February 2012

Dear Healthcare Professional,

Due to the current critical shortage of Methotrexate Injection, USP 1g/40mL (25 mg/mL) (Preservative-Free) in the United States (US) market, Hospira, Inc. is coordinating with the Food and Drug Administration (FDA) to increase the availability of the drug.

To alleviate the shortage, Hospira, Inc. has initiated temporary importation into the US market of a non-US-approved product, Methotrexate Injection, USP 1g/40mL (25 mg/mL) (Preservative Free) from Hospira Healthcare Corporation, Canada. The Canadian-approved Methotrexate Injection, USP 1 g/40 mL (25 mg/mL) (Preservative-Free) contains the same active ingredient, methotrexate, in the same concentration as the US-approved Methotrexate Injection, USP 1 g/40 mL (25 mg/mL) (Preservative-Free). This product is a clinically acceptable substitute for the out of stock product in the United States.

The Methotrexate Injection, USP from Hospira Healthcare Corporation, Canada is manufactured by Hospira, Inc. in Mulgrave, Australia, at an FDA inspected facility which is currently in compliance with FDA manufacturing standards.

At this time, no other entity except Hospira, Inc. is authorized by the FDA to import or distribute a non-US approved Methotrexate Injection, USP. Hospira Healthcare Corporation, Canada has appointed Hospira, Inc., as their distributor of this product in the US. Any sales of Canadian Methotrexate Injection, USP flip top vials (DIN 02182971) from any entity other than Hospira Healthcare Corporation, Canada or their distributor, Hospira, Inc., will be considered a violation of the Federal Food, Drug and Cosmetic Act and will be subject to enforcement by the FDA.

It is important to note that there are substantive differences in the format and content of the labeling between the US-approved Methotrexate Injection, USP and the Canadian Methotrexate Injection, USP.

For full prescribing information, refer to the Methotrexate Injection, USP (Preservative-Free) US package insert as there are significant differences in information such as adverse events, boxed warnings, and preparation and administration instructions. A copy of the US package insert can be found attached to this communication.

Please note the differences in the container label and carton labeling:

US Approved Methotrexate	Canadian Methotrexate
"Each vial contains: Methotrexate Sodium equivalent to 1000 mg Methotrexate and Sodium Chloride 0.490% w/v. Sodium Hydroxide and Hydrochloric Acid may be used as pH adjusters."	**"**Each mL contains: Methotrexate sodium equivalent to 25 mg of methotrexate and sodium chloride 4.9 mg for isotonicity. Sodium hydroxide and hydrochloric acid added for pH adjustment."
"Single Dose Vial"	"Single-Puncture, Multiple-Dispensing, Pharmacy Bulk Vial"
,Store at controlled room temperature 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).	"Store between 15 and 25°C"

Additionally, please follow these guidelines when using the Canadian-approved Methotrexate Injection, USP:

- The barcode used for Methotrexate Injection, USP is an international pharmaceutical manufacturing code and may not be appropriately recognized by scanning systems used in the United States. Institutions should confirm that barcode systems do not provide incorrect information when the product is scanned.

- Follow instructions in the US package insert to ensure that the drug product is being correctly prepared and administered.
- For questions regarding Methotrexate Injection, USP (Preservative-Free) in the United States, please contact the Hospira customer services team at 1-877-946-7747 (Monday to Friday 7 AM to 6 PM CST).

Customers can order directly from Hospira, Inc. by contacting Customer Services at:

Tel: 1-877-946-7747
Fax: 1-262-577-6917

Canadian Methotrexate Injection, USP flip top vials (DIN 02182971) are not returnable and not for resale.

Hospira, Inc. will be making reasonable attempts to fill your orders. We will be closely monitoring the distribution of Methotrexate Injection, USP to help manage supply.

If you have any additional questions, please contact Customer Service at 1-877-946-7747, Monday-Friday 7 AM-6 PM. This communication and updated product information is available on the Hospira, Inc. website (www.hospira.com) as well as on the FDA Drug Shortage web site (http://www.fda.gov/Drugs/DrugSafety/DrugShortage/default.htm)

To report adverse events, please call Hospira at 1-800-441-4100. Adverse events that may be related to the use of this product may also be reported to FDA's MedWatch Adverse Event Reporting Program either online, by regular mail or by fax:

- Online: www.fda.gov/medwatch/report.htm
- Regular Mail: use postage-paid FDA form 3500 available at:
  www.fda.gov/MedWatch/getforms.htm
  Mail to MedWatch, FDA, 5600 Fishers Lane, Rockville, MD 20852-9787
- Fax: 1-800-FDA-0178

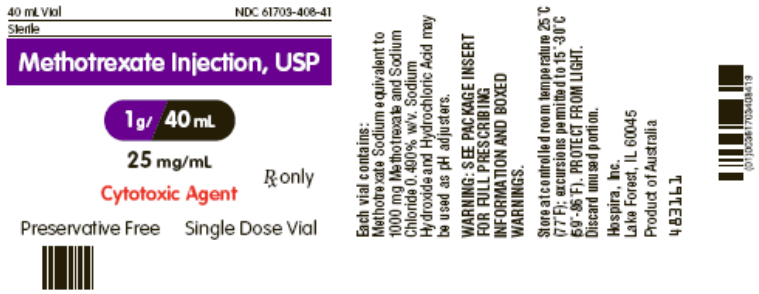
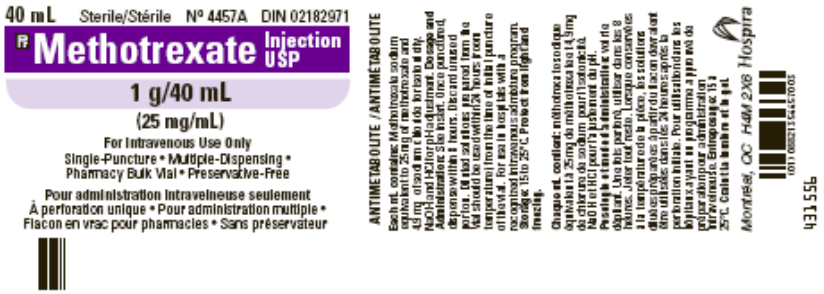
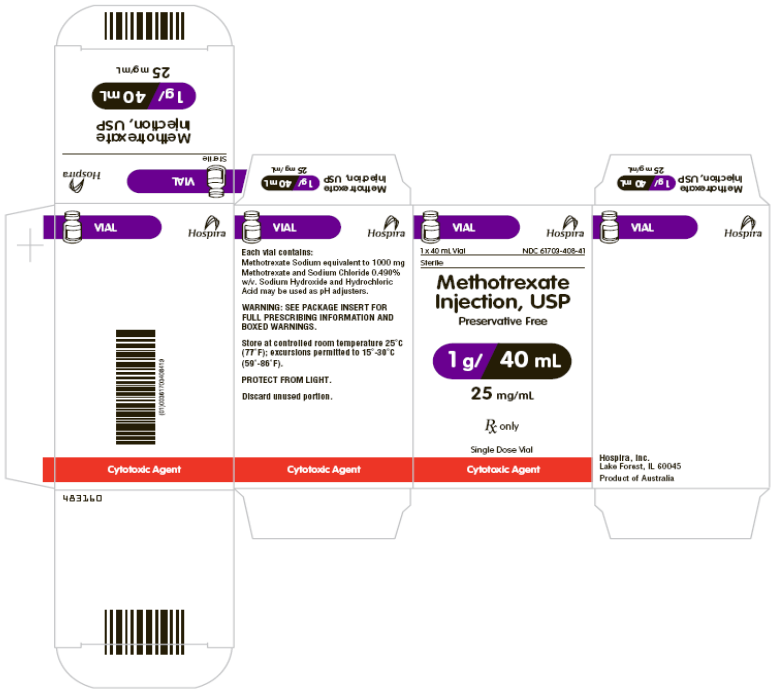
Please contact the Medical Information Department at 1-800-615-0187, 24 hours/day; 7 days/week if you have any questions about the information contained in this letter regarding the safe and effective use of Methotrexate Injection, USP 1g/40mL (25mg/mL)(Preservative-free).

Sincerely,

Judith Zutkis
VP, Global Regulatory Affairs
Hospira, Inc.

Hospira, Inc.
275 North Field Drive
Dept. 0389, Bldg. H2
Lake Forest, IL 60045
www.hospira.com

Comparison Table

US Methotrexate Injection USP 1g/40mL Preservative-Free	Canadian Methotrexate Injectable USP 1g/40mL Preservative-Free
Vial label	**Vial label**
	
Carton label	**Carton label**
	

WARNINGS

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

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

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

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

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

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

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

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

doses. It is not always fully reversible and fatalities have been reported. Pulmonary symptoms (especially a dry, nonproductive cough) may require interruption of treatment and careful investigation.

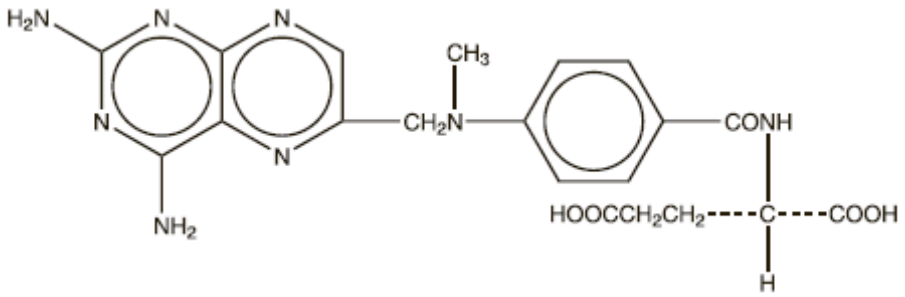
6. Diarrhea and ulcerative stomatitis require interruption of therapy: otherwise, hemorrhagic enteritis and death from intestinal perforation may occur.
7. Malignant lymphomas, which may regress following withdrawal of methotrexate, may occur in patients receiving low-dose methotrexate and, thus, may not require cytotoxic treatment. Discontinue methotrexate first and, if the lymphoma does not regress, appropriate treatment should be instituted.
8. Like other cytotoxic drugs, methotrexate may induce "tumor lysis syndrome" in patients with rapidly growing tumors. Appropriate supportive and pharmacologic measures may prevent or alleviate this complication.
9. Severe, occasionally fatal, skin reactions have been reported following single or multiple doses of methotrexate. Reactions have occurred within days of oral, intramuscular, intravenous, or intrathecal methotrexate administration. Recovery has been reported with discontinuation of therapy. (See **PRECAUTIONS, Organ System Toxicity,** *Skin*.)
10. Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy.
11. Methotrexate given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.

DESCRIPTION

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

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

The structural formula is:



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

Methotrexate Injection, USP is sterile and non-pyrogenic and may be given by the intramuscular, intravenous or intra-arterial route. (See **DOSAGE AND ADMINISTRATION.**) ***However, the preserved formulation contains Benzyl Alcohol and must not be used for intrathecal or high dose therapy.***

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

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

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

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

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

CLINICAL PHARMACOLOGY

Methotrexate inhibits dihydrofolic acid reductase. Dihydrofolates must be reduced to tetrahydrofolates by this enzyme before they can be utilized as carriers of one-carbon groups in the synthesis of purine nucleotides and thymidylate. Therefore, methotrexate interferes with DNA synthesis, repair, and cellular replication. Actively proliferating tissues such as malignant cells, bone marrow, fetal cells, buccal and intestinal mucosa, and cells of the urinary bladder are in general more sensitive to this effect of methotrexate. When cellular proliferation in malignant tissues is greater than in most normal tissues, methotrexate may impair malignant growth without irreversible damage to normal tissues.

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

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

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

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

Methotrexate in high doses, followed by leucovorin rescue, is used as a part of the treatment of patients with non-metastatic osteosarcoma. The original rationale for high dose methotrexate therapy was based on the concept of selective rescue of normal tissues by leucovorin. More recent evidence suggests that high dose methotrexate may also overcome methotrexate resistance caused by impaired active transport, decreased affinity of dihydrofolic acid reductase for methotrexate, increased levels of dihydrofolic acid reductase resulting from gene amplification, or decreased polyglutamation of methotrexate. The actual mechanism of action is unknown.

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

Two Pediatric Oncology Group studies (one randomized and one non-randomized) demonstrated a significant improvement in relapse-free survival in patients with nonmetastatic osteosarcoma, when high dose methotrexate with leucovorin rescue was used in combination with other chemotherapeutic agents following surgical

resection of the primary tumor. These studies were not designed to demonstrate the specific contribution of high dose methotrexate/leucovorin rescue therapy to the efficacy of the combination. However, a contribution can be inferred from the reports of objective responses to this therapy in patients with metastatic osteosarcoma, and from reports of extensive tumor necrosis following preoperative administration of this therapy to patients with non-metastatic osteosarcoma.

Pharmacokinetics

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

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

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

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

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

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

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

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

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

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

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

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

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

INDICATIONS AND USAGE

Neoplastic Diseases

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

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

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

Methotrexate in high doses followed by leucovorin rescue in combination with other chemotherapeutic agents is effective in prolonging relapse-free survival in patients with non-metastatic osteosarcoma who have undergone surgical resection or amputation for the primary tumor.

Psoriasis

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

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

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

CONTRAINDICATIONS

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

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

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

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

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

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

WARNINGS - SEE BOXED WARNINGS.

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

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

PRECAUTIONS

General

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

discontinued and appropriate corrective measures should be taken. If necessary, this could include the use of leucovorin calcium and/or acute, intermittent hemodialysis with a high-flux dialyzer. (See **OVERDOSAGE**). If methotrexate therapy is reinstituted, it should be carried out with caution, with adequate consideration of further need for the drug and increased alertness as to possible recurrence of toxicity.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Nursing Mothers
See **CONTRAINDICATIONS**.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Musculoskeletal System: stress fracture.

Ophthalmic: conjunctivitis, serious visual changes of unknown etiology.

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

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

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

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

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

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

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

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

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

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

Adverse Reactions in Psoriasis:
There are no recent placebo-controlled trials in patients with psoriasis. There are two literature reports (Roenigk, 1969, and Nyfors, 1978) describing large series (n=204, 248) of psoriasis patients treated with methotrexate. Dosages ranged up to 25 mg per week and treatment was administered for up to four years. With

the exception of alopecia, photosensitivity, and "burning of skin lesions" (each 3% to 10%), the adverse reaction rates in these reports were very similar to those in the rheumatoid arthritis studies. Rarely, painful plaque erosions may appear (Pearce, HP and Wilson, BB: *Am Acad Dermatol* 35: 835-838, 1996).

Adverse Reactions in JRA Studies

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

OVERDOSAGE

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

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

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

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

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

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

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

DOSAGE AND ADMINISTRATION

Neoplastic Diseases

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Bleomycin†	15 units/m^2 IV x 2 days	2,13,26,39,42
Cyclophosphamide†	600 mg/m^2 IV x 2 days	2,13,26,39,42
Dactinomycin†	0.6 mg/m^2 IV x 2 days	2,13,26,39,42

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

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

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

GUIDELINES FOR METHOTREXATE THERAPY WITH LEUCOVORIN RESCUE

1. Administration of methotrexate should be delayed until recovery if:
   - the WBC count is less than 1500/microliter
   - the neutrophil count is less than 200/microliter
   - the platelet count is less than 75,000/microliter
   - the serum bilirubin level is greater than 1.2 mg/dL
   - the SGPT level is greater than 450 U
   - mucositis is present, until there is evidence of healing
   - persistent pleural effusion is present; this should be drained dry prior to infusion.
2. Adequate renal function must be documented.
   a. Serum creatinine must be normal, and creatinine clearance must be greater than 60 mL/min, before initiation of therapy.
   b. Serum creatinine must be measured prior to each subsequent course of therapy. If serum creatinine has increased by 50% or more compared to a prior value, the creatinine clearance must be measured and documented to be greater than 60 mL/min (even if the serum creatinine is still within the normal range).
3. Patients must be well hydrated, and must be treated with sodium bicarbonate for urinary alkalinization.
   a. Administer 1,000 mL/m^2 of intravenous fluid over 6 hours prior to initiation of the methotrexate infusion. Continue hydration at 125 mL/m^2/hr (3 liters/m^2/day) during the methotrexate infusion, and for 2 days after the infusion has been completed.
   b. Alkalinize urine to maintain pH above 7.0 during methotrexate infusion and leucovorin calcium therapy. This can be accomplished by the administration of sodium bicarbonate orally or by incorporation into a separate intravenous solution.
4. Repeat serum creatinine and serum methotrexate 24 hours after starting methotrexate and at least once daily until the methotrexate level is below 5 x 10^{-8} mol/L (0.05 micromolar).
5. The table below provides guidelines for leucovorin calcium dosage based upon serum methotrexate levels. (See table below.‡)

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

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

CAUTION: DO NOT ADMINISTER LEUCOVORIN INTRATHECALLY.

Psoriasis, Rheumatoid Arthritis, and Juvenile Rheumatoid Arthritis

Adult Rheumatoid Arthritis: Recommended Starting Dosage Schedules

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

† Methotrexate Sodium Tablets for oral administration are available.

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

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

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

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

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

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

Psoriasis: Recommended Starting Dose Schedule:

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

†Methotrexate Sodium Tablets for oral administration are available.

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

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

HANDLING AND DISPOSAL

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

DILUTION INSTRUCTIONS FOR LIQUID METHOTREXATE INJECTION PRODUCT
Methotrexate Injection, USP, Isotonic Liquid, Contains Preservative

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

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

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

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

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

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

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

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

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

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

Hospira, Inc.
Lake Forest, IL 60045

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.

432925

PrMETHOTREXATE INJECTION USP

PART I: HEALTH PROFESSIONAL INFORMATION (PACKAGE INSERT FOR DOSING INFORMATION ONLY/ FOR COMPLETE PRESCRIBING INFORMATION, SEE PRODUCT MONOGRAPH)

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intramuscular, intravenous, intra-arterial, intrathecal	10 mg/mL, 25 mg/mL	Benzyl alcohol as preservative *For a complete listing see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.*

INDICATIONS AND CLINICAL USE

Two major fields of indication exist for Methotrexate:

- Neoplastic diseases
- Disease Modifying Antirheumatic Drug (DMARD)

Neoplastic Diseases

- Choriocarcinoma: Methotrexate - as single chemotherapy or in combination with other drugs.
- Intermediate-, or high grade Non-Hodgkin's Lymphoma as part of ProMACE-CytaBOM, ProMACE-MOPP, and Magrath protocols.
- Breast Cancer: as part of CMF (cyclophosphamide-methotrexate-fluorouracil) therapy.
- Acute Lymphoblastic Leukemia (ALL) - as maintenance therapy.
- Head and Neck Cancer - in combination with other chemotherapies.
- Gastric Cancer – palliative combination chemotherapy.
- Metastasis of unknown primary - as palliative combination chemotherapy.
- Osteogenic sarcoma (adjuvant) - high dose Methotrexate with leucovorin rescue (HDMTX-LV)
- Bladder Cancer (advanced) - as part of M-VAC regimen.
- Leptomeningeal spread of malignancies (carcinomatosis/leukemia/lymphoma) as a single chemotherapy or alternating with Ara-C
- Burkitt's lymphoma
- Advanced stages of childhood lymphoma (III and IV, St. Jude's Childrens' Research Hospital Staging System)
- Advanced cases of mycosis fungoids (cutaneous T-cell lymphoma).

Disease Modifying Antirheumatic Drug (DMARD)

The use of methotrexate as a DMARD in the following diseases where standard therapeutic interventions fail:

- Severe disabling psoriasis/psoriatic arthritis
- Severe disabling rheumatoid arthritis (RA)
- Severe disabling seronegative arthritides

In the treatment of psoriasis, methotrexate should be restricted to severe recalcitrant, disabling psoriasis, which is not adequately responsive to other forms of therapy, but only when the diagnosis has been established after dermatologic consultation.

Geriatrics:

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.

Pediatrics:
Safety and effectiveness in pediatric patients have not been established, other than in cancer chemotherapy.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section

- Pregnancy: Methotrexate can cause fetal death, embryotoxicity, abortion or teratogenic effects when administered to a pregnant woman. Methotrexate is contraindicated in pregnant patients 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 counselled on the serious risk to the fetus should they become pregnant while undergoing treatment. Pregnancy should be avoided if either partner is receiving methotrexate. The optimal time interval between the cessation of methotrexate treatment of either partner and pregnancy has not been clearly established. Published literature recommendations for time intervals vary from 3 months to one year.

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

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

- Methotrexate is contraindicated in patients with psoriasis or rheumatoid arthritis in the following situations:
    - Alcoholism, alcoholic liver disease or other chronic liver disease.
    - Overt or laboratory evidence of immunodeficiency syndromes.
    - Pre-existing blood dyscrasias, such as bone marrow hypoplasia, leucopenia, thrombocytopenia or significant anemia.

DRUG INTERACTIONS

Drug-Drug Interactions

The drugs listed below are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)
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 by increasing methotrexate levels.

In treating rheumatoid arthritis with methotrexate, acetyl salicyclic acid (ASA), NSAIDs, and/or low dose steroids may be continued.

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. Combined use of

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

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.

Leflunomide

Methotrexate in combination with leflunomide may increase the risk of pancytopenia.

Drugs Highly Bound to Plasma Proteins
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.

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

Nephrotoxic Drugs
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 clearance is decreased by cisplatinum.

Although not documented, other nephrotoxic drugs such as aminoglycosides, Amphotericin B and Cyclosporin could theoretically increase methotrexate toxicity by decreasing its elimination.

Penicillins and Sulfonamides
Penicillins and sulfonamides may reduce the renal clearance of Methotrexate; hematologic and gastrointestinal toxicity have been observed in combination with Methotrexate.

Oral Antibiotics
Oral antibiotics such as tetracycline, chloramphenicol, and non-absorbable 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. For example: Neomycin, Polymyxin B, Nystatin and Vancomycin decrease methotrexate absorption, whereas Kanamycin increases methotrexate absorption.

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.

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

Mercaptopurine
Methotrexate increases the plasma levels of mercaptopurine. Combination of methotrexate and mercaptopurine may therefore require dose adjustment.

Vitamins
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 cerebrospinal fluid (CSF) primarily as 5-methyl tetrahydrofolate 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.

In patients with rheumatoid arthritis or psoriasis, folic acid or folinic acid may reduce methotrexate toxicities such as gastrointestinal symptoms, stomatitis, alopecia and elevated liver enzymes.

Before taking a folate supplement, it is advisable to check B_{12} levels, particularly in adults over the age of 50, since folate administration can mask symptoms of B_{12} deficiency.

Folate deficiency states may increase methotrexate toxicity.

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

Hepatoxins
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 hepatotoxic agents (e.g., leflunomide, azathioprine, sulfasalazine, retinoids) should be closely monitored for possible increased risk of hepatotoxicity.

Cytarabine
Methotrexate given concomitantly with cytarabine may increase the risk of severe neurologic adverse events such as headache, paralysis, coma and stroke-like episodes.

Drug-Food Interactions
The bioavailability of orally administered methotrexate is reduced by food, particularly milk products.

DOSAGE AND ADMINISTRATION

Neoplastic Diseases

Dosing Considerations

- Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit.
- Methotrexate injection may be given by the intramuscular, intravenous, intra-arterial, intrathecal or intraventricular (via Ommaya reservoir into the CNS) routes. The preserved formulation contains benzyl alcohol and must not be used for intrathecal, intraventricular, or high dose therapy.
- Methotrexate may only be administered by physicians experienced in the treatment of neoplasia. The oncologist should consult the current literature for the treatment regimen to be used. Typical dosages reported in the literature for the following malignancies are listed in the following section.

Recommended Dose and Dosage Adjustment

Breast Cancer
The initial doses of CMF will be cyclophosphamide 100 mg/m^2 p.o. days 1 through 14, Methotrexate 40 mg/m^2 IV day 1, 8, and 5 - Fluorouracil 600 mg/m^2 IV day 1, 8. Cycle length will be 28 days ("2 weeks-on, 2 weeks-off"). In patients over 60 years of age, the dosage of Methotrexate will be 30 mg/m^2 IV day 1, 8.

If total bilirubin exceeds 1.5 mg/dL, decrease the dose of Methotrexate only by 50%.

Bladder Cancer
Typical dosage regimens for bladder cancer are the CMV Regimen and the “M-VAC Regimen" which are represented in the following tables.

*Table 1 - CMV Regimen**

Drugs**	Days		
	1	2	8¶
Cisplatin‡		100	
Vinblastine	4		4

Methotrexate***	30		30

* All doses in mg/m^2 with cycles repeated on day 22.
**Patients >70 years old receive 80% of all doses; if vomiting persists to day 8, no drug is given.
‡For each cycle adjust cisplatin to 100% for Ccr >60 mL/min; 50% of dose for Ccr 50-60 mL/min; none for Ccr <50 mL/min.
***No drug for a decrease on day 8 of >30 mL/min compared to day 1 or Ccr <50 mL/min or Cr >1.8 mg/dL.
¶ Major dose modifications for both drugs depending on myelosuppression.

*Table 2 - M-VAC Regimen**

Drugs	Days			
	1	2	15	22***
Methotrexate	30		30	30
Vinblastine		3	3	3
Doxorubicin		30**		
Cisplatin		70		

*All doses in mg/m^2 with cycles repeated every 28-32 days.
**Patients having prior pelvic irradiation equivalent to >2500 rad in 5 days, reduce the dose of Doxorubicin 15 mg/m^2.
***No doses given when the WBC <2500 cells/mm^3, platelets >100,000 cells/mm^3, or mucositis present.

Head and Neck Cancer
Methotrexate remains the standard of therapy for patients with recurrent or metastatic disease. It has been given in a wide variety of doses and schedules (a few of which are represented in the table below).

Table 3

Methotrexate Schedule*
0.8 mg/kg every 4 days IV
25 - 50 mg every 4 to 7 days
60 mg/m^2 weekly IV or 40 mg/m^2 biweekly IV
40 - 60 mg/m^2 weekly IV
80 mg/m^2 for 30 h every 2 wk with escalation to toxicity
40 mg/m^2 weekly IV
40-200 mg/m^2 IV on days 1, 4 weekly; Leucovorin on days 2,5
60 mg/m^2 IV weekly

** excerpt from Devita, et al: CANCER 3rd Ed, p. 496*

For palliation of patients with advanced incurable disease and acceptable renal function, it is appropriate to begin oral or intravenous methotrexate with weekly doses of 40-50 mg/m^2 or biweekly doses of 15 to 20 mg/ m^2 and escalate the dose in weekly increments until either mild toxicity or therapeutic response is achieved.

Gastric Cancer
A regimen used in a clinical trial in Belgium in patients with resectable gastric cancer follows: methotrexate (1.5 g/m^2 IV day 1, +5-Fluorouracil (1.5 g/m^2 IV) + Leucovorin (15 mg/m^2 orally or IV every 6 hours for 72 hours) + Adriamycin (30 mg/m^2 IV, day 15). The schedule is repeated on day 29 for 6 cycles.

Choriocarcinoma and similar trophoblastic diseases
Methotrexate is administered orally or intramuscularly in doses of 15 to 30 mg daily for a 5 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 gonadotrophin hormone (beta-HCG), which should return to normal or less than 50 IU/24 hours usually after the third or fourth course, and usually be

followed by a complete resolution of measurable lesions in four to six weeks. One to two courses of methotrexate after normalization of beta-HCG is usually recommended. Before each course of the drug, careful clinical assessment is essential. Cyclic combination therapy of methotrexate with other anti-tumour drugs has been reported as being useful.

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

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

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

The treatment of choice for localized histologically aggressive lymphoma is primary combination chemotherapy with or without involved-field radiation therapy. Frequently used regimens for intermediate, or high grade NHL that include methotrexate include groups: the ProMACE/MOPP, ProMACE-CytaBOM, Magrath Protocols. Represented in the table below for example, is the ProMACE-CytaBOM Regimen.

Table 4 – ProMACE-CytaBOM Regimen

ProMACE-CytaBOM	Day 1	Day 8	Day 14	Days 15-21
Cyclophosphamide 650 mg/m^2 IV	x			No therapy
Doxorubicin 25 mg/m^2 IV	x			
Etoposide 120 mg/m^2 IV	x			
Cytarabine 300 mg/m^2 IV		x		
Bleomycin 5 mg/m^2 IV		x		
Vincristine 1.4 mg/m^2 IV		x		
Methrotrexate 120 mg/m^2 IV		x with leucovorin rescue		
Prednisone 60 mg/m^2 PO	x----------~----------			x
Co-trimoxazole 2 PO bid throughout 6 cycles of therapy				

In early stage childhood non-Hodgkin's lymphoma, methotrexate is used effectively in combination chemotherapy regimens.

Mycosis Fungoides (cutaneous T-cell lymphoma)
Therapy with Methotrexate appears to produce a clinical response, in up to 50% of patients treated, but chemotherapy is not curative. Dosage is usually 2.5 to 10 mg daily by mouth for several weeks or months. Dose levels of drug and adjustment of dose regimen by reduction or cessation of drug are guided by patient response and hematologic monitoring. Methotrexate has also been given intramuscularly in doses of 50 mg once weekly or 25 mg 2 times weekly.

Leukemia
Acute lymphoblastic leukemia (ALL) in children 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 ALL. More recently, corticosteroid therapy in combination with other antileukemic drugs or in cyclic combinations with methotrexate, 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 remission 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, re-induction 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 ALL. The physician should be familiar with recent advances in antileukemic therapy.

Meningeal Leukemia
In the treatment or prophylaxis of meningeal leukemia, Methotrexate must be administered intrathecally.

For intrathecal administration, 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 children 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 children 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.

Leptomeningeal Carcinomatosis
Intrathecal administration of Methotrexate as a single-drug or in combination regimens, is the most common therapy for carcinomatous leptomeningitis.

Treatment is optimally administered through an Ommaya reservoir and is usually started with Methotrexate (10 mg/m^2) given twice weekly until the cerebrospinal fluid cytology becomes negative. The treatment regimen is gradually decreased, first to a weekly course, and eventually to a single administration every two months.

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

Drug*	Dose*	Treatment Week After Surgery
Methotrexate Leucovorin	12 g/m^2 IV as 4 hour infusion (starting dose) 15 mg orally every six hours for 10 doses starting at 24 hours after start of Methotrexate infusion.	4,5,6,7,11,12,15,16,29,30,44,45
Doxorubicin** as a single drug	30 mg/m^2/day IVx3 days	8,17
Doxorubicin** Cisplatin**	50 mg/m^2 IV 100 mg/m^2 IV	20,23,33,36 20,23,33,36
Bleomycin** Cyclophosphamide** Dactinomycin**	15 units/m^2 IV x 2 days 600 mg/m^2 IV x 2 days 0.6 mg/m^2 IV x 2 days	2,13,26,39,42 2,13,26,39,42 2,13,26,39,42

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

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

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

GUIDELINES FOR METHOTREXATE THERAPY WITH LEUCOVORIN RESCUE

1. Administration of Methotrexate should be delayed until recovery if:
   - The WBC count is less than 1500/microliter
   - The neutrophil count is less than 200/microliter
   - The platelet count is less than 75,000/microliter
   - The serum bilirubin level is greater than 1.2 mg/dL
   - The SGPT level is greater than 450 U
   - Mucositis is present, until there is evidence of healing
   - Persistent pleural effusion is present; this should be drained dry prior to infusion.

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

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

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

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

Patients who experience delayed early Methotrexate elimination are likely to develop non-reversible 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 (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.

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; than 15 mg IV q three hours, until Methotrexate level is less than 0.05 micormolar.

Psoriasis and Rheumatoid Arthritis

Dosing Considerations

- Refer to Neoplastic Diseases – Dosing Considerations
- The patient should be fully informed of the risks involved and should be under constant supervision of the physician.
- All dosage 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.

Recommended Dose and Dosage Adjustments

Psoriasis

Recommended Starting Dose Schedules

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

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, the 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

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

Administration
Dilution:
Methotrexate Injection, USP may be diluted with any of the solutions for IV infusion listed below in a concentration range of 0.4 mg/mL to 2 mg/mL. Dilutions should be used within 24 hours if kept at room temperature. Unused solution should be discarded after this time in order to avoid risk of microbial contamination.

Solutions:
0.9% Sodium Chloride Injection
5% Dextrose Injection
4% Dextrose and 0.18% Sodium Chloride Injection
Ringer's Injection

Since methotrexate is poorly soluble in acid media, use of potassium chloride solution is not advisable.

If a preservative free diluent is used, the solution should be used immediately because of the possibility of microbial growth. It is advisable to protect diluted solutions from light.

Due to the number of brands available, stability data of Methotrexate in plastic syringes and bags are not available.

Unused preservative free products should be discarded due to the possibility of microbial growth.

Dispensing of Pharmacy Bulk Vials:
Pharmacy Bulk Vials contain 25 mg/mL Methotrexate (as Methotrexate Sodium) in 20 mL, 40 mL or 100 mL of sterile, **unpreserved**, isotonic solution (see **Composition**).

The availability of Pharmacy Bulk Vials is restricted to hospitals with a recognized intravenous admixture program. Methotrexate Injection USP pharmacy bulk vials are packaged in an ONCO-TAIN™ sleeve to protect from breakage. It is recommended that the vial remains in the carton until time of use. The Methotrexate Injection USP vial should be inspected for damage and visible signs of leaks. If there are signs of breakage or leakage form the vial, do not use. Incinerate the unopened package.

Pharmacy Bulk Vials are intended for multiple dispensing FOR INTRAVENOUS USE ONLY employing a single puncture (see **Special Instructions - Handling and Disposal of Cytotoxic Drugs**).

The Pharmacy Bulk Vial content should be dispensed within eight hours. Any unused solution should be discarded. The diluted solutions prepared from the Pharmacy Bulk vial should be used within 24 hours from the time of the initial puncture of the Pharmacy Bulk Vial, when kept at room temperature.

Pharmacy Bulk Vials contain no preservatives. Care must be taken to minimize the potential for inadvertent introduction of micro-organisms during manipulation in the hospital environment.

Incompatibilities:
Other drugs should not be mixed with Methotrexate in the same infusion bottle.

Methotrexate has been reported to be incompatible with cytarabine, fluorouracil, and prednisolone sodium phosphate; however, its incompatibility with fluorouracil has been questioned. A mixture of Methotrexate with cytarabine and hydrocortisone sodium succinate in various infusion fluids has been reported to be visually compatible for at least 8 hours at 25°C, although precipitation did not occur on storage for several days.

Contact with acidic solutions should be avoided since Methotrexate is sparingly soluble in acid media and precipitation may occur.

OVERDOSAGE

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

Discontinue or reduce dosage at the first sign of ulceration or bleeding, diarrhea, or marked depression of the hematopoietic system. 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, neither standard 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.

There are published case reports of intravenous carboxypeptidase G2 treatment to hasten clearance of Methotrexate in cases of overdoses.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

STORAGE AND STABILITY

Keep in a safe place out of the reach of children.

Store Methotrexate Injection, USP vials between 15-25 °C. Protect from light.

Multidose vials (50 mg/2 mL and 500 mg/20 mL) Methotrexate with benzyl alcohol) should be stored at 2-8 °C after the vials are punctured for a maximum of four weeks (30 days). Protect from light. Aseptic techniques should be used when handling punctured vials to avoid contamination.

Methotrexate Injection USP vials are packaged in an ONCO-TAIN™ sleeve to protect form breakage. It is recommended that the vial remains in the carton until time of use. The Methotrexate Injection USP vial should be inspected for damage and visible signs of leaks. If there are signs of breakage or leakage form the vial, do not use. Incinerate the unopened package.

SPECIAL HANDLING INSTRUCTIONS

General:
Individuals who have contact with anti-cancer drugs or work in areas where these drugs are used, may be exposed to these agents in air or through direct contact with contaminated objects. Potential health effects may be reduced by adherence to institutional procedures, published guidelines and local regulations for preparation, administration, transportation and disposal of hazardous drugs.

Safe Handling and Disposal:
Methotrexate is a potent anti-neoplastic drug. Good medical practice will minimize exposure of persons involved with frequent handling of this drug as outlined below:

Handling:

1. Methotrexate has no vesicant properties and does not show acute toxicity on topical contact with the skin or mucous membranes. However, persons involved with handling cytotoxic drugs should avoid contact with skin and inhalation of airborne particles.

2. Preparation of antineoplastic solutions should be done in a vertical laminar flow hood (Biological Safety Cabinet - Class II).

3. Personnel preparing Methotrexate solutions should wear PVC gloves, safety glasses and protective clothing such as disposable gowns and masks.

4. Personnel regularly involved in preparation and handling of antineoplastics should have bi-annual blood examinations.

Disposal:

1. Avoid contact with skin and inhalation of airborne particles by use of PVC gloves and disposable gowns and masks.

2. All needles, syringes, vials and other materials for disposal which have come in contact with Methotrexate should be segregated in plastic bags, sealed and marked as hazardous waste. Incinerate at 1000°C or higher. Sealed containers may explode if a tight seal exists.

3. If incineration is not available, rinse all needles, syringes, tubing and other materials for disposal which have come in contact with Methotrexate solutions with water and discard in the sewer system with running water.

Rinse vials with the appropriate quantity of water with the aid of a hypodermic syringe. Withdraw the solution and discard in the sewer system with running water. Dispose of rinsed equipment and vials in a safe manner.

Cleaning:
Non-disposable equipment that has come in contact with methotrexate may be rinsed with water and washed thoroughly with soap and water.

Spillage/Contamination:
Wear gloves, mask and protective clothing. Place spilled material in an appropriate container (i.e. cardboard for broken glass) and then in a polyethylene bag; absorb remains with gauze pads or towels; wash area with water and absorb with gauze or towels again and place in bag; seal, double bag and mark as a hazardous waste. Dispose of waste by incineration or by other methods approved for hazardous materials. Personnel involved in clean up should wash with soap and water.

DOSAGE FORMS, COMPOSITION AND PACKAGING

(1) **Methotrexate Injection USP** is packaged in an ONCO-TAIN™ sleeve containing 20 mg, 50 mg and 500 mg of Methotrexate (as the sodium salt) as follows:

10 mg/mL Methotrexate	20 mg / 2 mL*	(contains no preservative)
25 mg/mL Methotrexate	50 mg / 2 mL*	(contains no preservative)
25 mg/mL Methotrexate	50 mg / 2 mL+	(contains preservatives)
25 mg/mL Methotrexate	500 mg / 20 mL+	(contains preservatives)

* Single use vials
+ Multidose vials

Note: 2 mL vials are available in packs of 5 vials. 20 mL vials are available as single vials.

(2) **Methotrexate Injection USP Pharmacy Bulk Vials, which is packaged in an ONCO-TAIN™ sleeve** are for intravenous use only and are supplied to hospitals with a recognized intravenous admixture program only, as follows:

25 mg/mL Methotrexate	500 mg / 20 mL	(contains no preservatives)
25 mg/mL Methotrexate	1 g / 40 mL	(contains no preservatives)
25 mg/mL Methotrexate	2.5 g / 100 mL	(contains no preservatives)

Composition: Methotrexate Injection, USP is a sterile, isotonic solution containing:

(1) Methotrexate Sodium equivalent to 10 mg/mL Methotrexate with 7.0 mg/mL Sodium Chloride, (unpreserved), with Sodium Hydroxide and Hydrochloric Acid as pH adjusters.
(2) Methotrexate Sodium equivalent to 25 mg/mL Methotrexate with 4.9 mg/mL Sodium Chloride, (unpreserved), with Sodium Hydroxide and Hydrochloric Acid as pH adjusters.
(3) Methotrexate Sodium equivalent to 25 mg/mL Methotrexate with 2.6 mg/mL Sodium Chloride and 0.9% v/v Benzyl alcohol (preserved), with Sodium Hydroxide and Hydrochloric Acid as pH adjusters.

Note: 50 mg/2 mL and 500 mg/20 mL Methotrexate Injection, USP, with benzyl alcohol (preservative) are supplied as multidose vials. Please see special storage conditions once the vials are punctured.

.

PART III: CONSUMER INFORMATION

Methotrexate Injection USP

This leaflet is part III of a three-part "Product Monograph" published when Methotrexate Injection USP was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Methotrexate Injection USP. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Methotrexate belongs to a group of medicines known as antimetabolites. It is used in high doses to treat many types of cancers, including breast cancer, Non-Hodgkin's lymphoma and leukemia. At lower doses, it may also be used to treat psoriasis and rheumatoid arthritis.

What it does:
Methotrexate works by blocking an enzyme needed by body cells to live. This interferes with the growth of some cells, such as skin cells in psoriasis that are growing rapidly. In rheumatoid arthritis, methotrexate acts on the inflammatory cells that cause joint swelling. Methotrexate therapy is used to control psoriasis and rheumatoid arthritis but it will not cure them. In cancer, Methotrexate works by blocking an enzyme process in cancer cells so that they cannot grow. Some normal cells in the body may be affected as well.

Your doctor may have prescribed Methotrexate for another purpose. Ask your doctor if you have any questions about why it has been prescribed for you.

When it should not be used:
Do not take Methotrexate Injection USP if you:

- Are allergic to any component of the drug (see What the important nonmedicinal ingredients are). Some of the symptoms of an allergic reaction to methotrexate may include rash, itching or hives on the skin, swelling of the face, lips, tongue or other parts of the body, shortness of breath, wheezing or troubled breathing.
- Have any blood disorders including:
  - bleeding from a lack of blood cells called platelets.
  - low iron in the blood (anemia).
- Have an immune system disorder such as AIDS (autoimmune deficiency syndrome) or HIV, the virus which causes AIDS.
- Have an infection.
- Have severe kidney or liver disorder.
- Suffer from alcoholism or alcoholic liver disease.
- Have a stomach ulcer.
- Have inflammation and bleeding from the rectum, with abdominal pain and diarrhea (ulcerative colitis).
- Are pregnant or breastfeeding.

What the medicinal ingredient is:
Methotrexate (meth-o-TREX-ate).

What the important nonmedicinal ingredients are:
Benzyl alcohol, hydrochloric acid, sodium chloride, sodium hydroxide and water for injection.

What dosage forms it comes in:
Methotrexate Injection USP 25 mg/mL and 10 mg/mL in the following presentations:

10 mg/mL
20 mg / 2 mL (no preservative) as a single use vial

25 mg/mL
50 mg / 2 mL (no preservative) as a single use vial
50 mg / 2 mL (with preservatives) as a multidose vial

500 mg / 20 mL (with preservatives) as a multidose vial

Methotrexate Injection USP 25 mg/mL is also available in Pharmacy Bulk vials in the following presentations:

500 mg/20 mL (no preservatives)
1 g/40 mL (no preservatives)
2.5 g/100 mL (no preservatives)

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- You should not plan to have children while taking Methotrexate or for a while after stopping treatment. (Talk to your doctor for further details.)
- Use a reliable method of birth control to prevent pregnancy.

Before Using This Medicine

Before you begin treatment with Methotrexate, you should talk to your doctor about the good this medicine will do as well as the risks of using it.

In deciding to use a medicine, the risks of taking the medicine must be weighed against the good it will do. This is a decision you and your doctor will make. For Methotrexate, the following should be considered:

Allergies:

- Tell your doctor if you have ever had any unusual or allergic reaction to methotrexate.

Pregnancy:

- Tell your doctor if you are pregnant or if you plan to have children. There is a good chance that this medicine may cause birth defects if either the male or female is taking it at the time of conception or if it is taken during pregnancy. Methotrexate may cause harm or even death of the fetus. Also, many cancer medicines may cause sterility, which could be permanent. Although sterility is probably rare with this medicine, the possibility should be kept in mind.

- Be sure that you have discussed this with your doctor before taking this medicine. It is best to use some kind of birth control while you are taking Methotrexate. Tell your doctor right away if you think you have become pregnant while taking Methotrexate.

Breast-feeding:

- Tell your doctor if you are breast-feeding or if you intend to breast-feed during treatment with this medicine. Because Methotrexate may cause serious side effects, breast-feeding is generally not recommended while you are taking it.

Children:

- Newborns and other infants may be more sensitive to the effects of Methotrexate. However, in other children it is not expected to cause different side effects or problems than it does in adults.

Older adults:

- Side effects may be more likely to occur in the elderly, who are usually more sensitive to the effects of Methotrexate.

Other medicines:

- When you are taking Methotrexate, it is important that your doctor know if you are taking any other prescription or nonprescription medicine. They should also be told if you have ever been treated with x-rays or cancer medicines or if you drink alcohol.

Other medical problems:

The presence of other medical problems may affect the use of Methotrexate. Tell your doctor if you have any other medical problems, especially:

- Alcohol abuse (or history of)
- Chickenpox (including recent exposure) or *Herpes zoster* (shingles)
- Colitis
- Disease of the immune system
- Gout (or history of)
- Kidney stones (or history of)
- Infection
- Intestine blockage
- Kidney disease
- Liver disease
- Mouth sores or inflammation
- Stomach ulcer

Precautions while using this medicine

It is very important that your doctor check your progress at regular visits to make sure that this medicine is working properly and to check for unwanted effects.

Do not drink alcohol while taking Methotrexate. Alcohol can increase the chance of liver problems.

Some patients who take Methotrexate may become more sensitive to sunlight than they are normally. Avoid too much sun exposure and do not use a sunlamp until you see how you react to the sun, especially if you tend to burn easily.

You should not receive certain vaccinations while taking Methotrexate. Discuss this with your doctor. Avoid anyone who has had oral polio vaccine for at least six weeks. Do not get close to them or stay in the same room for very long. If this is not possible, wear a mask over your nose and mouth.

Some side effects such as dizziness and fatigue may affect the ability to drive or operate machinery. These activities should be avoided. If you have any concerns, please consult your doctor.

Methotrexate can lower the number of white blood cells in your blood temporarily, increasing the chance of getting an infection. It can also lower the number of platelets, which are necessary for proper blood clotting. If this happens, there are certain precautions you can take, especially when your blood count is low to reduce the risk of infection or bleeding:

- If you can, avoid people with infections. Check with your doctor immediately if you think you are getting an infection or if you get a fever or chills, cough or hoarseness, lower back or side pain, or painful or difficult urination.
- Check with your doctor immediately if you notice any unusual bleeding or bruising; black, tarry stools; blood in urine or stools; or pinpoint red spots on your skin.
- Be careful when using a regular toothbrush, dental floss, or toothpick. Check with your doctor before having any dental work done.
- Do not touch your eyes or the inside of your nose unless you have just washed your hands.
- Be careful not to cut yourself when you are using sharp objects such as scissors or a razor.
- Avoid contact sports or other situations where bruising or injury could occur.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor and pharmacist what prescription and nonprescription medications you are taking. Methotrexate may interact with other medicines such as:

- acetyl salicyclic acid (ASA) and other pain killers or nonsteroidal anti-inflammatory drugs (NSAIDs)
- Some antibiotics (including penicillins and sulfonamides, and medicines to prevent malaria – pyrimethamine)
- some epilepsy treatments
- some cancer treatments
- some vaccines
- some medicines used to lower your cholesterol (including cholestyramine)

- azathioprine (used to prevent transplant organ rejection)
- cytarabine (used to treat leukemia)
- leflunomide (used to treat rheumatoid arthritis)
- mercaptopurine (used to treat leukemia)
- nitrous oxide anaesthesia
- probenicid (used to treat gout)
- retinoid medicines (used to treat acne)
- sulfonylureas (used to treat diabetes)
- sulfasalazine (used to treat Crohn's disease, rheumatoid arthritis and ulcerative colitis)
- theophylline (used to treat asthma)
- the vitamin folic acid
- phenytoins

The absorption of orally administered Methotrexate is reduced by food, particularly milk products.

It is very important to tell your doctor about all other medicines you are taking including those you buy without a prescription. You may need to receive different amounts of your medicine or you may need to receive different medicines.

Tell any doctor that is treating you that you are taking Methotrexate.

If you have not told your doctor or pharmacist about any of the above, tell them before you are given Methotrexate.

PROPER USE OF THIS MEDICATION

Take Methotrexate only as directed by your doctor. Do not take more or less of it, and do not take it more often than your doctor ordered. The exact amount of medicine you need has been carefully worked out. Taking too much may increase the chance of side effects, while taking too little may not improve your condition.

Methotrexate is often given together with certain other medicines. If you are using a combination of medicines, make sure that you take each one at the proper time and do not mix them. Ask your doctor or pharmacist to help you plan a way to remember to take your medicines at the right times.

While you are using Methotrexate, your doctor may want you to drink extra fluids so that you will pass more urine. This will help the drug to pass from the body, and will prevent kidney problems and keep your kidneys working well.

Methotrexate commonly causes nausea and vomiting. Even if you begin to feel ill, do not stop using this medicine without first checking with your doctor. Ask your doctor for ways to lessen these effects.

If you vomit shortly after taking a dose of Methotrexate, check with your doctor. You will be told whether to take the dose again or to wait until the next scheduled dose.

Usual dose:

The dose of Methotrexate will be different for different patients. The dose that is used may depend on a number of things, including what the medicine is being used for, the patient's size, whether the medicine is being given by mouth or by injection, and whether or not other medicines are also being taken. If you are taking or receiving Methotrexate at home, follow your doctor's orders or the directions on the label. If you have any questions about the proper dose of Methotrexate, ask your doctor.

If you take too much Methotrexate (overdose):

- In the event of overdosage, contact your doctor, hospital emergency department or regional Poison Control Centre.
- Do this even if you have no signs of discomfort.
- Always take the labelled medicine bottle with you, even if it is empty.

If you forget to take Methotrexate (missed dose):

- If it is almost time for your next dose, skip the dose you missed and take your next dose when you are meant to.

- Otherwise, take it as soon as you remember, then contact your doctor for advice on when to take the next dose.
- Do not try to make up for missed doses by taking more than one dose at a time.
- Contact your doctor or pharmacist if you have any doubts or concerns about missed doses.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Along with their needed effects, medicines like Methotrexate can sometimes cause unwanted effects. Also, because of the way these medicines act on the body, there is a chance that they might cause other unwanted effects that may not occur until months or years after the medicine is used. These delayed effects may include certain types of cancer, such as leukemia. Discuss these possible effects with your doctor.

The most common side effects include:

- Upset stomach, stomach pain, vomiting, nausea, loss of appetite, dizziness, chills and fever, diarrhea or sores on lips or mouth.
- A fall in the number of white blood cells. This may reduce your resistance to infection and increase your chances of cold sores, blood poisoning or swelling of blood vessels.

Less common side effects are:

- Headaches, hair loss, mood changes, confusion, ringing in the ears, sore eyes, skin rashes, increased sensitivity to sunlight or unexplained weight loss.
- A fall in the number of other blood cells. This may increase your chances of bruising, bleeding or tiredness.
- Damage to the lungs.
- Harm to the unborn baby.

Rarely and generally at higher doses for treatment of other diseases, Methotrexate can cause other side effects including:

- Liver damage, kidney damage, pain or difficulty urinating, lower back or side pain, blood in urine or stools, dark urine
- Fits, blurred vision, short term blindness
- Drowsiness, weakness
- Hoarseness
- Bloody vomit, black tarry stools or pin-point red spots on the skin
- Reddening or whitening of the skin, acne, boils, itching yellow skin or eyes
- Impotence or loss of interest in sex, decreased fertility, abortion
- Diabetes, thinning of the bones, painful muscles and joints

More rarely, it can cause:

- Skin rash and other skin disorders.
- Cancer of lymph glands, sudden death.
- Severe allergic reactions.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Diarrhea or mouth ulcers		√	
	Sore throat, fever, chills, or swelling of glands		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
		Talk with your doctor or pharmacist		
Less common	Chest pain, cough, shortness of breath or fever		√	
	Unusual bleeding or bruising		√	
Rare	Signs of severe allergic reaction: Skin rash, itching, chest tightness, wheezing, dizziness, hives, faintness, rapid heartbeat, shortness of breath, and/or a swollen face, lips or tongue			√
	Pain or difficulty urinating, lower back or side pain, blood in urine or stools, dark urine		√	

This is not a complete list of side effects. For any unexpected effects while taking Methotrexate Injection USP, contact your doctor or pharmacist.

HOW TO STORE IT

To store this medicine:

- Keep out of the reach of children.
- Store it at room temperature and away from heat and direct light. Avoid freezing Methotrexate Injection.
- Do not keep outdated medicine or medicine no longer needed. Be sure that any discarded medicine is out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report Online at www.healthcanada.gc.ca/medeffect
Call toll-free telephone: 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:
-Fax toll-free to 1-866-678-6789, or
-Mail to:.Canada Vigilance Program
Health Canada
Postal Locator 0701C
Ottawa ON KIA 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Hospira Healthcare Corporation,
at: 1-866-488-6088

This leaflet was prepared by
Hospira Healthcare Corporation.
Saint-Laurent, QC, H4M 2X6

Last revised: October 7, 2009