PRODUCT INFORMATION
Methoblastin tablets® 2.5 mg and 10 mg

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 and rheumatoid arthritis, 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 periportal 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 foetal 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 and rheumatoid arthritis 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 foetus 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, nonproductive cough) may require interruption of treatment and careful investigation. Pulmonary lesions can occur at all dosages. Infections (including pneumonia) needs to be excluded. Patients should be closely monitored for pulmonary symptoms.

11. Both the physician and the pharmacist should emphasise to the patient the importance of the weekly dosing regimen: mistaken daily use may cause serious and sometimes life-threatening or fatal toxicity. For the same reason great care should be taken with dispensing to ensure the correct tablet strength of Methoblastin is given to the patient. Methoblastin is available as 2.5 mg and 10 mg tablets.

NAME OF THE MEDICINE

Methotrexate; CAS number: 59-05-2

![Chemical Structure of Methotrexate]

DESCRIPTION

Methotrexate is a yellow or orange crystalline powder. It is practically insoluble in water, in alcohol, and in methylene hydrochloride. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides and carbonates.

Methoblastin tablets contains the active ingredient methotrexate.
Excipients: starch - maize, lactose, starch - pregelatinised maize, polysorbate 80, microcrystalline cellulose, magnesium stearate.
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, foetal 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.

In patients with rheumatoid arthritis, effects of methotrexate on articular swelling and tenderness can be seen as early as three to six weeks. Although methotrexate clearly ameliorates symptoms of inflammation (pain, swelling, stiffness) there is no evidence that it induces remission of rheumatoid arthritis nor has a beneficial effect been demonstrated on bone erosions and other radiological changes which result in impaired joint use, functional disability and deformity. Most studies of methotrexate in patients with rheumatoid arthritis are relatively short term (three to six months). Data from long term studies indicate that an initial clinical improvement is maintained for at least two years with continued therapy.

Pharmacokinetics

Orally administered, methotrexate is absorbed rapidly in most but not all patients, and reaches peak serum levels in 1 to 2 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.
INDICATIONS

Antineoplastic chemotherapy
Treatment of breast cancer, gestational choriocarcinoma and in patients with chorioadenoma destruens and hydatidiform mole. Palliation of acute and subacute lymphocytic 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. Methoblastin 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.

Psoriasis chemotherapy (See WARNINGS box and Precautions)
Because of the high risk attending to its use, Methoblastin 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.

Rheumatoid arthritis chemotherapy (See WARNINGS box and Precautions)
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. (See Precautions, Interactions with other drugs).

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 should not be given to:

- Pregnant patients with psoriasis or rheumatoid arthritis.
- Nursing mothers.
- Psoriasis and rheumatoid arthritis patients with severe hepatic disorders.
- Patients with severe renal impairment.
- Psoriasis and rheumatoid patients with alcoholism or alcoholic liver disease.
- Patients who have overt or laboratory evidence of immunodeficiency.
• Psoriasis and rheumatoid arthritis patients with bone marrow depression or pre-existing blood dyscrasias, such as bone marrow hypoplasia, leucopenia, thrombocytopenia or anaemia.

• Rheumatoid arthritis patients with active, infectious disease or psoriasis patients with serious infections.

• Patients with a known hypersensitivity to methotrexate or to any of the excipients.

• Psoriasis and rheumatoid arthritis patients with peptic ulcer disease or ulcerative colitis.

• An increased risk of hepatitis has been reported to result from combined use of methotrexate and etretinate. Therefore, the combination of methotrexate with retinoids such as acitretin is also contraindicated.

PRECAUTIONS (See WARNING box)

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 and rheumatoid arthritis, 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.

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 has occurred 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 radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.

It should be used with extreme caution in the presence of infection, peptic ulcer and ulcerative colitis. Methotrexate should be used with extreme caution in the presence of active infections, and is usually contraindicated in patients with overt or laboratory evidence of immunodeficiency syndromes. 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.

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.

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.

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.

**Check the following before and during use**

Methotrexate may cause renal damage that may lead to acute renal failure. Close attention should be given to renal function, including adequate hydration and urine alkalinisation. 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).

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.
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, leucopenia, 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. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid arthritis population.

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 rheumatoid arthritis, age at first use of methotrexate and duration of therapy have been reported as risk factors for hepatotoxicity. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid population. Liver function tests should be performed at baseline and at 4-8 week intervals in patients receiving methotrexate for rheumatoid arthritis. Pretreatment liver biopsy should be performed for patients with a history of excessive alcohol consumption, persistently abnormal baseline liver function test values, or chronic hepatitis B or C infection. During therapy, liver biopsy should be performed if there are persistent liver function test abnormalities, or there is a decrease in serum albumin below the normal range (in the setting of well controlled rheumatoid arthritis).

If the results of a liver biopsy show mild changes (Roenigk grades I, II, IIIa), methotrexate may be continued and the patient monitored according to the recommendations listed above. Methotrexate should be discontinued in any patient who displays persistently abnormal liver function tests.
function tests and refuses biopsy, or in any patient whose liver biopsy shows mild to severe changes (Roenigk grade IIIb or IV). When methotrexate is discontinued, a 'flare' of arthritis usually occurs within three to six weeks.

Both the physician 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 (see WARNINGS box and Precautions).

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 rheumatoid arthritis and 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.

Patients should be advised that adverse reactions to methotrexate, such as dizziness and fatigue, may affect their ability to drive or operate machinery.

Methoblastin tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

**Caution: Pharmacist**

Because of its potential to cause severe toxicity, methotrexate therapy requires close supervision of the patient by the physician. Pharmacists should dispense no more than a
seven day supply of the drug at one time. Refill of those prescriptions should be by direct order (written or oral) of the physician only.

Carcinogenicity/Genotoxicity/Effects on Fertility

No controlled human data exist regarding the risk of neoplasia with methotrexate. Methotrexate has been evaluated in a number of animal studies for carcinogenic potential with inconclusive results.

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.

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.

Assessment of the carcinogenic potential of methotrexate is complicated by conflicting evidence of an increased risk of certain tumours in rheumatoid arthritis. 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 foetal 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.

Men undergoing methotrexate therapy should use contraception during and for 3 months after treatment because methotrexate has in clinical studies caused increased number of abnormal and immobile spermatozoa.

Use in Pregnancy (Category D)

Methotrexate has caused foetal 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 or rheumatoid arthritis 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 foetus should they become pregnant while undergoing treatment.

Pregnancy should be avoided and reliable effective contraception used 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.

Interactions with other medicines

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, phenytoin, and some antibacterials such as penicillins, tetracycline, chloramphenicol, pristinamycin, probenecid and para-aminobenzoic acid. Hypolipidemic compounds such as cholestyramine proved preferential binding substrates compared to serum proteins when given in combination with methotrexate. These drugs, especially salicylates and sulphonamides, whether antibacterial, hypoglycaemic or diuretic, should not be given concurrently until the significance of these findings is established.

Renal tubular transport is diminished by probenecid; use of methotrexate with this drug should be carefully monitored. Penicillins and sulphonamides may reduce renal clearance of methotrexate, increase 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.

Despite the potential interactions, studies of methotrexate in patients with rheumatoid arthritis have usually included concurrent use of dosage regimens of NSAIDs, without apparent problems. It should be appreciated, however, that the doses used in rheumatoid arthritis (7.5 to 15 mg/week) are somewhat lower than those used in psoriasis and the larger doses could lead to unexpected toxicity. Therefore, until more is known about the NSAID/methotrexate interaction, it is recommended that methotrexate dosage be carefully controlled during treatment with NSAIDs.

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

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 azathioprine, retinoids, leflunomide and sulfasalazine are given concurrently with methotrexate. Methotrexate in combination with leflunomide may also increase the risk of pancytopenia.

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.

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

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).

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

Care should be exercised whenever packed red blood cells and methotrexate are given concurrently. Patients receiving 24 hour methotrexate infusion and subsequent transfusions have showed 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.

Bone marrow suppression and decreased folate levels have been described in the concomitant administration of triamterene and methotrexate.
Incompatibilities

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

ADVERSE EFFECTS

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:

Hypersensitivity and Skin: Anaphylactic reactions, 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.

Blood and Lymphatics: Bone marrow depression, leucopenia, neutropenia, thrombocytopenia, anaemia (including aplastic anaemia), eosinophilia, pancytopenia, agranulocytosis, hypogammaglobulinaemia, lymphadenopathy, proliferative disorders and decrease in serum albumin. 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 weekly methotrexate therapy. Folate supplementation may permit continuation of methotrexate therapy with resolution of anaemia.

Alimentary System: Mucositis (gingivitis, pharyngitis, stomatitis, glossitis), anorexia, nausea, vomiting, diarrhoea, abdominal distress, haematemesis, melaena, gastrointestinal ulceration and bleeding, intestinal perforation, enteritis, acute and chronic hepatic toxicity resulting in acute liver atrophy, necrosis, fatty metamorphosis, acute hepatitis, periportal fibrosis, hepatic cirrhosis, pancreatitis, elevated liver enzymes and 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 System: Renal failure, dysuria, azotaemia, cystitis, haematuria, defective oogenesis or spermatogenesis, transient oligospermia, urogenital or menstrual dysfunction,
infertility, abortion, foetal defects, foetal 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).

**Central Nervous System:** Headaches, drowsiness, blurred vision, eye discomfort, tinnitus, convulsions, aphasia, hemiindrome, speech impairment including dysartria, lethargy, motor dysfunction, cranial nerve palsies, leucoencephalopathy, encephalopathy, arachnoiditis, coma, dementia, depression and confusion have been reported.

Following low doses, occasional patients have reported transient subtle cognitive dysfunction, mood alteration or unusual cranial sensations.

**Pulmonary System:** 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, pleurisy, chest pain, hypoxaemia and / or radiological evidence of pulmonary infiltrates (usually diffuse and / or alveolar).

**Ophthalmic:** conjunctivitis, serious visual changes or unknown aetiology including transient blindness.

**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 cutaneous bacterial infections, pneumonia, sepsis, nocardiosis, histoplasmosis, cryptococcosis, *Herpes zoster*, *H. simplex* hepatitis, disseminated *H. simplex*, fatal sepsis and cytomegalovirus, including cytomegaloviral pneumonia.

**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.

**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, gynaecomastia, loss of libido, impotence and even sudden death has 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

Oral administration in tablet form is often preferred since absorption is rapid and effective serum levels are obtained.

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.

Choriocarcinoma and similar trophoblastic diseases

Methotrexate is administered orally 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.

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 in doses of 30 mg/m². If and when relapse does occur, reinduction of remission can again usually be obtained by repeating the initial induction regimen.
**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**

Therapy with methotrexate appears to produce clinical remissions in one half of the cases treated. Dosage is usually 2.5 to 10 mg daily by mouth for weeks or months. Dose levels of drug and adjustment of dose regimen by reduction or cessation of drug are guided by patient response and haematologic monitoring.

**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 twelve weeks following methotrexate therapy.

There are three commonly used general types of dosage schedules:

1. weekly oral 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. 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.

**Recommended Starting Dose Schedules**

1. Weekly single oral 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.

2. Divided oral dose schedule: 2.5 mg at 12 hour intervals for three doses or at 8 hour intervals for four doses, each week. With this dosage, 30 mg per week should not be exceeded.

3. Daily oral dose schedule: 2.5 mg daily for five days followed by at least a two day rest period. With this dosage schedule, 6.25 mg per day should not be exceeded.
Dosage in each schedule 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 each dosage schedule should be reduced to the lowest possible amount of drug and to the longest possible rest period. The use of methotrexate may permit the return to conventional topical therapy, which should be encouraged.

**Rheumatoid arthritis chemotherapy**

The patient should be fully informed of the risks involved and should be under constant supervision by the physician.

Assessment of haematological, hepatic, renal and pulmonary function should be made by history, physician 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 physician 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 12 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 12 weeks or more. The dosage in each schedule may be increased to 15 mg/week after six weeks in nonresponsive 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 possible 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.

**Instructions for Handling**

Pregnant staff should be excluded from working with this drug.

**OVERDOSAGE**

Symptoms commonly reported following oral overdose include those symptoms and signs reported at pharmacological doses, particularly haematological and gastrointestinal reactions. These signs and symptoms include leucopenia, thrombocytopenia, anaemia, pancytopenia, bone marrow suppression, mucositis, oral ulceration, nausea, vomiting, gastrointestinal
ulceration, gastrointestinal bleeding, anorexia, progressive weight loss and bloody diarrhoea. In some cases of overdose, 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.

Consider administration of activated charcoal in the event of a potentially toxic ingestion. Activated charcoal is most effective when administered within 1-hour of ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected.

After an inadvertent overdosage of methotrexate, calcium folinate (leucovorin calcium) should be given as soon as possible at 10 mg/m² IV or IM q 6 hours until the serum methotrexate levels are below 10⁻⁸M. 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 10⁻⁷M or higher, the doses of calcium folinate should be increased to 100 mg/m² IV q 3 hours until the methotrexate level is <10⁻⁸M. 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 <10⁻⁸M 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.

In cases of massive overdosage, hydration and urinary alkalisation may be necessary to prevent the precipitation of the drug and/or its metabolites in the renal tubules. Neither standard haemodialysis nor peritoneal dialysis have 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. However, effective clearance of methotrexate has been reported with acute, intermittent haemodialysis using a high-flux dialyzer.

Contact the Poisons Information Centre for advice on the management of an overdose.

PRESENTATION

Methoblastin (methotrexate) Tablets:

2.5 mg - yellow, round, biconvex, uncoated tablets engraved M 2.5 on one side and blank on the other, bottles of 30s

10 mg - yellow, capsule shaped, uncoated tablets engraved M 10 on the same side as the score line, bottles of 15s, 50s
NAME AND ADDRESS OF SPONSOR
Pfizer Australia Pty Ltd
ABN 50 008 422 348
38-42 Wharf Road
West Ryde NSW 2114
Australia

POISON SCHEDULE

S4  Prescription Only Medicine

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