TAJ PHARMA

PHARMACY MEDICINE
KEEP OUT OF REACH OF CHILDREN

Rx Only

Rx Methotrexate

Methotrexate BP 1000 mg/10 ml Injection

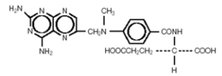
For I.M./I.V. Use Only

Methotrexate Injection BP 15 mg/3 mL,
50 mg/2 mL, 500 mg/5 mL, 1000 mg/10 mL
METHOTREXATE ™ 15 / 50 / 500 / 1000

COMPOSITION

METHOTREXATE™ 15
Methotrexate injection BP 15 mg / 3 mL
Each ml contains
Methotrexate BP 5 mg
ExcBPients q.s.
METHOTREXATE™ 50
Methotrexate Injection BP 50 mg / 2 mL
Each ml contains
Methotrexate BP 25 mg
ExcBPients q.s
METHOTREXATE™ 500
Methotrexate Injection BP 500 mg / 5 mL
Each ml contains
Methotrexate BP 100 mg
ExcBPients q.s.
METHOTREXATE™ 1000
Methotrexate Injection BP 1000 mg / 10 mL
Each ml contains
Methotrexate BP 100 mg
ExcBPients q.s.

DESCRBPTION



Chemically Methotrexate is N-[4-[[(2, 4-diamino-6 pteridinyl) methyl] methylamino] benzoyl]-L-glutamic acid. Molecular Weight: 454.45. The formula is C20H22N805. Methotrexate Injection is sterile and non-pyrogenic and may be given by the intramuscular, intravenous, intra-arterial or intrathecal route. Methotrexate Injection, is clear pale yellow colored solution.

CLINICAL PHARMACOLOGY

Methotrexate inhibits dihydrofolic acid reductase which reduces dihydrofolates to tetrahydrofolates by this 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. 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.

Pharmacokinetics

After intramuscular injection, peak serum concentrations occur in 30 to 60 minutes. At doses of 30 mg/m2 or less, Methotrexate is generally well absorbed with a mean bioavailability of about 60%. The absorption of doses greater than 80 mg/m2 is significantly less, possibly due to a saturation effect. In leukemic pediatric patients, oral absorption of Methotrexate appears to be dose dependent and vary widely (23% to 95%). A twenty fold difference between highest and lowest peak levels (Cmax: 0.11 to 2.3 micromolar after a 20 mg/m2 dose) has been reported. 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). The absorption of doses greater than 40 mg/m2 has been reported to be significantly less than that of lower doses. Food has been shown to delay absorption and reduce peak concentration. 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. After absorption, Methotrexate undergoes hepatic and intracellular metabolism to polyglutamated forms which can be converted back to Methotrexate by hydrolase enzymes. 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/m2). For patients receiving high doses of Methotrexate, the terminal half-life is eight to 15 hours. Renal excretion is the primary route of elimination, and is dependent upon dosage and route of administration. There is limited biliary excretion amounting to 10% or less of the administered dose.

INDICATIONS AND USAGE

Neoplastic Diseases
Methotrexate Injection is indicated in the treatment of gestational choriocarcinoma, chorioadenoma destruens and hydatidiform mole. 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, meningeal leukemia, osteosarcoma 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.

Psoriasis

In psoriasis Methotrexate is indicated in the symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of theraphy, but only when the diagnosis has been established, as by biopsy and/or after dermatologic consultation.
Methotrexate Injection is indicated in the management 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 theraphy including full dose non-steroidal anti-inflammatory agents (NSAIDs).

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 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. 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 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.

WARNING

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.

2. Methotrexate elimination is reduced in patients with impaired renal function, 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 and gastrointestinal toxicity have been reported with concomitant administration of Methotrexate (usually in high dosage) along with some nonsteroidal anti-inflammatory drugs (NSAIDs).

4. 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.

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

6. Methotrexate-induced lung disease is a potentially dangerous lesion, which may occur acutely at any time during therapy and which has been reported at doses as alow as 7.5 mg/week. It is not always fully reversible. Pulmonary symptoms (especially a dry, nonproductive cough) may require interruption of treatment and careful investigation.

7. 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.

8. Potentially fatal opportunistic infections, especially Pneumocystis carinii pneumonia, may occur with Methotrexate therapy.

PRECAUTIONS

General: Methotrexate has the potential for serious toxicity. 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. If Methotrexate therapy is reinstituted, it should be carried out with caution, with adequate consideration of further need for the drug and with increased alertness as to possible recurrence of toxicity.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No controlled human data exist regarding the risk of neoplasia with Methotrexate. 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: Methotrexate is in Pregnancy Category X. (See contraindications)

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

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

GI Toxicity: If vomiting, diarrhea, or stomatitis occurs, 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 Toxicity: Methotrexate can suppress hematopoiesis and cause anemia, aplastic anemia, leucopenia, and/or thrombocytopenia. In patients with malignancy and preexisting hematopoietic impairment, the drug should be used with caution, if at all. 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.

Hepatic Dysfunction: 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. Special caution is indicated in the presence of preexisting liver damage or impaired hepatic function. Liver function tests should be performed at baseline and at 4-8 week intervals in patients receiving Methotrexate for rheumatoid arthritis.

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. Potentially fatal opportunistic infections, especially Pneumocystis carinii pneumonia, may occur with Methotrexate therapy. When a patient presents with pulmonary symptoms, the possibility of

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