METOTREXATO KEMEX
METHOTREXATE 50 and 500 mg
Lyophilized Injectable
For Intravenous, Intrathecal, and Intramuscular Use

MADE IN ARGENTINA PRESCRIPTION ONLY

Qualitative and Quantitative Formula:
Methotrexate 50 mg
Each vial contains:
Methotrexate.....50.0 mg
Mannitol.....300.0 mg

Methotrexate 500 mg
Each vial contains:
Methotrexate.....500.0 mg
Mannitol.....300.0 mg

Methotrexate should be used only by physicians familiar with the use of antimetabolite therapy. Due to the potential for serious toxic reactions, patients should be informed by physicians about the associated risks and should be under constant medical supervision.
Deaths have been reported with the use of Methotrexate; it should be restricted to patients with severe, recalcitrant, disabling disease which is not adequately responsive to other forms of therapy, and only when the diagnosis has been established and after consultation with appropriate experts.

DESCRIPTION
Methotrexate is an antimetabolite used in the treatment of overt neoplastic diseases and severe psoriasis.
Chemically, Methotrexate is N – [-4[[- diamino – 6 – pteridinyl) methyl] methylamino] benzoyl] – L- glutamic acid.

CLINICAL PHARMACOLOGY
Methotrexate inhibits the reduction of dihydrofolic acid.
Methotrexate interferes with DNA synthesis, repair, and cellular replication.

INDICATIONS AND USAGE
Neoplastic Diseases:
Methotrexate is indicated in the treatment of gestational choriocarcinoma, chorioadenoma, and hydatidiform mole.

In Acute Lymphocytic Leukemia:
Methotrexate is indicated in the prophylaxis of meningeal leukemia and is used in maintenance therapy in combination with other chemotherapeutic agents.
Methotrexate is used alone or in combination with other antineoplastic agents in the treatment of breast cancer, skin cancer, head and neck cancer, mycosis fungoides, and lung cancer, particularly squamous cell, small cell, and advanced lymphomas.

Psoriasis:
Methotrexate is indicated in the symptomatic control of severe, recalcitrant, disabling psoriasis which is not adequately responsive to other forms of therapy, but only when the diagnosis has been established by biopsy.
It is important to ensure that psoriasis is not due to another concurrent disease affecting immune responses.

CONTRAINDICATIONS
Pregnancy.
Fertility disorders.
Lactation.
Patients with Psoriasis with alcoholism, alcoholic liver disease, or other chronic liver diseases should not receive Methotrexate.
Patients with known hypersensitivity to Methotrexate should not receive the drug.

GENERAL PRECAUTIONS
Toxic effects may be related in frequency and severity to the dose or frequency of administration but have occurred at all doses.
Most adverse reactions are reversible if detected early. When such effects or reactions do occur, the drug should be reduced in dosage or discontinued, and appropriate corrective measures should be taken.
This could include the use of calcium Leucovorin. If Methotrexate therapy is reinstituted, it should be carried out with caution, with adequate consideration of the need for the drug and increased alertness to possible recurrence of toxicity.

1) Methotrexate causes fetal death and/or congenital abnormalities. Therefore, it is not recommended for pregnant women. Pregnant patients with psoriasis should not receive Methotrexate.

2) Periodic monitoring for toxicity, including differential leukocyte count and platelet count, and tests of renal and hepatic function, is mandatory in the therapy. Periodic liver biopsies may be indicated for some patients. Patients at increased risk because of impaired Methotrexate elimination (renal dysfunction, pleuritis effusions, or ascites) should be monitored more frequently.

3) Methotrexate causes hepatotoxicity, fibrosis, and cirrhosis but generally only after prolonged use. Acute liver enzyme elevations occur frequently. These, generally, have correlated with histologic evidence of liver damage, and have been transient and reversible upon discontinuation of therapy. Persistent liver enzyme elevations >3 times the upper limit of normal should result in discontinuation of Methotrexate therapy.

4) Methotrexate can cause pulmonary disease, which can occur at any time during therapy. It is not always reversible.

5) Methotrexate can produce marked bone marrow depression, which can result in anemia, leukopenia, and/or thrombocytopenia.

6) Diarrhea and ulcerative stomatitis require discontinuation of therapy; otherwise, hemorrhagic enteritis and death from intestinal perforation may occur.

7) Therapy with Methotrexate in patients with impaired renal function should be undertaken with extreme caution, and with dosage reduction.

8) Bone marrow suppression and gastrointestinal toxicity have been reported with concurrent administration of Methotrexate (usually in high doses) along with some nonsteroidal anti-inflammatory drugs.

PATIENT INFORMATION
Patients should be informed of the early signs and symptoms of toxicity, which need to be reported to the physician as soon as they occur, and need continuous follow-up, including laboratory tests to monitor toxicity.
Both the physician and the pharmacist should emphasize to the patients the importance of adhering to the recommended dose schedule for psoriasis and that incorrect daily use of the recommended dose can result in potentially fatal toxicity.
Patients should be informed of the potential benefits and risks of Methotrexate. Risks of effects on reproduction should be discussed with both male and female patients taking Methotrexate.

DENTISTRY
Depression of the bone marrow effects can lead to increased microbial infections, delayed healing, and gingival bleeding; dental work should if possible be completed before the initiation of therapy and resumed after the blood count has recovered to normal levels. Patients should be instructed in proper oral hygiene and cautioned in the use of brushes, floss, and toothpicks.
May lead to stomatitis, which can be associated with significant discomfort.

LABORATORY TESTING
Patients undergoing Methotrexate therapy should be monitored periodically for toxic effects.

The following is especially important:
Blood urea nitrogen (BUN).
Hematocrit.
Platelet count.
Alanine aminotransferase (ALT/GPT).
Serum aspartate aminotransferase (AST/GOT).
Serum bilirubin.
Serum creatinine.
Serum lactate dehydrogenase (LDH).
Total and differential leukocyte count (recommended before initiating therapy and then as clinically indicated, drug, dose, and other concurrently used medications).
Bone Marrow Aspiration (recommended every 2 weeks until remission is achieved).

INTERACTIONS WITH OTHER DRUGS
Not to be coadministered with nonsteroidal anti-inflammatory drugs (NSAIDs), salicylates, phenytoin, phenylbutazone, sulfonamides, probenecid, oral antibiotics such as tetracycline, chloramphenicol, vitamin preparations with folic acid, folic acid deficiency states, trimethoprim, sulfamethoxazole.

CYTARABINE
Administration of cytarabine during the period from 48 hours before to 10 minutes after the start of Methotrexate therapy can result in synergism of cytotoxic effects. However, evidence is not definitive and dosage adjustment based on routine hematologic monitoring is recommended.

BONE MARROW DEPRESSANTS
Radiation therapy (simultaneous use may enhance the bone marrow depressant effects of these medications and radiation therapy: dosage reduction may be necessary).

LIVE VIRUS VACCINES
Due to suppressed normal defense mechanisms, concurrent use with live virus vaccines can enhance vaccine virus replication and/or decrease patient antibody response to the vaccine: immunization of these patients should be approached cautiously after careful review of the patient's hematologic status and only with the knowledge and consent of the physician supervising the Methotrexate therapy. The time interval between cessation of the immunosuppressive drug(s) and restoration of the ability to respond to the vaccine depends on the intensity and type of immunosuppressive therapy used, the underlying disease, and other factors, and is estimated to vary from 3 months to 1 year.
Patients in remission from leukemia should not receive live virus vaccines until at least 3 months after chemotherapy. Additionally, immunization with oral polio vaccine should be deferred for persons in close contact with the patient, particularly family members.

PEDIATRIC USE
Safety and effectiveness in children have not been established.

GASTROINTESTINAL SYSTEM
If vomiting, diarrhea, or stomatitis occur, leading to dehydration, Methotrexate should be discontinued until recovery occurs. Methotrexate should be used with extreme caution in the presence of peptic ulcer or ulcerative colitis.

HEMATOLOGY
Methotrexate can suppress hematopoiesis and cause anemia, leukopenia, and/or thrombocytopenia. Psoriasis.
Methotrexate should be immediately discontinued if there is a drop in blood count.
In the treatment of neoplastic diseases, Methotrexate should be continued only if the potential benefits outweigh the risks of severe myelosuppression.

PATIENTS WITH PROFOUND GRANULOCYTOPENIA AND FEVER
Should be promptly evaluated and often require antibiotic therapy.

LIVER
Methotrexate is hepatotoxic in the acute phase (elevated transaminases) and chronic phase (fibrosis and cirrhosis); chronic toxicity is potentially fatal and generally occurs after prolonged use (usually 2 years or more) and after total doses of 15 g or more.

INFECTION OR IMMUNOLOGICAL STATES
Methotrexate should be used with extreme caution in the presence of active infection and is usually contraindicated in patients with evidence of immunodeficiency syndromes. Immunization may be ineffective during Methotrexate therapy.

NEUROLOGICAL
After intrathecal use of Methotrexate, central nervous system toxicity can occur, which may be classified as:
Arachnoiditis, headache, back pain, fever, usually transient paresis, confusion, irritability, drowsiness, ataxia, dementia, and occasionally grand mal seizures.

LUNG
Pulmonary symptoms or nonspecific pneumonitis.
May induce potentially dangerous injury and requires treatment discontinuation and careful investigation.

SIDE EFFECTS - ADVERSE REACTIONS
Many adverse effects of antineoplastic therapy are unavoidable and represent the pharmacological action of the medication. Some of these (e.g., leukopenia and thrombocytopenia) are currently used as parameters to assist in individual dosage assessment.

More frequent:
Ulcerative stomatitis, leukopenia, nausea, abdominal pain, fatigue, fever, tiredness, immunosuppression.

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

Central Nervous System:
Headache, drowsiness, blurred vision, aphasia, hemiparesis, paresis, seizures.

Pulmonary System:
Severe chronic interstitial pneumonitis. Pulmonary disease.

Skin:
Erythematous rash, pruritus, urticaria, alopecia, telangiectasia, furunculosis.

Urogenital System:
Severe nephropathies, renal damage, azotemia, cystitis, hematuria.

Spermatogenesis:
Transient oligospermia.

Menstrual Dysfunction:
Fetal defects, infertility, abortion.

Very rare:
Arthralgias, myalgias, osteoporosis, and sudden death. Anaphylactic shock.

DOSAGE
Route of Administration:
- Preferably: intravenous
- Other routes: Intramuscular, intra-arterial, or intrathecal.

Choriocarcinomas, Hydatidiform Mole, and similar trophoblastic diseases: 15 to 30 mg per day for a course of 5 days.
Usually used in combination with other drugs.
Monitoring of urinary HCG is advisable.

Acute Lymphoblastic Leukemia:
Children and young adolescents in combination with prednisone:
Methotrexate: 3.3 mg/m². Prednisone: 60 mg/m daily for a period of 4 to 6 weeks.

Meningeal Leukemia:
Intrathecally: Dilute with preservative-free parenteral solutions to concentrations of 1 mg/ml.

Dose: 12 mg/m² (maximum: 15 mg/m²)

Dosing Chart/Age	
Age in years	Dose in mg/m²
< 1	6
1	8
2	10
3 or more	12

For 2.5 mg/kg/day at weekly intervals.

Preparation of the injection solution:
For intrathecal use: Dilute with preservative-free 0.98% sodium chloride solution to a concentration of 1 mg/ml.
For intravenous use: Dilute with 0.98% parenteral sodium chloride solution.

Storage of the reconstituted solution:
While the reconstituted solution remains stable for 48 hours in the refrigerator, it is recommended to use it immediately.

Handling and Disposal:
Like all cytotoxic preparations, precautions should be taken for their preparation, handling, and safe disposal.

1) Only trained personnel should handle the drug. This operation should exclude pregnant women.
2) Handling should be carried out in a specially designated area. The work surface should be covered with absorbent paper laminated on disposable plastic.
3) Adequate protective clothing should be used, i.e., PVC gloves, safety goggles, gowns, and disposable masks. In case of contact with the eyes or mucous membranes, rinse with plenty of water or saline solution.
4) Use syringes and equipment with LUER Lock fittings.
5) All unused material, needles, syringes, ampoules, and other items that have come into contact with cytotoxic drugs should be separated, placed in double-sealed polyethylene bags, and incinerated at 1000°C or higher.
Waste should receive similar treatment.

OVERDOSE
Treatment involves the use of calcium leucovorin from the onset of symptoms. There are regimens in which leucovorin is administered 24 hours before initiating Methotrexate therapy.
In case of overdose, seek medical attention at the nearest hospital or contact the Toxicology Center at:
- Hospital de Pediatría Dr. Ricardo Gutiérrez, Phone: 4821-6666
- Hospital Posadas, Phone: 4654-6648

STORAGE
Store below 30°C.

PRESENTATIONS: Packages containing 1, 2, and 5 vial ampoules.

KEEP OUT OF THE REACH OF CHILDREN.

Medicinal Speciality Authorized by The Ministry Of Health.
Certificate No. 54,934

Manufactured by:
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