WARNING

Methotrexate must be used only by physicians experienced in antimetabolite chemotherapy, or in the case of non-oncological conditions, by a specialist physician.

Because of the possibility of fatal or severe toxic reactions the patient should be fully informed by the physician of the risks involved and should be under his constant supervision.

Deaths have been reported with the use of methotrexate.

In the treatment of psoriasis, methotrexate should be restricted to severe, recalcitrant, disabling disease which is not adequately responsive to other forms of therapy, but only when the diagnosis has been established by biopsy and / or after appropriate consultation.

1. Methotrexate may produce marked depression of bone marrow, anaemia, aplastic anaemia, leucopenia, neutropenia, thrombocytopenia and bleeding.
2. Methotrexate may be hepatotoxic, particularly at high dosage or with prolonged therapy. Liver atrophy, necrosis, cirrhosis, fatty changes and perportal fibrosis have been reported. Since changes may occur without previous signs of gastrointestinal or haematological toxicity, it is imperative that hepatic function be determined prior to initiation of treatment and monitored regularly throughout therapy. Special caution is indicated in the presence of pre-existing liver damage or impaired hepatic function. Concomitant use of other drugs with hepatotoxic potential (including alcohol) should be avoided.
3. 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.
4. Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy.
5. Methotrexate given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.
6. Use in pregnancy: Pregnancy category D. Methotrexate has caused fetal death and / or congenital abnormalities. Therefore, it is not recommended in women of child bearing potential unless there is appropriate medical evidence that the benefits can be expected to outweigh the considered risks. Pregnant psoriatic patients should not receive methotrexate. Women of childbearing potential should not be started on methotrexate until pregnancy is excluded and should be fully counselled on the serious risk to the fetus should they become pregnant while undergoing treatment.
7. Impaired renal function is usually a contraindication.
8. Diarrhoea and ulcerative stomatitis are frequent toxic effects and require interruption of therapy; otherwise, haemorrhage enteritis and death from intestinal perforation may occur.
9. Unexpectedly severe (sometimes fatal) marrow suppression, aplastic anaemia and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high doses) along with nonsteroidal anti-inflammatory agents (NSAIDs).
10. 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 which has been reported at low doses. It is not always fully reversible and fatalities have been reported. Pulmonary symptoms (especially a dry, non-productive cough) may require interruption of treatment and careful investigation. Pulmonary lesions can occur at all dosages. Infection (including pneumonia) needs to be excluded. Patients should be closely monitored for pulmonary symptoms.
Methotrexate has been used in very high dosage followed by leucovorin (calcium folate) rescue in the experimental treatment of certain neoplastic diseases. This procedure is investigational and hazardous. It should not be attempted outside of facilities where the necessary expertise and resources have been assembled. The recent published literature should be consulted.

Name of Drug
Methotrexate

Description
Methotrexate is (S)-2-[4-[(2,4-diaminopteridin-6-yl)methyl]methylamino]benzoylamino]pentanedioic acid. It is a yellow or orange, crystalline powder, practically insoluble in water, in alcohol, in ether and in ethylene chloride. It dissolves in dilute solutions of mineral acids and in dilute solutions of alkali hydroxides and carbonates.

The structural formula is represented below.

![Structural formula of Methotrexate](image)

Molecular Formula: $\text{C}_{20}\text{H}_{22}\text{N}_8\text{O}_5$
Molecular Weight: 454.4
CAS Number: 59-05-2

Methotrexate Injection BP is a sterile, preservative-free yellow to orange solution available in three presentations containing Methotrexate BP and Sodium Hydroxide BP in Water for Injections BP. Sodium Chloride BP is added to the 50 mg in 2 mL and 500 mg in 20 mL presentations to render them isotonic. Methotrexate Injection BP 1000 mg in 10 mL is hypertonic.

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

**Pharmacokinetics**

After parenteral injection, peak serum levels are seen in about 0.5 – 2.0 hours. Approximately one half the absorbed methotrexate is reversibly bound to serum protein, but exchanges with body fluids easily and diffuses into the body tissue cells. Elimination is triphasic. The first phase probably describes distribution into organs; the second, renal excretion; and the third, passing of methotrexate into the enterohepatic circulation. Excretion occurs mainly through the kidneys. Approximately 41% of the dose is excreted unchanged in the urine during the first six hours; 90% within 24 hours. Repeated daily doses result in more sustained serum levels and some retention of methotrexate over each 24 hour period which may result in accumulation of the drug within the tissues. The liver cells appear to retain certain amounts of the drug for prolonged periods even after a single therapeutic dose. Methotrexate is retained in the presence of impaired renal function and may increase rapidly in the serum and in the tissue cells under such conditions. Methotrexate does not penetrate the blood cerebrospinal fluid barrier in therapeutic amounts when given orally or parenterally. High concentrations of the drug when needed may be attained by direct intrathecal administration.

**Indications**

- **Antineoplastic chemotherapy**
  Treatment of breast cancer, gestational choriocarcinoma and in patients with chorioadenoma destruens and hydatidiform mole. Palliation of acute and subacute lymphocytic and meningeal leukaemia. Greatest effect has been observed in palliation of acute lymphoblastic (stem cell) leukaemias. In combination with corticosteroids, methotrexate may be used for induction of remission. The drug is now most commonly used for the maintenance of induced remissions. Methotrexate is also effective in the treatment of the advanced stages (III and IV, Peters Staging System) of lymphosarcoma, particularly in children and in advanced cases of mycosis fungoides.

- **High dose therapy**
  The use of very high doses is made possible by vials for injection containing 500 mg and 1000 mg (See Precautions). Diseases treated with these doses administered in the form of single-drug or combination therapy, include osteogenic sarcoma, acute leukaemia, bronchogenic carcinoma and epidermoid carcinoma of the head and neck.

- **Psoriasis chemotherapy** (See WARNINGS box and Precautions).
  Because of the high risk attending to its use, Methotrexate Injection is only indicated in the symptomatic control of severe, recalcitrant, disabling psoriasis which is not adequately responsive to other forms of therapy, but only when the diagnosis has been established, as by biopsy and/or after dermatologic consultations.

**Contraindications**

Methotrexate should not be given to:

- Pregnant patients with psoriasis.
- Nursing mothers.
- Psoriasis patients with severe hepatic disorders.
- Patients with severe renal impairment.
- Psoriasis patients with alcoholism or alcoholic liver disease.
- Patients who have overt or laboratory evidence of immunodeficiency.
- Psoriasis patients with bone marrow depression or pre-existing blood dyscrasias, such as bone marrow hypoplasia, leucopenia, thrombocytopenia or anaemia.
- Psoriasis patients with serious infections.
• Patients with a known hypersensitivity to methotrexate or to any of the excipients.
• Psoriasis patients with peptic ulcer disease or ulcerative colitis.
• Radiotherapy to the central nervous system should not be given concurrently with intrathecal methotrexate.

Precautions
Use with caution in the following circumstances
Methotrexate must be used only by physicians experienced in antimetabolite chemotherapy or, in the case of non-oncological conditions, by a specialist physician. Because of the possibility of fatal or severe toxic reactions the patient should be fully informed by the physician of the risks involved and should be under his constant supervision. Close monitoring for toxicity is mandatory, particularly in high dose therapy or where drug elimination could be impaired (renal impairment, pleural effusion, ascites). Deaths have been reported with use of methotrexate in the treatment of malignancy and psoriasis.

• In the treatment of psoriasis, methotrexate should be restricted to severe, recalcitrant, disabling disease, which is not adequately responsive to other forms of therapy, but only when the diagnosis has been established, as by biopsy and/or after appropriate consultation.
• Methotrexate may produce marked depression of bone marrow, anaemia, leucopenia, thrombocytopenia and bleeding. It may be hepatotoxic, particularly at high dosage or with prolonged therapy. Liver atrophy, necrosis, cirrhosis, fatty changes and periportal fibrosis have been reported. Since changes may occur without previous signs of gastrointestinal or haematologic toxicity, it is imperative that hepatic function be determined prior to initiation of treatment and monitored regularly throughout therapy. Special caution is indicated in the presence of pre-existing liver damage or impaired hepatic function. Concomitant use of other drugs with hepatotoxic potential (including alcohol) should be avoided. Impaired renal function is usually a contraindication.

• Methotrexate should be used with extreme caution in the presence of debility and in extreme youth or age. Due to diminished hepatic and renal functions as well as decreased folate states in elderly patients, relatively low doses should be considered and these patients should be closely monitored.
• The risk of developing acute hepatitis and chronic hepatotoxicity in psoriatic patients seems to be correlated not only to the cumulative dose of the drug but also to the presence of concurrent conditions such as alcoholism, obesity, diabetes, advanced age and arsenical compounds. Chronic toxicity is potentially fatal; it generally occurs after prolonged use (generally 2 years or more) and after a total cumulative dose of at least 1.5 grams.
• In patients with malignant disease who have pre-existing bone marrow aplasia, leucopenia, thrombocytopenia or anaemia, the drug should be used with caution, if at all.
• Methotrexate given concomitantly with radiation may increase the risk of soft tissue necrosis and osteonecrosis.

• High-dose therapy
Methotrexate has been used in very high dosage followed by leucovorin rescue in the experimental treatment of certain neoplastic disease. This procedure is investigational and hazardous. It should not be attempted outside of facilities where the necessary expertise and resources have been assembled. The recent published literature should be consulted. Large doses should not be used in patients with impaired renal function or a third-space reservoir, such as ascites or large pleural effusion, because rapid drug excretion is important in limiting toxicity. Careful monitoring of renal function and methotrexate serum levels is required in order to reveal impending toxicity. Administration of calcium folinate is mandatory in high-dose methotrexate therapy. The administration of calcium folinate, hydration and urine alkalinisation should be carried out with constant monitoring of the toxic effects and the elimination of methotrexate.
Check the following before and during use:

- Methotrexate may cause renal damage that may lead to acute renal failure. Close attention to renal function including adequate hydration, urine alkalinisation and measurement of serum methotrexate and renal function are recommended.

- Methotrexate is excreted principally by the kidneys. Its use in the presence of impaired renal function may result in accumulation of toxic amounts or even additional renal damage. The patient's renal status should be determined prior to and periodically during methotrexate therapy and proper caution exercised should significant renal impairment be disclosed. Drug dosage should be reduced or discontinued until renal function is improved or restored. The urine should be kept alkaline throughout therapy with methotrexate (methotrexate is a weak acid and tends to precipitate at urine pH below 6.0).

- 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, using alkalinisation and measurement of serum methotrexate and creatinine levels are essential for safe administration.

- Vomiting, diarrhoea and ulcerative stomatitis are frequent toxic effects and require interruption of therapy; otherwise haemorrhagic enteritis and death from intestinal perforation may occur.

- Pulmonary symptoms (especially a dry non-productive cough) or a non-specific pneumonitis occurring during methotrexate therapy may be indicative of a potentially dangerous lesion and require interruption of treatment and careful investigation. Although clinically variable, the typical patient with methotrexate-induced lung disease presents with fever, cough, chest pain, dyspnoea, hypoxaemia and an infiltrate on X-ray. This lesion can occur at all dosages. Infection (including pneumonia) needs to be excluded.

- Systemic high doses or intrathecal administration of methotrexate may cause significant CNS toxicity. Patients should be closely monitored for neurologic symptoms and if these occur treatment should be discontinued and appropriate therapy instituted.

- Methotrexate has the potential for serious toxicity. Toxic effects may be related in frequency and severity to dose or frequency of administration, but have been seen at all doses. Because the toxic effects can occur at any time during therapy, it is necessary to follow the patients on methotrexate therapy very closely. When such reactions do occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken. If methotrexate therapy is reinstituted, it should be carried out with utmost caution, with adequate consideration of further need for the drug, and with increased alertness as to possible recurrence of toxicity.

- Pretreatment and periodic haematologic studies are essential to the use of methotrexate in chemotherapy because of its common effect of haematopoietic suppression, manifesting as anaemia, aplastic anaemia, pancytopenia, leukopenia, neutropenia and/or thrombocytopenia. This may occur abruptly and on apparent safe dosage, and any profound drop in blood cell count indicates immediate stoppage of the drug and appropriate therapy. If profound leucopenia occurs during therapy, bacterial infection may occur or become a threat. Cessation of the drug and appropriate antibiotic therapy is usually indicated. In severe bone marrow depression, blood or platelet transfusions may be necessary.

- Methotrexate causes hepatotoxicity, liver fibrosis and cirrhosis, but generally only after prolonged use. Liver enzyme elevations are frequently seen. These are usually transient and asymptomatic, and do not appear predictive of subsequent hepatic disease. Liver biopsy after sustained use often shows histological changes, and fibrosis and cirrhosis have been reported; these latter lesions may not be preceded by symptoms or abnormal liver function tests in the psoriasis population. Periodic liver biopsies are usually recommended for psoriatic patients who are under long-term treatment. In psoriasis, liver damage and function tests, including serum albumin and prothrombin time, should be performed several times prior to dosing. Liver function tests are often normal in
developing fibrosis or cirrhosis. These lesions may be detectable only by biopsy. It is recommended to obtain a liver biopsy at: 1) before start of therapy or shortly after initiation of therapy (2-4 months); 2) after a total cumulative dose of 1.5 grams; and 3) after each additional 1.0 to 1.5 grams. In case of moderate fibrosis or any cirrhosis, discontinue the drug; mild fibrosis normally suggests a repeat biopsy in 6 months. Milder histologic findings such as fatty change and low grade portal inflammation are relatively common before the start of therapy. Although these mild changes are normally not a reason to avoid or discontinue methotrexate therapy, the drug should be used with caution.

- In general, the following laboratory tests are recommended as part of essential clinical evaluation and appropriate monitoring of patients chosen for or receiving methotrexate therapy; a full blood count, haematocrit; urinalysis; renal function tests; liver function tests. A chest X-ray is also recommended. The tests should be performed prior to therapy, at appropriate periods during therapy, and after termination of therapy. During initial or changing doses, or during periods of increased risk of elevated methotrexate blood levels (e.g. dehydration), more frequent monitoring may also be indicated. During therapy for psoriasis, monitoring of these parameters is recommended: haematology at least monthly, and liver and renal function every 1 to 2 months. More frequent monitoring is usually indicated during antineoplastic therapy. It may be useful or important to perform liver biopsy or bone marrow aspiration studies where high dose or long term therapy is being followed.

- Methotrexate exits slowly from the third-space compartments (e.g. pleural effusions or ascites). This results in a prolonged terminal phase 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.

**Information for patients:**

Patients should be informed of the early signs and symptoms of toxicity, of the need to see their physician promptly if they occur, and the need for close follow-up, including periodic laboratory tests to monitor toxicity.

Patients should be informed of the potential benefit and risk in the use of methotrexate. The risk of effects on reproduction should be discussed with both male and female patients taking methotrexate.

Patients receiving methotrexate should avoid excessive unprotected exposure to sun or sunlamps because of possible photosensitivity reactions.

**Use in pregnancy: Category D**

Methotrexate has caused fetal death and / or congenital abnormalities; therefore, it is not recommended in women of childbearing potential unless there is appropriate medical evidence that the benefits can be expected to outweigh the considered risks. Pregnant psoriatic women should not receive methotrexate. Women of childbearing potential should not be started on methotrexate until pregnancy is excluded and should be fully counselled on the serious risk to the fetus should they become pregnant while undergoing treatment.

Pregnancy should be avoided if either partner is receiving methotrexate, during and for a minimum of 3 months after therapy has ceased, although the optimal time interval between the cessation of methotrexate treatment of either partner, and pregnancy, has not been clearly established.

**Use in lactation**

Methotrexate passes into breast milk and is contraindicated during breastfeeding. The highest breast milk to plasma concentration ratio reached was 0.08:1. Because of the potential for serious adverse reactions from methotrexate in breast fed infants, it is contraindicated in nursing mothers.

**Infection or immunological states**

- Methotrexate should be used with extreme caution in the presence of active infection, peptic ulcer and ulcerative colitis. Methotrexate therapy has immunosuppressive activity which can
potentially lead to serious or even fatal infections. This factor must be taken into consideration in evaluating the use of the drug where immune responses in a patient may be important or essential.

- Pneumonia (in some cases leading to respiratory failure) may occur. Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy. When a patient presents with pulmonary symptoms, the possibility of *Pneumocystis carinii* pneumonia should be considered.

- It is usually contraindicated in patients with overt or laboratory evidence of immunodeficiency.

- Immunisation may be ineffective when given during methotrexate therapy. Immunisation with live virus vaccines is generally not recommended. There have been reports of disseminated vaccinia infections after smallpox immunisation in patients receiving methotrexate therapy.

**Carcinogenicity and mutagenicity**

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. There is evidence that methotrexate causes chromosomal damage to animal somatic cells and human bone marrow cells. *In vitro*, methotrexate caused chromosomal aberrations in Chinese hamster A(T1) C1-3 cells, induced morphological transformation in mouse C3H/10T1/2 clone 8 cells and was associated with an increased incidence of large colony mutants at the tk locus in L5178Y/tk− mouse lymphoma cells. *In vivo*, it caused an increased incidence of polychromatic erythrocytes in mice and a transient and reversible increase in chromosomal aberrations in human bone marrow cells. The clinical significance of these findings is uncertain.

Benefit should be weighed against this potential risk before using methotrexate alone or in combination with other drugs, especially in children or young adults. Methotrexate causes embryotoxicity, abortion and fetal defects in humans. It has also been reported to cause impairment of fertility, oligospermia and menstrual dysfunction in humans, during and for a short period after cessation of therapy.

**Ability to drive or operate machinery**

Adverse reactions to methotrexate, such as dizziness and fatigue may affect the ability to drive or operate machinery.

**Interactions with other drugs**

- Methotrexate is bound in part to serum albumin after absorption and toxicity may be increased because of displacement by certain drugs such as salicylates, sulphonamides, sulphonylureas, phenylbutazone and phenytoin. Renal tubular transport is also diminished by probenicid; use of methotrexate with this drug should be carefully monitored. Hypolipidemic compounds such as cholestyramine proved preferential binding substrates compared to serum proteins when given in combination with methotrexate.

- Penicillins and sulphonamides may reduce the renal clearance of methotrexate; increased serum concentrations of methotrexate with concomitant haematologic and gastrointestinal toxicity have been observed with methotrexate. Use of methotrexate with penicillins and sulphonamides should be carefully monitored.

- Nonsteroidal anti-inflammatory drugs should not be administered prior to or concomitantly with the high dose methotrexate used in the treatment of osteosarcoma. Concomitant administration of NSAIDs with high-dose methotrexate therapy has been reported to elevate and prolong serum methotrexate levels, resulting in deaths from severe haematological 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 tubular secretion of methotrexate in an animal model and may enhance its toxicity.

- Unexpectedly severe (sometimes fatal) marrow suppression and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high doses) with some nonsteroidal anti-inflammatory agents (NSAIDs) including aspirin and other salicylates,
asapropazone, diclofenac, indomethacin and ketoprofen. Naproxen has been reported not to affect the pharmacokinetics of methotrexate but a fatal interaction has been reported.

- Folate deficiency states may increase methotrexate toxicity. Trimethoprim alone or in combination with 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. Increased bone marrow suppression has also been reported in patients receiving methotrexate and pyrimethamine. Conversely, multi-vitamin preparations including folic acid or its derivatives may alter responses to methotrexate and should not be given concomitantly.

- Methotrexate is often used in combination with other cytotoxic drugs. Additive toxicity may be expected in chemotherapy regimens which combine drugs with similar pharmacologic effects and special monitoring should be made with regard to bone marrow depression, renal, gastrointestinal and pulmonary toxicity. The dosage of methotrexate should be adjusted if it is used in combination with other chemotherapeutic agents with overlapping toxicities.

- 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).

- Oral antibiotics such as tetracycline, chloramphenicol and non-absorbable 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.

- The administration of asparaginase has been reported to antagonise the effect of methotrexate.

- An increased risk of hepatotoxicity has been reported when etretinate and other potential hepatotoxins such as leflunomide, azathioprine, retinoids and sulfasalazine are given concurrently with methotrexate. The use of nitrous oxide anaesthesia potentiates the effect of methotrexate on folate metabolism, yielding severe unpredictable myelosuppression and stomatitis. This effect can be reduced by the use of calcium folinate.

- Methotrexate in combination with leflunomide may also increase the risk of pancytopenia.

- Amiodarone administration to patients receiving methotrexate treatment for psoriasis has induced ulcerative skin lesions.

- Methotrexate increases the plasma levels of mercaptopurine. Combination of methotrexate and mercaptopurine may therefore require dose adjustment.

- Skin cancer has been reported in a few patients with psoriasis or mycosis fungoides (a cutaneous T-cell lymphoma) receiving concomitant treatment with methotrexate plus PUVA therapy (methoxalen and ultraviolet light).

- Care should be exercised whenever packed red blood cells and methotrexate are given concurrently. Patients receiving 24 hour methotrexate infusion and subsequent transfusions have shown enhanced toxicity probably resulting from prolonged serum-methotrexate concentrations.

- Methotrexate is an immunosuppressant and may reduce immunological response to concurrent vaccination. Severe antigenic reactions may occur if a live vaccine is given concurrently.

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

**Incompatibilities**

Methotrexate has been reported to be incompatible with cytarabine, fluorouracil and prednisolone.

**Adverse reactions**

The major toxic effects of methotrexate occur on normal, rapidly proliferating tissues, particularly the bone marrow and gastrointestinal tract. Ulcerations of the oral mucosa are usually the earliest signs of toxicity. The most common adverse reactions include ulcerative stomatitis, leucopenia, nausea and abdominal distress. Others reported are malaise, undue fatigue, chills and fever, headaches, dizziness, drowsiness, tinnitus, blurred vision, eye discomfort and decreased resistance to infection. In general,
the incidence and severity of side effects are considered to be dose and frequency related. Adverse reactions as reported for the various systems are as follows:

**Dermatological and Hypersensitivity:** Dermatitis, erythematous rashes, pruritus, urticaria, photosensitivity, depigmentation/hyperpigmentation, alopecia, vasculitis, petechiae, ecchymosis, telangiectasia, acne, folliculitis, furunculosis, nail changes. Burning and erythema may appear in psoriatic areas for 1 to 2 days following each dose. Lesions of psoriasis may be aggravated by concomitant exposure to ultraviolet radiation. Skin ulceration has been reported in psoriatic patients and a few cases of anaphylactoid reactions have been reported. Radiation dermatitis and sunburn may be “recalled”.

Severe, occasionally fatal, dermatological reactions, including toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, skin ulceration/necrosis and erythema multiforme have been reported in children and adults within days of methotrexate administration. Reactions were noted after single or multiple doses of methotrexate in patients with neoplastic and non-neoplastic diseases.

**Haematological and lymphatic system:** Bone marrow depression, leucopenia, neutropenia, thrombocytopenia, decrease in serum albumin, anaemia (including aplastic anaemia), eosinophilia, pancytopenia, agranulocytosis, hypogammaglobulinaemia, lymphadenopathy and proliferative disorders. Clinical sequelae such as fever, infections, haemorrhage from various sites and septicemia may be expected. Megaloblastic anaemia has also been reported, mainly in elderly patients receiving long-term methotrexate therapy. Folate supplementation may permit continuation of methotrexate therapy with resolution of anaemia.

**Gastrointestinal:** Mucositis (gingivitis, pharyngitis, stomatitis, glossitis), anorexia, nausea, vomiting, diarrhoea, abdominal distress, haematemeses, melena, gastrointestinal ulceration and bleeding, intestinal perforation, enteritis, acute and chronic hepatic toxicity resulting in acute liver atrophy, necrosis, fatty metamorphosis, acute hepatitis, perportal fibrosis, hepatic cirrhosis, pancreatitis, elevated liver enzymes, decreased serum albumin and hepatic failure. In rare cases the effect of methotrexate on the intestinal mucosa has led to malabsorption or toxic megacolon. Alteration of liver function tests (increases in transaminases and LDH levels) is commonly reported but usually resolves within one month after cessation of therapy.

**Urogenital:** Renal failure, dysuria, azotaemia, cystitis, haematuria, defective oogenesis or spermatogenesis, transient oligospermia, urogenital or menstrual dysfunction, infertility, abortion, fetal defects, fetal death, severe nephropathy, vaginitis, vaginal discharge.

**Cardiovascular:** Pericarditis, vasculitis, pericardial effusion, hypotension and thromboembolic events (including arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, thrombophlebitis and pulmonary embolism).

**Neurological:** Headaches, drowsiness, blurred vision, lethargy, motor dysfunction, cranial nerve palsies, leukoencephalopathy, encephalopathy and coma have been reported. Aphasia, hemiparesis, paresis, convulsions and Guillain-Barre syndrome, increased cerebrospinal fluid pressures have followed intrathecal administration. Following low doses, occasional patients have reported transient subtle cognitive dysfunction, mood alteration or unusual cranial sensations. Cognitive impairment has been recorded in children who received intrathecal methotrexate together with cranial irradiation. There have been reports of leukoencephalopathy following intravenous administration of methotrexate in high doses to patients who have had craniospinal irradiation.

After the the intrathecal or high-dose use of methotrexate, the central nervous system toxicity which may occur can be classified as follows: (1) chemical arachnoiditis manifested by such symptoms as headache, back pain, nuchal rigidity, and fever; (2) paresis, usually transient, manifested by paraplegia and increased CSF pressure associated with involvement with one or more spinal nerve roots; (3) a delayed syndrome occurring months to years after treatment characterised by necrotising leukoencephalopathy and manifested by confusion, stupor, irritability, somnolence, ataxia, dementia, occasionally major convulsions and rarely, death. The
effects are dose-related and occur particularly when intrathecal methotrexate is given at doses greater than 50 mg in combination with cranial irradiation and systemic methotrexate therapy.

- **Pulmonary:** Interstitial pneumonitis deaths, interstitial fibrosis and reversible eosinophilic pulmonary infiltrates have been reported and chronic interstitial obstructive pulmonary disease and alveolitis have occasionally occurred. Manifestations of methotrexate-induced pulmonary toxicity commonly include fever, cough (especially dry and non-productive), dyspnoea, chest pain, hypoxaemia and / or radiological evidence of pulmonary infiltrates (usually diffuse and / or alveolar).

- **Ophthalmic:** Conjunctivitis, serious visual changes of unknown aetiology including transient blindness.

- **Carcinogenicity:** Cytotoxic drugs have been reported to be associated with an increased risk of development of secondary tumours in humans. Reports of lymphoma, including reversible lymphomas and tumour lysis syndrome have been documented in patients treated with methotrexate. Evidence of chromosomal damage to animal somatic cells and human bone marrow cells has been reported with methotrexate.

- **Infections:** 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 infection. Other reported infections included pneumonia, sepsis, nocardiosis, histoplasmosis, cryptococcosis, *Herpes zoster, H. simplex* hepatitis, disseminated *H. simplex*, fatal sepsis and cytomegalovirus, including cytomegaloviral pneumonia.

- **Other:** Other reactions related to, or attributed to, the use of methotrexate are metabolic changes, precipitation of diabetes, osteoporotic effects (including aseptic necrosis of the femoral head), abnormal tissue cell changes, arthralgia/myalgia, proteinuria, nodulosis, stress fracture, loss of libido, impotence and even sudden death have been reported.

### 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.

**Antineoplastic chemotherapy**

Methotrexate may be administered by intramuscular, intravenous or intrathecal routes. METHOTREXATE INJECTION 1000MG IN 10ML SHOULD NOT BE USED INTRATHECALLY AS THE SOLUTION IS HYPERTONIC.

For intrathecal injection, Methotrexate Injection should be diluted to a strength of 1mg per mL with an appropriate preservative-free medium such as 0.9% Sodium Chloride Injection.

For conversion of mg/kg bodyweight to mg/m² of body surface area or the reverse, a ratio of 1:30 is given as a guideline. The conversion factor varies between 1:20 and 1:40 depending on age and body build.

- **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/m² intravenously on only the first and eighth days.

- **Choriocarcinoma and similar trophoblastic diseases**
  Methotrexate is administered intramuscularly in doses of 15-30 mg daily for a five day course. Such courses are usually repeated three to five times as required with a rest period of one or more
weeks interposed between courses, until any manifesting toxic symptoms subside. The effectiveness of therapy is ordinarily evaluated by 24 hour quantitative analysis of urinary chorionic gonadotrophin hormone (βHCG), which should return to normal or less than 50 units/24 hour usually after the 3rd or 4th course and usually followed by a complete resolution of measurable lesions in 4 to 6 weeks. One to two courses of methotrexate after normalisation of βHCG is usually recommended. Before each course of the drug, careful clinical assessment is essential. Cyclic combination therapy of methotrexate with other antitumour drugs has been reported as being useful. Since hydatidiform mole may precede or be followed by 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 choriocarcinoma.

- **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 alone or in combination with steroids was used initially for induction of remission of lymphoblastic leukaemias. More recently, corticosteroid therapy in combination with other antileukaemic drugs or in cyclic combination therapy including methotrexate, has produced rapid and effective remissions. When used for induction, in doses of 3.3 mg/m² in combination with prednisolone 60 mg/m² given daily, remission occurred in 50% of patients treated, usually within a period of 4 to 6 weeks. 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, by administering methotrexate 2 times weekly intramuscularly in 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.

- **Meningeal leukaemia**
  Patients with leukaemia are subject to leukaemic invasion of the central nervous system. This may manifest characteristic signs or symptoms or may remain silent and be diagnosed only by examination of the cerebrospinal fluid, 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 cerebrospinal fluid is minimal, for adequate therapy the drug is administered intrathecally.
  
  It is now common practice to administer methotrexate intrathecally as prophylaxis in all cases of lymphocytic leukaemia.
  
  By intrathecal injection the distribution of methotrexate is in the CSF, the volume of which is dependent on 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:

<table>
<thead>
<tr>
<th>Age (Yrs)</th>
<th>&lt;1</th>
<th>1</th>
<th>2</th>
<th>3+ Older</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg)</td>
<td>6</td>
<td>8</td>
<td>10</td>
<td>12</td>
</tr>
</tbody>
</table>

There is some indication that infants less than 4 months and adults ≥70 years may have increased acute toxicity with doses recommended and dose reduction may be indicated. The solution is made in a strength of 1 mg/mL with an appropriate, sterile, preservative-free medium such as 0.9% Sodium Chloride Injection BP.

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. At this point, one additional dose is advisable. 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 intrathecal route appears significantly in the systemic circulation and may cause systemic methotrexate toxicity. Therefore, systemic antileukaemic therapy with drug should be appropriately adjusted, reduced or discontinued. Focal leukaemic involvement of the CNS may not respond to intrathecal chemotherapy and is best treated with radiotherapy.

- **Lymphomas**
  In Burkitt’s tumour, stages I-II, methotrexate has produced prolonged remission in some cases. Recommended dosage is 10 to 25 mg per day orally for 4 to 8 days. In stage III, methotrexate is commonly given concomitantly with other antitumour agents. Treatment in all stages usually consists of several courses of the drug interposed with 7 to 10 day rest periods. Lymphosarcomas in stage III may respond to combined drug therapy with methotrexate given in doses of 0.625 mg to 2.5 mg/kg daily. Hodgkin’s Disease responds poorly to methotrexate and to most types of chemotherapy.

- **Mycosis fungoides**
  As an alternative to oral therapy, methotrexate 50 mg intramuscularly weekly or 25 mg intramuscularly twice weekly may be given.

- **High-dose therapy (See Precautions).**
  Dosage regimens have varied considerably in different studies, the nature and severity of the disease and the previous experience of the investigator are some of the factors influencing the choice of dosage and the duration of therapy. It must be emphasised that high dosages should be used only by qualified specialists and in hospitals where the necessary facilities are available.

**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 full blood count, 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 during and for at least three months following methotrexate therapy. The commonly used injectable dosage schedule is by weekly parenteral intermittent large doses. The schedules should be continually tailored to the individual patient. Dose schedules cited below pertain to an average 70 kg adult. An initial test dose one week prior to initiation of therapy is recommended to detect any idiosyncrasy. A suggested dose range is 5-10 mg parenterally.

**Recommended Starting Dose**
Weekly single IM or IV dose schedules: 10-25 mg per week until adequate response is achieved. With this dosage schedule, 50 mg per week should ordinarily not be exceeded.

Dosage may be gradually adjusted to achieve optimal clinical response, but not to exceed the maximum stated for each schedule. Once optimal clinical response has been achieved the 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.
Overdosage
Discontinue methotrexate at the first sign of ulceration or bleeding, diarrhoea or marked depression of the haematopoietic system. Symptoms commonly reported following oral overdose include those symptoms and signs reported at pharmacological doses, particularly haematological and gastrointestinal reactions. For example, leucopenia, thrombocytopenia, anaemia, pancytopenia, bone marrow suppression, mucositis, oral ulceration, nausea, vomiting, gastrointestinal ulceration, gastrointestinal bleeding. In some cases, no symptoms were reported. There have been reports of death following overdose. In these cases, events such as sepsis or septic shock, renal failure, and aplastic anaemia were also reported. As soon as possible after an inadvertent overdosage of methotrexate, calcium folinate (leucovorin calcium) should be given at 10 mg/m^2 IV or IM every 6 hours until the serum methotrexate levels are below 10^-8 M. In the presence of gastric stasis or obstruction leucovorin should be administered parenterally. Concomitant hydration (3 L/d) and urinary alkalisation with sodium bicarbonate should be employed. The bicarbonate dose should be adjusted to maintain a urinary pH at 7 or greater. Serum samples should be assayed for creatinine levels and methotrexate levels at 24 hour intervals. If the 24 hour serum creatinine level has increased 50% over baseline or if the 24 hour methotrexate level is >5 x 10^-6M or the 48 hour methotrexate level is 9 x 10^-7 M or higher, the doses of calcium folinate should be increased to 100 mg/m^2 IV every 3 hours until the methotrexate level is <10^-8 M. The infusion rate of calcium folinate should not exceed 16.0 mL (160 mg calcium folinate) per minute. Patients with significant third space accumulations should be considered high-risk and monitored until serum methotrexate levels are <10^-8 M regardless of their 24 hour serum concentration. The above mentioned statements on calcium folinate dosage do not apply with high-dosage methotrexate therapy. The dosages of calcium folinate have varied in different studies and the published literature on high-dosage methotrexate should be consulted. Neither standard haemodialysis nor peritoneal dialysis has been shown to significantly improve methotrexate elimination. Some clearance of methotrexate may be obtained by haemodialysis if the patient is totally anuric and no other therapeutic options are available. Effective clearance of methotrexate has been reported with acute, intermittent haemodialysis using a high-flux dialyser.

Handling precautions
As with all antineoplastic agents, trained personnel should prepare Methotrexate Injection BP. This should be performed in a designated area (preferably a cytotoxic laminar flow cabinet). Protective gown, mask, gloves and appropriate eye protection should be worn when handling methotrexate. Where solution accidentally contacts skin or mucosa, the affected area should be immediately washed thoroughly with soap and water. It is recommended that pregnant personnel not handle cytotoxic agents such as methotrexate. Luer-Lock fitting syringes are recommended. Large bore needles are recommended to minimise pressure and possible formation of aerosols. Aerosols may also be reduced by using a venting needle during preparation. Items used to prepare Methotrexate Injection BP, or articles associated with body waste, should be disposed of by placing in a double sealed polythene bag and incinerating at 1100°C.

Spills and disposal
If spills occur, restrict access to the affected area. Wear two pairs of gloves (latex rubber), a respirator mask, a protective gown and safety glasses. Limit the spread of the spill by covering with absorbent material such as absorbent towel or adsorbent granules. Collect up the towel of absorbent/adsorbent material and other debris from spill and place in a leak proof plastic container and label accordingly. Cytotoxic waste should be regarded as hazardous or toxic and clearly labelled ‘CYTOTOXIC WASTE FOR INCINERATION AT 1100°C’. Waste material should be incinerated at 1100°C for at least 1 second. Cleanse the remaining spill area with copious amounts of water.
Presentation
AUST R 10777: Methotrexate Injection BP 50 mg in 2 mL (sterile) Plastic Vial.
AUST R 47648: Methotrexate Injection BP 500 mg in 20 mL (sterile) Plastic Vial.
AUST R 10778: Methotrexate Injection BP 1000 mg in 10 mL (sterile) Plastic Vial.

Storage
Store below 25°C. Protect from light. Single use only. Discard unused portion.
The expiry date (month/year) is stated on the package after EXP.

Poison schedule
Australia - S4.

Sponsor in Australia
Pfizer Australia Pty Ltd
ABN 50 008 422 348
38-42 Wharf Road
West Ryde NSW 2114 Australia

Manufacturer
Pfizer (Perth) Pty Limited
ABN 32 051 824 956
15 Brodie Hall Drive
Bentley WA 6102 Australia

This information was approved by the TGA on 26 October 2000.

Date of most recent amendment: 16 March 2011