PRODUCT MONOGRAPH

Pr METOJECT®

methotrexate sodium

Solution for Injection 10 mg/mL

Single-Use Pre-Filled Syringes

Sterile

THERAPEUTIC CLASSIFICATION
Antimetabolite and Antirheumatic

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CAUTION

METOJECT (METHOTREXATE SODIUM) SHOULD BE USED ONLY BY PHYSICIANS WHOSE KNOWLEDGE AND EXPERIENCE INCLUDES THE USE OF ANTIMETABOLITE THERAPY.

ACTIONS AND CLINICAL PHARMACOLOGY

Methotrexate is a folate antagonist.

Methotrexate inhibits dihydrofolate reductase (DHFR), the enzyme that reduces folic acid to tetrahydrofolic acid. Tetrahydrofolate must be regenerated via the DHFR-catalyzed reaction in order to maintain the intracellular pool of tetrahydrofolate one-carbon derivatives for both thymidylate and purine nucleotide biosynthesis. The inhibition of DHFR by folate antagonists (Methotrexate) results in a deficiency in the cellular pools of thymidylate and purines and thus in a decrease in nucleic acid synthesis. Therefore, methotrexate interferes with DNA synthesis, repair, and cellular replication.

Methotrexate is most active against rapidly multiplying cells, because its cytotoxic effects occur primarily during the S phase of the cell cycle. Since cellular proliferation in malignant tissues is

greater than in most normal tissues, methotrexate may impair malignant growth without irreversible damage to normal tissues. As a result, 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 DHFR inhibition effects of methotrexate.

The cytotoxicity of methotrexate results from three important actions: inhibition of DHFR, inhibition of thymidylate synthase, and alteration of the transport of reduced folates. The affinity of DHFR to methotrexate is far greater than its affinity for folic acid or dihydrofolic acid, therefore, large doses of folic acid given simultaneously will not reverse the effects of methotrexate. However, Leucovorin Calcium, a derivative of tetrahydrofolic acid may block the effects of methotrexate if given shortly after the antineoplastic agent. 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 polyglutamination of methotrexate. The actual mechanism of action is unknown.

Methotrexate has immunosuppressive activity, this may be a result of inhibition of lymphocyte multiplication. The mechanisms of action in the management of rheumatoid arthritis of the drug is not known, although suggested mechanisms have included immunosuppressive and/or anti-inflammatory effects.

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.

Orally administered methotrexate is absorbed rapidly in most, but not all patients and reaches peak serum levels in 1 to 4 hours. Methotrexate is generally completely absorbed following parenteral administration, and after intramuscular injection peak serum concentrations occur in 30 to 60 minutes.

The terminal half-life reported for methotrexate is approximately 3 to 10 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 8 to 15 hours.

Excretion of single daily doses occurs through the kidneys in amounts from 80% to 90% within 24 hours. Repeated doses daily result in more sustained serum levels and some retention of methotrexate over each 24-hour period, which may result in accumulation of the drug within the tissues. The liver cells appear to retain certain amounts of the drug for prolonged periods even after a single therapeutic dose. Methotrexate is retained in the presence of impaired renal function and may increase rapidly in the serum and in the tissue cells under such conditions. Methotrexate does not penetrate the blood cerebrospinal fluid barrier in therapeutic amounts when given orally or parenterally. High concentrations of the drug, when needed, may be attained by direct intrathecal administration.

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

INDICATIONS AND CLINICAL USES

Two major fields of indication exists for METOJECT (methotrexate sodium):

1. Neoplastic diseases

2. Disease Modifying Antirheumatic Drug (DMARD)

1) <u>Neoplastic Diseases</u>

a) Choriocarcinoma: METOJECT - as single chemotherapy or in combination with other drugs
b) Intermediate-, or high grade Non Hodgkin's Lymphoma (NHL) as part of ProMACE-CytaBOM, ProMACE-MOPP, Magrath protocols.
c) Breast Ca-: as part of CMF
d) Acute Lymphoblastic Leukemia (ALL)- as maintenance therapy
e) Head and Neck Ca - in combination with other chemotherapies (CT)
f) Gastric Ca - palliative combination chemotherapy
g) Metastasis of unknown primary - as palliative combination chemotherapy
h) Osteogenic sarcoma (adjuvant) - high dose METOJECT with leucovorin rescue (HDMTX-LV)
i) Bladder Ca (advanced) - as part of M-VAC
j) Leptomeningeal spread of malignancies (carcinomatosis/leukemia/lymphoma) as a single chemotherapy or alternating with Ara-C
k) Burkitt's lymphoma
1) Advanced stages of childhood lymphoma (III and IV, St. Jude's Childrens' Research Hospital Staging System)
m) Advanced cases of mycosis fungoids

2) <u>Disease Modifying Antirheumatic Drug (DMARD)</u>

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

a) severe disabling psoriasis/psoriatic arthritis
b) severe disabling rheumatoid arthritis (RA)
c) severe, disabling seronegative arthritides

In the treatment of psoriasis, METOJECT 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.

CONTRAINDICATIONS

Pregnancy: METOJECT (methotrexate sodium) can cause fetal death or teratogenic effects when administered to a pregnant woman. METOJECT 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 METOJECT until pregnancy is excluded and should be fully counselled 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 METOJECT; during and for a minimum of three months after therapy for male patients, and during and for at least one ovulatory cycle after therapy for female patients (see **WARNINGS**).

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

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

Patients with psoriasis or rheumatoid arthritis who have pre-existing blood dyscrasias, such as bone marrow hypoplasia, leucopenia, thrombocytopenia or significant anemia, should not receive METOJECT.

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

WARNINGS

DEATHS HAVE BEEN REPORTED WITH THE USE OF METOJECT (METHOTREXATE SODIUM) IN THE TREATMENT OF MALIGNANCY, PSORIASIS, AND RHEUMATOID ARTHRITIS. THE USE OF METOJECT HIGH DOSE REGIMENS RECOMMENDED FOR OSTEOSARCOMA REQUIRES METICULOUS CARE (see **DOSAGE AND ADMINISTRATION**). HIGH DOSAGE REGIMENS FOR OTHER NEOPLASTIC DISEASES ARE INVESTIGATIONAL AND A THERAPEUTIC ADVANTAGE HAS NOT BEEN ESTABLISHED.

BECAUSE OF THE POSSIBILITY OF SERIOUS TOXIC REACTIONS, THE PATIENT SHOULD BE INFORMED BY THE PHYSICIAN OF THE RISKS INVOLVED AND SHOULD BE UNDER A PHYSICIAN'S CONSTANT SUPERVISION.

USE IN PREGNANCY

METOJECT 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 PATIENTS WITH PSORIASIS OR RHEUMATOID ARTHRITIS SHOULD NOT RECEIVE METOJECT (see **CONTRAINDICATIONS**).

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

1. Malignant lymphomas, which may regress following withdrawal of METOJECT, may occur in patients receiving low-dose METOJECT and, thus, may not require cytotoxic treatment. Discontinue METOJECT first and, if the lymphoma does not regress, appropriate treatment should be instituted.

2. Like other cytotoxic drugs, METOJECT may induce "tumour lysis syndrome" in patients with rapidly growing tumours. Appropriate supportive and pharmacologic measures may prevent or alleviate this complication.

3. Periodic monitoring for toxicity, including CBC with differential and platelet counts, and liver and renal function tests is a mandatory part of METOJECT therapy. Liver biopsies prior to METOJECT therapy are not indicated routinely. Liver function tests (LFTs) should be determined prior to the initiation of therapy with METOJECT and they should be monitored regularly throughout therapy. Patients at increased risk for impaired METOJECT elimination (e.g., renal dysfunction, pleural effusions, or ascites) should be monitored more frequently (see **PRECAUTIONS**).

4. METOJECT therapy in patients with impaired renal function should be undertaken with extreme caution, and at reduced dosages, because renal dysfunction will prolong METOJECT elimination.

5. METOJECT 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 METOJECT levels.

6. METOJECT 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 often are not preceded by symptoms or abnormal liver function tests (see **PRECAUTIONS**).

7. METOJECT-induced lung disease is a potentially dangerous lesion, which may occur acutely at any time during therapy and which has been reported at doses as low as 7.5

mg/week. It is not always fully reversible. Pulmonary symptoms (especially a dry, non-productive cough) may require interruption of treatment and careful investigation.

8. METOJECT should be used with caution in patients with impaired bone marrow function and previous or concomitant wide field radiotherapy. METOJECT may produce marked bone marrow depression, with resultant anemia, leucopenia, and/or thrombocytopenia.

9. Diarrhea and ulcerative stomatitis require interruption of therapy; otherwise, hemorrhagic enteritis and death from intestinal perforation may occur.

10. Unexpectedly severe (sometimes fatal) marrow suppression and gastrointestinal toxicity have been reported with concomitant administration of METOJECT (usually in high dosage) along with some non-steroidal anti-inflammatory drugs (NSAIDs) (see **PRECAUTIONS, Drug Interactions**).

11. Bone marrow and mucosal toxicity of METOJECT depend on: i) dose and ii) duration of exposure of high levels ($>2x10^{-8}$ mol/L (0.02 micromolar)) of METOJECT. Since the critical time factor has been defined for these organs as being 42 hours in humans, this has the following implications:
    i) when high doses of METOJECT are employed ($>1g/m^2$), drug levels in serum should be monitored;

    ii) when drug levels exceeding ($2x10^{-8}$ mol/L (0.02 micromolar)) the above for >42 hours may forecast significant toxicity;

    iii) when toxicity can be minimized by appropriate administration of Leucovorin Calcium;

    iv) when high-dose METOJECT (HDMTX) is employed, it is imperative to alkalinise the urine in order to prevent crystallisation of METOJECT and its 7-hydroxy metabolite in the urine, which may lead to acute renal failure.

12 Severe, occasionally fatal, skin reactions have been reported following single or multiple doses of METOJECT. Reactions have occurred within days of ~~oral~~, intramuscular, intravenous or intrathecal METOJECT administration. Recovery has been reported with discontinuation of therapy (see **PRECAUTIONS, Organ System Toxicity, Skin**).

13 Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with METOJECT therapy.

14 METOJECT given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.

PRECAUTIONS

General

METOJECT (methotrexate sodium) has the potential for serious toxicity (see **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 METOJECT 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 **SYMPTOMS AND TREATMENT OF OVERDOSAGE**). If METOJECT therapy is re-instituted, it should be carried out with caution, with adequate consideration of further need for the drug and with increased alertness as to possible recurrence of toxicity.

Elderly

The clinical pharmacology of METOJECT 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.

Pediatric Use

Safety and effectiveness in children have not been established, other than in cancer chemotherapy.

Use in Pregnancy (see **CONTRAINDICATIONS**)

Carcinogenesis, Mutagenesis, and Impairment of Fertility

No controlled human data exist regarding the risk of neoplasia with METOJECT. METOJECT has been evaluated in a number of animal studies for carcinogenic potential with inconclusive results. Although there is evidence that METOJECT causes chromosomal damage to animal somatic cells and human bone marrow cells, the clinical significance remains uncertain. Assessment of the carcinogenic potential of METOJECT is complicated by conflicting evidence of an increased risk of certain tumors in rheumatoid arthritis. Benefit should be weighed against this potential risk before using METOJECT alone or in combination with other drugs, especially in children or young adults. METOJECT 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.

Nursing Mothers (see **CONTRAINDICATIONS**)

Patients with Special Diseases and Conditions

(Organ System Toxicity)

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

Hematologic: METOJECT can suppress hematopoiesis and cause anemia, leucopenia, and/or thrombocytopenia. In patients with malignancy and pre-existing hematopoietic impairment, the drug should be used with caution, if at all. In controlled clinical trials in rheumatoid arthritis (n=128), leucopenia (WBC $<3000/mm^3$) was seen in 2 patients, thrombocytopenia (platelets $<1000,000/mm^3$) in 6 patients, and pancytopenia in 2 patients.

In psoriasis and rheumatoid arthritis, METOJECT should be stopped immediately if there is a significant drop in blood counts. In the treatment of neoplastic diseases, METOJECT 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: METOJECT 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 pre-existing liver damage or impaired hepatic function.

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.

In psoriasis, the usual recommendation is to obtain a liver biopsy at a total cumulative dose of 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 pre-therapy. Although these mild changes are usually not a reason to avoid or discontinue METOJECT therapy, the drug should be used with caution.

Clinical experience with liver disease in rheumatoid arthritis is limited, but the same risk factors would be anticipated. Liver function tests are also usually not reliable predictors of histological changes in this population.

When to perform a liver biopsy in rheumatoid arthritis patients has not been established, either in terms of cumulative METOJECT dose or duration of therapy. 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 1500 mg) 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.

Infection or Immunologic States: METOJECT 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 METOJECT therapy. Immunization with live virus vaccines is generally not recommended. There have been reports of disseminated vaccinia infections after smallpox immunization in patients receiving METOJECT therapy. Hypogammaglobulinemia has been reported rarely.

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

Neurologic: There have been reports of leucoencephalopathy following intravenous administration of METOJECT 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 METOJECT (1 mg/m^2). Symptomatic patients were commonly noted to have leucoencephalopathy and/or microangiopathic calcifications on diagnostic imaging studies. Chronic leucoencephalopathy has also been reported in patients with osteosarcoma who received repeated doses of high-dose METOJECT with leucovorin rescue even without cranial irradiation. Discontinuation of METOJECT does not always result in complete recovery.

A transient acute neurologic syndrome has been observed in patients treated with high dosage regimens. Manifestations of this neurologic disorder may include behavioral abnormalities, focal sensorimotor signs and abnormal reflexes. The exact cause is unknown.

After the intrathecal use of METOJECT, the central nervous system toxicity which may occur can be classified as follows: chemical arachnoiditis manifested by such symptoms as headache, back pain, nuchal rigidity, and fever; paresis, usually transient, manifested by paraplegia associated with involvement with one or more spinal nerve roots; leucoencephalopathy manifested by confusion, irritability, somnolence, ataxia, dementia, and occasionally major convulsions.

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

Renal: High doses of METOJECT used in the treatment of osteosarcoma may cause renal damage leading to acute renal failure. Nephrotoxicity is due primarily to the precipitation of METOJECT and 7-hydroxy methotrexate in the renal tubules. Close attention to renal function including adequate hydration, urine alkalinization and measurement of serum METOJECT 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 METOJECT administration. Reactions were noted after single or multiple, low, intermediate or high doses of METOJECT in patients with neoplastic and non-neoplastic diseases.

Other Precautions: METOJECT should be used with extreme caution in the presence of debility.

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

Drug Interactions

Nonsteroidal anti-inflammatory drugs should not be administered prior to or concomitantly with the high doses of METOJECT used in the treatment of osteosarcoma. Concomitant administration of some NSAIDs with high dose METOJECT therapy has been reported to elevate and prolong serum METOJECT 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 METOJECT. These drugs have been reported to reduce the tubular secretion of METOJECT thereby enhancing its toxicity.

Despite the potential interactions, studies of METOJECT 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.

METOJECT 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 METOJECT with this drug should be carefully monitored.

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

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

Oral antibiotics such as tetracycline, chloramphenicol, and non-absorbable broad spectrum antibiotics, may decrease intestinal absorption of METOJECT 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 METOJECT absorption, whereas Kanamycin increases METOJECT absorption.

Trimethoprim/sulfamethoxazole has been reported rarely to increase bone marrow suppression in patients receiving METOJECT, probably by an additive antifolate effect.

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

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

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

Laboratory tests Patients undergoing METOJECT 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, and liver and renal function every 1 to 3 months. More frequent monitoring is usually indicated during antineoplastic therapy. During initial or changing doses, or during periods of increased risk of elevated METOJECT (methotrexate sodium) blood levels (e.g., dehydration), more frequent monitoring may also be indicated.

A relationship between abnormal liver function tests and fibrosis or cirrhosis of the liver has not been established. Transient liver function test abnormalities are observed frequently after METOJECT administration and are usually not cause for modification of METOJECT therapy. Persistent liver function test abnormalities just prior to dosing and/or depression of serum albumin may be indicators of serious liver toxicity and require evaluation.

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

Information for Patients

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

Both the physician and pharmacist should emphasize to the patient that the recommended dose is taken weekly in rheumatoid arthritis and psoriasis, and that mistaken daily use of the recommended dose has led to fatal toxicity.

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

ADVERSE REACTIONS

IN GENERAL, THE INCIDENCE AND SEVERITY OF ACUTE SIDE EFFECTS ARE RELATED TO DOSE, FREQUENCY OF ADMINISTRATION, AND THE DURATION OF THE EXPOSURE TO SIGNIFICANT BLOOD LEVELS OF METHOTREXATE SODIUM TO THE TARGET ORGANS. THE MOST SERIOUS REACTIONS ARE DISCUSSED ABOVE UNDER PATIENTS WITH SPECIAL DISEASES AND CONDITIONS (ORGAN SYSTEM TOXICITY) IN THE PRECAUTION SECTION. THAT SECTION SHOULD ALSO BE CONSULTED WHEN LOOKING FOR INFORMATION ABOUT ADVERSE REACTIONS WITH METHOTREXATE SODIUM.

The most frequently reported adverse reactions include ulcerative stomatitis, leucopenia, 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 Sodium are listed below by organ system. In the oncology setting, concomitant treatment and the underlying disease make specific attribution of a reaction to Methotrexate Sodium difficult.

Hematopoietic:
Methotrexate Sodium can suppress hematopoiesis and cause anemia, leucopenia, and/or thrombocytopenia (see **PRECAUTIONS, Organ Toxicity**).

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

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. Aphasia, hemiparesis, paresis and convulsions have also occurred following administration of Methotrexate Sodium. Following low doses, there have been occasional reports of transient subtle cognitive dysfunction, mood alteration, or unusual cranial sensations, leucoencephalopathy, or encephalopathy.

Infection:
There have been case reports of sometimes fatal opportunistic infections in patients receiving Methotrexate Sodium therapy for neoplastic and non-neoplastic diseases. *Pneumocystis carinii* pneumonia was the most common infection. Other reported infections included nocardiosis, histoplasmosis, cryptococcosis, *Herpes zoster, H. simplex hepatitis*, and disseminated *H. simplex*.

Pulmonary System:
Interstitial pneumonitis deaths have been reported, and chronic interstitial obstructive pulmonary disease has occasionally occurred.

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

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

Rare reactions:
Related to or attributed to the use of Methotrexate Sodium such as nodulosis, vasculitis, herpes zoster, sepsis, arthralgia/myalgia, loss of libido/impotence, diabetes, osteoporosis sudden death, lymphomas, tumor lysis syndrome, soft tissue necrosis and osteonecrosis. A few cases of anaphylactoid reactions have been reported.

Malignant lymphomas, which may regress following withdrawal of Methotrexate Sodium, may occur in patients receiving low-dose Methotrexate Sodium, and thus may not require cytotoxic treatment. Discontinue Methotrexate Sodium first and, if the lymphoma does not regress, appropriate treatment should be instituted.

ADVERSE REACTIONS REPORTED IN RHEUMATOID ARTHRITIS
Incidence greater than 10%: elevated liver enzymes 15%, nausea/vomiting 10%.
Incidence 3% to 10%: stomatitis, thrombocytopenia.
Incidence 1% to 3%: rash/pruritus/dermatitis, alopecia, diarrhea, dizziness, leukopenia and pancytopenia.

ADVERSE REACTIONS IN PSORIASIS
The adverse reaction rates reported are very similar to those in the rheumatoid arthritis studies. Rarely, painful psoriatic plaque erosions may appear.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

See **PRECAUTIONS** -*Organ System Toxicity*

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 METOJECT (methotrexate sodium). Leucovorin administration

should begin as promptly as possible. As the time interval between METOJECT administration and leucovorin initiation increases, the effectiveness of leucovorin in counteracting toxicity decreases. Monitoring of the serum METOJECT concentration is essential in determining the optimal dose and duration of treatment with leucovorin (see **DOSAGE AND ADMINISTRATION**).

In cases of massive overdosage, hydration and urinary alkalinization may be necessary to prevent the precipitation of METOJECT and/or its metabolites in the renal tubules. Generally, neither hemodialysis nor peritoneal dialysis has been shown to improve METOJECT elimination. However, effective clearance of METOJECT has been reported with acute intermittent hemodialysis using a high-flux dialyzer.

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

DOSAGE AND ADMINISTRATION

Neoplastic Diseases

METOJECT (methotrexate sodium) may be given by the intramuscular, intravenous, intra-arterial, intrathecal or intraventricular (via Ommaya reservoir into the CNS) routes.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. METOJECT 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:

Breast Cancer

The initial doses of CMF will be cyclophosphamide 100 mg/m^2 p.o. days 1 through 14, METOJECT 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 METOJECT will be 30 mg/m^2 IV day 1, 8.

If total bilirubin exceeds 1.5 mg per dL, decrease the dose of METOJECT 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.

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 <50mL/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.

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

METOJECT 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).

METOJECT 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 intravenous METOJECT 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: METOJECT (1.5 g/m^2 IV day 1, + 5-Fluorouracil (1.5 g/m^2 IV) + Leucovorin (15 mg/m^2 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

METOJECT is administered 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 followed by a complete resolution of measurable lesions in 4 to 6 weeks. One to two courses of METOJECT after normalization of beta-HCG is usually recommended. Before each course of the drug, careful clinical assessment is essential. Cyclic combination therapy of METOJECT with other anti-tumour drugs has been reported as being useful.

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

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

Lymphomas

In Burkitt's tumour, Stages I-II, METOJECT has produced prolonged remissions in some cases. In Stage III, METOJECT 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 METOJECT 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 METOJECT include groups: the ProMACE/MOPP, ProMACE-CytaBOM, Magrath Protocols. Represented in the table below for example, is the ProMACE CytaBOM Regimen.

ProMACE-CytaBOM	**Day 1**	**Day 8**	**Day 14**	**Day 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		
Methotrexate Sodium 120 mg/m^2 IV		X with Leucovorin rescue		

ProMACE-CytaBOM	Day 1	Day 8	Day 14	Day 15-21
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, METOJECT is used effectively in combination chemotherapy regimens.

Mycosis Fungoides

Therapy with METOJECT appears to produce a clinical response 70% of the time, but chemotherapy is not curative. Dose levels of drug and adjustment of dose regimen by reduction or cessation of drug are guided by patient response and hematologic monitoring. METOJECT can be 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.

METOJECT alone or in combination with steroids was used initially for induction of remission in acute lymphoblastic leukemias (ALL). More recently, corticosteroid therapy in combination with other antileukemic drugs or in cyclic combinations with METOJECT included, has appeared to produce rapid and effective remissions. When used for induction, METOJECT in doses of 3.3 mg/m^2 in combination with 60 mg/m^2 of prednisone, given daily, produced remission in 50% of patients treated usually within a period of 4 to 6 weeks. METOJECT 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: METOJECT is administered 2 times weekly 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 occurs, 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 acute lymphoblastic leukemia (ALL). The physician should be familiar with recent advances in antileukemia therapy.

Meningeal Leukemia

In the treatment or prophylaxis of meningeal leukemia, METOJECT must be administered intrathecally.

For intrathecal administration, METOJECT 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 METOJECT *administration* at a dose of 12 mg/m^2 (maximum 15 mg) has been reported to result in low CSF METOJECT 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 sodium 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 METOJECT 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. METOJECT 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. METOJECT given by the intrathecal route appears significantly in the systemic circulation and may cause systemic METOJECT 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 METOJECT 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 METOJECT (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 METOJECT 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 METOJECT treatment is 12 grams/m^2. If this dose is not sufficient to produce a

peak serum METOJECT concentration of 1,000 micromolar (10^{-3}mol/L) at the end of the METOJECT 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 METOJECT infusion.	4,5,6,7,11,12,15,16,29,30,44,45
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** 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 METOJECT are to be administered, the following safety guidelines should be closely observed.

GUIDELINES FOR METOJECT *THERAPY WITH LEUCOVORIN RESCUE*

1. Administration of METOJECT 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 METOJECT infusion. Continue hydration at 125 mL/m^2 /hr (3 liters/m^2/day) during the METOJECT infusion, and for 2 days after the infusion has been completed.

    b) Alkalinize urine to maintain pH above 7.0 during METOJECT 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 METOJECT 24 hours after starting METOJECT and at least once daily until the METOJECT level is below $5x10^{-8}$mol/L (0.05 micromolar).

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

Patients who experience delayed early METOJECT 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 METOJECT 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 METOJECT elimination, or abnormalities in

renal function following METOJECT 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 METOJECT (e.g., medications which may interfere with METOJECT 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 METOJECT

Clinical Situation	**Laboratory Findings**	**Leucovorin Dosage and Duration**
Normal METOJECT Elimination	Serum METOJECT 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 METOJECT infusion).
Delayed Late METOJECT Elimination	Serum METOJECT 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 METOJECT level is less than 0.05 micromolar.
Delayed Early METOJECT Elimination and/or Evidence of Acute Renal Injury	Serum METOJECT 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 METOJECT 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 METOJECT level is less than 1 micromolar; than 15 mg IV q three hours, until METOJECT level is less than 0.05 micromolar.

PSORIASIS AND RHEUMATOID ARTHRITIS

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**).

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 (see **ADVERSE REACTIONS**). Maximal myelosuppression usually occurs in seven to ten days.

Psoriasis
Recommended Starting Dose Schedule

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

The dosage may be gradually adjusted to achieve optimal clinical response; 30 mg/week should not ordinarily be exceeded.

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

Rheumatoid Arthritis
Recommended Starting Dosage Schedule

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

PHARMACEUTICAL INFORMATION

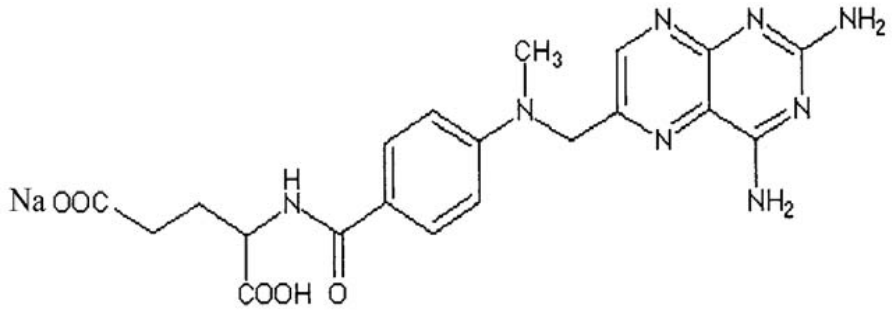
Drug Substance

Proper name: Methotrexate

Chemical name: N-[4-[[(2,4-diamino-6-pteridinyl)methylamino]benzoyl]-L-glutamic acid

Molecular formula and molecular mass: $C_{20}H_{22}N_8O_5$ (454.45 g/mol)

Chemical Structure:



Physical Form: A yellow to orange-crystalline powder. Contains not more than 12% water. Methotrexate is a mixture of 4-amino-10-methylfolic acid and closely related compounds and is equivalent to not less than 94.0% of $C_{20}H_{22}N_8O_5$ calculated on the anhydrous basis. The parenteral solution is prepared with the sodium salt, but potency is always expressed on the basis of the acid.

Solubility: Methotrexate is practically insoluble in water, ethanol, chloroform, and diethylether; freely soluble in dilute solutions of alkali and carbonates; slightly soluble in dilute hydrochloric acid.

COMPOSITION

METOJECT (methotrexate sodium) 10 mg/mL solution for injection is available in single-use pre-filled syringes. Non-medicinal ingredients include sodium chloride, sodium hydroxide and water.

Stability and Storage Recommendations:

Store between 15-30ºC. Any unused solution should be discarded. Protect from light

Incompatibilities:

Other drugs should not be mixed with METOJECT.

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

See **PRECAUTIONS** for clinical incompatibilities.

Special Instructions - Handling and Disposal of Cytotoxic Drugs

METOJECT 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. METOJECT 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 METOJECT should wear PVC gloves, safety glasses and protective clothing such as disposable gowns and masks.

4. Personnel regularly involved in the 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 METOJECT 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 METOJECT with water and discard in the sewer system with running water.

4. 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 METOJECT may be rinsed with water and washed thoroughly with soap and water.

Spillage/Contamination

Wear gloves, mask, 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.

AVAILABILITY OF DOSAGE FORMS

METOJECT (methotrexate sodium) 10 mg/mL solution for injection is available in single-use pre-filled syringes. Non-medicinal ingredients include sodium chloride, sodium hydroxide and water.

METOJECT is available as follows;

* 1 mL syringe with 0.75 mL solution for injection, equivalent to 7.5 mg methotrexate
* 1 mL syringe with 1 mL solution for injection, equivalent to 10 mg methotrexate
* 2.25 mL syringe with 1.5 mL solution for injection, equivalent to 15 mg methotrexate
* 2.25 mL syringe with 2 mL solution for injection, equivalent to 20 mg methotrexate
* 3 mL syringe with 2.5 mL solution for injection, equivalent to 25 mg methotrexate

All syringes are available in cartons of 1, 5 or 10 single-use pre-filled syringes.

PHARMACOLOGY

Human 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 children, oral absorption has been reported to vary widely (23% to 95%). A twenty fold difference between highest and lowest peak levels (C_{max}: 0.11 to 2.3 micromolar after a 20 mg/m^2 dose) has been reported. Significant inter-individual variability has also been noted in time to peak concentration (T_{max} :0.67 to 4 hrs after a 15 mg/m^2 dose) and fraction of dose absorbed. Food has been shown to delay absorption and reduce peak concentration. Methotrexate is generally completely absorbed from parenteral routes of injection. After intramuscular injection, peak serum concentrations occur in 30 to 60 minutes.

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

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

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

Metabolism - After absorption, methotrexate undergoes hepatic and intracellular metabolism to polyglutamated forms which can be converted back to methotrexate by hydrolase enzymes. These polyglutamates act as inhibitors of dihydrofolate reductase and thymidylate syntheses. 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-hydroxy methotrexate 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-hydroxy methotrexate is 3 to 5 fold lower than the parent compound. Methotrexate is partially metabolized by intestinal flora after oral administration.

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

Methotrexate clearance rates vary widely and are generally decreased at higher doses. Delayed drug clearance has been identified as one of the major factors responsible for methotrexate toxicity. It has been postulated that the toxicity of methotrexate for normal tissues is more dependent upon the duration of exposure to the drug rather than the peak level achieved. When a

patient has delayed drug elimination due to compromised renal function, a third space effusion, or other causes, methotrexate serum concentrations may remain elevated for prolonged periods.

The potential for toxicity from high dose regimens or delayed excretion is reduced by the administration of leucovorin calcium during the final phase of methotrexate plasma elimination. Pharmacokinetic monitoring of methotrexate serum concentrations may help identify those patients at high risk for methotrexate toxicity and aid in proper adjustment of leucovorin dosing. Guidelines for monitoring serum methotrexate levels, and for adjustment of leucovorin dosing to reduce the risk of methotrexate toxicity, are provided in **DOSAGE AND ADMINISTRATION**.

TOXICOLOGY

The acute toxicity (LD_{50}) of methotrexate in mice ranges from 65 to 70 mg/kg intravenously and 45 to 90 mg/kg intraperitoneally.

The acute oral toxicity (LD_{50}) in rats is 317 mg/kg; subcutaneously, it is 58 mg/kg and intraperitoneally it ranges from 80 to 464 mg/kg.

In a 22 month carcinogenicity study in rats that received methotrexate at doses of 0.1, 0.2 and 0.4 mg/kg/day, 5 days/week every other week, little or no effect of the drug was observed. It has been concluded that methotrexate is apparently remarkably free from toxic effects when otherwise lethal doses are administered utilizing an intermittent dosage schedule providing for a recovery period of 9 days. For example, daily oral doses of 0.4 mg/kg are lethal doses both in dogs and rats when administered for up to two weeks; when 0.5 mg/kg and 0.4 mg/kg doses, respectively, were administered daily five times a week every other week for three months to dogs and ten months to rats, they were found to be essentially without toxicity.

Methotrexate is often used clinically in doses that are nearly toxic and may cause severe depression of all blood cellular elements. Constant supervision is recommended and signs of gastrointestinal ulceration and bleeding, including bleeding from the mouth, bone marrow

depression, primarily of the white cell series and alopecia are indications of toxicity. In general, toxicity is in direct proportion to dose and exposure time to methotrexate.

Toxicity of methotrexate to the bone marrow and gastrointestinal epithelium is not so much dependent on dosage as on the duration of exposure of these organs to the drug and its extracellular (plasma) concentration. For bone marrow and gastrointestinal tract, the critical time factor has been defined as about 42 hours and the critical plasma concentration as $2xl0^{-8}$M. Both factors must be exceeded for toxicity to occur to these organs.

Doses of methotrexate resulting in plasma levels in excess of $2xl0^{-8}$M circulating for greater than 42 hours will be toxic to both the bone marrow and gastrointestinal epithelium. This toxicity can be minimized by the appropriate administration of LEUCOVORIN CALCIUM.

Methotrexate may be hepatotoxic, particularly at high dosage and with prolonged therapy. Liver atrophy, necrosis, cirrhosis, fatty changes and periportal fibrosis have been reported.

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