For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

Methotrexate Injection USP

ZEXATE® SOLUTION FOR INJECTION OR INFUSION 25MG/ML

SAFETY WARNINGS

EMBRYO-FETAL TOXICITY, HYPERSENSITIVITY REACTIONS, BENZYL ALCOHOL TOXICITY, and OTHER SERIOUS ADVERSE REACTIONS

Methotrexate Injection can cause embryo-fetal toxicity, including fetal death. For non-neoplastic diseases, Methotrexate Injection is contraindicated in pregnancy. Advise females and males of reproductive potential to use effective contraception.

Methotrexate Injection is contraindicated in patients with a history of severe hypersensitivity reactions to methotrexate, including anaphylaxis.

Formulations with benzyl alcohol can cause severe central nervous toxicity or metabolic acidosis. Use only preservative-free Methotrexate Injection for treatment of neonates or low-birth weight infants and for intrathecal use. Do not use benzyl alcohol-containing formulations for high-dose regimens unless immediate treatment is required, and preservative-free formulations are not available.

Other serious adverse reactions, including death, have been reported with methotrexate. Closely monitor for infections and adverse reactions of the bone marrow, kidneys, liver, nervous system, gastrointestinal tract, lungs, and skin. Withhold or discontinue Methotrexate Injection as appropriate.

DESCRIPTION:

Methotrexate is a potent cytotoxic antimetabolite. Methotrexate injection is a clear yellow solution free from particulate matter with a pH of 7.0-9.0.

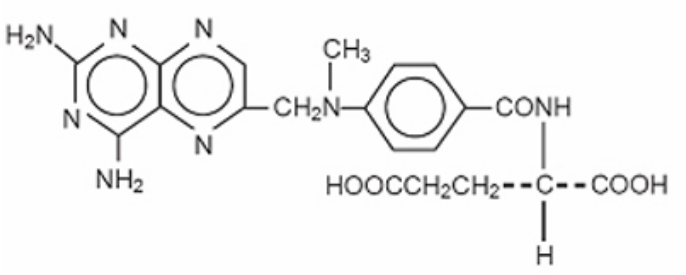
COMPOSITION:

Methotrexate Injection USP

Each ml contains:

Methotrexate Sodium equivalent to Methotrexate USP	25.0 mg
Sodium Chloride USP	4.9 mg
Sodium Hydroxide USNF	to adjust pH
Hydrochloric Acid USNF	to adjust pH
Water for Injection USP	q.s.

CHEMICAL STRUCTURE:



Chemically methotrexate is *N*-[4-[[(2,4-diamino-6-pteridinyl) methyl]methylamino]benzoyl]-L-glutamic acid. Molecular formula of Methotrexate is $C_{20}H_{22}N_8O_5$ and molecular weight is 454.45.

PHARMACOLOGY:

Mechanism of action

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.

The mechanism of action in rheumatoid arthritis, pJIA, and in psoriasis is unknown.

Pharmacodynamics

Methotrexate has as its principal mechanism of action the competitive inhibition of the enzyme folic acid reductase. Folic acid must be reduced to tetrahydrofolic acid by this enzyme in the process of DNA synthesis and cellular replication. Methotrexate inhibits the reduction of folic acid and interferes with tissue cell reproduction. Methotrexate is a phase specific substance. Its main effect is directed to the S-phase of cell division. Actively proliferating tissues such as malignant cells, bone marrow, fetal cells, dermal epithelium, buccal and intestinal mucosa and cells of the urinary bladder are in general more sensitive to the effects of methotrexate. Cellular proliferation in malignant tissue is greater than in most normal tissue and thus methotrexate may impair malignant growth without irreversible damage to normal tissues.

Pharmacokinetics

Distribution

After intravenous administration, the initial volume of distribution is approximately 0.18 L/kg (18% of body weight) and steady-state volume of distribution is approximately 0.4 to 0.8 L/kg (40 to 80% of body weight). Methotrexate competes with reduced folates for active transport across cell membranes by means of a single carrier-mediated active transport process. At serum concentrations greater than 100 micromolar, passive diffusion becomes a major pathway by which effective intracellular concentrations can be achieved. Methotrexate in serum is approximately 50% protein bound. Methotrexate 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 intravenously, intramuscularly, or subcutaneously.

Elimination

The terminal half-life reported for methotrexate is approximately 3 to 10 hours for patients receiving treatment for psoriasis, or rheumatoid arthritis or low-dose antineoplastic therapy (less than 30 mg/m^2). Following intravenous administration of high-dose methotrexate, the terminal half-life is 8 hours to 15 hours.

Metabolism
Methotrexate undergoes hepatic and intracellular metabolism to polyglutamated forms that can be converted back to methotrexate by hydrolase enzymes. These polyglutamates act as inhibitors of dihydrofolate reductase and thymidylate synthetase. Small amounts of methotrexate polyglutamates may remain in tissues for extended periods. The retention and prolonged drug action of these active metabolites vary among different cells, tissues and tumors. Methotrexate undergoes minor metabolism to 7-hydroxymethotrexate, and accumulation may become significant following high dosages. The aqueous solubility of 7-hydroxymethotrexate is 3- to 5-fold lower than the solubility of methotrexate.

Excretion
Renal excretion is the primary route of elimination and is dependent upon dosage and route of administration. With intravenous administration, 80% to 90% of the administered dose is excreted unchanged in the urine within 24 hours. There is limited biliary excretion amounting to 10% or less of the administered dose. Enterohepatic recirculation of methotrexate has been proposed.

Renal excretion occurs by glomerular filtration and active tubular secretion. Nonlinear elimination due to saturation of renal tubular reabsorption has been observed in psoriatic patients at doses between 7.5 and 30 mg.

Specific Populations

Pediatric Patients
In pediatric patients receiving methotrexate for acute lymphoblastic leukemia (6.3 mg/m^2 to 30 mg/m^2), or for JIA (3.75 mg/m^2 to 26.2 mg/m^2), the terminal half-life has been reported to range from 0.7 to 5.8 hours or from 0.9 to 2.3 hours, respectively.

Patients with Renal impairment
The elimination half-life of methotrexate increases with the severity of renal impairment, with high interindividual variability.

Route of Administration:
Methotrexate may be administered by intramuscular, intravenous, intra-arterial or intrathecal injection.

INDICATIONS:

Antineoplastic chemotherapy
Methotrexate has a broad spectrum of antineoplastic activity. It is indicated for the treatment of breast cancer, gestational choriocarcinoma, and in patients with chorioadenoma destruens and hydatidiform mole.

Methotrexate may be used in combination with other chemotherapeutic agents for the palliative treatment of acute leukaemias, particularly acute lymphoblastic leukaemia. It may also be used in the treatment of Burkitt lymphoma, advanced stages (III and IV, Petersa Staging System) of lymphosarcoma, especially in children, and in advanced cases of mycosis fungoides.

High dose therapy
In high-dose schedules, methotrexate may be effective alone or in combination therapy, in the treatment of epidermoid cancers of the head and neck, osteogenic sarcoma and bronchogenic carcinoma.

Calcium folinate (leucovorin calcium) must be used in conjunction with high dose methotrexate therapy.

Psoriasis chemotherapy
Methotrexate may be of value in the symptomatic control of severe, recalcitrant, disabling psoriasis which is not adequately responsive to other forms of treatment. However, due to the high risk associated with its use, methotrexate should be used after the diagnosis has been definitely established, as by biopsy and/or after dermatologic consultation.

Rheumatoid arthritis chemotherapy
Management of severe, recalcitrant, active rheumatoid arthritis in adults not responding to, or intolerant of, an adequate trial of NSAIDs and one or more disease modifying drugs.

Aspirin, NSAIDs and/or low dose steroids may be continued, although the possibility of increased toxicity with concomitant use of NSAIDs including salicylate has not been fully explored.

Steroids may be reduced gradually in patients who respond to methotrexate.

Combined use of methotrexate with gold, penicillamine, hydroxychloroquine, sulfasalazine or cytotoxic agents has not been studied and may increase the incidence of adverse effects. Rest and physiotherapy as indicated should be continued.

CONTRAINDICATIONS:
Methotrexate Injection is contraindicated in:

• Patients with history of severe hypersensitivity to methotrexate

• Pregnancy in patients with non-neoplastic diseases

ADVERSE EFFECTS:

The following adverse reactions are described, or described in greater detail, in other sections:
Hypersensitivity Reactions
Myelosuppression
Serious Infections
Renal Toxicity
Hepatotoxicity
Neurotoxicity
Gastrointestinal Toxicity
Pulmonary Toxicity
Dermatologic Reactions
Secondary Malignancies
Tumor Lysis Syndrome
Increased Risk of Adverse Reactions due to Third Space Accumulation

The following adverse reactions have been identified during post-approval use of methotrexate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: Aplastic anemia, lymphadenopathy, hypogammaglobulinemia

Cardiovascular disorders: Thromboembolic events (including arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, thrombophlebitis, and pulmonary embolus), pericarditis, pericardial effusion, hypotension, sudden death

Endocrine: Diabetes

Eye disorders: Optic neuropathy, blurred vision, ocular irritation, conjunctivitis, xerophthalmia

Gastrointestinal disorders: Hemorrhagic enteritis, intestinal perforation, gingivitis, pancreatitis, pharyngitis, hematemesis, melena, gastrointestinal ulceration and bleeding

Hepatobiliary disorders: Acute hepatitis, decreased serum albumin, fibrosis, cirrhosis, liver failure

Immune system disorders: Anaphylaxis, anaphylactoid reactions, vasculitis

Metabolism: Hyperglycemia

Musculoskeletal disorders: Stress fracture, soft tissue necrosis, arthralgia, myalgia, osteoporosis

Nervous system disorders: Headaches, drowsiness, blurred vision, speech impairment (including dysarthria and aphasia), transient cognitive dysfunction, mood alteration, unusual cranial sensations,

paresis, encephalopathy, leukoencephalopathy, and convulsions. Also, spinal radiculopathy with intrathecal use

Renal disorders: Severe renal toxicity including renal failure, azotemia, hematuria, proteinuria, cystitis

Reproductive disorders: Defective oogenesis or spermatogenesis, loss of libido, impotence, gynecomastia, menstrual dysfunction

Respiratory disorders: Pulmonary fibrosis, respiratory failure, chronic interstitial obstructive pulmonary disease, pleuritic pain and thickening, alveolitis

Skin disorders: Toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, skin necrosis, and erythema multiforme, erythematous rashes, pruritus, alopecia, skin ulceration, accelerated nodulosis, urticaria, pigmentary changes, ecchymosis, telangiectasia, photosensitivity, acne, furunculosis

DRUG INTERACTIONS:

Effects of Other Drugs on Methotrexate

Drugs that Increase Methotrexate Exposure

Coadministration of methotrexate with the following products may increase methotrexate plasma concentrations, which may increase the risk of methotrexate severe adverse reactions.

Increased organ specific adverse reactions may also occur when methotrexate is coadministered with hepatotoxic or nephrotoxic products. If coadministration cannot be avoided, monitor closely for methotrexate adverse reactions when coadministered with:

• Penicillin or sulfonamide antibiotics
• Highly protein-bound drugs (e.g., oral anticoagulants, phenytoin, salicylates, sulfonamides, sulfonylureas, and tetracyclines)
• Proton pump inhibitors
• Probenecid
• Antifolate drugs (e.g., dapsone, pemetrexed, pyrimethamine and sulfonamides)
• Aspirin and other nonsteroidal anti-inflammatory drugs

Unexpectedly severe and fatal gastrointestinal toxicity can occur with concomitant administration of methotrexate (primarily at high dose) and nonsteroidal anti-inflammatory drugs (NSAIDs)

• Mercaptopurine
• Hepatotoxic products
• Weak acids (e.g., salicylates)
• Nephrotoxic products

<u>Nitrous Oxide</u>

Coadministration of methotrexate with nitrous oxide anesthesia potentiates the effect of methotrexate on folate-dependent metabolic pathways, which may increase the risk of severe

methotrexate adverse reactions. Avoid nitrous oxide anesthesia in patients receiving methotrexate. Consider alternative therapies in patients who have received prior nitrous oxide anesthesia.

Folic Acid
Coadministration of methotrexate with folic acid or its derivatives decreases the clinical effectiveness of methotrexate in patients with neoplastic diseases. Methotrexate competes with reduced folates for active transport across cell membranes. Instruct patients to take folic or folinic acid only as directed by their healthcare provider.

Effects of Methotrexate on Other Drugs

Theophylline
Coadministration of methotrexate with theophylline increases theophylline plasma concentrations which may increase the risk of theophylline adverse reactions. Monitor theophylline levels and adjust the theophylline dosage in accordance with approved product labeling.

PRECAUTIONS AND WARNINGS:

Embryo-Fetal Toxicity
Based on published reports and its mechanism of action, methotrexate can cause embryo-fetal toxicity, including fetal death when administered to a pregnant woman.

Methotrexate Injection is contraindicated for use in pregnant women with non-neoplastic diseases. Advise pregnant women with neoplastic diseases of the potential risk to a fetus. The preservative benzyl alcohol can cross the placenta; when possible, use the preservative-free formulation when Methotrexate Injection is needed during pregnancy to treat a neoplastic disease.

Advise females of reproductive potential to use effective contraception during Methotrexate Injection treatment and for 6 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during Methotrexate Injection treatment and for 3 months after the final dose.

Hypersensitivity Reactions
Hypersensitivity reactions, including anaphylaxis, can occur with methotrexate. If signs or symptoms of anaphylaxis or any other serious hypersensitivity reaction occurs, immediately discontinue Methotrexate Injection and institute appropriate therapy.

Risks of Serious Adverse Reactions due to Benzyl Alcohol-Preservative
Formulations with benzyl alcohol can cause severe central nervous toxicity or metabolic acidosis, if used in neonates or low-birth weight infants, intrathecally, or in high-dose regimens. Use only preservative-free Methotrexate Injection for treatment of neonates or low-birth weight infants and for intrathecal use. Do not use benzyl alcohol-containing formulations for high-dose regimens unless immediate treatment is required, and preservative-free formulations are not available. The preservative benzyl alcohol can cross the placenta; when possible, use the preservative-free formulation when Methotrexate Injection is needed during pregnancy to treat a neoplastic disease.

Serious and Fatal Adverse Reactions Including Gasping Syndrome in Neonates and Low-Birth Weight Infants

Serious and fatal adverse reactions including "gasping syndrome" can occur in neonates and low birth weight infants treated with drugs containing benzyl alcohol, including Methotrexate Injection with preservative. The "gasping syndrome" is characterized by central nervous system (CNS) depression, metabolic acidosis, and gasping respirations.

When prescribing in infants (non-neonate, non-low-birth weight), if a preservative-free formulation of Methotrexate Injection is not available and use of a benzyl alcohol-containing formulation is necessary, consider the combined daily metabolic load of benzyl alcohol from all sources including Methotrexate Injection (Methotrexate Injection contains 9.4 mg of benzyl alcohol/per mL) and other drugs containing benzyl alcohol. The minimum amount of benzyl alcohol at which serious adverse reactions may occur is not known.

Neurotoxicity Due to Intrathecal Administration
Serious neurotoxicity can occur following the intrathecal administration of Methotrexate Injection containing the preservative benzyl alcohol.

Metabolic Acidosis with High-Dose Therapy
Severe metabolic acidosis can occur with Methotrexate Injection that contains the preservative benzyl alcohol**.**

Myelosuppression
Methotrexate suppresses hematopoiesis and can cause severe and life-threatening pancytopenia, anemia, aplastic anemia, leukopenia, neutropenia, and thrombocytopenia.

Obtain blood counts at baseline and periodically during treatment. Monitor patients for possible clinical complications of myelosuppression. Provide supportive care and withhold, reduce dose, or discontinue Methotrexate Injection as needed.

Serious Infections
Patients treated with methotrexate are at increased risk for developing life-threatening or fatal bacterial, fungal, or viral infections including opportunistic infections such as Pneumocystis jiroveci pneumonia, invasive fungal infections, hepatitis B reactivation, tuberculosis primary infection or reactivation, and disseminated Herpes zoster and cytomegalovirus infections.

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with Methotrexate Injection. Withhold or discontinue Methotrexate Injection in patients who develop serious infections.

Renal Toxicity
Methotrexate can cause renal toxicity including irreversible acute renal failure. Monitor renal function and withhold or discontinue methotrexate as needed for severe renal toxicity.

For patients receiving high-dose regimens, follow recommendations to decrease the risk of renal injury and mitigate renal toxicity.

Patients with impaired renal function are at increased risk for methotrexate toxicity.

Consider administration of glucarpidase in patients with toxic plasma methotrexate concentrations (>1 micromole per liter) and delayed clearance due to impaired renal function.

Hepatotoxicity

Methotrexate can cause severe and potentially irreversible hepatotoxicity including fibrosis, cirrhosis, and fatal liver failure.

In patients with psoriasis, fibrosis or cirrhosis may occur in the absence of symptoms or abnormal liver function tests. In patients with psoriasis, the risk of hepatotoxicity appears to increase with total cumulative dose and generally occurs after receipt of a total cumulative dose of 1.5 g or more.

The safety of Methotrexate Injection in patients with liver disease is unknown. Avoid use of Methotrexate Injection in patients with chronic liver disease, unless benefits clearly outweigh the risks. The risk of hepatotoxicity is increased with heavy alcohol consumption.

Assess liver function prior to initiating Methotrexate Injection and monitor liver function tests during treatment. Withhold or discontinue Methotrexate Injection as appropriate.

Neurotoxicity

Methotrexate can cause severe acute and chronic neurotoxicity which can be progressive, irreversible, and fatal. Serious neurotoxicity, including generalized and focal seizures, have occurred in pediatric patients. Monitor patients for signs of neurotoxicity and withhold or discontinue Methotrexate Injection when appropriate.

Leukoencephalopathy

Leukoencephalopathy can occur with intermediate and high-dose intravenous regimens, intrathecal methotrexate, and low-dose methotrexate therapy. The risk of leukoencephalopathy is increased with prior cranial radiation.

Transient Acute Neurologic Syndrome

A transient acute stroke-like syndrome can occur with high-dose methotrexate. Clinical manifestations include confusion, hemiparesis, transient blindness, seizures, and coma.

Neurologic Adverse Reactions Associated with Intrathecal Administration

Intrathecal methotrexate can cause the following additional neurologic adverse reactions:

- Acute chemical arachnoiditis manifested by symptoms such as headache, back pain, nuchal rigidity, and fever.
- Subacute myelopathy characterized by paraparesis or paraplegia.

Avoid the intrathecal use of Methotrexate Injection that contains the preservative benzyl alcohol because of the risk of serious neurotoxicity.

Gastrointestinal Toxicity

Methotrexate can cause diarrhea, vomiting, stomatitis, hemorrhagic enteritis and fatal intestinal perforation. Patients with peptic ulcer disease or ulcerative colitis are at a greater risk of developing severe gastrointestinal adverse reactions.

Withhold or discontinue Methotrexate Injection for severe gastrointestinal toxicity, and institute appropriate supportive care as needed.

Pulmonary Toxicity

Methotrexate-induced pulmonary toxicity including acute or chronic interstitial pneumonitis and irreversible or fatal cases can occur at all dose levels. Monitor patients for signs of pulmonary toxicity and withhold or discontinue Methotrexate Injection as appropriate.

Dermatologic Reactions

Severe, including fatal, dermatologic reactions, such as toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, skin necrosis, and erythema multiforme, can occur with methotrexate.

Psoriasis may be aggravated by concomitant exposure to ultraviolet radiation.

Methotrexate can also cause radiation recall dermatitis and photodermatitis (sunburn) reactivation.

Monitor patients for signs of dermatologic toxicity and withhold or permanently discontinue Methotrexate Injection for severe dermatologic adverse reactions. Counsel patients to avoid excessive sun exposure and use sun protection measures.

Folic Acid Supplementation

Neoplastic Diseases

Products containing folic acid or its derivatives may decrease the clinical effectiveness of methotrexate. Avoid use of products containing folic acid or folinic acid unless clinically indicated.

Non-neoplastic Diseases

Folate deficiency may increase methotrexate adverse reactions. Administer folic acid or folinic acid to patients with rheumatoid arthritis, pJIA, and psoriasis.

Secondary Malignancies

Secondary malignancies can occur at all dose levels of methotrexate. In some cases, lymphoproliferative disease that occurred during therapy with low-dose methotrexate regressed completely following withdrawal of methotrexate. If lymphoproliferative disease occurs, discontinue Methotrexate Injection and institute appropriate treatment if lymphoma does not regress.

Tumor Lysis Syndrome

Methotrexate can induce tumor lysis syndrome in patients with rapidly growing tumors. Institute appropriate treatment for prevention and management of tumor lysis syndrome**.**

Immunization and Risks Associated with Live Vaccines

Immunization during Methotrexate Injection treatment may be ineffective.

Disseminated infections following administration of live vaccines have been reported.

Update immunizations according to immunization guidelines prior to initiating Methotrexate Injection. Immunization with live vaccines is not recommended during treatment. The interval between live vaccinations and initiation of Methotrexate Injection should be in accordance with current vaccination guidelines for patients on immunosuppressive therapies.

Infertility

Based on published reports, methotrexate can cause impairment of fertility, oligospermia, and menstrual dysfunction. It is not known if the infertility may be reversible in affected patients. Discuss the risk of effects on reproduction with female and male patients of reproductive potential.

Increased Risk of Adverse Reactions Due to Third Space Accumulation

Methotrexate can exit slowly from third space accumulations resulting in prolonged terminal plasma half-life and toxicity. Evacuate significant third-space accumulations prior to Methotrexate Injection administration.

Increased Risk of Soft Tissue and Bone Toxicity with Concomitant Radiotherapy

Concomitant radiation therapy increases the risk of soft tissue necrosis and osteonecrosis associated with methotrexate.

Risk of Serious Adverse Reactions with Medication Errors

Serious adverse reactions, including death, have occurred due to medication errors. Most commonly, these errors occurred in patients who were taking methotrexate daily when a weekly dosing regimen was prescribed. Ensure that patients receive the recommended dosage, because medication errors have led to death.

Carcinogenicity, Mutagenicity and Impairment of Fertility

Methotrexate has been evaluated in a number of animal studies for carcinogenic potential with inconclusive results. There is evidence that methotrexate causes chromosomal damage to animal somatic cells and human bone marrow cells.

Pregnancy

Risk Summary

Methotrexate Injection is contraindicated in pregnant women with non-neoplastic diseases. Based on published reports and its mechanism of action, methotrexate can cause embryo-fetal toxicity and fetal death when administered to a pregnant woman. There are no animal data that meet current standards for nonclinical developmental toxicity studies. Advise pregnant women with neoplastic diseases of the potential risk to a fetus. The preservative benzyl alcohol can cross the placenta; when possible, use the preservative-free formulation when Methotrexate Injection is needed during pregnancy to treat a neoplastic disease.

Nursing Mothers

Risk Summary
Limited published literature reports the presence of methotrexate in human milk in low amounts, with the highest breast milk to plasma concentration ration reported to be 0.08:1. No information is available on the effects of methotrexate on a breastfed infant or on milk production. Because of the potential for serious adverse reactions from methotrexate in breastfed infants, advise women not to breastfeed during treatment with Methotrexate Injection and for 1 week after the final dose.

Females and Males of Reproductive Potential
Methotrexate can cause malformations and fetal death at doses less than or equal to the recommended clinical doses.

Pregnancy Testing
Verify the pregnancy status of females of reproductive potential prior to initiating Methotrexate Injection.

Contraception

Females
Advise females of reproductive potential to use effective contraception during and for 6 months after the final dose of Methotrexate Injection therapy.

Males
Methotrexate can cause chromosomal damage to sperm cells. Advise males with female partners of reproductive potential to use effective contraception during and for 3 months after the final dose of Methotrexate Injection therapy.

Infertility

Females
Based on published reports of female infertility after therapy with methotrexate, advise females of reproductive potential that Methotrexate Injection can cause impairment of fertility and menstrual dysfunction during and after cessation of therapy. It is not known if the infertility may be reversed in all affected females.

Males
Based on published reports of male infertility after therapy with methotrexate, advise males that Methotrexate Injection can cause oligospermia or infertility during and after cessation of therapy. It is not known if the infertility may be reversed in all affected males.

Pediatric Use
The safety and effectiveness of Methotrexate Injection in pediatric patients have been established for ALL, meningeal leukemia prophylaxis and treatment, non-Hodgkin lymphoma, osteosarcoma and in pJIA. Clinical studies evaluating the use of methotrexate in pediatric patients with pJIA demonstrated safety comparable to that observed in adults with RA. The safety and effectiveness of Methotrexate Injection have not been established in pediatric patients for the treatment of breast

cancer, squamous cell carcinoma of the head and neck, gestational trophoblastic neoplasia, rheumatoid arthritis, and psoriasis. Additional risk information is described below.

Risks of Serious Adverse Reactions due to Benzyl Alcohol-Preservative
Due to the risk of serious adverse reactions and fatal gasping syndrome following administration of intravenous solutions containing the preservative benzyl alcohol in neonates, use only preservative-free Methotrexate Injection in neonates and low-birth weight infants. The "gasping syndrome" is characterized by CNS depression, metabolic acidosis, and gasping respirations.

Serious adverse reactions including fatal reactions and the "gasping syndrome" occurred in premature neonates and low-birth weight infants in the neonatal intensive care unit who received drugs containing benzyl alcohol as a preservative. In these cases, benzyl alcohol dosages of 99 to 234 mg/kg/day produced high levels of benzyl alcohol and its metabolites in the blood and urine (blood levels of benzyl alcohol were 0.61 to 1.378 mmol/L). Additional adverse reactions include gradual neurological deterioration, seizures, intracranial hemorrhage, hematological abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Preterm, low-birth weight infants may be more likely to develop these reactions because they may be less able to metabolize benzyl alcohol.

When prescribing in infants (non-neonate, non-low-birth weight), if a preservative-free formulation of Methotrexate Injection is not available and use of a benzyl alcohol-containing formulation is necessary, consider the combined daily metabolic load of benzyl alcohol from all sources including Methotrexate Injection (Methotrexate Injection contains 9.4 mg of benzyl alcohol/per mL) and other drugs containing benzyl alcohol. The minimum amount of benzyl alcohol at which serious adverse reactions may occur is not known.

Do not administer methotrexate formulations containing benzyl alcohol intrathecally due to the risk of severe neurotoxicity.

Leukemia/Lymphoma
Serious neurotoxicity, frequently manifested as generalized or focal seizures, has been reported with unexpectedly increased frequency among pediatric patients with acute lymphoblastic leukemia who were treated with intermediate-dose intravenous methotrexate (1 gm/m^2).

Geriatric Use
In general, dose selection for an elderly patient should be cautious reflecting the greater frequency of decreased hepatic and renal function, concomitant disease or other drug therapy (i.e., that interfere with renal function, methotrexate or folate metabolism) in this population.

Renal Impairment
Methotrexate elimination is reduced in patients with renal impairment [creatinine clearance (CLcr) less than 90 mL/min, calculated using Cockcroft-Gault]. Patients with renal impairment are at increased risk for methotrexate adverse reactions.

Follow recommendations to promote methotrexate elimination and decrease risk of acute kidney injury and other methotrexate toxicities in patients who are receiving intermediate- or high-dose

regimens. Consider reducing the dose or discontinuing Methotrexate Injection in patients with renal impairment as appropriate.

Hepatic Impairment
The pharmacokinetics and safety of methotrexate in patients with hepatic impairment is unknown Patients with hepatic impairment may be at increased risk for methotrexate adverse reaction based on elimination characteristics of methotrexate. Consider reducing the dose or discontinuing Methotrexate Injection in patients with hepatic impairment as appropriate.

DOSAGE AND ADMINISTRATION:

Because of its potential to cause severe toxicity, methotrexate therapy requires close supervision with particular caution to distinguish between daily and weekly dosage regimens. Weekly dosage prescriptions should specify a particular day of the week.

(a) Antineoplastic chemotherapy

Methotrexate may be administered by intramuscular, intravenous, intra-arterial or intrathecal injection. Non-isotonic solutions of methotrexate injection should not be administered intrathecally.

A guideline of a ratio of 1:30 is given for the conversion of mg/kg body weight to mg/m^2 body surface area. The conversion factor varies between 1:20 and 1:40 depending on age and body build.

Trophoblastic neoplasms
The usual dosage is 15 to 30 mg daily orally or IM for 5 days. A repeat course may be given after a period of one or more weeks provided all signs of toxicity have disappeared. Three to five courses of therapy are usually employed. The effectiveness of therapy is ordinarily evaluated by 24-hour quantitative analysis of urinary chorionic gonadotropin hormone (CGH) which should return to normal or less than 50 IU/24 hours, usually after the 3rd or 4th course. Complete resolution of measurable lesions usually occurs 4 to 6 weeks later. One to two courses of methotrexate after normalization of CGH are usually recommended. Before each course of methotrexate, careful clinical assessment is essential. Cyclic combination therapy of methotrexate with other antineoplastic drugs has been reported as being useful.

Since hydatidiform mole may precede choriocarcinoma, prophylactic chemotherapy with methotrexate has been recommended. Chorioadenoma destruens is considered to be an invasive form of hydatidiform mole. Methotrexate is administered in these disease states in doses similar to those recommended for trophoblastic neoplasms.

Breast carcinoma
Prolonged cyclic combination chemotherapy with cyclophosphamide, methotrexate and fluorouracil has given good results when used as adjuvant treatment to radical mastectomy in primary breast cancer with positive axillary lymph nodes. Methotrexate dosage was 40 mg/m^2 intravenously on the first and eighth days.

Leukaemia

Acute lymphatic (lymphoblastic) leukaemia in children and young adolescents is the most responsive to present day chemotherapy. In young adults and older patients, clinical remission is more difficult to obtain and early relapse is more common. In chronic lymphatic leukaemia, the prognosis for adequate response is less encouraging.

Methotrexate in doses of 3.3 mg/m^2 orally in combination with prednisolone 60 mg/m^2 daily has been given for induction of remission of lymphoblastic leukaemia. When remission and general clinical improvement have been attained, a maintenance dosage of methotrexate 30 mg/m^2 orally or IM twice weekly may be given. This treatment is expected to produce remission in 50% of patients treated, usually within 4 to 6 weeks.

Alternatively, 2.5 mg/kg IV every 14 days may be given. Should relapse occur, reinduction of remission can again usually be obtained by repeating the initial induction regimen. A variety of dosage schedules for both induction and maintenance of remission with various combinations of alkylating and antifolic agents have recently been introduced. Multiple drug therapy with several agents, including methotrexate given concomitantly, appears to be gaining increasing support in both the acute and chronic forms of leukaemia.

Acute granulocytic leukaemia is rare in children but common in adults. This form of leukaemia responds poorly to chemotherapy and remissions are short with relapses common. Resistance to therapy also develops rapidly.

Meningeal leukaemia

Patients with leukaemia are subject to leukaemic invasion of the central nervous system. This may manifest characteristic signs or symptoms or remain silent and be diagnosed only by examination of the cerebrospinal fluid (CSF), which contains leukaemic cells in such cases. Therefore, the CSF should be examined in all leukaemic patients. Since passage of methotrexate from blood serum to the CSF is minimal, for adequate therapy the drug is administered intrathecally. Only preservative-free methotrexate should be used for intrathecal administration.

It is now common practice to administer methotrexate intrathecally as prophylaxis in all cases of acute lymphocytic leukaemia.

By intrathecal injection the distribution of methotrexate is in the CSF, the volume of which is dependent upon age and not body surface area. The CSF is at 40% of adult volume at birth and reaches adult volume in several years. The recommended dose by age is:

Age (yrs)	**less than 1**	**1**	**2**	**3+ older**
Dose (mg)	6	8	10	12

There is some indication that infants less than 4 months and adults 70 years of age or older may have increased acute toxicity with the doses recommended and dose reduction may be indicated.

For the treatment of meningeal leukaemia, intrathecal methotrexate may be given at intervals of 2 to 5 days, however there is some indication that doses given at intervals of less than one week may result in increased toxicity.

Methotrexate is administered until the cell count of the cerebrospinal fluid returns to normal, then one additional dose of the drug is administered.

For prophylaxis against meningeal leukaemia, the dosage is the same as for treatment except for the intervals of administration. On this subject, it is advisable for the physician to consult the medical literature.

Large doses may cause convulsions. Untoward side effects may occur with any given intrathecal injection and are commonly neurological in character.

Methotrexate given by the intrathecal route appears in significant concentrations in the systemic circulation and may cause systemic methotrexate toxicity. Therefore, systemic antileukaemic therapy with the drug should be appropriately adjusted, reduced or discontinued. Focal leukaemic involvement of the central nervous system may not respond to intrathecal chemotherapy and is best treated with radiotherapy.

Lymphomas
The usual dosage of methotrexate for the treatment of stage I or II of Burkitt lymphoma is 10 to 25 mg per day orally for 4 to 8 days. In stage III methotrexate is commonly given concomitantly with other antineoplastic agents. In all stages, several courses of drug therapy are usually administered interposed with 7 to 10-day rest periods. Lympho sarcomas in stage III may respond to combined drug therapy with methotrexate given in doses of 0.625 mg to 2.5 mg/kg daily.

Methotrexate is of no value in the treatment of Hodgkin's Disease.

Mycosis fungoides
Dosage of methotrexate for the treatment of mycosis fungoides is usually 2.5 to 10 mg orally each day for weeks or months. Initial dosage and dosage adjustment are determined by patient response and haematologic monitoring.

Methotrexate has also been given IM in doses of 50 mg once weekly or 25 mg twice weekly.
Methotrexate appears to produce clinical remissions in 50% of the cases treated.

High-dosage therapy
Recent published literature should be consulted for details; dosage regimens have varied considerably in different studies depending upon the nature and severity of the disease, the experience of the investigator etc. It must be emphasised that high dosages should be only used by qualified specialists and in hospitals where the necessary facilities are available.

In order to prevent precipitation of methotrexate in the renal tubules, the patients should maintain an adequate urine flow by drinking plenty of fluids for 2 days after a high dose injection (greater than 200 mg), and keep the urine alkaline by using sodium bicarbonate continuously for at least 24 hours afterwards.

(**b) Psoriasis chemotherapy**
The patient should be fully informed of the risks involved and should be under constant supervision of the physician.

Assessment of renal function, liver function and blood elements should be made by history, physical examination and laboratory tests (such as haemogram, urinalysis, serum creatinine, liver function studies and liver biopsy if indicated) before beginning methotrexate, periodically during methotrexate therapy and before reinstituting methotrexate therapy after a rest period. Appropriate steps should be taken to avoid conception for at least 12 weeks following methotrexate therapy.

There are three commonly used general types of dosage schedules:
(1) weekly oral or parenteral intermittent large doses;
(2) divided dose intermittent oral schedule over a 36-hour period;
(3) daily oral with a rest period.

All schedules should be continually tailored to the individual patient. A single test dose of 5 to 10 mg parenterally one week prior to initiation of therapy is recommended to detect any idiosyncratic reaction.

Recommended dose schedules for a 70 kg adult are:
(1) Weekly single dose schedule: 10 to 25 mg orally, IM or IV per week until adequate response is achieved. Weekly dosage should not exceed 50 mg.
(2) Divided dose schedule: 2.5 mg orally at 12-hour intervals for three doses or at 8-hour intervals for four doses each week. Weekly dosage should not exceed 30 mg.
(3) Daily dose schedule: 2.5 mg orally daily for five days followed by a rest period of at least 2 days. Daily dosage should not exceed 6.25 mg.

Dosage in each schedule may be gradually adjusted to achieve optimal clinical response, but not to exceed the maximum stated. After optimal response has been achieved, each dosage schedule should be reduced to the lowest possible dose with the largest possible rest period. Conventional topical therapy should be resumed as soon as possible.

(c) Rheumatoid arthritis chemotherapy
The patient should be fully informed of the risks involved and should be under constant supervision of the doctor.

Assessment of haematological, hepatic, renal and pulmonary function should be made by history, physical examination and laboratory tests before beginning, periodically during and before reinstituting methotrexate therapy. Appropriate steps should be taken in men and women to avoid conception during methotrexate therapy.

Both the doctor and the pharmacist should emphasise to the patient the importance of the weekly dosage regimens: mistaken daily use may cause serious and sometimes life threatening or fatal toxicity.

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. Complete blood count with platelets should be evaluated seven to ten days later.

Recommended starting dosage schedules are single oral doses of 7.5 mg once weekly or divided oral doses of 2.5 mg at twelve-hour intervals for three doses given as a course once weekly.

Therapeutic response usually begins within three to six weeks and the patient may continue to improve for another twelve weeks or more. The dosage in each schedule may be increased to 15 mg/week after six weeks in non-responsive patients. If necessary, dosage may be gradually increased further to achieve optimal response, but not ordinarily to exceed a total weekly dosage of 20 mg. Once response has been achieved, each schedule should be reduced, if possible, to the lowest possible amount of drug and with the longest rest period.

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

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 0.9% Sodium Chloride Injection, USP.

OVERDOSE:

Manifestations
Overdosage, including fatal overdosage, has occurred with methotrexate.

Manifestations of overdosage include adverse reactions reported at pharmacologic doses, particularly hematologic and gastrointestinal reactions (e.g., leukopenia, thrombocytopenia, anemia, pancytopenia, myelosuppression, mucositis, stomatitis, oral ulceration, nausea, vomiting, gastrointestinal ulceration, or gastrointestinal bleeding). In some cases, no symptoms were reported; however, sepsis or septic shock, renal failure, and aplastic anemia were also reported.

Manifestations of intrathecal overdosage include CNS symptoms (e.g., headache, nausea and vomiting, seizure or convulsion, and acute toxic encephalopathy). In some cases, no symptoms were reported; however, cerebellar herniation associated with increased intracranial pressure and acute toxic encephalopathy have also been reported.

Management
Leucovorin and levoleucovorin are indicated to diminish the toxicity and counteract the effect of inadvertently administered overdosages of methotrexate. Administer leucovorin or levoleucovorin as soon as possible after overdosage (refer to the leucovorin or levoleucovorin prescribing information). Monitor serum methotrexate concentrations closely to guide leucovorin or levoleucovorin therapy. Monitor serum creatinine concentrations closely because high serum methotrexate concentrations may cause renal damage leading to acute renal failure.

Glucarpidase is indicated for the treatment of toxic methotrexate concentrations in patients with delayed methotrexate clearance due to impaired renal function (refer to the glucarpidase prescribing information). If glucarpidase is used, do not administer leucovorin within 2 hours before or after a dose of glucarpidase because leucovorin is a substrate for glucarpidase.

Hydration and urinary alkalinization may be necessary to prevent the precipitation of methotrexate and/or its metabolites in the renal tubules. 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.

STORAGE:
Store below 25°C. Protect from light.

INCOMPATIBILITIES:
Immediate precipitation or turbidity results when combined with certain concentrations of droperidol, heparin sodium, metoclopramide hydrochloride, ranitidine hydrochloride in syringe.

SHELF LIFE:
24 months.

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.

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

PRESENTATION:
ZEXATE® Solution For Injection or Infusion 25mg/ml is available as:

- 2 ml single dose vial containing 50 mg of methotrexate in unit carton.
- 20 ml single dose vial containing 500 mg of methotrexate in unit carton.

REFERENCES:

1. Prescribing Information, Methotrexate Injection, Hospira Inc., Lake Forest, IL 60045, USA. Revised 03/2021.
2. Prescribing Information, Methotrexate Injection, Pfizer Australia Pty Ltd., Revised 18 Jan 2019.
3. Prescribing Information, DBL Methotrexate Injection BP 50mg/2ml (MAL19950049ARZ)

MANUFACTURERS INFORMATION:

Manufactured in India by:
Fresenius Kabi Oncology Ltd.
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P.O. Guru Majra
Tehsil-Nalagarh
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