METHOTREXATE INJECTION, USP

50 mg/2 mL (25 mg/mL), 250 mg/10 mL (25 mg/mL) and 1 g/40 mL (25 mg/mL)
(Preservative Free)

Rx ONLY

WARNINGS

METHOTREXATE SHOULD BE USED ONLY BY PHYSICIANS WHOSE KNOWLEDGE AND EXPERIENCE INCLUDE THE USE OF ANTIMETABOLITE THERAPY, BECAUSE OF THE POSSIBILITY OF SERIOUS TOXIC REACTIONS (WHICH CAN BE FATAL).

METHOTREXATE SHOULD BE USED ONLY IN LIFE THREATENING NEOPLASTIC DISEASES, OR IN PATIENTS WITH PSORIASIS OR RHEUMATOID ARTHRITIS WITH SEVERE, RECALCITRANT, DISABLING DISEASE WHICH IS NOT ADEQUATELY RESPONSIVE TO OTHER FORMS OF THERAPY. DEATHS HAVE BEEN REPORTED WITH THE USE OF METHOTREXATE IN THE TREATMENT OF MALIGNANCY, PSORIASIS, AND RHEUMATOID ARTHRITIS. PATIENTS SHOULD BE CLOSLY MONITORED FOR BONE MARROW, LIVER, LUNG AND KIDNEY TOXICITIES. (See PRECAUTIONS.) PATIENTS SHOULD BE INFORMED BY THEIR PHYSICIAN OF THE RISKS INVOLVED AND BE UNDER A PHYSICIAN’S CARE THROUGHOUT THERAPY. THE USE OF METHOTREXATE HIGH DOSE REGIMENS RECOMMENDED FOR OSTEOSARCOMA REQUIRES Meticulous CARE. (See DOSAGE AND ADMINISTRATION.) HIGH DOSE REGIMENS FOR OTHER NEOPLASTIC DISEASES ARE INVESTIGATIONAL AND A THERAPEUTIC ADVANTAGE HAS NOT BEEN ESTABLISHED. METHOTREXATE FORMULATIONS AND DILUENTS CONTAINING PRESERVATIVES MUST NOT BE USED FOR INTRATHECAL OR HIGH DOSE METHOTREXATE THERAPY.

1. Methotrexate has been reported to cause fetal death and/or congenital anomalies. Therefore, it is not recommended for women of childbearing potential unless there is clear medical evidence that the benefit can be expected to outweigh the considered risks. Pregnant women with psoriasis or rheumatoid arthritis should not receive methotrexate. (See CONTRAINDICATIONS).

2. Methotrexate elimination is reduced in patients with impaired renal functions, ascites, or pleural effusions. Such patients require especially careful monitoring for toxicity, and require dose reduction or, in some cases, discontinuation of methotrexate administration.

3. Unexplained severe (sometimes fatal) bone marrow suppression, aplastic anemia, and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high dosage) along with some nonsteroidal anti-inflammatory drugs (NSAIDs). (See PRECAUTIONS, Drug Interactions.)

4. Methotrexate causes hepatitis, fibrosis and cirrhosis, but generally only after prolonged use. Acutely, liver enzyme elevations are frequently seen. These are usually transient and asymptomatic, and also do not appear predictive of subsequent hepatic disease. Liver biopsy after sustained use often shows histologic changes, and fibrosis and cirrhosis have been reported; these latter lesions may not be preceded by symptoms or abnormal liver function tests in the psoriatic population. For this reason, periodic liver biopsies are usually recommended for psoriatic patients who are under long-term treatment. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid arthritis population. (See PRECAUTIONS, Organ System Toxicity, Hepatic.)

5. Methotrexate-induced lung disease, including acute or chronic interstitial pneumonitis, is a potentially dangerous lesion, which may occur acutely at any time during therapy and has been reported at low doses. It is not always fully reversible and fatalities have been reported. Pulmonary symptoms (especially a dry, nonproductive cough) may require interruption of treatment and careful investigation.

6. Diarrhea and ulcerative stomatitis require interruption of therapy. Otherwise, hemorrhagic enteritis and death from intestinal perforation may occur.

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

8. Like other cytotoxic drugs, methotrexate may induce "tumor lysis syndrome" in patients with rapidly growing tumors. Appropriate supportive and pharmacologic measures may prevent or alleviate this complication.

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

10. Potentially fatal opportunistic infections, especially pneumonia, may occur with methotrexate therapy.

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

DESCRIPTION

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

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

The structural formula is:

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{CH}_3 \\
\text{CH}_3 & \quad \text{CH}_2\text{CH}_2\text{COOH} \\
\text{HOOC} & \quad \text{CH}_2\text{CH}_2\text{COOH}
\end{align*}
\]

Molecular weight: 454.45  \( \text{C}_{29}\text{H}_{22}\text{N}_5\text{O}_5 \)

Methotrexate Injection, USP is sterile and non-pyrogenic and may be given by the intramuscular, intravenous, intra-arterial or intrathecal route. Only the preservative free formulation of Methotrexate Injection, USP may be administered by the intrathecal route. (See DOSAGE AND ADMINISTRATION.)

Methotrexate Injection, USP, Isotonic Liquid, Preservative Free, for single use only, is available in 50 mg/2 mL, 250 mg/10 mL and 1 g/40 mL vials.
CLINICAL PHARMACOLOGY

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

The mechanism of action of methotrexate in rheumatoid arthritis is unknown, it may affect immune function. Two reports describe in vitro methotrexate inhibition of DNA precursor uptake by stimulated mononuclear cells, and another describes in animal polyarthritis partial correction by methotrexate of spleen cell hyporesponsiveness and suppressed IL-2 production. Other laboratories, however, have been unable to demonstrate similar effects.

Clarification of methotrexate’s effect on immune activity and its relation to rheumatoid immunopathogenesis awaits further studies.

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

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

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

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

In a 6-month double-blind, placebo-controlled trial of 127 pediatric patients with juvenile rheumatoid arthritis (JRA) (mean age, 10.1 years; age range, 2.5 to 18 years; mean duration of disease, 5.1 years) on background nonsteroidal anti-inflammatories (NSAIDs) and/or prednisone, methotrexate given weekly at an oral dose of 10 mg/m² provided significant clinical improvement compared to placebo as measured by either the physician’s global assessment, or by a patient composite (25% reduction in the articular-severity score plus improvement in parent and physician global assessment of disease activity). Over two-thirds of the patients in this trial had polyarticular course JRA, and the numerically greatest response was seen in this subgroup treated with 10 mg/m²/wk methotrexate. The overwhelming majority of the remaining patients had systemic-course JRA. All patients were unresponsive to NSAIDs; approximately one-third were using low dose corticosteroids. Weekly methotrexate at a dose of 5 mg/m² was not significantly more effective than placebo in this trial.

Two Pediatric Oncology Group studies (one randomized and one non-randomized) demonstrated a significant improvement in relapse-free survival in patients with nonmetastatic osteosarcoma, when high dose methotrexate with leucovorin rescue was used in combination with other chemotherapeutic agents following surgical resection of the primary tumor. These studies were not designed to demonstrate the specific contribution of high dose methotrexate/leucovorin rescue therapy to the efficacy of the combination. However, a contributory effect can be inferred from the reports of objective responses in this therapy in patients with metastatic osteosarcoma, and from reports of extensive tumor necrosis following preoperative administration of this therapy in patients with non-metastatic osteosarcoma.

Pharmacokinetics

Absorption

In adults, oral absorption appears to be dose dependent. Peak serum levels are reached within one to two hours. At doses of 30 mg/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 also appears to be dose dependent and has been reported to vary widely (23% to 95%). A twenty-fold difference between highest and lowest peak levels C max (0.11 to 2.3 micromolar after a 20 mg/m² dose) has been reported. Significant interindividual variability has also been noted in time to peak concentration (T max; 0.67 to 4 hrs after a 15 mg/m² dose) and fraction of dose absorbed. 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 is generally completely absorbed from parenteral routes of injection. After intramuscular injection, peak serum concentrations occur in 30 to 60 minutes. As in leukemic pediatric patients, a wide interindividual variability in the plasma concentration of methotrexate has been reported in pediatric patients with JRA. Following oral administration of methotrexate in doses of 6.4 to 11.2 mg/m²/week in pediatric patients with JRA, mean serum concentrations were 0.59 micromolar (range, 0.33 to 1.49) at 1 hour, 0.44 micromolar (range, 0.01 to 1.00) at 2 hours, and 0.29 micromolar (range, 0.06 to 0.58) at 3 hours. In pediatric patients receiving methotrexate for acute lymphocytic leukemia (6.3 to 30 mg/m²), or for JRA (3.75 to 26.2 mg/m²), the terminal half-life has been reported to range from 0.7 to 5.8 hours or 0.9 to 2.3 hours, respectively.

Distribution

After intravenous administration, the initial volume of distribution is approximately 0.18 L/kg (18% of body weight) and steady-state volume of distribution is approximately 0.18 L/kg (40% 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. 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.

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Because they can occur at any time during therapy, it is necessary to follow patients on methotrexate. Methotrexate has the potential for serious toxicity. (See General PRECAUTIONS.)

Patients with a known hypersensitivity to methotrexate should not receive the drug. 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 psoriasis or rheumatoid arthritis who have overt or laboratory evidence of immunodeficiency syndromes should not receive methotrexate. Patients with psoriasis or rheumatoid arthritis who have preexisting blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anemia, should not receive methotrexate. Patients with a known hypersensitivity to methotrexate should not receive the drug.

**WARNINGS**

(SEE BOXED WARNINGS) Methotrexate formulations and diluents containing preservatives must not be used for intrathecal or high dose methotrexate therapy.

**PRECAUTIONS**

General

Methotrexate has the potential for serious toxicity. (See BOXED WARNINGS) Toxic effects may be related in frequency and severity to dose or frequency of administration but have been seen at all doses. Because they can occur at any time during therapy, it is necessary to follow patients on methotrexate.
Psoriasis and rheumatoid arthritis: Methotrexate is in Pregnancy Category X. See Pregnancy after cessation of therapy. Impairment of fertility, oligospermia and menstrual dysfunction in humans, during and for a short period causes embryotoxicity, abortion, and fetal defects in humans. It has also been reported to cause lymphoma treatment. Benefits should be weighed against the potential risk before using methotrexate have regressed completely following withdrawal of methotrexate, without requiring active anti-

No controlled human data exist regarding the risk of neoplasia with methotrexate. Methotrexate has been reported rarely to increase bone marrow suppression in patients receiving methotrexate, probably by decreased tubular secretion and/or an additive antifolate effect. Vitamin preparations containing folic acid or its derivatives may decrease responses to systemically administered methotrexate. Preliminary animal and human studies have shown that small quantities of intravenously administered leucovorin enter the CSF primarily as 5-methyltetrahydrofolate and, in humans, remain in 3 orders of magnitude lower than the usual methotrexate concentration following intrathecal administration. However, high doses of leucovorin may reduce the efficacy of intrathecally administered methotrexate.

Methotrexate increases the plasma levels of mercaptopurine. The combination of methotrexate and mercaptopurine may therefore require dose adjustment. Oral antibiotics such as enrofloxacin, chloramphenicol, and nonsteroidal broad spectrum antibiotics, may decrease intestinal absorption of methotrexate or interfere with the enterohepatic circulation by inhibiting bowel flora and suppressing metabolism of the drug by bacteria. Penicillins may reduce the renal clearance of methotrexate; increased serum concentrations of methotrexate with concomitant hemolytic and gastrointestinal toxicity have been observed with high and low dose methotrexate. Use of methotrexate with penicillins should be carefully monitored. The potential for increased hepatotoxicity when methotrexate is administered with other hepatotoxic agents has not been evaluated. However, hepatotoxicity has been reported in such cases. Therefore, patients receiving concomitant therapy with methotrexate and other potential hepatotoxins (e.g., azathioprine, trimethoprim, sulfonamides) should be closely monitored for possible increased risk of hepatotoxicity.

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

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Carcinogenesis, Mutagenesis, Impairment of Fertility

No controlled human data exist regarding the risk of neoplasia with methotrexate. Methotrexate has been evaluated in a number of animal studies for carcinogenic potential with inconclusive results. Although there is evidence that methotrexate causes chromosomal damage to animal somatic cells and human bone marrow cells, the clinical significance remains uncertain. Non-Hodgkin’s lymphoma and other tumors have been reported in patients receiving low-dose oral methotrexate. However, there have been instances of malignant lymphoma arising during treatment with low-dose oral methotrexate, which have regressed completely following withdrawal of methotrexate, without requiring active anti-

Drug Interactions

Nonsteroidal anti-inflammatory drugs should not be administered prior to or concomitantly with the high doses of methotrexate, such as used in the treatment of osteosarcoma. Concomitant administration of some NSAIDs with high dose methotrexate therapy has been reported to elevate and prolong serum methotrexate levels, resulting in deaths from severe hemolytic and gastrointestinal toxicity. Caution should be used when NSAIDs and salicylates are administered concomitantly with lower doses of methotrexate. These drugs have been reported to reduce the tubular secretion of methotrexate in an animal model and may enhance its toxicity. Despite the potential interactions, studies of methotrexate in patients with rheumatoid arthritis have usually included concurrent use of constant dosage regimen 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 osteosarcoma and that larger doses could lead to unexpected toxicity. Methotrexate is partially bound to serum albumin, and toxicity may be increased because of displacement by certain drugs, such as salicylates, phenylbutazone, phenytoin, and sulfonamides. Renal tubular transport is also diminished by probenecid; use of methotrexate with this drug should be carefully monitored.

In the treatment of patients with osteosarcoma, caution must be exercised if high-dose methotrexate is administered in combination with a potentially nephrotoxic chemotherapeutic agent (e.g., cisplatin). Methotrexate increases the plasma levels of mercaptopurine. The combination of methotrexate and mercaptopurine may therefore require dose adjustment. Oral antibiotics such as enrofloxacin, chloramphenicol, and nonsteroidal broad spectrum antibiotics, may decrease intestinal absorption of methotrexate or interfere with the enterohepatic circulation by inhibiting bowel flora and suppressing metabolism of the drug by bacteria. Penicillins may reduce the renal clearance of methotrexate; increased serum concentrations of methotrexate with concomitant hemolytic and gastrointestinal toxicity have been observed with high and low dose methotrexate. Use of methotrexate with penicillins should be carefully monitored.

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

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

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Pregnancy

Psoriasis and rheumatoid arthritis: Methotrexate is in Pregnancy Category X. See
Methotrexate injectable formulations containing the preservative benzyl alcohol are not recommended for use in neonates. There have been reports of "gasping syndrome" in neonates (children less than one month of age) following the administration of intravenous solutions containing the preservative benzyl alcohol. Symptoms include a striking onset of gasping respiration, hypotension, bradycardia, and cardiovascular collapse.

Serious neurotoxicity, frequently manifested as generalized or focal seizures, has been reported with unexplained increased frequency among pediatric patients with acute lymphoblastic leukemia who were treated with intermediate-dose intravenous methotrexate (15mg/m²)(See PRECAUTIONS, Organ System Toxicity, Neurologic.)

Infectious Disease

Pneumonia should be considered.
Neurologic

There have been reports of leukoencephalopathy following intravenous administration of methotrexate to patients who have had cranial irradiation. Severe neurotoxicity, frequently manifested as generalized or focal seizures, has been reported in unexpectedly increased frequency among pediatric patients with acute lymphoblastic leukemia who were treated with intermediate-dose intravenous methotrexate (1 g/m²). Symptomatic patients were commonly noted to have leukoencephalopathy and/or microangiopathic calcifications on diagnostic imaging studies. Chronic leukoencephalopathy has also been reported in patients who received repeated doses of high-dose methotrexate with leukovorin rescue even without cranial irradiation. Discontinuation of methotrexate does not always result in complete recovery. A transient acute neurologic syndrome has been observed in patients treated with high dose regimens. Manifestations of this stroke-like encephalopathy may include confusion, hemiparesis, transient blindness, seizures and coma. The exact cause is unknown. After the intrathecal use of methotrexate, the central nervous system toxicity which may occur can be classified as follows: acute chemical arachnoiditis manifested by such symptoms as headache, back pain, nuchal rigidity, and fever; sub-acute myelopathy characterized by paresthesias/paraplegia associated with involvement of one or more spinal nerve roots; chronic leukoencephalopathy manifested by confusion, irritability, somnolence, ataxia, dementia, seizures and coma. This condition can be progressive and even fatal.

Pulmonary

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

Renal

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

Skin

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

Other precautions

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

Methotrexate exit 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 accumulation, it is advisable to evacuate the fluid before treatment and to monitor plasma methotrexate levels.

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

ADVERSE REACTIONS

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

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

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

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

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

Cardiovascular:
Pericarditis, pericardial effusion, hypertension, 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 confusion have also occurred following administration of methotrexate. Following low doses, there have been occasional reports of transient subtle cognitive dysfunction, mood alteration or unusual cranial sensations, leukoencephalopathy, or encephalopathy.

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

Infection:
There have been case reports of sometimes fatal opportunistic infections in patients receiving methotrexate therapy for neoplastic and non-neoplastic diseases. Pneumocystis carinii Pneumonia was the most common opportunistic infection. There have also been reports of infections, pneumonia, Cryptococcosis, Herpes zoster, H. simplex hepatitis, and disseminated H. simplex.

Musculoskeletal System:
Stress fracture.

Ophthalmic:
Conjunctivitis, serious visual changes of unknown etiology.

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

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

Urogenital System:
Severe nephropathy or renal failure, azotemia, cystitis, hematuria, proteinuria; defective oxygenation or spermogenesis, transient oligospermia, menstrual dysfunction, vaginal discharge, and gynecomasia; infertility, abortion, fetal death, fetal defects.

Other rarer adverse events related to or attributed to the use of methotrexate include nodulosis, vasculitis, arthralgia/myalgia, loss of libido/imotence, diabetes, osteoporosis, sudden death, lymphoma, including reversible lymphoma, tumor lysis syndrome, soft tissue necrosis and osteonecrosis. Anaphylactic reactions have been reported.

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

OVERDOSAGE
Leucovorin is indicated to diminish the toxicity and counteract the effect of inadvertently administered overdosages of methotrexate. Leucovorin administration should begin as promptly as possible. As the time interval between methotrexate administration and leucovorin initiation increases, the effectiveness of leucovorin in countering 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 alkalization may be necessary to prevent the precipitation of methotrexate and/or its metabolites in the renal tubules. Generally speaking, neither hemodialysis nor peritoneal dialysis has been shown to improve methotrexate elimination. However, effective clearance of methotrexate has been reported with acute, intermittent hemodialysis using a high-flux dialyzer (Wall, SM et al: Am J Kidney Dis 28 (6):846-854, 1996).

Adverse Reactions in Psoriasis:
There are no recent placebo-controlled trials in patients with psoriasis. There are two literature reports (Riemschneider, 1969 and Nolte, 1978) describing large series (n=204, 245) of psoriasis patients treated with methotrexate. Dosages ranged up to 25 mg per week and treatment was administered for up to 4 years. With the exception of alopecia, photosensitivity, and "burning of skin lesions" (each 3% to 10%), the adverse reaction rates in these reports were very similar to those in the rheumatoid arthritis studies. Rarely, painful plaque erosions may appear (Pearce, HP and Wilson, BB: Am Acad Dermatol 35: 835-838, 1996).

Adverse Reactions in JRA Studies:
The approximate incidences of adverse reactions reported in pediatric patients with JRA treated with oral, weekly doses of methotrexate (5 to 20 mg/m²wk or 0.1 to 0.65 mg/kg/wk) were as follows (virtually all patients were receiving concomitant nonsteroidal anti-inflammatory drugs, and some were also taking low dosages of corticosteroids): elevated liver function tests 14%, gastrointestinal reactions (e.g., nausea, vomiting, diarrhea), 11%; stomatitis, 2%; leukopenia, 2%; headache, 1.2%; alopecia, 0.5% dizziness, 0.2%; and rash, 0.2%. Although there is experience with dosing up to 30 mg/m²wk in JRA, the published data for doses above 20 mg/m²wk are too limited to provide reliable estimates of adverse reaction rates.

DOSAGE AND ADMINISTRATION:
Neoplastic Diseases:
Oral administration in tablet form is often preferred when low doses are being administered since absorption is rapid and effective serum levels are obtained. Methotrexate Injection, USP (preservative free) formulations may be given by the intramuscular, intravenous, intra-arterial or intrathecal route.

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

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

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

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

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

Methotrexate alone or in combination with steroids was used initially for induction of remission in acute lymphoblastic leukemias. More recently, corticosteroid therapy, in combination with other antileukemic drugs or in cyclic combination with methotrexate included, has appeared to produce rapid and effective remissions.

When used for induction, methotrexate in doses of 3.3 mg/m² in combination with 60 mg/m² of prednisone, given daily, produced remissions in 50% of patients treated, usually within a period of 4 to 6 weeks. Methotrexate in combination with other agents appears to be the drug of choice for securing maintenance of drug-induced remissions. When remission is achieved and supportive care has produced general clinical improvement, maintenance therapy is initiated, as follows: Methotrexate is administered 2 times weekly either by mouth or intramuscularly in total weekly doses of 30 mg/m². It has also been given in doses of 2.5 mg/kg intravenously every 14 days. If and when relapse does occur, reinduction of remission can again usually be obtained by repeating the initial induction regimen.

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

Mononuclear Leukemia:
In the treatment of prophylaxis of mononuclear leukemia, methotrexate must be administered intravenously.

Preservative free methotrexate is diluted to a concentration of 1 mg/mL in an appropriate sterile, preservative free medium such as 0.9% Sodium Chloride Injection, USP.

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

Intrathecal methotrexate administration at a dose of 12 mg/m² (maximum 15 mg) has been reported to result in low CSF methotrexate concentrations and reduced efficacy in pediatric patients and high concentrations and neurotoxicity in adults. The following dosage regimen is based on age instead of body surface area:

<table>
<thead>
<tr>
<th>AGE (years)</th>
<th>DOSE (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>6</td>
</tr>
<tr>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>3 or older</td>
<td>12</td>
</tr>
</tbody>
</table>

In one study in patients under the age of 40, this dosage regimen appeared to result in more consistent CSF methotrexate concentrations and less neurotoxicity. Another study in pediatric patients with acute lymphocytic leukemia compared this regimen to a dose of 12 mg/m² (maximum 15 mg), a significant reduction in the rate of CNS relapse was observed in the group whose dose was based on age.

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

For treatment of mononuclear leukemia, intrathecal methotrexate may be given at intervals of 2 to 5 days. However, administration at intervals of less than one week may result in increased subacute toxicity. Methotrexate is administered until the cell count of the cerebrospinal fluid returns to normal.

Uremic side effects may occur with any given intrathecal injection and are commonly neurological in character. Large doses may cause convulsions. Methotrexate given by the intrathecal route appears significantly less toxic than systemic methotrexate toxicity. Therefore, systemic antileukemic therapy with the drug should be appropriately adjusted, reduced or discontinued.

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

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

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

Methotrexate alone or in combination with other agents appears to be the drug of choice for securing maintenance of drug-induced remissions. When remission is achieved and supportive care has produced general clinical improvement, maintenance therapy is initiated, as follows: Methotrexate is administered 2 times weekly either by mouth or intramuscularly in total weekly doses of 30 mg/m². It has also been given in doses of 2.5 mg/kg intravenously every 14 days. If and when relapse does occur, reinduction of remission can again usually be obtained by repeating the initial induction regimen.

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

Meningeal Leukemia:
In the treatment of prophylaxis of meningoleukemia, methotrexate must be administered intrathecally.

Preservative free methotrexate is diluted to a concentration of 1 mg/mL in an appropriate sterile, preservative free medium such as 0.9% Sodium Chloride Injection, USP.

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

Intrathecal methotrexate administration at a dose of 12 mg/m² (maximum 15 mg) has been reported to result in low CSF methotrexate concentrations and reduced efficacy in pediatric patients and high concentrations and neurotoxicity in adults. The following dosage regimen is based on age instead of body surface area:

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Uremic side effects may occur with any given intrathecal injection and are commonly neurological in character. Large doses may cause convulsions. Methotrexate given by the intrathecal route appears significantly less toxic than systemic methotrexate toxicity. Therefore, systemic antileukemic therapy with the drug should be appropriately adjusted, reduced or discontinued.

Focal leukemic involvement of the central nervous system may not respond to intrathecal chemotherapy and is best treated with radiotherapy.

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

Mycosis fungoides (cutaneous T cell lymphoma):
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Osteosarcoma:
An effective adjuvant chemotherapy regimen requires the administration of several cytotoxic chemotherapeutic agents. In addition to high-dose methotrexate with leucovorin rescue, these agents may include doxorubicin, cisplatin, and the combination of bleomycin, cyclophosphamide and dacarbazine (BCD) in the doses and schedule shown in the table below. The starting dose for high-dose methotrexate treatment is 12 gram/m². If this dose is not sufficient to produce a peak serum methotrexate concentration of 1,000 micromolar (10⁻⁴ mol/L) at the end of the methotrexate infusion, the dose may be escalated to 15 gram/m² 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.

<table>
<thead>
<tr>
<th>Drug†</th>
<th>Dose†</th>
<th>Treatment Week After Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>12 g/m²</td>
<td>2 IV as 4 hour infusion (starting dose)</td>
</tr>
<tr>
<td>Leucovorin</td>
<td>35 mg orally every six hours for 10 doses starting at 24 hours after start of methotrexate infusion</td>
<td>- - -</td>
</tr>
<tr>
<td>Doxorubicin†</td>
<td>80 mg/m² day IV x 3 days</td>
<td>8,17</td>
</tr>
<tr>
<td>Cisplatin†</td>
<td>80 mg/m² 2 IV</td>
<td>20,23,33,36</td>
</tr>
<tr>
<td>Bleomycin†</td>
<td>30 units/m² IV</td>
<td>2,13,26,39,42</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>600 mg/m² IV</td>
<td>2,13,26,39,42</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>0.6 mg/m² IV</td>
<td>2,13,26,39,42</td>
</tr>
</tbody>
</table>

†See each respective package insert for full prescribing information. Dosage modifications may be necessary because of age.
When these higher doses of methotrexate are to be administered, the following safety guidelines should be closely observed.

**GUIDELINES FOR METHOTREXATE THERAPY WITH LEUCOVORIN RESCUE**

1. Administration of methotrexate should be delayed until recovery if:
   - the WBC count is less than 5,000/mcroliter
   - the neutrophil count is less than 2,000/mcroliter
   - the platelet count is less than 75,000/mcroliter
   - the serum bilirubin level is greater than 1.2 mg/dL
   - the SGPT level is greater than 450 U
   - macroscopis 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/m² of intravenous fluid over 6 hours prior to initiation of the methotrexate infusion. Continue hydration at 250 mL/m²/hr (1 liter/m²/day) during the methotrexate infusion, and for 2 days after the infusion has been completed.
   - b. Alkalize urine to maintain pH above 6.0 during methotrexate infusion and leucovorin calcium therapy. This can be accomplished by the administration of sodium bicarbonate orally or by incorporation into a separate intravenous solution.

4. Repeat serum creatinine and serum methotrexate 24 hours after starting methotrexate and at least once daily until the methotrexate level is below 5 x 10⁻⁶ mol/L (0.05 micromolar).

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

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

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

**CAUTION: DO NOT ADMINISTER LEUCOVORIN INTRATHELECTY.**

**Psoriasis, Rheumatoid Arthritis, and Juvenile Rheumatoid Arthritis: Adult Rheumatoid Arthritis:**

Recommended Starting Dosage Schedules

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

1 Methotrexate Sodium Tablets for oral administration are available.

**Polyarticular-Course Juvenile Rheumatoid Arthritis:** The recommended starting dose is 10 mg/m² given once weekly.

For either adult RA or polyarticular-course JRA, dosages may be adjusted gradually to achieve an optimal response. Limited experience shows a significant increase in the incidence and severity of serious toxic reactions, especially bone marrow suppression, at doses greater than 20 mg/wk in adults. Although there is experience with doses up to 30 mg/m²/wk in children, there are too few published data to assess how doses over 20 mg/m²/wk might affect the risk of serious toxicity in children. Experience does suggest, however, that children receiving 20 to 30 mg/m²/wk (0.65 to 1.0 mg/kg/wk) may have better absorption and fewer gastrointestinal side effects if methotrexate is administered either intramuscularly or subcutaneously.

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

The optimal duration of therapy is unknown. Limited data available from long-term studies in adults indicate that the initial clinical improvement is maintained for at least 2 years with continued therapy. When methotrexate is discontinued, the arthritis usually worsens within 3 to 6 weeks.

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

All schedules should be continually tailored to the individual patient. An initial test dose may be given prior to the regular dosing schedule to detect any extreme sensitivity to adverse effects (see ADVERSE REACTIONS). Maximal myelosuppression usually occurs in 7 to 10 days.

**Psoriatic: 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.

1 Methotrexate Sodium Tablets for oral administration are available.

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

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

**HANDLING AND DISPOSAL:**

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

**DILUTION INSTRUCTIONS FOR LIQUID METHOTREXATE INJECTION PRODUCT:**

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

**HOW SUPPLIED:**

Parenteral: Methotrexate Injection, USP (Preservative Free) is supplied in single dose vials.
LEUCOVORIN RESCUE SCHEDULES FOLLOWING TREATMENT WITH HIGHER DOSES OF METHOTREXATE

<table>
<thead>
<tr>
<th>Clinical Situation</th>
<th>Laboratory Findings</th>
<th>Leucovorin Dosage and Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Methotrexate Elimination</td>
<td>Serum methotrexate level approximately 10 micromolar at 24 hours after administration, 1 micromolar at 48 hours, and less than 0.2 micromolar at 72 hours.</td>
<td>35 mg PO, IM, or IV q 6 hours for 60 hours (10 doses starting at 24 hours after start of methotrexate infusion).</td>
</tr>
<tr>
<td>Delayed Late Methotrexate Elimination</td>
<td>Serum methotrexate level remaining above 0.2 micromolar at 72 hours, and more than 0.05 micromolar at 96 hours after administration.</td>
<td>Continue 15 mg PO, IM, or IV q six hours, until methotrexate level is less than 0.05 micromolar.</td>
</tr>
<tr>
<td>Delayed Early Methotrexate Elimination and/or Evidence of Acute Renal Injury</td>
<td>Serum methotrexate level of 50 micromolar or more at 24 hours, or 1 micromolar or more at 48 hours after administration, or; a 100% or greater increase in serum creatinine level at 24 hours after methotrexate administration, (e.g., an increase from 0.5 mg/dL to a level of 1 mg/dL or more).</td>
<td>350 mg IV q three hours, until methotrexate level is less than 1 micromolar; then 15 mg IV q three hours until methotrexate level is less than 0.05 micromolar.</td>
</tr>
</tbody>
</table>

**REFERENCES**

4. National Study Commission on Cytotoxic Exposure-Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD, Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
5. Clinical Oncological Society of Australia: Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. Available from Louis P. Jeffrey, ScD, Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
# METHOTREXATE

## Methotrexate Injection

### Product Information

- **Product Type**: HUMAN PRESCRIPTION DRUG
- **Route of Administration**: INTRA-ARTERIAL, INTRAMUSCULAR, INTRATHECAL, INTRAVENOUS

### Active Ingredient/Active Moiety

<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Basis of Strength</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>METHOTREXATE</td>
<td>METHOTREXATE</td>
<td>25 mg in 1 mL</td>
</tr>
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<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>SODIUM CHLORIDE</td>
<td></td>
</tr>
<tr>
<td>SODIUM HYDROXIDE</td>
<td></td>
</tr>
<tr>
<td>HYDROCHLORIC ACID</td>
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</table>

### Inactive Ingredients

- SODIUM CHLORIDE
- SODIUM HYDROXIDE
- HYDROCHLORIC ACID

### Packaging

<table>
<thead>
<tr>
<th>#</th>
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<th>Marketing End Date</th>
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<td>03/07/2014</td>
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<td>40 in 1 VIAL, Type B: Not a Combination Product</td>
<td>03/07/2014</td>
<td></td>
</tr>
</tbody>
</table>

### Marketing Information

- **Marketing Category**: ANDA
- **Application Number**: ANDA040716
- **Marketing Start Date**: 03/07/2014
- **Marketing End Date**: 03/07/2014

### Labeler

- **Labeler Name**: Accord Healthcare, Inc.
- **Establishment Name**: Intas Pharmaceuticals Limited
- **Address**: 723479138
- **Business Operations**: manufacture(16729-277)

### Establishment

- **Establishment Name**: Intas Pharmaceuticals Limited
- **Address**: 8163707871
- **Business Operations**: manufacture(16729-277)