INJECTION / TABLET

PHARMATREXATE

U.S.P Specs.

(METHOTREXATE U.S.P)

انجکشن / گولیاں

فارماٹریگزیٹ

(میتھوٹریگزیٹ) یو۔ایس۔پی

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 with out irreversible damage to normal tissues.

PHARMACOKINETICS : Methotrexate is a weak dicarboxylic acid with pKa 4.8 and 5.5, and thus it is mostly ionized at physiologic pH. Oral absorption is saturable and thus dose-dependent, with doses less than 40 mg/m^2 having 42% bioavailability and doses greater than 40 mg/m^2 only 18%. Mean oral bioavailability is 33% (13-76% range), and there is no clear benefit to subdividing an oral dose. Mean intramuscular bioavailability is 76%. Methotrexate is metabolized by intestinal bacteria to the inactive metabolite 4-amino-4-deoxy-N-methylpteroic acid (DAMPA), which accounts for less than 5% loss of the oral dose. Factors that decrease absorption include food, oral non absorbable antibiotics (e.g. vancomycin, neomycin, and bacitracin), and more rapid transit through the gastrointestinal tract (GI) tract, such as diarrhea, while slower transit time in the GI tract from constipation will increase absorption. Methotrexate is also administered in the placenta accreta, inhibiting the blood circulation to the target site.

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 menigeal leukemia and is used in maintenance therapy in combination with other chemotherapeutic agents. 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, small cell types and 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 a 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 arthriteis (ACR criteria), 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 nonsteroidal anti-inflammatory agents (NSAIDs).

CONTRAINDICATIONS : 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. Pregnancy should be avoided if either partner is receiving methotrexate; during and for a minimum of 3 months after therapy for male patients, and during and for at least one ovulatory cycle after therapy for female patients. 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 a laboratory evidence of immuno-deficiency syndromes should not receive methotrexate. Patients with psoriasis or rheumatoid arthritis who have prexexisting blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anemia, should not receive methotrexate. Patients with known hypersensitivity to methotrexate should not receive the drug.

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 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 haemodialysis 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 increased alertness as to possible recurrence of toxicity.

Drug Interactions : Penicillins may decrease the elimination of methotrexate and thus increase the risk of toxicity.While they may be used together, increased monitoring is recommended. Probenecid inhibits methotrexate excretion, which increases the risk of methotrexate toxicity. Additionally, methotrexate neurotoxicity, -- which may cause seizures, -- is known to be induced by phenobarbital and carbamazepine, which are antiepileptic drugs.Its effects can be reversed by folinic acid (leucovorin), in a process known as "leucovorin rescue."

ADVERSE REACTIONS :

IN GENERAL. THE INCIDENCE AND SEVERITY OF ACUTE SIDE EFFECTS ARE RELATED TO DOSE AND FREQUENCY OF ADMINISTRATION.

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.

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

Boood and Lympthtic System Disorders:Suppressed hematopoiesis, anemia, aplastic anemia, pancytopenia, leukopenia, neutropenia, thrombocytopenia, agranulocytosis, eosinophillia, 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 subtile cognitive dysfunction, mood alteration, unusual cranial sensations, leukoencepalopathy, or encephalopathy.

Hepatobillary Disorders:Hepatoxicity, 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 penumonia was the most common opportunistic infection. There have also been reports of infections, pneumonia, cytomegalovirus infection, including cytomegaloviral pneumonia, sepsis, fatal sepsis, nocardiosis, histoplasmosis, cryptococosis. Herpes zoster, H. simplex hepatitis and disseminted H. simplex.

Musculoskletal System: Stress fracture.

Ophthalmic: Conjunctivitis, serious visual changes of unknown etiology.

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

Skin: Erythematous rashes prunitus, 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, spermatogenesis, transient oligospermia, menstrual dysfunction, vaginal discharge, and gynecomastia; infertility, abortion, fetal death, fetal defects. Other rarer reaction related to or attributed to the use of methotrexate such as nodulosis, vasculitis, arthralgia/myalgia, loss of libido/impotence, diabetes, osteoporosis, sudden death,reversible lymphomas tumor lysis syndrome, soft tissue necrosis, and osteonecrosis. Anaphylactoid reactions have been reported.

OVERDOSAGE : Leucovorin is indicated to diminish the toxicity and counteract the effect of inadevertently 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 have been shown to improve methotrexate elimination.

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 sodium injectable products may be given by the intramuscular and intravenous route.

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 gonadatropin (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.

Leukemia:

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 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, maintencance therapy is intiated, 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

Osteosarcoma:

An effective adjuvant chemotherapy regimen required 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. 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 patients is vomiting or is unable to tolerate oral medication leucovorin is given IV or IM at the same dose schedule.

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 hours intervals for 3 doses given as a course once weekly.

Polyarticular-Course Juvenile Rhematoid Arthritis.

The recommended starting dose is 10 mg/m^2 given once weekly.

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.

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.

RECONSTITUTION: Reconstitute immediately prior to use.

AVAILABILITY :

Pharmatrexate Injection: Glass Vial containing methotrexate U.S.P 50 mg as methotrexate sodium in sterile powder form, packed in unit carton. Preservative free.

Pharmatrexate - 2.5 Tablets: Each tablet contains methotrexate U.S.P. 2.5mg. Pack of 100 tablets in blisters.

Pharmatrexate - 10 Tablets: Each tablet contains methotrexate U.S.P. 10mg. Pack of 10 tablets in blisters.

DOSAGE: As directed by the physician.

INSTRUCTIONS: Store below 25°C.

Protect from heat, light and moisture.

Keep all medicines out of the reach of children.

To be sold on prescription of registered medical practitioner only.

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات: 25 ڈگری سینٹی گریڈ سے کم پر رکھیں۔

گرمی، نمی اور روشنی سے بچائیں۔

تمام ادویات بچوں کی پہنچ سے دور رکھیں۔

صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

Manufactured by:

PHARMEDIC LABORATORIES (PVT) LIMITED.

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