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

6. Diarrhea and ulcerative stomatitis require interruption of therapy; otherwise, hemor-
hagic 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 metho-
trexate and, thus, may not require cyto-
toxic 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 hematologic measures may prevent or alleviate this complication.

9. Severe, occasionally fatal, skin reactions have been reported following single or 
multiple doses of methotrexate. Reac-
tions 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 pulmonary pneumo-
nia, 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 antime-
tabolite used in the treatment of certain neoplastic diseases, severe psoriasis, and adult rheumatoid arthritis.

Chemically, methotrexate is \( \text{H}_\text{N}[-\text{[L-2,4-diamino-6-pteridinyl]} \text{methyl][methylamino][benzoyl]}\text{L-gluta-
tamic acid.}

The structural formula is:

\[
\text{C}_{20}\text{H}_{22}\text{N}_8\text{O}_5
\]

CLINICAL PHARMACOLOGY:
Methotrexate inhibits dihydrofolate reductase. Dihydrofolates must be reduced to tetrahydrofo-
lates by this enzyme before they can be utilized as carriers of one-carbon units in the synthesis of purine nucleotides and thymidylate. Therefor-
e, methotrexate interferes with DNA synthe-
sis, repair, and cellular replication. Actively pro-
liferating 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 pro-
duction. Other laboratories have confirmed 
unusual demineralization effects. Clarification 
of methotrexate toxicity and its relation to 
rheumatoid immunopathogenesis awaits 
more 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 
chronic arthritis or inflammation (pain, swelling, stiffness), there is no evidence that it induces remission of rheumatoid 
arthritis nor has a beneficial effect been demon-
strated on bone erosions and other radiologic changes which result in impaired joint use, func-
tional 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 indi-
icate 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 proliferative 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 primary osteosarcoma or metastatic osteosarcoma. The original rationale for high-dose methotrexate treatment was on the concept of selective rescue of normal tissue cells by leucovorin. More recent evidence suggests that high-dose methotrexate alone can also induce marked resistance caused by impaired active transport, decreased affinity of dihydrofolic acid reductase for the drug, and increased levels of dihydrofolic acid reductase resulting from gene amplification, or decreased polyglutamation of methotrexate. The complete success of this approach is unknown.

In a 6-month double-blind, placebo-controlled trial in patients with juvenile rheumatoid arthritis (JRA) (mean age, 10.1; range, 2.5 to 18; years; mean duration of disease, 5.1; years; 102 patients), no difference in outcome was found between patients who received methotrexate and patients who received placebo. A significant clinical improvement compared to placebo as measured by either the physician's or the parent's evaluation involved approximately 40% to 50% of the patients in each group, which was not statistically significant. Although the small sample size of this study may affect the results, the conclusion of this study is that methotrexate may be effective in a subgroup of patients with juvenile rheumatoid arthritis where disease progression is not controlled with conventional treatment.

Methotrexate has been shown in clinical studies to be effective in the treatment of non-metastatic osteosarcoma, when high-dose methotrexate with leucovorin rescue was used in conjunction with other chemotherapeutic agents following surgical resection of the primary tumor. These agents have been designed to block the specific contribution of high-dose methotrexate to the efficacy of the drug. However, a contribution can be inferred from the reports of objective responses to this therapy in patients with metastatic osteosarcoma who had extensive disease. Methotrexate has been used in conjunction with other chemotherapeutic agents and bone marrow transplantation in the treatment of osteosarcoma. For example, patients (see PRECAUTIONS). In patients with metastatic osteosarcoma, the disease is often progressive and the benefit of salvage methotrexate therapy is not clear. However, the use of this agent in this setting has been reported in clinical studies to improve survival rates.

Pharmacokinetics

Absorption

In adults, oral absorption appears to be dose dependent. Peak serum levels are reached within one hour. At doses of 30 mg/m² or less, methotrexate is generally well absorbed with a mean bioavailability of about 60% The absorption of oral methotrexate is decreased in patients with inflammatory bowel disease and in patients with bone marrow depression from other chemotherapy. The absorption of oral methotrexate is decreased in patients with inflammatory bowel disease and in patients with bone marrow depression from other chemotherapy.

Dosing

Methotrexate is generally administered orally once daily. The dose should be adjusted to achieve adequate serum concentrations, which are usually transient and asymptomatic, and elevations are frequently seen. These are usually transient and asymptomatic, and elevations are frequently seen. These are not be preceded by symptoms or abnormalities. The dose may be increased slowly as tolerated by the patient. The dose should be reduced or the interval between doses increased when hematopoietic (granulocytic, platelet, and thrombocytic) toxicity develops, or when there is evidence of fibrosis or cirrhosis in the rheumatoid arthritis population.

Organ System Toxicity

In adults, renal abnormalities have usually included concurrent use of constant aspirin, (NSAIDs), and/or low-dose steroids may be necessary in patients receiving low-dose methotrexate due to impaired active transport. Decreased affinity of dihydrofolic acid reductase for the drug, and increased levels of dihydrofolic acid reductase resulting from gene amplification, or decreased polyglutamation of methotrexate. The complete success of this approach is unknown.

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Methotrexate is partially bound to serum albumin, and toxicity may be increased by displacement from protein binding sites as with salicylates, phenytoin, phenobarbital, and sulfonamides. Renal tubular transport is also diminished by pro- benicid; use of probenicid with this drug should be carefully monitored.

In the treatment of patients with osteoarthritis, caution must be exercised if high-dose methotre- xate is administered in combination with a poten- tially nephrotoxic chemotherapeutic agent (e.g., cisplatin).

Methotrexate increases the plasma levels of mercaptopurine and 6-mercaptopurineurine. Thus, mercaptopurine and 6-mercaptopurine may therefore require dose adjustment.

Oral antineoplastic agents such as tetracycline, chloramphenicol, and nonabsorbable broad spectrum antibiotics, can interfere with or diminish absorption of methotrexate or interfere with the enterohepatic circulation by inhibiting bowel flora and suppress- ing metabolism. Use of these agents in combination with methotrexate or folate metabolites should be carefully monitored for possible increased risk of hepatotoxicity.

Methotrexate may decrease the clearance of theophylline; theophylline levels should be moni- tored when theophylline is administered in combina- tion with methotrexate.

Vitamin preparations containing folic acid or its derivatives may decrease responses to sys- temically administered methotrexate. Preliminary animal and human studies have shown that small quantities of intravenously-administered leucovorin can reverse the CSF primarily as 5-methyltetrahydrofolate and, in humans, remain 1 to 3 orders of magnitude lower than the parent drug concentrations following intrathecally administered drug. Higher doses of leucovorin may reduce the efficacy of intrathecally administered methotrexate.

Folate deficiency states may increase metho- trexate toxicity. Improved response to methotrexate has been reported rarely to increase bone marrow suppression in patients receiving methotrexate, probably by decreasing the 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 limited number of clinical studies for carcinogenic potential with inconclusive results. Although there is evidence that methotrexate causes chromosome breaks in animal somatic cells and human bone marrow cells, the clinical significance remains uncertain. Non-Hodgkin’s lymphoma has been reported in patients receiving low-dose oral methotrexate. However, the incidence of myeloma, lymphoma arising during treatment with low-dose oral methotrexate, which have regressed com- pletely following withdrawal of methotrexate, not requiring active anti-lymphoma treat- ment. 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. Methotre- xate causes embryotoxicity, abortion, aneuploidy, and fetal defects in humans. It has also been reported to cause impaired spermatogenesis 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 CONTRAINDI- CATIONS).

Nursing Mothers See CONTRAINDICATIONS.

Pediatric Use

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

Pediatric studies evaluating the use of methotrexate in children and adolescents (i.e., patients 2 to 16 years of age) with JRA demonstrated to be very similar to that observed in adults with rheumatoid arthritis (see CLINICAL PHARMACOLOGY: CLINICAL PHARMACOLOGY: EFFECTS ON IMMUNITY AND IMMUNOSUPPRESSION; DOSAGE AND ADMINISTRATION).

Methotrexate injectable formulations containing the preservative benzyl alcohol are not recom- mended for use in neonates. There have been reports of fetal ‘gassing syndrome’ in neonates (children less than one month of age) following the administrations of intravenous methotrexate, the preservative benzyl alcohol. Symptoms include a striking onset of gasping respiration, hypoten- sion, bradycardia, and cyanosis.

Serious neurotoxicity, frequently manifested as generalized or focal seizures, has been reported with unexpected increased frequency of seizures in pediatric patients with acute lymphoblastic leukemia who were treated with a single low-dose intravenous methotrexate (1 g/m²) (see PRE- CAUTIONS, Organ System Toxicity, Neurologic).
or cirrhosis in this population. There is a combined reported experience in 217 rheumatoid arthritis patients, where 74 patients both below 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 cirrhosis and 0.1% cases of cirrhosis. Of the 64 cases of fibrotic changes, 10 were secondary. The relative stain is more sensitive for early fibrosis and its use may increase these figures. It is unknown whether even long-term survivors are free of hepatic injury.

Liver function tests should be performed at baseline and after 8 weeks in patients receiving 1 gm/m2. Liver biopsy should be performed for patients with worsening alcohol consumption, persistently abnormal baseline liver function test values or chronic hepatitis B or C infection. During therapy, liver function tests should be performed if there are persistent liver function test abnormalities or there is a decrease in serum albumin below the normal range (the setting of well-controlled rheumatoid arthritis).

If the results of a liver biopsy show mild changes (Reye's syndrome), liver function tests should be continued in any patient who displays persistently abnormal liver function tests and refuses liver biopsy. A continuation of liver biopsy should show marked to severe changes (Roenigk grade I/II).

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 autoimmune or viral states. Immunosuppression may be ineffective when given during methotrexate therapy. Immune responses to multiple viral infections and patients receiving methotrexate therapy. Hypogammaglobulinemia has been reported rarely. Methotrexate-induced opportunistic infections, especially Pneumocystis carinii pneumonia, may occur with methotrexate therapy. When a patient presents with new or unusual symptoms, the possibility of Pneumocystis carinii pneumonia should be considered.

Neurologic
There have been reports of leukoencephalopathy following intravenous administration of methotrexate to those who have had cranial irradiation. Serious neurotoxicity, frequently manifested as generalized or focal seizures, has been reported with unexpectedly increased frequency among pediatric patients with acute lymphocytic leukemia who were treated with intermediate-dose intravenous methotrexate (1 gm/m2). Symptomatic patients were commonly receiving methotrexate therapy. Hypogammaglobulinemia has been reported rarely. Methotrexate should be used with extreme caution in the presence of active infection (e.g., plague eruptions or ascites). These results in a prolonged terminal plasma half-life and increased toxicity. In patients with significant third space accumulations, it is advisable to evacuate the fluid compartment 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 
Infections and Severe and Acute Side Effects are Related to Dose and Frequency of Administration. The Adverse Reactions are Discussed Above Under Organ System Toxicity (except for Cytopenias). That Section Should Also Be Consulted When Looking for Information About Adverse Reactions with Methotrexate.

The most frequently reported adverse reactions include urologic disturbances (hesitancy, frequency, pain), nausea, and abdominal distress. Other frequently reported adverse effects are malaise, undue fatigue, chills and fever, diarrhea, and prodromal signs and symptoms of infection. Other adverse reactions that have been reported with methotrexate are listed below by organ system.

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

Blood and Lymphatic System Disorders: suppression of hematopoiesis, anemia, aplastic anemia, pancytopenia, leukopenia, neutropenia, thrombocytopenia, agranulocytosis, eosinophilia, lymphadenopathy and lymphoproliferative disorders (including respiratory papillomatosis and hypogammaglobulinemia) has been reported rarely.

Cardiovascular: pericarditis, pericardial effusion, hypotension, and severe cardiovascular events (including arterial thrombosis, cerebral thrombosis, deep vein thrombosis, stroke, thrombophlebitis, and pulmonary embolism).

Central Nervous System: headaches, drowsiness, blurred vision, blindness, speech disturbances, headache, vomiting, convulsion, and acute toxic encephalopathy. In one study of 248 patients with psoriasis treated with methotrexate, dosages ranged up to 25 mg per week and the drug was continued for up to 4 years. With the exception of alopecia and dermatitis, the frequency of adverse reactions was low (each 3% to 10%). The adverse reaction rates in these reports were very similar to those in the controlled trials. A rare central nervous system reaction (headache, drowsiness, or convulsions) that appears to be toxic in nature may occur and may be prolonged.

ADVERSE REACTIONS IN JRA Studies
There are no recent placebo-controlled trials in patients with psoriasis. There are two literature reports (Roenigk, 1969, and Nyfors, 1975) describing large series (n = 204, 248) of psoriasis patients treated with methotrexate. Dosages ranged up to 25 mg per week and the drug was continued for up to 4 years. With the exception of alopecia and dermatitis, the frequency of adverse reactions was low (each 3% to 10%). The adverse reaction rates in these reports were very similar to those in the controlled trials. A rare central nervous system reaction (headache, drowsiness, or convulsions) that appears to be toxic in nature may occur and may be prolonged.

OVERDOSAGE: Leucovorin is indicated to diminish the toxicity and counteract the effect of inadvertently administered overdoses of methotrexate. Leucovorin administration may be indicated after the patient is asymptomatic, but may be necessary. Atropine has been used to counteract hyperventilation. Atropine is a frequently used antidote for methotrexate toxicity and may be effective in reducing methotrexate levels. However, the use of atropine in the treatment of methotrexate toxicity is controversial. Leucovorin has been shown to be effective in reducing methotrexate levels. However, the use of atropine in the treatment of methotrexate toxicity is controversial.

In case of massive overdosage, hydration and urinary alkalization may be necessary to prevent the precipitation of methotrexate and/or its metabolites in the renal tubules. Although toxicity may be diminished, neither hemodialysis nor peritoneal dialysis has been shown to improve methotrexate elimination. However, effective clearance has been reported with acute, intermittent hemodialysis using a high-flux dialyzer. The most critical factor in determining the optimal dose and duration of treatment with leucovorin. In case of massive overdosage, hydration and urinary alkalization may be necessary to prevent the precipitation of methotrexate and/or its metabolites in the renal tubules. Although toxicity may be diminished, neither hemodialysis nor peritoneal dialysis has been shown to improve methotrexate elimination. However, effective clearance has been reported with acute, intermittent hemodialysis using a high-flux dialyzer. The most critical factor in determining the optimal dose and duration of treatment with leucovorin. In case of massive overdosage, hydration and urinary alkalization may be necessary to prevent the precipitation of methotrexate and/or its metabolites in the renal tubules. Although toxicity may be diminished, neither hemodialysis nor peritoneal dialysis has been shown to improve methotrexate elimination. However, effective clearance has been reported with acute, intermittent hemodialysis using a high-flux dialyzer. The most critical factor in determining the optimal dose and duration of treatment with leucovorin. In case of massive overdosage, hydration and urinary alkalization may be necessary to prevent the precipitation of methotrexate and/or its metabolites in the renal tubules. Although toxicity may be diminished, neither hemodialysis nor peritoneal dialysis has been shown to improve methotrexate elimination. However, effective clearance has been reported with acute, intermittent hemodialysis using a high-flux dialyzer. The most critical factor in determining the optimal dose and duration of treatment with leucovorin.
Reports of oral overdose often indicate accidental daily administration instead of repeated (single or divided) doses. Patients commonly report that following oral overdose include those symptoms and side effects that are the same as those following intramuscular or intravenous injection. However, important factors in the management of oral overdose include the presence of active infection and the need to exclude any possible drug interaction (including pneumonia) needs to be excluded. Synergism of immunodeficiency syndromes.

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

**AGE (years)**

<table>
<thead>
<tr>
<th>MEASURE</th>
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<tr>
<td>&lt; 1</td>
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<tr>
<td>1 to 2</td>
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<td>3 or older</td>
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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. In patients with acute lymphocytic leukemia, the dosage was 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 intrathoracic injection and are commonly neurological in character. Large doses may cause convulsions. Methotrexate given by the intrathoracic 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 intrathoracic 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 usually consists of several courses of the drug interposed with 7 to 10 day rest periods. In Stages III and IV, methotrexate 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 10 mg/m^2 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 use of several cytotoxic chemotherapeutic agents. In addition to high-dose methotrexate for rescue, these agents may include doxorubicin, cisplatin, and the combination of bleomycin, cyclophosphamide and dacarbazine (BCD) in the doses and schedule shown in the table below. The starting dose for high-dose methotrexate treatment is 12 grams/m^2. If this dose is not sufficient to produce a peak serum methotrexate concentration of 1.0 micromolar (10^-6 M) at the end of the methotrexate infusion, the dose may be escalated to 15 grams/m^2 in subsequent treatments.

If the patient is vomiting or unable to tolerate oral medication, leucovorin is given IV at the dose and schedule.
hours (total 14 doses over 84 hours) in subsequent courses of therapy. The possibility that the patient is taking other medications which interact with methotrexate (e.g., medications which may interfere with methotrexate binding to serum albumin, or elimination) should always be reconsidered when laboratory abnormalities or clinical toxicities are observed.

CAUTION: DO NOT ADMINISTER LEUCOVORIN INTRATHECALLY.

Psoriasis, Rheumatoid Arthritis, and Juvenile Rheumatoid Arthritis

Adult Rheumatoid Arthritis

Recommended Starting Dosage Schedules
1. Single oral doses of 7.5 mg once weekly.
2. Divided oral dosages of 2.5 mg at 12 hour intervals for 3 doses given as a course once weekly.

*Methotrexate Sodium Tablets for oral administration are available.

Polyarticular-Course Juvenile Rheumatoid Arthritis

The recommended starting dose is 10 mg/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 depression, 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 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 hemoglobin, hepatic, renal, and pulmonary function should be made by history, physical examination, and laboratory tests before beginning, periodically during, and before reinitiating methotrexate therapy (see PRECAUTIONS). Appropriate steps should be taken to avoid conception during methotrexate therapy (see PRECAUTIONS and CONTRAINDICATIONS).

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

Psoriasis

Recommended Starting Dose Schedule
1. Weekly single oral, IM or IV dosage schedule: 10 to 25 mg per week until adequate response is achieved.
2. Divided oral dosage 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. 1-3 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.

<table>
<thead>
<tr>
<th>Clinical Situation</th>
<th>Laboratory Findings</th>
<th>Leucovorin Dosage and Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Methotrexate Elimination</td>
<td>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</td>
<td>15 mg PO, IM, or IV q 6 hours for 60 hours (10 doses starting at 24 hours after start of methotrexate infusion).</td>
</tr>
<tr>
<td>Delayed Late Methotrexate Elimination</td>
<td>Serum methotrexate level remaining above 0.2 micromolar at 72 hours, and more than 0.05 micromolar at 96 hours after administration.</td>
<td>Continue 15 mg PO, IM, or IV q 6 hours, until methotrexate level is less than 0.05 micromolar.</td>
</tr>
<tr>
<td>Delayed Early Methotrexate Elimination and/or Evidence of Acute Renal Injury</td>
<td>Serum methotrexate level of 50 micromolar or more at 24 hours, or 5 micromolar or more at 48 hours after administration. DR, 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).</td>
<td>150 mg IV q 3 hours, until methotrexate level is less than 1 micromolar, then 15 mg IV q 3 hours, until methotrexate level is less than 0.05 micromolar.</td>
</tr>
</tbody>
</table>

HOW SUPPLIED:

Parenteral

Methotrexate Injection, USP, Isotonic Liquid, Contains Preservative

Each mL contains methotrexate sodium equivalent to 25 mg methotrexate.

Product

<table>
<thead>
<tr>
<th>NDC</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>102302</td>
<td>63323-123-02</td>
</tr>
<tr>
<td>102310</td>
<td>63323-123-10</td>
</tr>
</tbody>
</table>

2 mL - 50 mg
10 mL - 250 mg

Store at controlled room temperature, 20° to 25°C (68° to 77°F). Protect from freezing. Protect from light.

This container closure is not made with natural rubber latex.

REFERENCES:

4. National Study Commission on Cytoxic Exposure–Recommendations for Handling Cytoxic Agents. Available from Dr. P. Jeffrey, Sc.D., Chairman, National Study Commission on Cytoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.