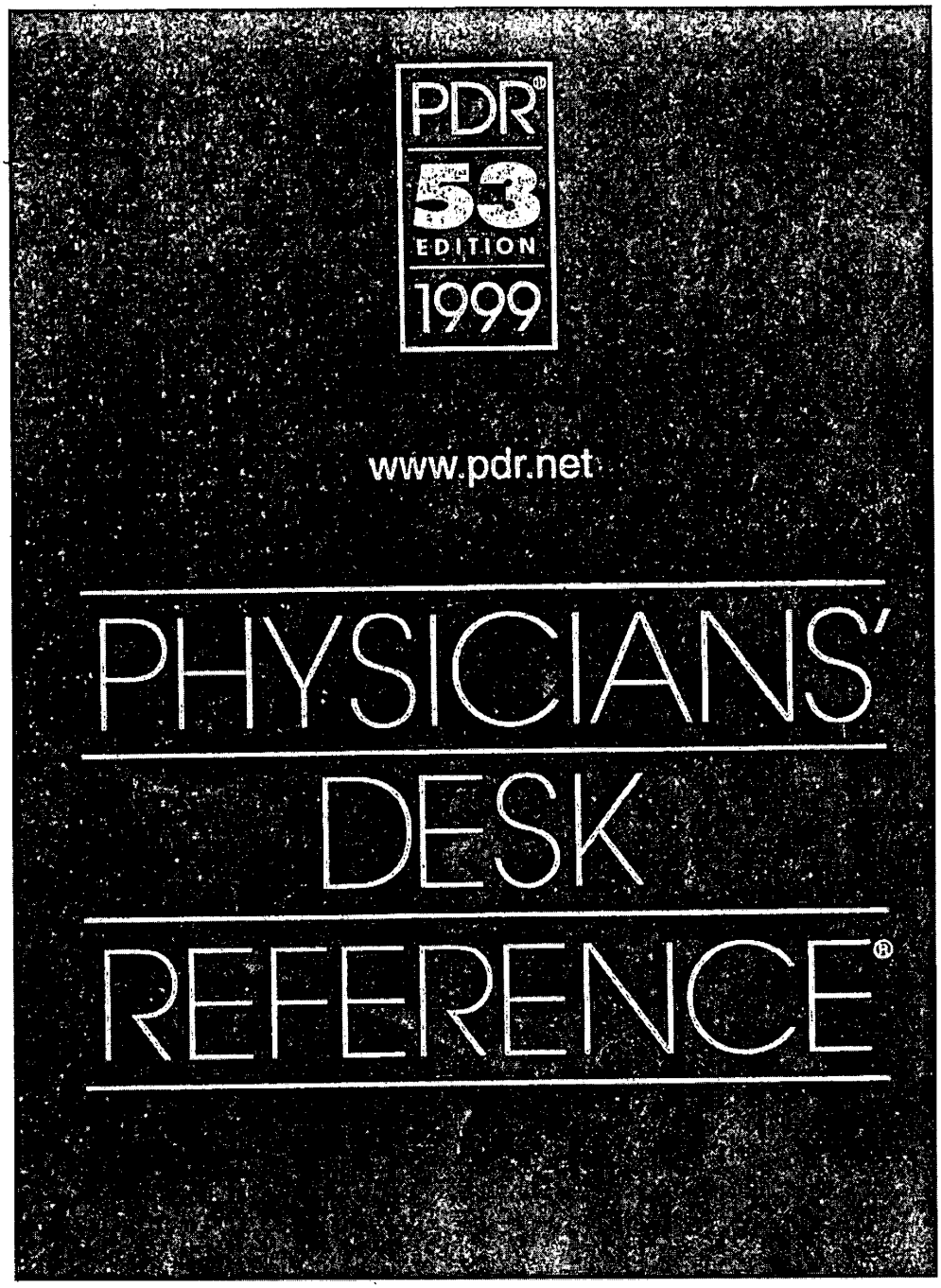

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PHYSICIANS' DESK REFERENCE®

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METHOTREXATE SODIUM TABLETS ℞
METHOTREXATE SODIUM FOR INJECTION ℞
METHOTREXATE LPF® SODIUM ℞
(METHOTREXATE Sodium Injection) and
METHOTREXATE SODIUM INJECTION ℞

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.

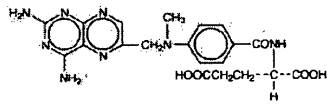
METHOTREXATE FORMULATIONS AND DILUENTS CONTAINING PRESERVATIVES MUST NOT BE USED FOR INTRATHECAL OR HIGH DOSE METHOTREXATE THERAPY.

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

DESCRIPTION

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

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



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

Methotrexate Sodium Tablets for oral administration are available in bottles of 100 and in a packaging system designated as the RHEUMATREX® Methotrexate Sodium Dose Pack for therapy with a weekly dosing schedule of 5 mg, 7.5 mg, 10 mg, 12.5 mg and 15 mg. Methotrexate Sodium Tablets contain an amount of methotrexate sodium equivalent to 2.5 mg of methotrexate and the following inactive ingredients: Lactose, Magnesium Stearate and Pregelatinized Starch. May also contain Corn Starch.

Methotrexate Sodium Injection and 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.**) However, the preservative formulation contains Benzyl Alcohol and must not be used for intrathecal or high dose therapy.

Methotrexate Sodium Injection, Isotonic Liquid, Contains Preservative is available in 25 mg/mL, 2 mL (50 mg) and 10 mL (250 mg) vials.

Each 25 mg/mL, 2 mL and 10 mL vial contains methotrexate sodium equivalent to 50 mg and 250 mg methotrexate respectively, 0.90% 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 LPF® Sodium (methotrexate sodium injection), Isotonic Liquid, Preservative Free, for single use only, is available in 25 mg/mL, 2 mL (50 mg), 4 mL (100 mg), 8 mL (200 mg) and 10 mL (250 mg) vials.

Each 25 mg/mL, 2 mL, 4 mL, 8 mL and 10 mL vial contains methotrexate sodium equivalent to 50 mg, 100 mg, 200 mg and 250 mg methotrexate respectively, and the following inactive ingredients: Sodium Chloride 0.490% 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. The 2 mL, 4 mL, 8 mL and 10 mL solutions contain approximately 0.43 mEq, 0.86 mEq, 1.72 mEq and 2.15 mEq of Sodium per vial, respectively, and are isotonic solutions.

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 necesary, 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. Dihydrololates 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.

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 to 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 has been reported to vary widely (23% to 95%). A twenty fold difference between highest and lowest peak levels (C_{max}: 0.11 to 2.3 micromolar after a 20 mg/m^2 dose) has been reported. Significant interindividual variability has also been noted in time to peak concentration (T_{max}: 0.67 to 4 hrs after a 15 mg/m^2 dose) and fraction of dose absorbed. Food has been shown to delay absorption and reduce peak concentration.

Continued on next page

Methotrexate Sodium—Cont.

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

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

Methotrexate does not penetrate the blood-cerebrospinal fluid barrier in therapeutic amounts when given 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 dihydrolase 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 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 0.08:1.

INDICATIONS AND USAGE

Neoplastic Diseases

Methotrexate is indicated in the treatment of gestational choriocarcinoma, chorioadenoma destruens and hydatidiform mole.

In acute lymphocytic leukemia, methotrexate is indicated in the prophylaxis of meningeal leukemia and is used in maintenance therapy in combination with other chemotherapeutic agents. Methotrexate is also indicated in the treatment of meningeal leukemia.

Methotrexate is used alone or in combination with other anticancer agents in the treatment of breast cancer, epidermoid cancers of the head and neck, advanced mycosis fungoides, and lung cancer, particularly squamous cell and small cell types. Methotrexate is also used in combination with other chemotherapeutic agents in the treatment of advanced stage non-Hodgkin's lymphomas.

Methotrexate in high doses followed by leucovorin rescue in combination with other chemotherapeutic agents is effective in prolonging relapse-free survival in patients with nonmetastatic 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

Methotrexate is indicated in the management of selected adults with severe, active, classical or definite rheumatoid arthritis (ARA criteria) who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of first-line therapy including full dose NSAIDs and usually a trial of at least one or more disease-modifying antirheumatic drugs.

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

CONTRAINDICATIONS

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

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

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

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

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

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

WARNINGS—SEE BOXED WARNINGS.

PRECAUTIONS

General

Methotrexate has the potential for serious toxicity. (See Boxed **WARNINGS.**) Toxic effects may be related in frequency and severity to dose or frequency of administration but have been seen at all doses. Because they can occur at any time during therapy, it is necessary to follow patients on methotrexate closely. Most adverse reactions are reversible if detected early. When such reactions do occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken. If necessary, this could include the use of leucovorin calcium. (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 Patients 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

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

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

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).

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

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

Patients receiving concomitant therapy with methotrexate and etretinate or other retinoids should be monitored closely for possible increased risk of hepatotoxicity.

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

Vitamin preparations containing folic acid or its derivatives may decrease responses to systemically administered methotrexate. Preliminary animal and human studies have shown that small quantities of intravenously administered

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