

Methoblastin[®]

Methotrexate 2.5mg, 10mg tablets

Presentation

Oral preparations

Each 2.5 mg, yellow, round, convex tablet contains Methotrexate 2.5 mg. The tablets are engraved with “M 2.5” on one side and blank on the other.

Each 10 mg, yellow, capsule shaped tablet contains Methotrexate 10 mg. The tablets are engraved with “M10” on the same side as the score line.

Uses

Pharmacodynamic Properties

Methotrexate (4-amino-10 methyl folic acid) is an antimetabolite and an analogue of folic acid. The drug enters the cells *via* an active transport system for reduced folates and, due to a relatively irreversible binding, the drug inhibits the enzyme dihydrofolate reductase which catalyses the reductive process of folic acid into tetrahydrofolic acid. The inhibited formation of tetrahydrofolates results in an interference with DNA synthesis, repair and cell replication. The affinity of dihydrofolate reductase for methotrexate is far greater than its affinity for folic or dihydrofolic acid and, therefore, even very large amounts of folic acid given simultaneously will not reverse the effects of methotrexate. The drug seems also to cause an increase in intracellular deoxyadenosine triphosphate, which is thought to inhibit ribonucleotide reduction and polynucleotide ligase, an enzyme concerned in DNA synthesis and repair.

Actively proliferating tissues such as malignant cells, bone marrow, foetal cells, buccal and intestinal mucosa, spermatogonia and cells of the urinary bladder are in general more sensitive to the pharmacological actions of methotrexate.

Pharmacokinetics

Absorption. Low oral doses (up to 25 - 30mg/m²) are rapidly absorbed from the gastrointestinal tract but absorption at higher doses is erratic, possibly because of a saturation effect. A variability in methotrexate absorption has been however detected in subjects receiving oral treatment due to drug-induced epithelial denudation, motility changes and alterations in intestinal flora. In addition, food has been shown

to delay absorption and reduce peak concentration. Peak serum levels are reached within 1-4 hrs following oral administration.

Distribution. Approximately 50% of absorbed methotrexate is reversibly bound to serum protein but is easily diffused into body tissue cells, where the drug is actively transported across the cell membranes.

Methotrexate is widely distributed into body tissues with highest concentrations in the kidneys, gallbladder, spleen, liver and skin. Small or insignificant amounts cross the blood-brain barrier and enter CSF following oral or parenteral administration; this may be increased when giving higher doses. Small amounts have been detected in saliva and breast milk. The drug crosses the placental barrier.

Methotrexate is retained for several weeks in the kidneys and for months in the liver, even after a single therapeutic dose. Sustained serum concentrations and tissue accumulation of methotrexate may result from repeated daily doses.

The drug enters slowly into third-space collections of fluid, such as pleural effusions, ascites and marked tissue oedemas.

Metabolism. At low doses the drug does not appear to undergo significant metabolism; following high-dose therapy methotrexate undergoes hepatic and intracellular metabolism to polyglutamated forms which can be converted back to methotrexate by hydrolase enzymes. A small amount of metabolism to the 7-hydroxy derivative may occur at doses commonly prescribed.

Before absorption, methotrexate may be partly metabolised by the intestinal flora to 2,4-diamino-N¹⁰-methylpteroic acid, a pharmacologically inactive metabolite.

Excretion. Clearance from plasma is reported to be triphasic: the first phase probably involves distribution into organs, the second renal excretion and the third the methotrexate passage into the enterohepatic circulation.

The terminal half-life after low oral doses is in the range 3 to 10 hrs. Total clearance averages 12 L/h, but there is wide interindividual variation, delayed drug clearance having been identified as one of the major factors responsible for drug toxicity.

Excretion is mainly through the kidneys via glomerular filtration and active transport. The pattern of elimination, however, varies considerably according to the dosage. Methotrexate excretion is impaired and accumulation occurs more rapidly in patients with impaired renal function. In addition, simultaneous administration of weak organic acids such as salicylates may suppress methotrexate clearance. The drug is slowly released from third-space compartments, giving prolongation of plasma disappearance and increased risk of toxicity.

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, Methoblastin 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 states (III and IV, Peters Staging System) of lymphosarcoma, particularly in children and in advanced cases of mycosis fungoides.

Psoriasis Chemotherapy

See Warnings. 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.

Dosage and Method of Administration

Antineoplastic Chemotherapy:

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 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 gonadotropin hormone (CGH), which should return to normal or less than 50 units/24 hour usually after the 3rd or 4th course and usually be followed by a complete resolution of measurable lesions in 4 to 6 weeks. One to two courses of methotrexate after normalisation of CGH 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. Choriodenoma destruens is considered to be an invasive form of hydatidiform mole. Methoblastin is administered in these disease states in doses similar to those recommended for choriocarcinoma.

Leukaemia. Methoblastin alone or in combination with steroids was used initially for induction of remission of lymphoblastic leukaemias. When used for induction, in doses of 3.3 mg/m² in combination with prednisone 60 mg/m² given daily, remission occurred in 50% of patients treated, usually within a period of 4 to 6 weeks.

Methoblastin alone, or in combination with other agents appears to be the drug of choice for securing maintenance of drug induced remissions. When remission is achieved and supportive care has produced general clinical improvement, maintenance therapy is initiated, as follows: Methoblastin is administered 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, Methoblastin has produced prolonged remissions in some cases. Recommended dosage is 10 to 25 mg per day orally for 4 to 8 days. In stage III, Methoblastin 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 Methoblastin given in doses of 0.625 mg to 2.5 mg/kg daily.

Mycosis fungoides. Therapy with Methoblastin 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.

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 should be continually tailored to the individual patient. Dose schedules cited below pertain to an average 70kg 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 schedule: 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 Methoblastin may permit the return to conventional topical therapy, which should be encouraged.

Contraindications

Known hypersensitivity to methotrexate and severe renal impairment are contraindications for the use of the drug.

The presence of liver impairment, alcoholism, alcoholic liver disease, bone marrow depression or pre-existing blood dyscrasias such as bone marrow hypoplasia, leucopenia, thrombocytopenia or anaemia, serious infections, overt or laboratory evidence of immunodeficiency, peptic ulcer disease or ulcerative colitis warrant extreme caution in using methotrexate for antineoplastic therapy while they represent contra-indications for its use in patients with psoriasis.

Methotrexate should not be given to pregnant patients with psoriasis.

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.

Warnings and Precautions

As a general rule, the administration of methotrexate should be carried out under the supervision of physicians fully trained in the use of cytotoxic drugs. A close monitoring for toxicity is mandatory, particularly in the case of delivering high drug dosages and long term therapy. Deaths have been reported with use of methotrexate in the treatment of malignancy and psoriasis.

The treatment of non-oncological conditions should also always be instituted and supervised by a specialised physician.

Although toxic effects are likely to be related in frequency and severity to dose and/or frequency of drug administration, toxicity can occur at all doses.

Patients should be fully informed by the attending physician of the risk of toxicity before undergoing methotrexate treatment. Patients need to be closely monitored throughout treatment, and particular attention is recommended for patients with renal impairment, as it may lead to renal failure, as well as for those with pleural effusions or other third-space compartments (e.g. ascites) since drug elimination could be impaired. Methotrexate exits slowly from the third-space compartments and 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.

Routine baseline assessment should include a complete blood cell count, haematocrit; urinalysis, hepatic and renal function tests, and a chest x-ray. The tests should be performed prior to therapy, at appropriate periods during therapy, and after termination of therapy. On initiating therapy or changing doses, or during periods of increased risk of elevated methotrexate blood levels (e.g. dehydration), more frequent monitoring may also be indicated.

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 and may not be preceded by symptoms. 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. During therapy for psoriasis, monitoring of haematological parameters (at least one monthly) and liver and renal function (every one to two months) is recommended.

In oncological patients more frequent monitoring is usually indicated. The urine should be kept alkaline throughout therapy with methotrexate. 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.

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.

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

Methotrexate may produce marked depression of bone marrow, anaemia, aplastic anaemia, leucopenia, neutropenia, thrombocytopenia and bleeding. 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.

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.

Outpatients under methotrexate therapy should be informed of the early signs and symptoms of toxicity, of the need to see their physician promptly if they occur and of the need of a close follow-up, including regular laboratory tests for monitoring toxicity.

In the treatment of psoriasis, 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.

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.

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.

Special warnings and precautions apply to the following areas:

Infections. 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. Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy. 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. Signs/symptoms of infection should be carefully observed and aggressive antibiotic therapy may be necessary.

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.

Gastrointestinal toxicity. Methotrexate should be used with extreme caution in the presence of peptic ulcer and ulcerative colitis. Vomiting, diarrhoea and ulcerative

stomatitis are frequent toxic effects. If severe and recurrent vomiting, severe and recurrent diarrhoea or extensive ulcerative stomatitis occur, methotrexate therapy should be discontinued given the risk of haemorrhagic enteritis and intestinal perforation.

Hepatotoxicity. Transient abnormalities of liver function test (elevated transaminases) are observed frequently after methotrexate administration and do not usually require modification of methotrexate therapy. Liver biopsy after sustained use often shows histological changes. Liver atrophy, necrosis, cirrhosis, fatty changes and periportal fibrosis have been reported. Chronic (fibrosis and cirrhosis) liver toxicity is potentially fatal and may occur following prolonged (2 years or longer) treatment and high cumulative drug doses of at least 1.5 grams. Although liver biopsy is currently believed to be the only reliable measure of methotrexate-induced hepatotoxicity, liver function tests should be determined prior to initiation of treatment and repeated periodically during the treatment period, since changes may occur without previous signs of gastrointestinal or haematologic toxicity. Special caution is indicated in the presence of pre-existing liver damage or impaired hepatic function. Persistent abnormalities and/or significant decreases in serum albumin may be indicators of serious liver toxicity and require evaluation. Concomitant use of other drugs with hepatotoxic potential (including alcohol) should be avoided.

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.

Pulmonary toxicity. 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) or a non-specific pneumonitis occurring during methotrexate therapy may 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. Pulmonary lesions can occur at all dosages.

Infection (including pneumonia) needs to be excluded. 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. Patients should be closely monitored for pulmonary symptoms.

Neurotoxicity. Systemic high-doses of methotrexate may cause significant CNS toxicity: patients should be closely monitored for neurologic signs/symptoms. If such manifestations occur the treatment should be discontinued and appropriate therapy instituted.

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

Renal function. Impaired renal function is usually a contraindication. Methotrexate is not nephrotoxic but is almost completely excreted by the kidney. Risk of renal damage leading to acute renal failure due primarily to the precipitation in the kidney of the unchanged drug and metabolite (7-hydroxy methotrexate) can be reduced by close attention to renal function including adequate oral hydration, urine alkalinisation (methotrexate is a weak acid and tends to precipitate at urine pH below 6.0), measurement of serum methotrexate and creatinine levels. Renal function tests should be performed periodically. Drug dosage should be reduced or discontinued until renal function is improved or restored.

Interactions

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.

Reduced oral methotrexate absorption from the gastrointestinal tract has been seen in the presence of *oral antibiotics*. 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.

After absorption, methotrexate is partly bound to serum albumin: the concurrent use of other drugs competing for the same binding site may result in a displacement of methotrexate, increased plasma concentrations and risk of toxicity. *Salicylates*, *sulfonamides*, *sulfonylureas*, *phenytoin*, *phenylbutazone*, *aminobenzoic acid* some antibiotics such as *penicillins*, *tetracycline*, *pristinamycin*, *probenecid* and *chloramphenicol* have an inhibiting/competitive effect with methotrexate on serum protein binding.

Renal tubular transport is also diminished by *probenecid*; use of methotrexate with this drug should be carefully monitored. *Penicillins* and *sulfonamides* may reduce 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 sulfonamides should be carefully monitored.

Caution should be used when *non-steroidal anti-inflammatory drugs (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.

Also, hypolipidemic compounds such as *cholestyramine* proved preferential binding substrates compared to serum proteins when given in combination to methotrexate.

Unexpectedly severe (sometimes fatal) marrow suppression and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high doses) with some *NSAIDs*, including *aspirin* and other *salicylates*, *azapropazone*, *diclofenac*, *indomethacin* and *ketoprofen*. The mechanism is uncertain but may include both displacement of methotrexate from protein-binding sites or an inhibiting effect of NSAIDs on prostaglandin E2 synthesis yielding to a significant decrease of blood renal flow, resulting in reduced methotrexate excretion. *Naproxen* has been reported not to affect the pharmacokinetics of methotrexate, but a fatal interaction has been reported.

The concurrent use of *pyrimethamine* or *trimethoprim/sulfamethoxazole* may increase bone marrow suppression in patients receiving methotrexate probably by decreased tubular secretion and/or an additive antifolate effect. Conversely, *multivitamin preparations* including folic acid or its derivatives may alter responses to methotrexate and should not be given to patients concomitantly.

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

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

An increased risk of hepatotoxicity has been reported when methotrexate and *etretinate* and other potential hepatotoxins such as *azathioprine*, *retinoids*, *leflunomide*, *sulfasalazine* and *alcohol* 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 folinic acid rescue.

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

Skin cancer has been reported in few patients with psoriasis or mycosis fungoides (a cutaneous T-cell lymphoma) receiving a concomitant treatment with methotrexate plus *PURA 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-hr methotrexate infusion and subsequent transfusions have showed enhanced toxicity probably resulting from prolonged high 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.

Pregnancy and Lactation

Pregnant psoriatic patients should not receive methotrexate.

Embryotoxicity, abortion, foetal death and/or congenital abnormalities have occurred in pregnant women receiving methotrexate. 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.

Women of childbearing potential should not receive the drug until pregnancy is excluded and should be advised to use a reliable contraceptive method during and until about 3 months after discontinuation of the drug. If the drug is administered during pregnancy or if the patient becomes pregnant while receiving methotrexate, information on the potential serious hazard to the foetus should be provided.

Men undergoing methotrexate therapy should also use contraception because methotrexate has in clinical studies caused increased number of abnormal and immobile spermatozoa.

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.

Methotrexate is contraindicated during breastfeeding. Mothers should be advised not to breast-feed while on methotrexate, since the drug is excreted in breast milk and could be a potential cause of serious adverse effects.

Preclinical Safety Data

The intraperitoneal LD50 of methotrexate was 94 and 6-25 mg/kg for mice and rats, respectively. The oral LD50 of the compound in rats was 180 mg/kg. The tolerance

to methotrexate in mice increased with age. In dogs, the intravenous dose of 50 mg/kg was lethal. The main targets after a single dose were the hemolymphopoietic system and G.I. tract.

The toxic effects after repeated administration of methotrexate were investigated in mice and rats. The main targets of methotrexate in the above animal species were the haemolymphopoietic system, G.I. tract, lung, liver, kidney, testes, and skin. The tolerance of mice to chronic methotrexate doses increased with age.

Carcinogenicity. Cytotoxic drugs have been reported to be associated with an increased risk of development of secondary tumours in humans. However, 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.

Evidence of chromosomal damage to animal somatic cells and human bone marrow cells has been reported with methotrexate.

Methotrexate was genotoxic in several of the *in vitro* and *in vivo* tests performed, toxic to the male reproductive organs, and embryotoxic and teratogenic in mice, rats and rabbits. No evidence of carcinogenicity was found in life-span studies in mice and hamsters. Nevertheless, methotrexate, like other cytotoxic drugs, must be considered potentially carcinogenic.

Effects on the Ability to Drive and Use Machines

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

Adverse Effects

Many side effects of methotrexate therapy are unavoidable being due to the pharmacological actions of the drug. However, the adverse effects are generally reversible if detected early. The major toxic effects of methotrexate occur on normal, rapidly proliferating tissues, particularly the bone marrow and the gastrointestinal tract. Ulcerations of the oral mucosa are usually the earliest signs of toxicity. The most common adverse reactions include stomatitis, leucopenia, thrombocytopenia, nausea and abdominal distress; however, as for other cytotoxic drugs, different toxicities may occur with different frequency/intensity according to different doses/routes of administration. Others reported are malaise, undue fatigue, chills and fever, headaches, dizziness, drowsiness, tinnitus, blurred vision, eye discomfort and decreased resistance to infection.

Adverse reactions as reported for the various organ systems are as follows.

Haematologic Effects. Bone marrow depression, leucopenia, neutropenia, thrombocytopenia, anaemia (including aplastic anaemia), eosinophilia, pancytopenia, agranulocytosis, hypogammaglobulinaemia, lymphadenopathy, proliferative disorders and decrease in serum albumin is expected following methotrexate therapy. Leukocytes and neutrophils may occasionally show two depressions, the first occurring in 4-7 days and a second nadir after 12-21 days, followed by recovery. Clinical sequelae such as fever, infections and haemorrhage from various sites and septicaemia 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.

Gastrointestinal Effects. Mucositis (stomatitis, gingivitis, glossitis, pharyngitis, enteritis) as well as nausea, vomiting and diarrhoea may occur. Clinical consequences of such toxicities may be ulceration and bleeding of the mucosal membranes of the mouth and/or other portions of the gastrointestinal tract, intestinal perforation, haematemesis, malaena, abdominal distress, anorexia. In rare cases the effect of methotrexate on the intestinal mucosa has led to malabsorption or toxic megacolon.

Methotrexate administration has been associated with acute and chronic hepatotoxicity such as acute liver atrophy, necrosis, fatty metamorphosis, periportal fibrosis or hepatic cirrhosis, pancreatitis. Alteration of liver function tests (increases in transaminases and LDH levels) is commonly reported but usually resolve within one month's after cessation of therapy. A more important hepatic fibrosis or cirrhosis may follow long-term (2 years or longer) treatments and high cumulative drug doses. The risk of developing 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 the use of arsenical compounds.

Hypersensitivity and Dermatologic Effects. Anaphylactic reaction, erythematous rashes, urticaria and pruritus have been reported following methotrexate administration. Dermatitis, acne/furunculosis/folliculitis, nail changes, vasculitis, petechiae, ecchymoses, telangiectasia, photosensitivity, skin depigmentation/hyperpigmentation and alopecia may also occur. Burning and erythema may appear in psoriatic areas for 1-2 days following each dose, aggravated by concomitant exposure to ultraviolet radiation. 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.

Pulmonary Effects. Interstitial pneumonitis, interstitial fibrosis, reversible eosinophilic pulmonary infiltrates may occur. Chronic interstitial pulmonary disease has occasionally been reported. Manifestations of methotrexate-induced pulmonary toxicity commonly include fever, cough (especially dry and non-productive), dyspnoea, chest pain, hypoxemia and/or radiological evidence of pulmonary infiltrates (usually diffuse and/or alveolar).

Cardiovascular Effects. 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, speech impairment including dysarthria, lethargy, motor dysfunction, cranial nerve palsies, aphasia, hemiparesis, 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.

Urogenital and Reproductive Effects. Severe nephropathy, renal failure, azotemia, cystitis, dysuria, haematuria may occur. Defective oogenesis or spermatogenesis, transient oligospermia, urogenital dysfunction, menstrual dysfunction, vaginitis, vaginal discharge, gynaecomastia, loss of libido, impotence, infertility, abortion, foetal defects and foetal death have also been reported.

Carcinogenicity. Cytotoxic drugs have been reported to be associated with an increased risk of development of secondary tumours in humans. Evidence of chromosomal damage to animal somatic cells and human bone marrow cells has been reported with methotrexate (see also Preclinical Safety Data).

Other Adverse Effects. Other adverse effects reported in association with the use of methotrexate include metabolic changes, precipitating diabetes and osteoporotic effects (including aseptic necrosis of the femoral head). Abnormal tissue cell changes, arthralgia/myalgia, proteinuria, nodulosis, stress fracture and even sudden death have also been reported.

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, 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/m^2 IV or IM q 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 alkalinisation 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 $>5 \times 10^{-6} \text{ M}$ or the 48 hour methotrexate level is $9 \times 10^{-7} \text{ M}$ or higher, the doses of calcium folinate should be increased to 100 mg/m^2 IV q 3 hours until the methotrexate level is $<10^{-8} \text{ M}$. 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 $<10^{-8} \text{ M}$ 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.

In case of massive overdosage, hydration and urinary alkalinisation 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.

Pharmaceutical Particulars

List of Excipients

2.5 mg and 10 mg tablet

Lactose

Maize starch

Pregelatinized maize starch

Polysorbate 80

Microcrystalline cellulose
Magnesium stearate

Incompatibilities

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

Shelf Life

2.5 mg and 10 mg tablets: 5 years

Special Precaution for Storage

Methotrexate tablets should be protected from light and stored below 25°C.

Instructions for Use/Handling

Pregnant staff should be excluded from working with this drug.

Package Quantities

The 2.5 mg tablets are available in a pack size of 30 tablets.

The 10 mg tablets are available in a pack size of 50 tablets.

Medicine Classification

Prescription Medicine

Name and Address

Pfizer New Zealand Ltd.
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Auckland
New Zealand
Toll Free Number: 0800736 363

Date of Preparation

31 March 2010

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