrants (the risk of avere mysiosuppression. Patients with profound granulocytopenia, and fever should be exclusive immediately and usualty require parenteral broad-spectrum antibiotic therapy.

Hepatic: Methotecapectrolin induced relative Hepatic: Methotecapectrolin induced relative aminases) and chronic (Broais and cirrhosis) hepatotecicity. Chronic losicity is potentially Istall in generality has occurred ether prolinged use (generally two years or more) and after a total dose of alloast 1.5 grans, in studies in possible patients, hepatotocicity appeared to be a function of total comulative dose and appeared to be inhanced by alcohotechin, obesity diabetes and advanced age. An accurate incidence rate has not been determined, the mite of progression and reversibility of listicities is not factore. Special data tion is indicated in the presence of presusting liver danalige of impaired hepatic function.

Imparent nepus: Insciont In piperase, the function tests, instuding serum albumin, should be performed periodically prior to dosing but are olimin normal in the faise of developing throsis or criminosis. Those tealors may be detectable only by biopsy. The usual recommendation is to obtain a liver hooty st 1 preminerapy or shortly after initia-tion of therapy (2 - 4 months), 2) a total cumulative dose of 1.5 grams, and 2) after each additional 1.0 to 1.5 grams. Moderalle librosis or any circhosis normally leads to discontinuation of the drug, mid biosis normality leads to discontinuation of the drug, mid biosis normality usgeds a repeat blogs in 6 months. Milder histologic findings such as latty change and low grade portal inflammation, are relatively common pretherapy. Athough these mild changes are usually not a rea-son to avoid or discontinue methotiexate therapy, the drug should be used with caution.

Infection or Immunologic States: Methotrevate should be used with estimate caution in this presence of active infection, and is usually contraindicated in patients with over or laboratory evi-dence of immunodeficiency syndromes. Immunitation may be ineffective when given during methotrevate herapy. Immun-zation with ive withs vaccines is generally not recommended. There have been reports of disseminated vaccina infections after smallpoor immunizations in patients receiving methotra-ate herapy Hypogenmaglobulinemia has been reported rarely

Potenliałly fatal opportunistic inflections, especially Pneumocystis carnis pneumonia, may occur with metholiteraalli titeraray. When a patienti presents with pulmonary symptoms, the possibility of Pneumocystis carnii pneumonia should be considered.

Neurologic There have been reports of levicencephalopathy following nitravenous administration of methodrescale to petients who have had cannosprail invaliancy. Services neurotoxich, fre-quentiv manifested as generalized or local scitures, has been reported with unexpectedly increased flequency among pedi-atric patients with acute lymphoblastic leukema who water treated with intermediated-obse intravenous methodrescale (1 priv m²). Symptomatic patients were commonly noted to have fleu-cencephalopathy and/or microangiopathic catolications on dayopath among the subcass who received repeated does of high-dose methotrestale with leucavoin rescue even without

cranial irreduction. Discontinuation of metholrexate does not alays result in complete recovery

A transient acute neurologic syndrome has been observed in pa-tients treated with high dose regimens. Manifestations of this stroke-file encephalopatty may include couldwark, hernquinsis, selcures and coma: The exact cause is unknown:

After the intrathecal use of methol/resister. After the intrathecal use of methol/resister, the central nervous exitie choical anchronodins manifested by such symptoms as headdachaical anchronodins manifested by such symptoms headdachaical anchronodins manifested by such symptoms headdachaical anchronodins manifested by back mytelopathy anactarized by paraparesizion projection as associated with involvement and nerve involvement associated with involvement and nerve rous print antwork rous involvement and nerve rous print antwork rous print network and the surgers and come and come. This condition can be progressive and even latal

Pulmonary: Pulmionary symptoms (especially a dry nonproductive couph) or a non-specific pneumonitis occurring during metholisis-ale fiberapy may be indicative of a potentially dangerous lesion and regram interruption of trainterni and careful investigation. Although clinically variable, the typical patient with metholereate indicated ung disease presents with lever, cough, dyspine. Typosemia, and an infiliate on chest x-ray, intection needs to be excluded. This lesion can occur at all dosages.

Renat: High does of methotriscale used in the treatment of os-teosarcoma may cause renal damage leading to acute renal failum. Neghridoxicity is due primarity to the precipitation of methoterastie and 7-hybridoxicity is due primarity to the precipitation of methoterastie and 2-hybridoxicity and the most blueback. Close alteritor is measurement of alroy adequate hydraticn, urine altalanization and measurement of alroy methoterastie and creating levels are ba-sential for sale administration.

Skin: Severil, occasionality latal, dermatologic reactions, includ-ing too: apidermal necrolysis, Stevens-Johnson syndrome antoliative dermaities, skin necrosis, and enytheme multiforme. have been réported in children and adults, within days of oral, intramuscular, intravenous, or intramecal methodretate admin-sitration. Reactions were noted after single or multiple low, intermediate, or high doses of methodresate in patients with neoplessic and non-neoplastic diseases.

Other precautions: Methodrexate should be used with extreme cau-tion in the presence of debility

Methotre state exits slowly from third space compartments (eg. pieural effusions or asones). This results in a prolonged faminual plasma half We and unseptical lookity. In patients with significant third space accumulations, it is advisable to evacuate the fixed before treatment and to movitor plasma methotrecate levels.

Lesions of psoniasis may be apgravated by concorrelant exposure to ultraviolet radiation. Rectation dermetitis and surburn may be "recalled" by the use of methotrevale.

ADVERSE REACTIONS

INCENSE NEACTIONS INCENSENT THE INCREMENT AND SEVERITY OF ACUTE SIDE EFFECTS ARE RELATED TO DOSE AND FREQUENCY OF AD-MINISTRATION. 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 ulsurative stornalitis, enukopena, nausea, and abdominal districts. Differ fra-quently reported adverse effects are mailaise, undue (angue, chais and lover; disziness and discreased resistance to inflection.

Other adverse reactions that have been reported with mathetres-ale are fisted below by organ system. In the oncology setting, concentratin treatment and the underlying detests make specific athribution of a reaction to methotrecale difficult.

Almentary System gingvitis, phanynges, stomatits, anorexia, nau-sea, vomiting, dairthea, hematismesis, melena, gastrointestinal iAceration and bleeding, ententis, pancreatitis.

Cardiovascular pericardets, pencardial ethusion, hypotension, and thromboembolic events (including anterial thromboels, carebral thromboels, deep vein thromboels, retinal vein thromboels, throm-bophlebits, and pulmorary embolus).

Central Mervous System: hexitaches, drowsiness, blurned vision Aphasia, hexingaresis, paresis and convusions have also occurred following administration of methodisata. Fotowing low does, there have been occasional report of dransmit subte cognitive dysfunc-tion, mood alteration or unusual cranial sensations.

Intection There have been case reports of sometimes fatal oppor-funistic infections in patients receiving methor/resate therapy for

neoplastic and non-neoplastic diseases. Pneumocyclis carini monia was the most common infliction. Other reported infer included nocardioxis, histoplasmosis, cryptococcoss, Herges z H. simplex hepatitis, and disseminated H. simplex.

Ophthalmic, conjunctivitis, serious visual changes of unknown etc.

Pulmonary System intensitial pneumoniths deaths have been ported, and chronic intensitial obstructive pulmonary disease sociasionally occurred

Skin erythematous rashes, pruntus, urticana, photosen: ity oigmentary changes, alopecia, ecchymous, letangliects acre, fururculosis, erythema multiforme, toxic epide necrolysis, Stevens-Johnson syndrome, skin necrosis, erfolative dematitis.

Urogenital System, severs nephropathy or ranal takers, acoter cystilis, hematuria, defective orgenesis or spormalogenesis, h seni oligosemia, menstual dystancion, vaginal decharge, gynecomasta: intertility, abortion, letal defects

Other rarer reactions related to or attributed to the use of me of reasts such as nodulosis, vasculitis, arthratgia/myalga, L af felido/impolence, oiabeles, osteoporosis, sudden death, versible lynghomas, and umor lysis syndrome. Anaphylact reactions have been reported

Adverse Reactions in Peoriasis: There are no incort placebo-controlled traits in patients with psor sr. The same how ternature reports (Roanigh, 1969, and Myko 1978) does any how ternature reports (Roanigh, 1969, and Myko 1978) does not how the same size of the same stranged up to 25 mg per were and trained were adversaria. Dosages ranged up to 25 mg per were and trained were adversarial to possible the same size of the copieton of adversaria. Photosensativity and "burning of skin tesser (reach 3% to 10%), fin adversaria maction raises in these reports we very similar to those in the rheumatoid artivitis studies.

OVERDOSAGE

Execution is indicated to dimensity the loadily and ocumensat the effect of indivertiently administered overdosages of methodraxal-Leu-ocvern administration should begin as growing as possible. As the time manyal between methodraxata administration and leu-covern ministration methodraxata administration and leu-covern ministration methodraxata administration and leu-covern ministration methodraxes. He effortune de leucovern in counteracting toxicity decreases. Monitoring of the serium method arate concernization is exercised. In decremental in determining the optimal dos and duration of treatment with loucoverni.

In cases of massive overdosage, hydration and umany alkalenza toor may be necessary to prevent the precipitation of methodnacal and/or its metabolities in the revail tubules. Neither hemolulyee nor perior-neal dialysis has been shown to umprove methodnacal elimination.

Accidential intrathecal overdosage may require intensive systemic, support, high-dose systemic leucovoin, alkaine druresis and rapid CSF drainage and ventriculolumbar perfusion

DOSAGE AND ADMINISTRATION

Neoplastic Deseases Oral administration in tablet form is often preferred when tow does are being administration in tablet form is often preferred when tow does are being administered since absorption is rapid and efective sorum levels are obtained. Methotexate for Injection may be green by the inframuscular, mitravenous, intra-arterial, or in-trathecal route

Or in-tratinecal route Chonocarcinome and similar trophoblastic diseases. Matholinovate is administered oraby or initramuscularly in doese of 15 to 30 mg dayl fina i live-day course. Such courses are usually oralised far 3 to 5 times as required, with insit periods of one or more weeks interposed between courses, until any mandesting local symptoms subside. The effectiveness of therapy is orinianly individed by 23 hour quantita-trie analysis of unmary choronic generation (hCG), which should return to normalize lations of UI/26 hour subling after the third or fourth course and usually be followed by usually after the third or fourth course in 416 diverses. One to incourses of method results after normalization of hCG is usually account mended. Belgee each course of the origin general divide as essential antihumo dhugs has been reported as being useful.

Since hydalidilorm mole may precede chorocarcinoma, prophy-lactic chemistherapy with methotrexate has been recommended.

Chonoadenoma destruens is considered to be an invasive form of hydatiditorm mole. Metholirezate is administered in these disease states in doses similar to those recommended for chonocarcinoma.

Leukemia, Acute lymphobiastic leukemia in podalitic patients and young adolescents is the most responsive to privisen day chamo-therapy. In young adults and older patients, chickai temission is more difficult to obtain and early oxidose is more common.

Mattheore sate above or in combination with steroids was used initially for induction of remission in action lymphobles is leader mittally for induction of remission in action lymphobles is leader more antisource of the sate of the sate of the sate of the offer antisource of the sate of the sate of the sate of the remissions. When used for induction, methotreaste in doesn of 3.3 mg/m² in combination with 60 mg/m² of parbinsons, given daily, produced remissions in 50% of parbins treated, usually writin a period of 4 to 8 weaks. Methotreaste in combination with other sgents appears to be the dug of choice for securing anthreaster of drug-induced remissions. When remission is achieved and supporters care has produced general clinical metharmaculary in total vesible doesn't of any morth or provement, in table reade induction of methods in days it and when dispass does occur, method on the days it and also been given in doesn't be be care distributed as follows alwy to balanced by repeating the indial school method and the methods and a control the spectrum of the sate been given in doesn't be beneficient of methods on the mg/m tables and also been doesn't care the produced penetral clinical methods and a control of the state in the sate been given in doesn't be beneficient of methods on the mg/m usu-ally the oblamed by repeating the indial school methods and the tortholestion domethods are been used a careful of combination domethods and the methods and the sate to a control of combination domethods and and be oblamed by repeating the indial school method and the sate of a school bean tool and bean tablestice the methods and the sate to a control of combination domethod and the sate to a control of combination domethod and bean tablestice the sate to a control of combination domethod and bean tablestice the sate to a control of combination domethod and bean tablestice the sate to a control of combination domethod and bean tablestice the sate to a control of combination do

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A variety of combination chemotherapy regimens have been use for both induction and maintenance therapy in acute hymphoblast leu-lamia. The physician should be familiar with the new advance in antileutenic therapy

Meningial Laukama, in the treatment or prophylaxis of meningial laukamis, methotissale must be administered entrathroadly. Preser-vative free methotissate is distilled to a concentration of 1 mg/mL in an appropriate sterile, preservative free medium such as 0.9% So-dium Chitonie Injecton.

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.

Infrathecal methotrexate administration at a dose of 12 mg/ m⁴ (maximum 15 mg), has been reported to result in low CSF methotizatie concentrations and educed efficacy in pediatric patients and high concentrations and neurotoxic-ity in adults. The following dosage regimen is based on age instead of body surface area.

AGE (years)	DOSE (mg)
51	6
1	8
2	01
3 or older	12

In one study in patients under the spe of 40, this dosage regimen appaared to result in more consistent CSF methotracele concentra-from and less neuroblacks. Another slody in prodiction patients with acute hypothodyle louterma compared this regimen to a dose of 12, regimer (maximum 15 mg), a segminicant reduction in the rate of CNS relepse 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 foukemia, intrafflecal methotres-ate may be given al infarvals of 2 to 5 days. However, administration at infervals of tess than 1 week may result in in-resease subscula toxicith. Methotrazale as administered until the cell count of the cembrospinal 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 escopt for the intervals of administration. On this subject, it is administer for the physician to consult the medical literature.

Untoward side afflicts may occur with any given intrittiecal injec-tion and are commonly neurological in character. Large doass may cause convulsions, Medifolmsate given by the intrafficial route ap-geans sig-intraffly in the systemic circulation and may cause systemic methotizisate loxicity. Therefore, systemic antibiation herapy with leding should be appropriately adjusted, reduced of discontinued. Focal isotemic involvement of the central intrivous system may not respond to intrafficial chemotherapy and is best treated with radiatherapy.

Lymphomas. In Burket's terrior, Steges Hil, methotraszle has pro-duced gradanged remspoths in some cases. Recommended dosage is 10 to 25 mg/say crashy to 4 to 8 days. In Stage III, methotmaxie is commonly given conconitantly with other antitumor agents. Treat-ment in all stages, usually consists of several courses of the dog interposed with 7 to 10 day rest pendet. Lymphosarcomas in Stage III may re-spond to combined rough therapy with methotrasate given in doses of 0.625 to 2.5 mg/sg daily.

Mycosis Fungodes: Therapy with metholineate appears to produce direct nervisions in one half of the cases treated. Dissage is usually 2 5 to 10 or Gafly by mouth for weaks an invertils. Does levels of drug and adjustiment of does regimen by reduction or censation of drug are guided by patient insponse and himitatioger molion-ing Methodimisation has been given intransacidarily in doese of 50 mg and such software weakly.

Osteosarcona: An effective adjuvant chemotherapy mgimen re-quires the administration of several cytotoxic chemotherapyuto; opers, in addision to high-obse methotoxusch with secondors mo-cus, these agents may include dosoublich, clapters, and the combination of bielomycen, cytophosphamics and dacfinomycin (BCO) in the doses and achedule stown in the table below. The starting dose is not sufficient to produce a peak securit method-rasite concentration of 1,000 micromolar (10° molf), at the end of the methotoxusce intestion, the dose may be escalated to 15 grams/ in it subsets the table, the patient is vorting or is unable to kierate oral medication, issue-volin e given IV or Mil at the same docks and schedule.

Octore and schedule		
Onug' Dose' After Surgery	Treatment Week	
Methotrexate	12g/m² IV as 4 hour miusion (starting dase)	4,5,6,7,11,12, 15, 16, 29,30,44,45
Laucovonn	15 mg orally every six hours for 10 does starting at 24 hours after start of methotrexale infusion.	
Doxolubicin' as a single drug	30 mg/m² day IV z 3 days	8,17
Dosorubican Caplasin	50 mg/m² IV 100 mg/m² IV	20,23,33,36 20,23,33,36
Bleamycin	15 units/m² IV x 2 days	2,13,26,39,42
Cyclophosphamide*	600 mg/m² IV a 2 days	2,13,26,39,42
Dactnomycin	0.6 mg/m² IV s 2 days	2,13,26,39,42

¹ Link MP, Gooin AM, Maer AW, et al. The effect of adjuvant chemo-therapy on religne-free sunnyal in patients with deteosarcoma of the extremity. N Engl J of Med 1986; 314(No.25); 1600-1606

*See each respective package insert for full prescribing informa-tion. Desage modifications may be necessary because of drug-induced toxicity.

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

GUIDELINES FOR METHOTREXATE THERAPY WITH LEUCOVORIN RESCUE

Administration of metholminate should be delayed until recov-Administration of methotmiste should be detayed until recov-bry if • The WBC count is less than 1500/microhiter • The electrophi count is less than 200/microhiter • The platelet count is less than 200/microhiter • The Source Twicken kerel is gradier than 1.2 mg/dl • the SOUPT level is gradier than 450 U. • possibilities present, until gradier than 450 U. • possibilities present, until previo available of healing • possibilities present, until previous the should be drained dry provide inhuston.

2

Adequate renal function must be documented a Serum creatinere must be normal, and creasine clearance must be greater than 60 multimit, before intribution of therapy. b Serum creatinere must be measured prior to each subsequent course of therapy II serum creatinere has increased by 50 % or more compared to a prior value, the creatinere doarance must be measured and documented to be greater than 60 mL/ min (even if the serum creatinine is shit within the normal range).

- 3. Failents must be well hydraled, and must be inteled with so-dium boarbonate for unnary alkainvation. a Admission of the methodreaste infusion. Continue hydrabon al 125 m/th/h (3 lies/mix/day) during the methodreaste infu-sion, and for 2 days after the infusion has been completed b. Afkainize unine to marken pH ablev 7 0 during methodreaste infu-sion, and inscoverin calcium therapy. This can be soom pidehid by the administration of lacdum thecationale orally on by incorporation into a separate infravenous solution.

Repeal serum creatinine and serum metholrexale 24 hours al for starting metholrexate and at least once daily until the metholrexatir level is below 5 x 10° moVL (0.05 mcromolar)

The table below provides guidelines for leucovorni calcium dos-age based upon serum methotrexate levels. (See table below 1)

Patients who expenence delayed early methotrexate elimination

are likely to develop nonreversible obgutor moal bakere. In addition to appropriate lexicorent therapy, freeds patients require continu-ng hydrosion and urinary akalemisation, and obsee monitoring of fuid and electricitie status, until the serum methodmicate level has balen to be-low 0.05 micromotar and the instal failure has recorved.

6. Some patients will have abnormaticies in methotinscia elemination, or abnormaticies in renai function following methodresate administration, which are aguiticant but less severe than the abnormatikies described in the table below. These abnormatikes may not be associated with significant chincal toxicity. It eignificant chincal toxicity is observed, hugovonn rescue should be extended for an additional (but the later additional to a second to a subscription of the table). The possibility that the patient is taking other medications which interact with methotisuse (e.g. medications which may interfere with metholismus be indicated with any or eight of all solutions) is subscription. The possibility that the patient is taking other medications which interact with methotismuste (e.g. medications which may interfere with methotismuste briding to serve abnormatibles or chincal longities are observed.

CAUTION DO NOT ADMINISTER LEUCOVORIN

Peortesia: 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, enand, and pulmonary function should be made by history, physical examination, and laborar information before beginning, parodicatify during, and before reinstituting metho-trevate therapy. (See PRECAUTIONS). Appropriate therapy (See PRECAUTIONS AND CONTRAINDICATIONS).

All schedules should be continually tailored to the individual pa-tient. An initial test dose may be given prior to the regular dosing schedule to detect any extreme sensitivity to advense effects (See ADVERSE REACTOORS). Maximal mysicouppression usually occurs in seven to lan days

Psonasis: Recommended Starting Dose Schedule

Weekly single oral IM or IV dosage schedule. 10 to 25 mg per week until adequate response is acheved.

2 Divided oral dose schedule 2.5 mg at 12 hour intervals tor

Dosages in each schedule may be gradually adjusted to achieve op-timal clinical response. 30 mg/week should not ardinarily be exceeded

Once optimal chincal response has been achieved, each dos-age schedule should be reduced to the lowest possible amount of drug and to the longest possible rest pend. The use of meth-olreasile may permit the return to conventional lopical therapy, which should be encouraged.

HANDLING AND DISPOSAL

Procedures for proper handling and disposal of anticancer drugs should be considered. Several pudelense on this subject have been published. ** Them is no general agreement that all of the proce-dures recommended in the guidelines are necessary or appropriate.

Parenteral drug products should be inspected visually for par-ticulate matter and discoloration prior to administration, whenever solution and container permit.

RECONSTITUTION OF LYOPHILIZED POWDER Reconstitute immediately prior to use

Methotresate for injection should be reconstituted with an appropri-ate stepile preservaive free medium such as 5% Destrose Solution. To Solum Choloid hipdcion. The 1 gram visit should be reconsti-tuted with 19.4 mJ, to a concentration of 50 mg/mL. When high doses of metholicitatia are administered by 1V infusion, the total doses is billed in 5% Destrose Solution.

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

HOW SUPPLIED

for Injection USP, Lyophilized, Preservative Free, for Single Use Only

Each 1 g vial of tyophilized powder contains methotrexate sodium equivalent to 1 g methotrexate

Ignal

Store at controlled noom temperature 15-30°C (59°-86°F). Pro-tect From Light. Relain in carton until time of use Discard

unused pertion

See package insert for routes of administrati Rx only

Manufactured by: Bigma/ Pharmoceuticals SA Barbengo, Switzerland

Manufactured for: Bigmar, Inc. Johnstown, OH 43031

Rev 06, November 1998

REFERENCES

Roengk HH, Aunbach R, Malbach HI, et al. Methotrex Pso-flass: Revised Guidelines. J Am Acad Dermatol 19:145-156.

2 Kremer JM, et al. Metholrexate for Rheumatoid Arthritis gested Guidelines for Monitoring Liver Toxicity. Arth R. 1994; 37:316-328

Recommendations for the Safe Handling of Paren Antinoplas to Drugs. NIH Publication No. 83:2621. For si the Superintendent of Documents, U.S. Government Pri Office, Washington, DC 20402

AMA Council Report Guidelines for Handling Paren Animeoplastics JAMA 1985 253(11):1590-1592

National Study Commission on Cytotoxic Exposure Recom-diations for Handling Cytotoxic Agents. Available from Lot Johny, ScD. Chairman, National Study Commission of 1 toxic Exposures. Massachusetts College of Pharmacy and / Health Sciences, 179 Longwood Avenue, Boston, Massa setts 02115.

Clinical Oncological Society of Australia: Guidelines and Rer mendations for Sale Handling of Antineoplastic Agents. M Australia 1983; 1:426-428.

Jones RB, et al. Sale Handling of Chemotherapeutic Agen Report From the Mount Sinai Medical Center Cat-A Cancer-nal for Clinicians Sept/Oct 1983, 258-263

American Society of Hospital Pharmacists Technical Assiste Bulletin on Handling Cylotoxic and Hazardous Drugs. Am J F Pharm 1990; 47:1033-1049

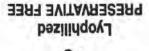
9 OSHA Work, Practice Guidelines for Personnel Dealing with C loxic (Antineoplastic) Drugs. Am J Hosp Pharm, 15 43 1193-1204

LEUCOVORIN RESCUE SCHEDULES FOLLOWING THE MENT WITH HIGHER DOSES OF METHOTREXATE

Clinical Siluation: Normal Methotreaste Elemention (Jaboratory Findings: Serum methotnaste level approximate) micromalar at 24 hours alter administration, 1 micromolar at hours, and less than 0.2 micromolar at 72 hours Laucovortin Desage and Duration; 15 mg PO, IM, or IV hours for 66 hours 10 doales staming at 24 hours after star metholrerate infusion)

Clinical Situation: Delayed Late Methotrexate Elimination Laboratory Findings: Serum methotrexate level remaining ac-02 miccronolitar at 72 hours, and more than 0.05 miccronolis at hours after administration Leuceovorth Desings and Duration: Continue. 15 mg PO, M, or 9 6 hours, until methotrecate level is than 0.05 micromolar

Clinical Situation: Delayed Early Metriotrexate Elimination a or Evidence of Acute Renal Input, Laboratory Filosifique: Sum metholoreate level of 50 micron lat or more at 24 hours, or 5 micronolar or more at 48 hours at diamin-stration, GH at 100% or graater increase in sorum cre-nice level at 24 hours after methotexate administration (eg. increase Ironol 5 might), to a level of 1 mg/til or more) Laucevortin Desege and Duration: 150 mg IV g 3 hours, no metholitexate level as less than 1 micromolar, then 15 mg IV hours until metholitexate level is less than 0.05 micronolar



61

METHOTREXATE ROR INJECTION USP

METHOTREXATE FOR INJECTION USP

1 g

Lyophilized PRESERVATIVE FREE

1 g Single Dose Vial Sterile

See package insert for routes of administration.



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.



Store between 15° - 30°C (59° - 86°F), PRO-TECT 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 INFORMA-TION AND BOXED WARNINGS.

Manufactured by: Bigmar Pharmaceuticals SA Barbengo, Switzerland

Manufactured for: Bigmar, Inc. Johnstown, OH 43031

Lot # Exp. Date

Page 00187

Usual Dosage: Consult package insert for dosage and full prescribing information. METHOTREXATE Intomazion. Reconstitute Immediately prior to use with 19.4 mL of an appropriate sterile, preservative-free medium to a concentration of 50 mg/mL. Each vial contains hyphilized Methothesate Sodium equivalent to 1009 mg, methothesate and upproximately 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. Store between 15° - 30°C (SS² + 88°F), PROTECT FROM LIGHT, Retain in carton until time of use. Decard unused portion. WARNING: SEF BACKAGE INSERT FOR EUL (DEESCEURING INFOR-FOR INJECTION USP 2 6 999 1 g Lyophilized PRESERVATIVE FREE 1 g Single Doee Vial Stortle See package insert for routes of administration. Storfle Lot FEB WARNING: SEE PACKAGE INSERT FOR FULL PRESCRIBING INFOR-MATION AND BOXED WARNINGS. Manufactured by: Manufactured for: Sina Bigmar Pharmaceuticals SA Barbengo, Switzerland Bigmar, Inc. Johnstown, OH 43031 Rx only

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1.0

Approval Package for:

APPLICATION NUMBER: ANDA 40-385

Name:	Trexall Tablets (Methotrexate Tablets USP)		
Sponsor:	Barr Laboratories, Inc.		
Approval Date:	March 21, 2001		

APPLICATION NUMBER: ANDA 40-385

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APPLICATION NUMBER: ANDA 40-385

APPROVAL LETTER

ANDA 40-385

MAR 2 1 2001

Barr Laboratories, Inc. Attention: Christine Mundkur 2 Quaker Road P.O. Box 2900

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

El 3/9/01 WMSmall BC3/12/01 WMSmall

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Endorsements: HFD-625/E.Schaefer/ HFD-625/M.Smela/ HFD-617/M.Dillahunt/3/8/01 NDullahurt 3/14/07 HFD-613/A.Payne/ Cyfur HFD-613/J.Grace/ Jz 3/12/2005

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F/T by: DJ 3/8/01

APPROVAL

APPLICATION NUMBER: ANDA 40-385

APPROVED LABELING

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21009270101

Trexall[™] (inethotrexate tablets, USP)

Revised JANUARY 2001

21009270101

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ROVED

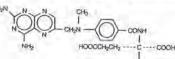
WARNINGS:

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 INFORMATION ON THE THREATENING INFORMATIO DISEASES, OR IN PATIENTS WITH PSORIASIS OR RHEUMATOID ARTHRITIS WITH SEVERE, RECALCITRANT, DIS-ABLING 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.
- MALIGNANCY, PSOHIASIS, AND RHEUMATOID ARTHRITIS. PATIENTS SHOULD BE CLOSELY MONITORED FOR BONE MARROW, LIVER, LUNG AND KIDNEY TOXICITIES. (See **PRECAUTIONS.**)
- A PHYSICIAN'S CARE THROUGHOUT THERAPY.
- A PHISTICIAN'S CARE INNOTATION OF THEMETY. 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 psonasis or rheumatoid arthritis should not receive methotrexate. (See CONTRAINOICATIONS.)
- 2.Methotrexate elimination is reduced in patients with impaired renal function, ascites, or pleural effusions. Such patients require especially careful monitoring for loxicity, 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.)
- some nonsteroidal anti-initiammatory drugs (NSAIDs). (See PRECAUTIONS, Drug Interactions.) 4. Methotraxale causes hepatoloxicity, 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 log-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.)
- Exactly, repaire.)
 5.Metholrexate-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.
- "Analignant 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 alteviate 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.)
- Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy.
- Methotrexate given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.

DESCRIPTION:

TrexaliTM (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 *M*-[4]([2,4-diamino-6-pteridinyi) methyl] methyl-amino]benzoy]-t-glutamic acid. The structural formula is:



C20H22N805

Molecular Weight: 454,45

TrexalI™ (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.

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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 another of methodocate solution equivalent to 15 mg of methodocate, methylcellulose, magnesium stearate, microorystalline 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 itanium 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. Thereform, 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 uniary 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 rheumatois increasible usingle to normal ussues. The mechanism of action in rheumatois 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 turther studies.

In patients with rheumatiol 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 rheumaloid arthrilis Pragere 00196m (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 epitheliai cells in the skin is oreatly 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 with-in 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.

The 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 con-centration (T_{MAX} : 0.67 to 4 hours 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, saficylates, letracyclines, 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 turnors. A small amount of metabolism to 7-hydroxymethotrexate may occur at doses commonly prescribed. The aqueous solubility of 7-hydroxy-methotrexate 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 clear-ance 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.

Methotraxate 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;

TrexallTM (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 chemotherapautic agents in the treatment of advanced stage non-Hodgkin's lymphomas.

Psoriasis:

TrexallTM (methotrexate tablets) are indicated in the symptomatic control of severe, recalcitrant, dis-abling psortasis 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. Rheumaloid Arthritis:

TrexalITM (methotrexale 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, Orug 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 outweights 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; guring and for a minimum of three months after therapy for male patients, and during and for at least one ovulatory cycle after therapy for lemale patients. (See Boxed WARNINGS.)

Because of the potential for serious adverse reactions from metholrexate 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 metholrexate.

Patients with psoriasis or rheumatold 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 thrangy, 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 DVERDOSAGE.) 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 osoriasis, and that mistaken daily use of the recommended dose has led to tatal 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 differentiat and platelet counts, hepatic enzymes, renal function tests, and a chest X-ray. During therapy of rheumatoid arthritis and pso-riasis, 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 librosis or cirrhosis in the rheumatoid arthritis population.

Pulmonary function tests may be useful if methotrexate-induced long 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 ani mal 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 saficylates, phenylbutazone, phenytoin, and sultonamides. 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 enterothepatic 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., azathio-prine, 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-methyltetrahydrotolate 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 palients 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 signification-ternains uncertain. Non-Hodgkin's lymphome and other turnors flave 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 letal detects in humans. It has also been reported to cause impairment of fertility, oligosper-mia 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 stomatifis 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 collits. Hematologic: Methotrexate can suppress hematopoiesis and cause anemia, leukopenia, and/or thrombo-

cytopenia. In patients with mahgnancy and preexisting hematopoletic 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 granuloo topenia 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 cir-rhosis) hepatotoxicity. Chronic toxicity is potentially fatal; it generally has occurred after prolonged use (generally two years or more) and after a total dose of al 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 greence of pre-existing liver damage or impaired hepatic function. existing liver damage or impaired hepatic function.

In psortasis, liver function tests, including serum albumin, should be performed periodically prior to dos-ing but are often normal in the face of developing fibrosis or circthosis. These lesions may be detectable only by biopsy. The usual recommendation is to obtain a liver biopsy at 1) preferacy or shortly after in-tiation 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 circhosis normally leads to discontinuation of the drug, mild fibro-sis normally suggests a repeat biopsy in 6 months. Milder histologic findings such as faity change and low grade portal inflammation are relatively common pretherapy. Although these mild changes are usually not a reason to avoid or discontinue methorexate therapy, the drug should be used with caution. In cheumatoid arthritis, ane at first use of methotrexate and duration of therator have been reported as risk

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 psoriais; 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 experi-ence in 217 rheumatoid arthritis patients with liver blopsies both before and during treatment (after a cumulative dose of at least 1.5 g) and in 714 patients with a blopsy 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 mid. 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.

Whener even longer use will increase triese risks. Liver function tests should be performed at baseline and at 4-8 week intervals in patients receiving methotexate for meeurated or patients with a history of excessive alcohol consumption, persistently abnormal baseline liver function test values or chronic hepatitis 8 or C infection. During therapy, liver blopsy 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).

setting of well controlled rheumatoid arthritis). If the results of a liver biopsy show mild changes (Roenigk grades I, II, IIIa), methotrexate may be contin-ued 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 over or laboratory evidence of incidency ficiency syndromes. Immunization may be ineffective when given during methotrexate therapy. Immunization with live virus vaccines is generally not recommended. There have been reports of dissem-inated vaccinia infections after smallpox immunization in patients- receiving methotrexate therapy. Hvoogammaglobulinemia has been reported rarely. 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.

Carini pneumonia snowie bec considered. Neurologic: There have been reports of leukoencephalopathy following intravenous administration of methotexate to patients who have had craniospinal irradiation. Serious neurotoxicity, trequently mani-fested as generalized or local seizures, has been reported with unexpectedly lincreased frequency among pediatric patients with acute lymphoblastic leukemia who were treated with intermediate-dose intravenous methotexate (1 gm/m²). Symptomatic patients were commonly noted to have subcencephalopathy and/or microangiopathic calcifications on diagnostic imaging studies. Chronic leukoencephalopathy also been reported in patients who received repeated doses of high-dose methotexate with leucovorin rescue even without cranial irradiation. Discontinuation of methotexate does not always result in com-olete 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 upknown.

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, dyspinea, hypoxemia, and an infiltrate on chest X-ray; infection needs to be excluded. This lesion can occur at all dosages. Peral-blich dosast of methotrevale used in the treatment of neterserving may raise read damage leading.

Cliess Ardy, intection needs to be excluded, this response in occur at an observation and a service of the serv

Skin: Severe, occasionally fatal, dematologic reactions, including toxic epidermal necrolysis, Stevens-Johnson Syndrome, exfoliative dermatilis, skin necrosis, and erythema multiforme, have been reported in children and adults, within days of oral, intramuscular, intravenous, or intrathecal methotrexate adminis-tration. 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 ascres). 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

Lesions of psoriasis may be aggravated by concomitant exposure to ultraviolet radiation. Radiation der matitis and sunburn may be "recalled" by the use of methotrexate. **ADVERSE REACTIONS:**

ADVENSE 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 CON-SULTED WHEN LOOKING FOR INFORMATION ABOUT ADVENSE REACTIONS WITH METHOTREXATE.

The most frequently reported adverse reactions include ulcerative stornalitis, leukopenia, nausea, and The most inequency reported adverse reactions include uncertainty stomatos, reutopenia, nausea, and addominal disterss. 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 encology setting, concomitant treatment and the underlying disease make specific attribution of a reac-tion to methotrexate difficult.

Alimentary System: Gingivitis, pharyngitis, stomatilis, anorexia, nausea, vomiting, diarrhea, hematemesis, melena, gastrointestinal ulceration and bleeding, enteritis, parcreatitis.

Cardiovascular: Pericarditis, pericardial effusion, Trypotension, 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, herriparesis, paresis and conbeing resident reports of transient subtle cognitive dystunction, mood alteration, unusual cranial sensa-been occasional reports of transient subtle cognitive dystunction, mood alteration, unusual cranial sensation, leukoencephalopathy, or encephalopathy.

bilin ierkoencepnaropauty, or encepnaropauty. Inlection: 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.

Pulnionary 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, ecchymo-sis, telangiectasia, acne, furunculosis, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson Syndrome, skin necrosis, and extoliative dermatritis.

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

Other rarer reactions related to or attributed to the use of methotnexate such as nodulosis, vasculitis, arthrai gia/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 subtracled) adverse reactions in 12 In TR week double-blind studies of patients (n=128) with rhaumatoid arthritis treated with low-dose oral

(7.5 to 15 mg/week) pulse methotrexate, are listed below. Virtually all of these patients were on concomi-tant 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/pruntus/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, arthrafgias, 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 fesions" (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,

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 infliction increases, the effectiveness of leu-covorin in counteracting toxicity decreases. Monitoring of the serum methotrexate concentration is essen-tial 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 pre-cipitation of methotrexate and/or its metaboliths in the renal tubules. Generally speaking, neither hemodial-ysis nor peritoneal dialysis have been shown to improve methotrexate elimination. However, effective clear-ance of methotrexate has been reported with acute, intermittent hemodialysis using a high-flux dialyzer. (Walt, SM et al: AM J Kinney 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 absorp-tion is rapid and effective serum levels are obtained.

tion is rapid and effective serum levels are obtained. *Choriocarcinoma and similar trophoblastic diseases:* Methotrexate is administered orally or intramuscu-larly 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 analy-ally 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 methotexate after normalization of hGG 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, prophylacilic chemotherapy with methotrexate has

Since hydatidiform mole may precede choriocarcinoma, prophylactic chemotherapy with methotraxate 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 recommanded for choriocarcinoma. Leukamia: 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 reliable is more common. relapse is more common.

Methotrexate alone or in combination with steroids was used initially for induction of remission in acute 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 does of 3.3 mg/m² in combination with 60 mg/m² of predinsone, given daily, produced remissions in 50% of patients treated, usually within a period of 4.10 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 does 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 remis-sion 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 ther-

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

And covering menapy. 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 com-monly given concomitantity with other antitumor agents. Treatment in all stages usually consists of sever-al 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 methodexate given in does of 0.020 to 2.5 mg/ng dany. Mycosis fungoides: Therapy with methodexate 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. Methotexate has also been given intramuscularly in doses of 50 mg once week-by or 25 mg 2 times wawfue. ly or 25 mg, 2 times weekly.

Psorlasis and Rheymatoid Attrilis:

The patient stroud 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 sheuld 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 sin-gle weekly dose. All schedules should be continually failored 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 AOVERSE 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

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 methotrex-ate 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 recom-mended in the guidelines are necessary or appropriate.

HOW SUPPLIED:

5 mg: .

TrexallTM (methotrexate tablets, USP) are available as:

- Green, oval-shaped, lim-coaled, scored, biconvex tablet. Debossed with **b** on one side and **927/s** 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
- Blue, oval-shaped, film-coated, scored, biconvex tablet. Debossed with 6 on one side and 928/7-// on the other side. Each 7.5 mg tablet contains an amount of methotrexate sodium equivalent to 7.5 mg of methotrexate. 7.5 mg:
 - Available in bottles of: 30 NDC 0555-0928-01
 - NDC 0555-0928-09
 - 60 100 NDC 0555-0928-02
- 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 equiv-10 mg: alent to 10 mg of methotrexate. Available in bottles of:

 - 30 NDC 0555-0929-01
 - 60 NDC 0555-0929-09
 - 100 NDC 0555-0929-02
- 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 equiv-15 mg: alent 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.
- 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.
- Anational 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.
- 5.Clinical Oncological Society of Australia: Guidelines and recommendations for safe handling of anti-neoplastic 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 SeptVoct 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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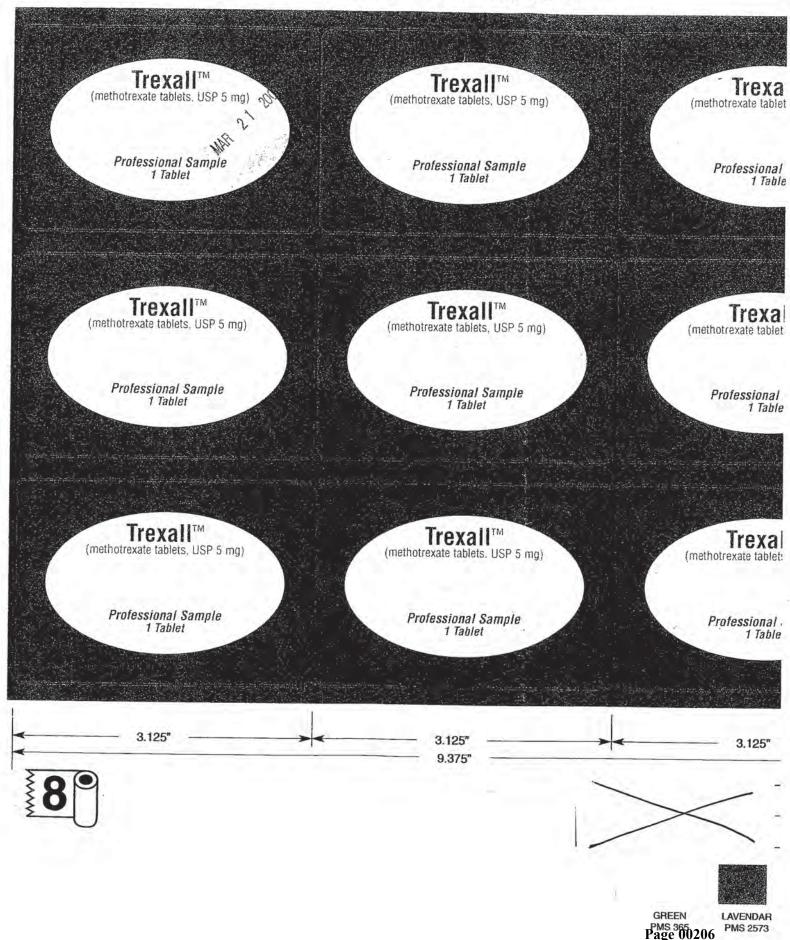


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NON-VINYL (BACK/PAPER) SIDE

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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.

Rx only

Professional Samples

10 Samples x 1 5 mg Tablet

QUPOND



SAMPLE



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.

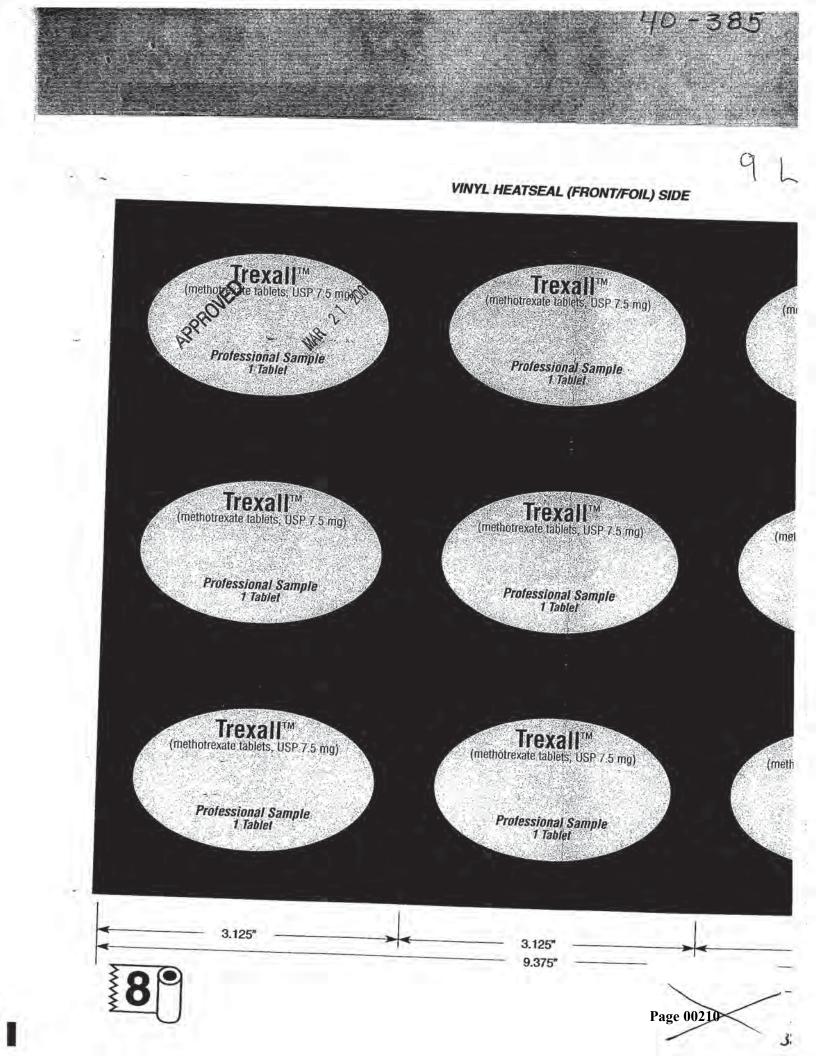


Professional Samples

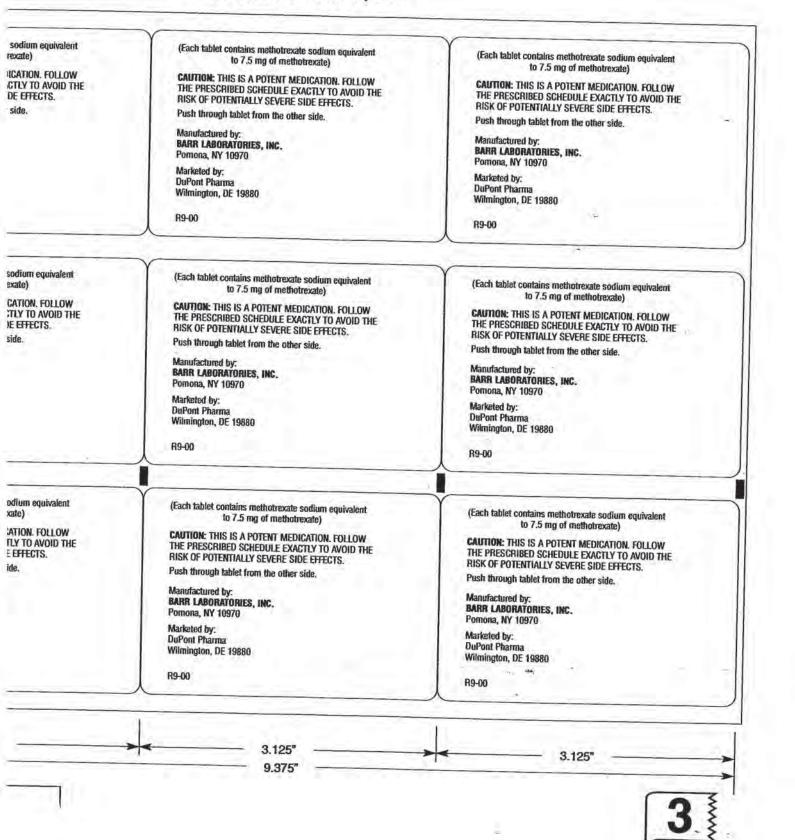
10 Samples x 1 5 mg Tablet

Manufactured by: BARR LABORATORIES, INC. Pomona, NY 10970

Marketed by: DuPont Pharma Wilmington, DE 19880



NON-VINYL (BACK/PAPER) SIDE





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

OII HIN



Pull tab to open

H Idilling

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.



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

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:

- 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?	11.	x	
s this product a USP item? If so, USP supplement in which verification was assured. USP 23	x		
s this name different than that used in the Orange Book?	1	x	-
f 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	A	
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?	I.C.	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	0 ==
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	1
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 faisely inconsistent between labels and labeling? Is "Jointly Manufactured by", statement needed?		×	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?	1.00	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.	Doctor	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	

Does th	e product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
_	of the inactives differ in concentration for this route of administration?	x		
	verse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
	e a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
	e term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
	to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
	to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?	1	x	11
-	to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		x	
	SSUES: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)		1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 -	
Do col	ntainer recommendations fail to meet or exceed USP/NDA recommendations? If so, are the mendations supported and is the difference acceptable?		x	
	USP have labeling recommendations? If any, does ANDA meet them?	x	1	100
-	product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	x		-
Failur	e of DESCRIPTION to meet USP Description and Solubility Information? If so, USP Information should ed. However, only include solvents appearing in innovator labeling.		x	
Bioe	QUIVALENCE ISSUES: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 ate study acceptable)			
	labeling references a food effect or a no-effect? If so, was a food study done?	1123	x	1.1
	LINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		x	12
Pate	ent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for cation of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if please state.		x	
OR	THE RECORD:		()	
1. 2. 3. 4. 5. 6.	 The reference listed drug for this product is Methotrexate Sodium Tablets, NDA#08-085/S-048; Approved October 29, 1999. The firm cites suitability petition docket number 97P-0279/CP1, approved a the basis for the 5 mg and 15 mg strength submission. See Vol. 1.1, page The firm certifies there are no patents/exclusivities in effect for this drug pr page 03-00001. The product is manufactured by Barr Laboratories, Inc., 2150 Perrowville F 24551. See Vol. 1.2, page 09-00002. Outside firms are utilized for testing only. See Vol. 1.2, page 10-00002. 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 	August 02-0000 roduct. Road, F	22, 19 05. See Vo	97, as ol. 1.1,
	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 :

7.

-

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

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: JWatt	Date: 12/21/99	
Team Leader Julia	Date: 12/21/1989	
CC: ANDA: 40-385 DUP/DIVISION FILE		

DUP/DIVISION FILE HFD-613/TWatkins/JGrace (no cc) V:\FIRMSAM\BARR\LTRS&REV\40385na1.I Review

8.

REVIEW OF PROFESSIONAL LABELING DIVISION OF LABELING AND PROGRAM SUPPORT LABELING REVIEW BRANCH

		lumber:		Date of Submission: April 14, 2000
Es	tablis	shed Nan		Tablets USP, 5 mg, 7.5 mg, 10mg and 15 mg , TREXALL™, and
La	belin	g Deficie	ncies:	
	GE			four proposed proprietary names are under review. We defer comment at
2.	co		R (30's, 60's and	
	i. II.		Temperature R gs- Delete ° —	Recommendation- include "Protect from light.".
3.	PH	YSICIAN	'S SAMPLE BO	TTLE (4's) – See comments under CONTAINER.
4.	PH	YSICIAN	'S SAMPLE UN	IT DOSE BLISTER (1's)- See GENERAL COMMENTS.
5.	PH	YSICIAN	'S SAMPLE UN	T DOSE BLISTER CARTON (1's)- See GENERAL COMMENTS.
6.			'S SAMPLE DIS COMMENTS.	SPENSER (10 unit dose cartons per dispenser)-See comments under
7.		SERT		
	1000	the second second	NERAL COMMI	- 031 5 7
	b.	INDICA	TIONS AND US	AGE
		i. Neo	oplastic Disease	s – Delete '
1	¢.	which re		nation for Patients) – Second paragraph- Delete the penultimate sentence
	d.	PRECA	UTIONS (Organ	System Toxicity; Neurologic) – Include the following to appear as the nces of paragraph one of this subsection:
		with une who we patients	expectedly increated with in	equently manifested as generalized or focal seizures, has been reported ased frequency among pediatric patients with acute lymphoblastic leukemia atermediate-dose intravenous methotrexate (1 gm/m²). Symptomatic y noted to have leukoencephalopathy and/or microangiopathic calcifications tudies.

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.

 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	
s this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
s this name different than that used in the Orange Book?		x	
f 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		Alandsside
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	1
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.	117	x	1
Does the package proposed have any safety and/or regulatory concerns?	12.40.2	X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?	1	x	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	i i
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?	11.00	x	1-1
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	1.4	x	1.0
Are there any other safety concerns?		x	11
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	1
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)	1111	x	4
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	Ŵ
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?	1	X	ir
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?	1	X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?	1	X	1

nactive Ingredients: (FTR: List page # in application where inactives are listed)	A COLORADOR AND A COLORADOR	120000	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
oes the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
to any of the inactives differ in concentration for this route of administration?	X		
ny adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?	11	X	1
s there a discrepancy in inactives between DESCRIPTION and the composition statement?	11	X	1
tas the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	-
allure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?	-	x	
	1	X	1
ailure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?	-	x	-
ailure to list dyes in imprinting Inks? (Coloring agents e.g., iron oxides need not be listed)		-	
JSP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)		x	
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the ecommendations supported and is the difference acceptable?		^	1.1
Does USP have labeling recommendations? If any, does ANDA meet them?	X		
s 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)			
nsert labeling references a food effect or a no-effect? If so, was a food study done?	141-6-5-4	X	
tas CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.	1011-1	X	1
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	
mg, 7.5 mg, 10 mg and 15 mg strength submission. See Vol. 1.1 & 4.1, page 02-00005. The firm certifies there are no patents/exclusivities in effect for this drug product. See Vol. The product is manufactured by Barr Laboratories, Inc., 2150 Perrowville Road, Forest, V page 09-00002. Outside firms are utilized for testing only. See Vol. 1.2, page 10-00002. Container/Closure	A 24551.	See Vo	ol. 1.2,
The firm certifies there are no patents/exclusivities in effect for this drug product. See Vol. The product is manufactured by Barr Laboratories, Inc., 2150 Perrowville Road, Forest, V page 09-00002. Outside firms are utilized for testing only. See Vol. 1.2, page 10-00002. Container/Closure 30's – bottle: 75 cc, HDPE, White, Wide mouth, Round 33/400, Cap: Metal, with Inner lin ————————————————————————————————————	A 24551. er 33/400 ner liner 3	See Vo , (Two 3/400,	ol. 1.2, -piece
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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

CC:

Reviewer: 1. Watt Team Leader:

Date: 5/3/2000 Date: 5-17-2000

ANDA: 49-385 DUP/DIVISION FILE HFD-613/TWatkins/JGrace (no cc) V:FIRMSAM/BARR/LTRS&REV/40385NA2.I Review

> APPEARS THIS WAY 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	1	1.1
Is this name different than that used in the Orange Book?	11-00	X	1
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis		1 Sh	1
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		1
Packaging	10213	1.	1
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	1
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	

the strength and/or concentration of the product unsupported by the insert labeling? X it the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect? X dividual catnom required? itsues for FTR: Innovator individually cartoned? Light sensitive product which X abeling X as applicant Tailed to clearly differentiate multiple product strengths? X as applicant Tailed to clearly differentiate multiple product strengths? X as policant Tailed to clearly differentiate multiple product strengths? X as policant Tailed to clearly differentiate multiple product strengths? X as policant Tailed to clearly differentiate multiple product strength vs Aduit; Oral Solution vs X obser RLD make special differentiatem florecrect of tailey inconsistent between labels and labeling? X "Jointly Maurifactured by," statement incorect of tailey inconsistent between labels and labeling? X "Jointly Maurifactured by," statement incorect of tailey supported. X Scoring: Describe social oral dosage form identifying markings in HOW SUPPLIED? X as the fina failed to describe the socing in the HOW SUPPLIED section? X as the fina failed to describe the socing in the HOW SUPPLIED section? X as the fina failed to	
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Patent/Exclusivity issues (; FTR: check the orange book edition of cumulative supplement for	
none, please state.	

FOR THE RECORD:

The reference listed drug for this product is Methotrexate Sodium Tablets, 2.5 mg (Lederle; NDA#08-085/S-048; 1. Approved October 29, 1999. CSO cannot provide S-046 at this time more changes and FPL needed of RLD.

The firm cites suitability petition docket number 97P-0279/CP1, approved August 22, 1997, as the basis for the 5 2. mg, 7.5 mg, 10 mg and 15 mg strength submission. See Vol. 1.1 & 4.1, page 02-00005.

The firm certifies there are no patents/exclusivities in effect for this drug product. See Vol. 1.1, page 03-00001. 3.

The product is manufactured by Barr Laboratories, Inc., 2150 Perrowville Road, Forest, VA 24551. See Vol. 1.2, 4.

- page 09-00002.
- Outside firms are utilized for testing only. See Vol. 1.2, page 10-00002. 5.
- 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, (Twopiece ' _____ 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

 strength Physician sample : Film:-1 Tablet Blister Card for 5 mg -, Foil: -See Vol. 1.3, ---- aluminum foil, "--

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
	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
	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
Tal	Inactive:Sodium Carbonate, Microcrystalline Cellulose, Anhydrous Lactose, Pregelatinized Starch, Crospovidone, c, Magnesium Stearate
Ian	5 mg only – F
	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-
	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 roor 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.
Re	te of Review: Jan. 31, 2001 & Feb. 8, 2001 Date of Submission: Jan. 12, 2001 & Feb 2, 2001 Date: 1/31/01 & 2/8/2001
Tea	am Leader: John Grace July July 2/12/2001
	ANDA: 40-385
cc:	DUP/DIVISION FILE
cc:	DUP/DIVISION FILE HFD-613/ARayne/JGrace (no cc)
cc:	DUP/DIVISION FILE HFD-613/ARayne/JGrace (no cc) V:VFIRMSAM\BARR\LTRS&REV\40385ap.I Review

1.

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. <u>ANDA # 40385</u>

- <u>NAME AND ADDRESS OF APPLICANT</u> Barr Laboratories, Inc. Attention: Christine Mundkur 2 Quaker Road PO Box 2900 Pomona, NY 10970-0519
- 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. <u>SUPPLEMENT(s)</u> N/A
- <u>PROPRIETARY NAME</u>

 However, the labeling reviewer will inform Barr that the proposed proprietary name is unacceptable.
- 7. <u>NONPROPRIETARY NAME</u> Methotrexate Tablets, USP
- <u>SUPPLEMENT(s) PROVIDE(s) FOR:</u> N/A
- 9. AMENDMENTS AND OTHER DATES:

Vol.	Submission date	Submission type
A1.1 – 1.10 (A1.2 – 1.7 are Bio)	07/23/99	Original
A2.1	08/06/99	NC - CMC electronic submission
W	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. <u>PHARMACOLOGICAL CATEGORY</u> antineoplastic, antirheumatic and antipsoriatic

11. <u>Rx or OTC</u> Rx

12. <u>RELATED IND/NDA/DMF(s)</u>

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)
1 1	III: Packaging	12 - 12 - 14 - 14 - 14 - 14 - 14 - 14 -	
	III: Packaging	1	1
	III: Packaging	Y 12 1	
	III: Packaging		1
∇	II: Drug Substance		
$\overline{\Lambda}$	III: Packaging	1	1.000
	III: Packaging		1.000
	III: Packaging	12.00	C
	III: Packaging		
	III: Packaging		

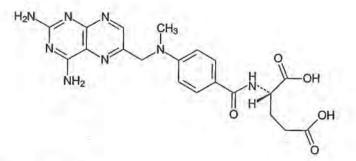
See DMF Checklist for further details.

- 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]-. C₂₀H₂₂N₈O₅. 454.45. 59-05-2.



16. <u>RECORDS AND REPORTS</u>

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. <u>REVIEWER:</u> Eugene L. Schaefer, Ph.D.

DATE COMPLETED: 2/28/2000

DATE REVISED: 3/6/2000

APPEARS THIS WAY ON ORIGINAL

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information from

CHEMISTRY REVIEW #1

Endorsements:

HFD-625/ELSchaefer, Chemist/3-6-00 HFD-625/MSmela, Chemistry Team Leader/3-7-00 HFD-617/MDillahunt, Project Manager/3-7-00 M Jullehurt 3/8/W ISAM\BARR\LTRS&REV\40385.DOC TRY REVIEW - Not APPROVANT

V:\FIRMSAM\BARR\LTRS&REV\40385.DOC

CHEMISTRY REVIEW - Not APPROVABLE - Major

cc:

1. CHEMISTRY REVIEW NO. 2

ANDA # 40385

2.

- <u>NAME AND ADDRESS OF APPLICANT</u> Barr Laboratories, Inc. Attention: Christine Mundkur
 Quaker Road PO Box 2900 Pomona, NY 10970-0519
- <u>LEGAL BASIS FOR SUBMISSION</u> Approved ANDA Suitability Petition for change in strength
- 5. <u>SUPPLEMENT(s)</u> N/A
- <u>PROPRIETARY NAME</u>

 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. <u>NONPROPRIETARY NAME</u> Methotrexate Tablets, USP
- 8. <u>SUPPLEMENT(s) PROVIDE(s) FOR:</u> N/A

9. <u>AMENDMENTS AND OTHER DATES:</u>

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, <u>which was used for making the original exhibit</u> 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. <u>PHARMACOLOGICAL CATEGORY</u> 11. <u>Rx or OTC</u> antineoplastic, antirheumatic and antipsoriatic Rx
- 12. RELATED IND/NDA/DMF(s)

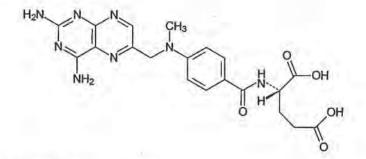
Approved ANDA 81-099, Methotrexate Tablets USP, 2.5 mg, Barr Laboratories, Inc.

Bio-IND 15-304, Methotrexate Tablets USP, 15 mg, Barr Laboratories, Inc.

See DMF Checklist.

- 13. DOSAGE FORM tablet
- 14. <u>STRENGTHS</u> 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]-. C₂₀H₂₂N₈O₅. 454.45. 59-05-2.



16. <u>RECORDS AND REPORTS</u> 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. <u>REVIEWER:</u> Eugene L. Schaefer, Ph.D.

DATE COMPLETED: 10/24/2000

REVISED: 10/27/00

APPEARS THIS WAY ON ORIGINAL

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confidential commercial

information from

CHEMISTRY REVIEW #2

1. CHEMISTRY REVIEW NO. 3

- <u>NAME AND ADDRESS OF APPLICANT</u> Barr Laboratories, Inc. Attention: Christine Mundkur 2 Quaker Road PO Box 2900 Pornona, NY 10970-0519
- 4. <u>LEGAL BASIS FOR SUBMISSION</u> Approved ANDA Suitability Petition for change in strengths (4)
- 5. <u>SUPPLEMENT(s)</u> N/A

7

- <u>PROPRIETARY NAME</u> in the original submission was unacceptable. Trexall[™] in the minor amendment of 1/12/01 is acceptable.
- 7. <u>NONPROPRIETARY NAME</u> Methotrexate Tablets, USP
- 8. <u>SUPPLEMENT(s) PROVIDE(s) FOR:</u> 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
n.	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
9	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. <u>PHARMACOLOGICAL CATEGORY</u> 11. antineoplastic, antirheumatic and antipsoriatic

Rx or OTC Rx

12. RELATED IND/NDA/DMF(s)

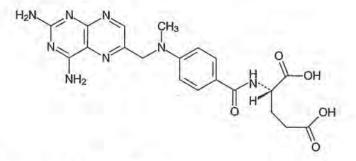
Approved ANDA 81-099, Methotrexate Tablets USP, 2.5 mg, Barr Laboratories, Inc.

Bio-IND 15-304, Methotrexate Tablets USP, 15 mg, Barr Laboratories, Inc.

See DMF Checklist.

- 13. <u>DOSAGE FORM</u> 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]-. C₂₀H₂₂N₈O₅. 454.45. 59-05-2.



- 16. <u>RECORDS AND REPORTS</u> 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 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

APPEARS THIS WAY ON ORIGINAL

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confidential commercial

information from

CHEMISTRY REVIEW #3

cc: ANDA 40-385 DUP DIV FILE Field Copy

Endorsements:

ES 2/2/01 MSmelas.

HFD-625/ELSchaefer, Chemist/1/31/01 HFD-625/MSmela, Chemistry Team Leader/2/1/01 HFD-617/MDillahunt, Project Manager/2/2/01 Willohuut 2/2/01 F/t by: DJ 2/2/01 V:\FIRMSAM\BARR\LTRS&REV\40385cr3.DOC

CHEMISTRY REVIEW - Not APPROVABLE - Minor

APPEARS THIS WAY ON ORIGINAL 1. CHEMISTRY REVIEW NO.

2.

- <u>NAME AND ADDRESS OF APPLICANT</u> Barr Laboratories, Inc. Attention: Christine Mundkur 2 Quaker Road PO Box 2900 Pomona, NY 10970-0519
- 4. <u>LEGAL BASIS FOR SUBMISSION</u> Approved ANDA Suitability Petition for change in strengths (4)

4

5. <u>SUPPLEMENT(s)</u> N/A

 $\hat{\mathbf{n}}$

- <u>PROPRIETARY NAME</u> in the original submission was unacceptable. Trexall[™] in the minor amendment of 1/12/01 is acceptable.
- 7. <u>NONPROPRIETARY NAME</u> Methotrexate Tablets, USP
- <u>SUPPLEMENT(s) PROVIDE(s) FOR:</u> N/A
- 9. <u>AMENDMENTS AND OTHER DATES:</u>

A1.1 - 1.10	07/23/99	Original
(A1.1 & 1.8 - 1.10 are Chem)		
(A1.2 - 1.7 are Bio)		12 July 19 19 19 19 19
A2.1	09/21/99	"Acceptable for Filing" letter
A3.1	10/07/99	Bio telephone amendment
A1.1	03/09/00	NA – Major
9	03/23/00	Fax from Barr re packaging and stability
'n	03/28/00	Telecon re 3/23
A4.1 - 4.5	04/14/00	Major amendment
(A4.2 is labeling)		
A4.1	08/09/00	Labeling comments to firm via voicemail
	11/13/00	NA – Minor
A5.1 - 5.3	01/12/01	Minor amendment
(5.2 & 5.3 are labeling.)		and to other a series of the series of the
A5.1	02/02/01	NC Labeling
	02/06/01	NA-Minor
н.	02/08/01	Fax from Barr re 02/06/01*
	02/13/01	Chem telecon re 02/06/01*
	02/15/01	Minor amendment*
н	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.

 PHARMACOLOGICAL CATEGORY
 11.
 Rx or OTC

 antineoplastic, antirheumatic and antipsoriatic
 Rx

12. RELATED IND/NDA/DMF(s)

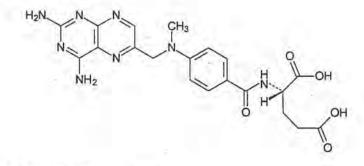
Approved ANDA 81-099, Methotrexate Tablets USP, 2.5 mg, Barr Laboratories, Inc.

Bio-IND 15-304, Methotrexate Tablets USP, 15 mg, Barr Laboratories, Inc.

See DMF Checklist.

- 13. DOSAGE FORM tablet
- 14. <u>STRENGTHS</u> 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]-. C₂₀H₂₂N₈O₅. 454.45. 59-05-2.



16. <u>RECORDS AND REPORTS</u> N/A

17. <u>COMMENTS</u>

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. <u>REVIEWER:</u> 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

ANDA 40-385 cc:

> DIV FILE Field Copy

Endorsements:

In al MSmele 1.1 HFD-625/ELSchaefer, Chemist/3/7/01 HFD-625/MSmela, Chemistry Team Leader/3/7/01 HFD-617/MDillahunt, Project Manager/3/8/01 Whellahu F/T by: DJ 3/8/01 V:\FIRMSAM\BARR\LTRS&REV\40385cr4.doc

E\$ 3/91

CHEMISTRY REVIEW - APPROVED

ANDA APPROVAL SUMMARY

ANDA:	CHEMIST:	DATE:
40-385	Eugene L. Schaefer, Ph.D.	3/7/01
DRUG PRODUCT: Methotrexate		
FIRM: Barr Laboratori	ies, Inc.	
DOSAGE FORM:	STRENGTHS:	- 13 (State)
Tablets, USP	5 mg, 7.5 mg,	10 mg, 15 mg
cGMP: The facilities were four	nd acceptable on 10/	30/00.
BIO: No further questions 2/1	16/00 and 6/1/00.	1
VALIDATION - (Description of o same as in firm's ANDA?): N/A DS and DP are in USP 24.		by FDA lab
STABILITY:		
The containers in the sta those in the container se		identical to
LABELING:		
Container, carton, and ir Angela Payne on 2/8/01.	nsert labeling were	approved by
STERILIZATION VALIDATION (If a N/A	applicable):	
SIZE OF BIO BATCH (Firm's sour	rce of NDS ok?): Yes	, DMF OK.
15-mg tablets		A CALLER AND
SIZE OF STABILITY BATCHES (If they manufactured via the same		batch, were
5 mg: table	ets	
7.5 mg: table	ets	
10 mg: table	ets	
15 mg: —— table	ets	
PROPOSED PRODUCTION BATCHES-MA	ANUFACTURING PROCESS	SAME?: Yes
5 mg: — table	ets .	
7.5 mg: table	ets	
10 mg: table	ets	
15 mg: ——— table	ets A	1. Sec. 1.
Signature of chemist: 3/9/01 Eugene L. Schaefer, Ph.D.	Signature of Team Michael Smela	Leader: MSml 3/12/2

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: ANDA 40-385

BIOEQUIVALENCE REVIEW(S)

Methotrexate Sodium 15 mg and 5 mg Tablets ANDA # 40-385 Reviewer: André Jackson Barr Laboratories Pomona, N.Y. Submission Date: 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.	
Principal	1.	
Investigator:	2.	\langle
Clinical Study	Period I	Period II
Date:	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:		

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Principal Investigator:	
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:

3

Patients with Mild	Y			
to Severe Psoriasis:				
IRB Approval:	Y			
Informed Consent	Y			
Obtained:				
No. of Subjects	38	(22	males,16	females)
Enrolled:				
Inclusion/Exclusion criteria	vc	1:1	.1 ; pages	s: 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	В
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:		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:

4

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	В	1,6,7,11
GRII	В	A	2,3,5,9,12,13
2.GRI	A	В	14,15,18,20,23, 24,21,33
GRII	В	А	16,17,19,22,34

3.GRI	A	B	26,27,30,48
GRII	В	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 Core: Methotrexate, USP^a

1.11

mg

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:

Parameter	A
lethod	1
Internal Standard	†∖ /
Sensitivity/LOQ	t \ /
inearity (Standard curve samples)	
Quality Control (QC) Samples	
Precision of Standards (%CV)	$ \land / $
Precision of QC Samples (%CV)	T X
Accuracy of Standards (%)	
Accuracy of QC Samples (%)	
Stability	$\frac{1}{2}$
Freeze-thaw	

Table 2: Validation data for methotrexate.

Processed Sample Stability at RT	
Long term at -25° C	
Recovery	t ×
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 loglinear 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 Table 3. Mean plasma levels of 36 subjects. Values are mean \pm sd.

	TEST		REFERENC	CE
HOURO	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 \pm sd.

	TEST		REFERENC	CE	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	

AUC 0 to last measured concentration
 AUC to time infinity
 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.

Methotrexate, USP ^a		15	5
1.57			1
			10.0
			10
SI-1			
			1.0
			1
			- 1 Ave.
			14
< B.			
			1
		_	4
			-
a Theoretical quantities are	based on the		

Page 00259

c.Dependent on Methotrexate, USP assay.

d.Used but not retained, except as allowed in

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 # ----- 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 <u>in</u> <u>vitro</u> 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 bioavailability 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. \mathcal{U} Division of Bioequivalence Review Branch I

RD INITIALED YCHuang FT INITIALED YCHuang

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Concur At

Date

Date

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

Drug (Gene	ric Name):	Methotrexate	sodium			
Dose Stren	gths:5 mg a	nd 15 mg				
ANDA No.:4	0-385			*		
Firm: Barr						
	Date: July					
File Name:	40385SDW.79	9				
I. Con	ditions for	Dissolution	Testing:			
USP	XXIII Bask	et: Paddle:	x RPM:	50		
	Units Test					
	lium: 0.1N					
	elength: 30					
2.2.7	ume: 900 mL					
	cifications					
	'75% in 45		o oodina			
		: Methotrexat				
	usp Methodol	ogy: UV Spect	говсору			
a cherry tel sector and	OSE METHOD					
TT Rec	ults of In	Vitro Dissolu	tion Test	ing.		-
and the second second second second	ults of In	Vitro Dissolu Test Product	tion Test		erence Drody	act
Sampling		Test Product	tion Test		erence Produ	
Sampling Times	Lot	Test Product # 409277R01	tion Test	Ref	Lot # 457-0	37
Sampling	Lot	Test Product	tion Test %CV	Ref		2.5
Sampling Times	Lot Stre	Test Product # 409277R01 ength(mg) 5		Ref	Lot # 457-0 Strength(mg)	37
Sampling Times (Minutes)	Lot Stre Mean	Test Product # 409277R01 ength(mg) 5 Range	%CV	Ref Mean	Lot # 457-0 Strength(mg) Range)37 2.5 %CV
Sampling Times (Minutes) 10	Lot Stre Mean 87	Test Product # 409277R01 ength(mg) 5 Range 77-92	%CV 6.3	Ref Mean 52	Lot # 457-0 Strength(mg) Range 49-56)37 2.5 %CV 4.7 2.2
Sampling Times (Minutes) 10 20 30	Lot Stre Mean 87 88	Test Product # 409277R01 ength(mg) 5 Range 77-92 80-93	%CV 6.3 5.2	Mean 52 97	Lot # 457-0 Strength(mg) Range 49-56 94-100)37 2.5 %CV 4.7
Sampling Times (Minutes) 10 20 30	Lot Stre Mean 87 88 89	Test Product # 409277R01 ength(mg) 5 Range 77-92 80-93 82-93	%CV 6.3 5.2 4.5	Ref Mean 52 97 99	Lot # 457-0 Strength(mg) Range 49-56 94-100 96-104	037 2.5 %CV 4.7 2.2 2.8
Sampling Times (Minutes) 10 20 30 45	Lot Stre Mean 87 88 89 91	Test Product # 409277R01 ength(mg) 5 Range 77-92 80-93 82-93 84-94	%CV 6.3 5.2 4.5 4.2	Ref Mean 52 97 99 100 99	Lot # 457-0 Strength(mg) Range 49-56 94-100 96-104 97-105	037 2.5 %CV 4.7 2.2 2.8 2.9 2.6
Sampling Times (Minutes) 10 20 30 45 75	Lot Stre Mean 87 88 89 91 92	Test Product # 409277R01 ength(mg) 5 Range 77-92 80-93 82-93 84-94 87-95	%CV 6.3 5.2 4.5 4.2	Ref Mean 52 97 99 100 99	Lot # 457-0 Strength(mg) Range 49-56 94-100 96-104 97-105 96-104	037 2.5 %CV 4.7 2.2 2.8 2.9 2.6 1ct
Sampling Times (Minutes) 10 20 30 45 75 Sampling	Lot Stre Mean 87 88 89 91 92 Lot	Test Product # 409277R01 ength(mg) 5 Range 77-92 80-93 82-93 84-94 87-95 Test Product	%CV 6.3 5.2 4.5 4.2	Ref Mean 52 97 99 100 99 Ref	Lot # 457-0 Strength(mg) Range 49-56 94-100 96-104 97-105 96-104 erence Produ	037 2.5 &CV 4.7 2.2 2.8 2.9 2.6 1Ct 037
Sampling Times (Minutes) 10 20 30 45 75 Sampling Times	Lot Stre Mean 87 88 89 91 92 Lot	Test Product # 409277R01 ength(mg) 5 Range 77-92 80-93 82-93 82-93 84-94 87-95 Test Product # 409457R01	%CV 6.3 5.2 4.5 4.2	Ref Mean 52 97 99 100 99 Ref	Lot # 457-0 Strength(mg) Range 49-56 94-100 96-104 97-105 96-104 erence Produ Lot # 457-0)37 2.5 %CV 4.7 2.2 2.8 2.9 2.6 1ct 37 2.5
Sampling Times (Minutes) 10 20 30 45 75 Sampling Times (Minutes)	Lot Stre Mean 87 88 89 91 92 Lot Stre	Test Product # 409277R01 ength(mg) 5 Range 77-92 80-93 82-93 82-93 84-94 87-95 Test Product # 409457R01 ength(mg) 15	%CV 6.3 5.2 4.5 4.2 3.2	Ref Mean 52 97 99 100 99 Ref	Lot # 457-0 Strength(mg) Range 49-56 94-100 96-104 97-105 96-104 erence Produ Lot # 457-0 Strength(mg)	037 2.5 %CV 4.7 2.2 2.8 2.9 2.6 1ct 037 2.5 %CV
Sampling Times (Minutes) 10 20 30 45 75 Sampling Times (Minutes) 10	Lot Stre Mean 87 88 89 91 92 Lot Stre Mean	Test Product # 409277R01 ength(mg) 5 Range 77-92 80-93 82-93 84-94 87-95 Test Product # 409457R01 ength(mg) 15 Range	%CV 6.3 5.2 4.5 4.2 3.2 %CV	Ref Mean 52 97 99 100 99 Ref Mean	Lot # 457-0 Strength(mg) Range 49-56 94-100 96-104 97-105 96-104 Erence Produ Lot # 457-0 Strength(mg) Range	037 2.5 %CV 4.7 2.2 2.8 2.9 2.6 1ct 037 2.5 %CV 4.7
Sampling Times (Minutes) 10 20 30 45 75 Sampling Times	Lot Stre Mean 87 88 89 91 92 Lot Stre Mean 89	Test Product # 409277R01 ength(mg) 5 Range 77-92 80-93 82-93 84-94 87-95 Test Product # 409457R01 ength(mg) 15 Range 76-95	%CV 6.3 5.2 4.5 4.2 3.2 %CV 7.2	Ref Mean 52 97 99 100 99 Ref Mean 52	Lot # 457-0 Strength (mg) Range 49-56 94-100 96-104 97-105 96-104 Errence Produ Lot # 457-0 Strength (mg) Range 49-56	037 2.5 &CV 4.7 2.2 2.8 2.9 2.6 1Ct 037
Sampling Times (Minutes) 10 20 30 45 75 Sampling Times (Minutes) 10 20	Lot Stre Mean 87 88 89 91 92 Lot Stre Mean 89 91	Test Product # 409277R01 ength(mg) 5 Range 77-92 80-93 82-93 84-94 87-95 Test Product # 409457R01 ength(mg) 15 Range 76-95 81-95	%CV 6.3 5.2 4.5 4.2 3.2 %CV 7.2 5.0	Ref Mean 52 97 99 100 99 Ref Mean 52 97	Lot # 457-0 Strength(mg) Range 49-56 94-100 96-104 97-105 96-104 Erence Produ Lot # 457-0 Strength(mg) Range 49-56 94-100	037 2.5 %CV 4.7 2.2 2.8 2.9 2.6 1ct 037 2.5 %CV 4.7 2.2

APPENDIX

Site 1

Variable	N	Mean TEST	Std	Mean REFERENC	Std CE	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 REFERENC	Std E (7	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	1
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	1. T
KEL hr-1	13	0.24	0.06	0.20	0.05	
THALF hr	13	2.98	0.64	3.63	1.07	

S	i	te	3

Variable N

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 AM 2/16/00

V:\Firmsam\Barr\Ltr&Rev\40385SDW.799

BIOAVAILABILITY - ACCEPTABLE Submission Date: July 23, 1999 FASTING STUDY (STF) old 1. Strength: 15 mg Tablet Clinical: 1. 2. 3. Analytical: Outcome: AC 2. Dissolution WAIVER (DIW) Strength: 5 mg Tablet OIL Outcome: AC Submission Date: October 7, 1999 3. STUDY AMENDMENT (STA) Strength: 15 mg Disk and Additional Information Outcome: AC

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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,

lonner

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 Labo	ratories	
DRUG AND	DOSAGE	FORM :	Methotrexate	Sodium	Tablets		
STRENGTH TYPES OF	a strange of the second s	the second se	Jle Dose				
CLINICAL	STUDY SI	TE(S) :1 2. 3.					
ANALYTIC	CAL SITE(s): —		-			
STUDY SU	MMARY :	See Revi	iew			-	

DISSOLUTION : See Submission

	DSI INSPECTION	STATUS
Inspection needed: <u>YES</u> / NO	Inspection status:	Inspection results:
First Generic 🛛 🏂	Inspection requested: (date)	
New facility For cause Other	Inspection completed: (date)	
PRIMARY REVIEWE	R : Andre Jackson BRAN	ICH : I 9/2000
TEAM LEADER : Y	C. Huang BRANCH : I	
INITIAL :	DATE: 2/	19/2000
DIRECTOR, DIVISION	N OF BIOEQUIVALENCE : DAL $- \qquad \qquad DATE : \frac{2}{2}$	

411 Smelves

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
ethotrexate, USP ^(a)	5	7.5	10	15
a.				

Comments:

- 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.
- 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	Tablet Strength	vs Test 15 mg
	Strength	the standard second	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. (Lud Division of Bioequivalence Review Branch I

RD INITIALED YCHuang FT INITIALED YCHuang

5/23/2000 Date

Date 4

Concur: (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:

I√ JSP 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

IN-Vitro COMPARATIVE DISSOLUTION STUDY

Sampling	Test Product	Reference Product
Times	Lot # 409289R01	Lot # 457-037
(Minutes)	Strength 7.5 mg	Strength 2.5 mg

% Dissolved

% Dissolved

Sample No. 1	10 min.	20 min.	30 min.	45 min.	75* min.	Sample No. 1	10 min.	20 min.	30 min.	45 min.	75* min.
2 3						2					
3						3					
4						4					
5						5					1
6						1					
7						7					
8						8					
9						9					
10						10					1
11						11					
12	L					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	83
%RSD.	4.6	4	3.7	3.3	3	%RSD.	4.8	2.9	2.2	6.8	5
*	Addition	al time n	oint at th	e same ro	tation sr	need					

Additional time point at the same rotation speed.

IN-Vitro COMPARATIVE DISSOLUTION STUDY

Sampling	Test Product	Reference Product
Times	Lot # 409299R01	Lot # 457-037
(Minutes)	Strength 10 mg	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					1					1
2						2					
2 3	1					3					- 11
3 4 5 6 7	1					4					
5						5					1
5 6	1					6			~		1
1	1					7	8				
8						8					
						9					ł
10	1					10					
11						11					- 1
12						12					1
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
A 6											

*Additional time point at the same rotation speed.

	Sampling Test Product				Reference Product						
Times Lot # 409459R01			Lot # 409457R01								
Minutes) Strength 15 mg			5 mg		Strength 15 mg						
*		% Dis	solved					%	Dissolve	d	
Sample	10	20	30	45	75*	Sample	10	20	30	45	75*
No.	min.	min.	min.	min.	min.	No.	min.	min.	min.	min.	min.
1	-					1					
2						2					
3 4 5						3					
4						4					1
5					12.1	5					
6						1					1
7						7					1
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, Pharm. D. Director, Division of Bioequivalence Office of Generic Drugs Center for Drug Evaluation and Research

OFFICE OF GENERIC DRUGS DIVISION OF BIOEQUIVALENCE

	6				
ANDA # : 40-385	SPONSOR : Ba	arr Laboratories, Inc.			
DRUG AND DOSAGE	FORM : Methotrexate Sodi	um Tablets			
STRENGTH(S) : 15	img, 10 mg, 7.5 mg and 5.0	0 mg			
TYPES OF STUDIES	s : Single Dose BA stady	on 15 mg / waiver on 10 mg.			
CLINICAL STUDY S	SITE (S) :1.	, Jizna and znd .			
	2.				
ANALYTICAL SITE(STUDY SUMMARY : DISSOLUTION : See	See Review(Approval was pending	DSI inspection completed on (9/29/2000) DSI: Acceptable UN			
	DSI INSPECTION S	TATUS			
Inspection needed: YES / <u>NO</u>	Inspection status:	Inspection results:			
First Generic	Inspection requested: (date)				
New facility	Inspection completed: (date)				
For cause	1 14				
Other		-			
PRIMARY REVIEWE	R : Andre Jackson BRANC	CH:I			
INITIAL :	2 // DATE: 12/4	1/2000Ø			
TEAM LEADER : Y	r.C. Huang BRANCH : I				
INITIAL : 4/-	DATE : 12/	4/2000			
DIRECTOR, DIVISION	N OF BIOEQUIVALENCE : DALE	P. CONNER, Pharm. D.			
INITIAL : Garbo		-			

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: ANDA 40-385

ADMINISTRATIVE DOCUMENTS

a request for

882 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	DATE February 13, 2001			
request a telecon to discuss comment 2 of the deficiency letter. (see attached fax).	ANDA NUMBER 40-385			
Mike Smela reviewed the fax and I	IND NUMBER			
telephoned the firm and left the following voice mail message for Mr. Sharif Ahmed: It is policy to	TELECON			
require full term data if accelerated	INITIATED BY			
show adverse trends.	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 Mullahut Allahut			

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.

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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

M. Smela M. Smela M. Dillahunt M. Dillahunt M. Dillahunt 2-1

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 guestion about the tradename they propose to use for their product. Mr. Smela referred the firm to contact John Grace for questions about the tradename.

V:\FIRMSAM\BARR\TELECONS\40385.tcon3.doc ANDA 40-385

.CC:

Division File Chem Div I, T-con Notebook 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

SIGNATURE

M.Smela

M.Dillahunt

(914) 353-8432

Page 00282

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: ANDA 40-385

CORRESPONDENCE

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

July 23, 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

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 sector tion that the information in the electronic submission is the same as the information will be provided in the paper submission.



Page 00284

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.

à Mundhe

Christine Mundkur Vice President, Quality and Regulatory Counsel

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

August 6, 1999

NEW LIDERSEP

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

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 Vice President, Quality and Regulatory Courter ER FOR Drift RUE AUE Page 00286

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

September 20, 1999

NEWCOMES

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 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
1.
2.
3.
4.
5.
6.

Function

Clinical Site

Clinical Site

Clinical Site

Clinical Site

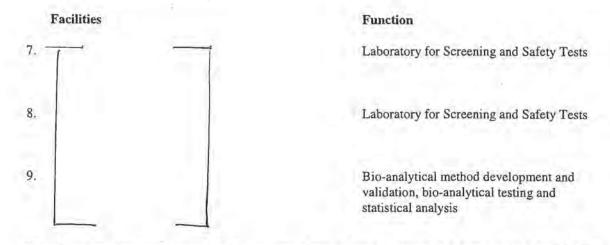
Laboratory for Screening and Safety Tests

Laboratory for Screening and Safety Tests



ANDA 40-385 METHOTREXATE TABLETS, USP 5 MG AND 15 MG GENERAL CORRESPONDENCE

Page 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

Page 00288

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,

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 DUP/Jacket cc: Division File Field Copy HFD-610/R.West HFD-92 HFD-615/M.Bennett Endorsement: HFD-615/NMahmud, Chief RSB HFD-615, GDavis, CSO an 99 Z HFD-600, MSmela, Sup. Chem. date Word File v:\firmsam\barr\ltrs&rev\40385.ack FT\njg\9\21\99 ANDA Acknowledgment Letter!

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

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



MAJOR AMENDMENT

ANDA 40-385

2000 MAR

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.

> Christine Mundkur ATTN:

FROM: Michelle Dillahunt

PHONE: (914) 362-1100 FAX: (914) 353-3859

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(i) 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

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED

FROM DISCLOSURE UNDER APPLICABLE LAW. If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address..

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information from

3/9/2000 FOA 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:

- 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.
- 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 – <u>http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html</u>.
 - 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.F.

Director Division of Labeling and Program Support Office of Generic Drugs Center for Drug Evaluation and Research

NO.163 P.1



2 Quaker Road P.O. Box 2900 Pomona, NY 10970 914-362-1100

Fax Transmission

Date:	March 23, 2000		
То:	Michelle Dilahunt Project Manager, OGD	Phone Number: Fax Number:	(301) 827-5848 (301) 594 -0180
From:	Sharif Ahmed Manager of Regulatory Affairs Barr Laboratories, Inc.	Phone Number: Fax Number:	(913) 353-8476 (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.

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.

The information contained in this facsimile message is privileged and confidential information intended only for the use of the individual or entity named above. If the reader of this message is not the intended recipient, or the employee or agent responsible to deliver it to the intended recipient, you are hereby notified that any dissemination, distribution or conving of this communication is strictly prohibited.

If you have received this communication in error, please immediately notify us by telephone, and return the original message to us at the cover address via the U.S. Postal Service. Thank You

Verification Name/Number:

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

ORIG AMENDMENT

April 14, 2000

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:

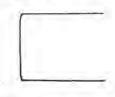
ANDA 40-385 Methotrexate Tablets, USP 5 mg and 15 mg Additional Strengths: Methotrexate Tablets, USP 7.5 mg and 10 mg MAJOR AMEDMENT

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:

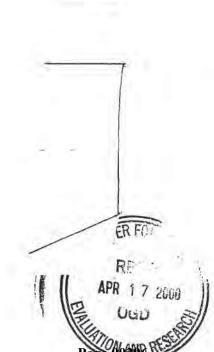
CHEMISTRY DEFICIENCIES

A. Deficiencies

COMMENT 1:



RESPONSE:



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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

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) NOV 13 2000



TO: APPLICANT; Barr Laboratories, Inc.

TEL: (914) 362-1100

ATTN: Christine Mundkur

FAX: (944) 353-3859 (\$45) PROJECT MANAGER: 301-827-5848

FROM: Michelle Dillahunt

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 Methrotrexate 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 habeling Comments Included.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

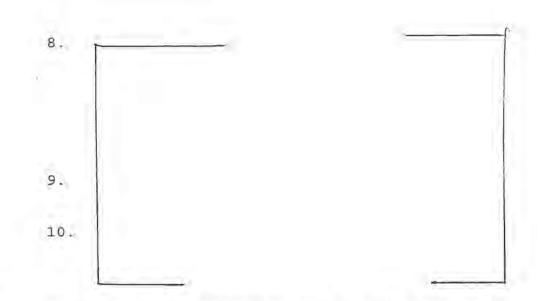
It received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, discentination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

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information from 11/13/2000 FDA FAX



- B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:
 - 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

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

January 12, 2001

ORIG AMENDMENT

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

Office of Generic Drugs

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:



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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 ' –

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 ____

--- 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/m²). 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 TrexallTM 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 TrexallTM 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 TrexallTM with the previously submitted draft labeling for TrexallTM 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.

unt

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.

Mundle

Christine Mundkur Vice President, Quality and Regulatory Counsel Barr Laboratories, Inc.

Jan. 12, 2001

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

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/m²). 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.



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.

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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 26 2001



TO: APPLICANT: Barr Laboratories, Inc.

ATTN: Christine Mundkur

FROM: Michelle Dillahunt

TEL: (845) 362-1100 FAX: (845) 353-3859 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 (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:

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

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FEB 6 ANI

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:

٦

2,

Sincerely yours,

Paul - Sureof

Rashmikant^M. Patel, Ph.D. Director Division of Chemistry I Office of Generic Drugs Center for Drug Evaluation and Research



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
		Phone Number:	(913) 353-8476
From:	Sharif Ahmed Manager of Regulatory Affairs	Fax Number:	(914) 353-3859
	of Pages 9 ng cover):		

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

The information contained in this facsimile message is privileged and confidential information intended The information contained in this facsimile is privileged and confidential information intended only for the use of the individual or entity numed above. If the reader of this message is not the intended recipient, or the employee or agent responsible to deliver it to the intended recipient, you are hereby notified that any dissemination, distribution or copying of this communication is strictly prohibited.

If you have received this communication in error, please immediately notify us by telephone, and return the original message to us at the above address via the U.S. Postal Service, Thank You.

Verification Name/Number:

Ples advise them it is policy to require full term data if accelerated show adverse trends. By they still want TCon, sit up for rack 100513 for want TCon, sit up for rack 100513 for

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

February 15, 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 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:

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 2 page(s)

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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.

Date

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

tea dins 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:



RESPONSE:

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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 Agence comment 7.

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2/22/2001 BARR LETTER

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^{\rm IM} 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

- 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/m² 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)

FULL PRESCRIBING INFORMATION: CONTENTS* WARNING: SEVERE TOXIC REACTIONS, INCLUDING EMBRYO-FETAL TOXICITY AND DEATH

1 INDICATIONS AND USAGE

1.1 Rheumatoid Arthritis including Polyarticular Juvenile Idiopathic Arthritis

- 1.2 Psoriasis
- 1.3 Limitation of Use

2 DOSAGE AND ADMINISTRATION

- 2.1 Important Dosing Information 2.2 Rheumatoid Arthritis including Polyarticular Juvenile Idiopathic
- Arthritis
- 2.3 Psoriasis
- 2.4 Administration and Handling

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

-----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)

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 FDAapproved patient labeling.

Revised: 11/2014

5 WARNINGS AND PRECAUTIONS

- 5.1 Organ System Toxicity
- 5.2 Embryo-Fetal Toxicity
- 5.3 Effects on Reproduction
- 5.4 Laboratory Tests
- 5.5 Risks from Improper Dosing
- 5.6 Patients with Impaired Renal Function, Ascites, or Pleural Effusions
- 5.7 Dizziness and Fatigue
- 5.8 Malignant Lymphomas
- 5.9 Tumor Lysis Syndrome
- 5.10 Concomitant Radiation Therapy
- 6 ADVERSE REACTIONS
 - 6.1 Clinical Trials Experience 6.2 Other Adverse Reactions
- 7 DRUG INTERACTIONS

7.1 Aspirin, Nonsteroidal Anti-Inflammatory Drugs, and Steroids

7.2 Proton Pump Inhibitors (PPIs)
7.3 Oral Antibiotics
7.4 Hepatotoxins
7.5 Theophylline
7.6 Folic Acid and Antifolates
7.7 Mercaptopurine
7.8 Other Drugs
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mothers
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8.6 Females and Males of Reproductive Potential
8.7 Renal Impairment

8.8 Hepatic Impairment 10 OVERDOSAGE **11 DESCRIPTION** 12 CLINICAL PHARMACOLOGY 12.1 Mechanism of Action 12.2 Pharmacodynamics 12.3 Pharmacokinetics 13 NONCLINICAL TOXICOLOGY 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility 14 CLINICAL STUDIES 14.1 Rheumatoid Arthritis 14.2 Polyarticular Juvenile Idiopathic Arthritis 15 REFERENCES 16 HOW SUPPLIED/STORAGE AND HANDLING 17 PATIENT COUNSELING INFORMATION *Sections or subsections omitted from the full prescribing information are not listed

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/m²/wk in children, there are too few published data to assess how doses over 20 mg/m²/wk might affect the risk of serious toxicity in children. Experience does suggest, however, that children receiving 20 to 30 mg/m²/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 drugs¹.

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)].

<u>Preexisting Blood Dyscrasias</u>

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/mm³) was seen in 2 patients, thrombocytopenia (platelets <100,000/mm³) 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/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, 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/mm³).

Incidence 1% to 3%: Rash/pruritis/dermatitis, diarrhea, alopecia, leukopenia (WBC less than 3000/mm³), 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/m²/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/m²/wk in pJIA, the published data for doses above 20 mg/m²/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.

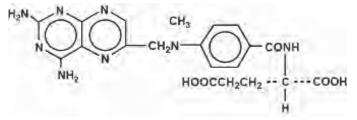
Symptoms of intrathecal overdose are generally central nervous system (CNS) symptoms, including headache, nausea and vomiting, seizure or convulsion, and acute toxic encephalopathy. In some cases, no symptoms were reported. There have been reports of death following intrathecal overdose. In these cases,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



M.W. = 454.45

 $C_{20}H_{22}N_8O_5$

Otrexup contains methotrexate in a sterile, preservative-free, unbuffered solution with a 27 gauge ¹/₂ 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/m² 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/m² dose) and fraction of dose absorbed. The absorption of doses greater than 40 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 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/m²/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/m²). 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/m²), or for JIA (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 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/m²/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 selfadminister 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 Otrexup™ is subject of US Patent Nos. RE44,846, 8,021,335, 6,746,429, RE44,847, 8,480,631, 8,562,564 and 8,579,865.

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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:

o gastrointestinal	o nerve
o bone marrow	o lung
o liver	o kidneys
o immune system	o 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:

o vomiting	o neck stiffness
o diarrhea	o paralysis
o mouth sores	o irritability
o fever	o sleepiness
o confusion	o problems with
o weakness	coordination
o temporary blindness	o dry cough
o seizures	o trouble breathing
o headache	o severe skin rash
o back pain	

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 FDAcleared 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 ©2014 Antares Pharma, Inc., Ewing, NJ 08628

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