Methotrexate Tablets, USP

WARNINGS

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

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

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

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

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

1. Methotrexate has been reported to cause fetal death and/or congenital anomalies. Therefore, it is not recommended for women of childbearing

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

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.

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

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

xate has been detected in human breast milk. The highest breast milk to oncentration ratio reached was 0.08:1.

ONS AND USAGE

ic Diseases

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

xate is used in maintenance therapy in combination with other erapeutic agents.

xate is used alone or in combination with other anticancer agents in the t of breast cancer, epidermoid cancers of the head and neck, advanced fungoides (cutaneous T cell lymphoma), and lung cancer, particularly s cell and small cell types. Methotrexate is also used in combination with motherapeutic agents in the treatment of advanced stage non-Hodgkin's as.

s

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

toid Arthritis including Polyarticular-Course Juvenile Rheumatoid

xate is indicated in the management of selected adults with severe, active, id arthritis (ACR criteria), or children with active polyarticular-course heumatoid arthritis, who have had an insufficient therapeutic response to, olerant of, an adequate trial of first-line therapy including full dose non-anti-inflammatory agents (NSAIDs).

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

INDICATIONS

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

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

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

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

with psoriasis or rheumatoid arthritis who have preexisting blood s, 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.

Information for Patients

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

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

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

Laboratory Tests

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

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

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

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

Drug Interactions

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

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

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

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

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

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

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

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

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

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

The use of nitrous oxide anesthesia potentiates the effect of methotrexate on folate-dependent metabolic pathways, resulting in the potential for increased toxicity such as stomatitis, myelosuppression, and neurotoxicity. Avoid concomitant nitrous oxide anesthesia in patients receiving methotrexate. Use caution when administering methotrexate after a recent history of nitrous oxide administration.

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 (ie, patients 2 to 16 years of age) with JRA demonstrated safety comparable to that observed in adults with rheumatoid arthritis. (See **CLINICAL PHARMACOLOGY, ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**.)

Geriatric Use

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

Organ System Toxicity

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

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

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

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

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

In rheumatoid arthritis, age at first use of methotrexate and duration of therapy

have been reported as risk factors for hepatotoxicity; other risk factors, similar to those observed in psoriasis, may be present in rheumatoid arthritis but have not been confirmed to date. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in this population. There is a combined reported experience in 217 rheumatoid arthritis patients with liver biopsies both before and

encephalopathy.

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

Infection: There have been case reports of sometimes fatal opportunistic infections

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

DOSAGE AND ADMINISTRATION

Neoplastic Diseases

often preferred when low doses are being l and effective serum levels are obtained.

lastic diseases: Methotrexate is administered l 5 to 30 mg daily for a five-day course. Such 5 times as required, with rest periods of one ourses, until any manifesting toxic symptoms is ordinarily evaluated by 24 hour quantitative opin (hCG), which should return to normal or third or fourth course and usually be followed le lesions in 4 to 6 weeks. One to two courses f hCG is usually recommended. Before each assessment is essential. Cyclic combination antitumor drugs has been reported as being

choriocarcinoma, prophylactic chemotherapy nded.

red to be an invasive form of hydatidiform these disease states in doses similar to those

ukemia in pediatric patients and young present day chemotherapy. In young adults is more difficult to obtain and early relapse is

with steroids was used initially for induction ukemias. More recently corticosteroid therapy, emic drugs or in cyclic combinations with l to produce rapid and effective remissions. in doses of 3.3 mg/m^2 in combination with 60 duced remissions in 50% of patients treated, eks. Methotrexate in combination with other ce for securing maintenance of drug-induced ed and supportive care has produced general erapy is initiated, as follows: Methotrexate is by mouth or intramuscularly in total weekly ven in doses of 2.5 mg/kg intravenously every cur, reinduction of remission can again usually luction regimen.

y regimens have been used for both induction phoblastic leukemia. The physician should be leukemic therapy.

es I-II, methotrexate has produced prolonged nded dosage is 10 to 25 mg/day orally for 4 is commonly given concomitantly with other tages usually consists of several courses of y rest periods. Lymphosarcomas in Stage III py with methotrexate given in doses of 0.625

ell lymphoma): Therapy with methotrexate clinical responses in up to 50% of patients lly 5 to 50 mg once weekly. Dose reduction or se and hematologic monitoring. Methotrexate ekly in doses ranging from 15 to 37.5 mg in weekly therapy.

l Juvenile Rheumatoid Arthritis

nded Starting Dosage Schedules

ce weekly.

g at 12 hour intervals for 3 doses given as a

toid Arthritis: The recommended starting dose

urse JRA dosages may be adjusted gradually ited experience shows a significant increase ous toxic reactions, especially bone marrow mg/wk in adults. Although there is experience ren, there are too few published data to assess affect the risk of serious toxicity in children. that children receiving 20 to 30 mg/m^2/wk ter absorption and fewer gastrointestinal side l either intramuscularly or subcutaneously.

within 3 to 6 weeks and the patient may eks or more.

known. Limited data available from long-term tial clinical improvement is maintained for at py. When methotrexate is discontinued, the weeks.

f of the risks involved and should be under ian. (See **Information for Patients** under matologic, hepatic, renal, and pulmonary , physical examination, and laboratory tests and before reinstituting methotrexate therapy. s should be taken to avoid conception during **IONS** and **CONTRAINDICATIONS**.)

tailored to the individual patient. An initial he regular dosing schedule to detect any extreme sensitivity to adverse effects. (See **ADVERSE REACTIONS**.) Maximal myelosuppression usually occurs in seven to ten days.

Psoriasis: Recommended Starting Dose Schedules

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

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

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

HANDLING AND DISPOSAL

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

HOW SUPPLIED

Oral:

Description

Methotrexate Tablets, USP contain an amount of methotrexate sodium equivalent to 2.5 mg of methotrexate and are round, convex, yellow tablets, scored in half on one side, engraved with M above the score, and 1 below.

NDC 67253-320-36 - bottle of 36 count

NDC 67253-320-10 - bottle of 100 count

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

REFERENCES

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4. Jones RB, et al. Safe handling of chemotherapeutic agents: A report from the Mount Sinai Medical Center. CA - *A Cancer Journal for Clinicians* Sept/Oct 1983; 258-263.
5. American Society of Hospital Pharmacists technical assistance bulletin on handling cytotoxic and hazardous drugs. *Am J Hosp Pharm* 1990; 47:1033-1049.

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