

Methoblastin®
2.5mg, 10mg tablets and 2.5mg/ml, 25mg/ml injection - Methotrexate

Composition

Oral preparations

Each 2.5mg yellow round convex tablet contains Methotrexate sodium 2.5mg. The tablets are engraved with “M2.5”.

Each 10mg yellow round convex tablet contains Methotrexate sodium 10mg. The tablets are engraved with “M10” and are scored on one side.

Injection solutions

2.5 mg/ml vials: A clear, slightly yellow solution free from visible particulate matter containing Methotrexate sodium

25 mg/ml vials: A clear, slightly yellow solution free from visible particulate matter containing Methotrexate sodium.

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, 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.

High Dosage Therapy

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. 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:

Methoblastin parenteral may be given by intramuscular, intravenous, intra arterial, intrathecal or oral route.

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 $40\text{mg}/\text{m}^2$ intravenously on the first and eighth days.

Choriocarcinoma and similar trophoblastic diseases. Methotrexate is administered orally or intramuscularly in doses of 15-30mg 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 50units/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. Methotrexate is administered in these disease states in doses similar to those recommended for choriocarcinoma.

Leukaemia. Methotrexate alone or in combination with steroids was used initially for induction of remission of lymphoblastic leukaemias. When used for induction, in doses of $3.3\text{mg}/\text{m}^2$ in combination with prednisone $60\text{mg}/\text{m}^2$ 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, as follows: Methotrexate is administered in doses of $30\text{mg}/\text{m}^2$. It has also been given in doses of $2.5\text{mg}/\text{kg}$ 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. Some patients with leukaemia are subject to leukaemic invasion of the CNS. Since passage of methotrexate from blood serum to the cerebrospinal fluid is minimal, for adequate therapy the drug is administered intrathecally. The common approach is to treat such patients as may actually manifest leukaemic involvement by direct intrathecal instillation of methotrexate.

Methotrexate is administered by intrathecal injection of the sodium salt in solution, in doses of 0.2 to 0.5 mg/kg/bodyweight. Administration is at intervals of 2 to 5 days and is usually repeated until the cell count of the cerebrospinal fluid returns to normal. At this point on additional dose is advised. A second common course of administration is methotrexate $12\text{mg}/\text{m}^2$ once weekly for two weeks then once monthly. Large doses may cause convulsions. Untoward side effects may occur with any given 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 central nervous system may not respond to intrathecal chemotherapy and is best treated with radiotherapy.

Lymphomas. In Burkitts tumour, stages I-II, Methotrexate has produced prolonged remissions in some cases. Recommended dosage is 10 to 25mg 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 0.625mg to 2.5mg/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 10mg 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. Methotrexate has also been given intramuscularly in doses of 50mg once weekly or 25mg twice weekly.

High-dose therapy. See Warnings. 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.

There are three commonly used general types of dosage schedules:

1. weekly oral or parenteral intermittent large doses,
2. divided dose intermittent oral schedule over a 36 hour period
3. daily oral with a rest period. All schedules should be continually tailored to the individual patient. 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. A suggested dose range is 5-10mg parenterally.'

Recommended starting dose schedules.

1. Weekly single oral, IM or IV dose schedules: 10-25mg per week until adequate response is achieved. With this dosage schedule, 50mg per week should ordinarily not be exceeded.
2. Divided oral dose schedule: 2.5mg at 12 hour intervals for three doses or at 8 hour intervals for four doses each week. With this dosage, 30mg per week should not be exceeded.
3. Daily oral dose schedule: 2.5mg daily for five days followed by at least a two day rest period. With this dosage schedule, 6.25mg 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 contra-indications for the use of the drug.

The presence of liver impairment, alcoholism, bone marrow depression, serious infections, 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 or rheumatoid arthritis.

Special Warnings and Special Precautions for Use

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.

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 well as for those with pleural effusions or other third-space compartments (e.g. ascites) since drug elimination could be impaired.

Routine baseline assessment should include a complete blood cell count, hepatic and renal function tests, and a chest x-ray. During therapy of rheumatoid arthritis and psoriasis, monitoring of haematological parameters (at least one monthly) and liver and renal function (every one to three months) is recommended. In oncological patients more frequent monitoring is usually indicated. The urine should be kept alkaline throughout therapy with methotrexate.

Outpatients under methotrexate therapy should be informed of the 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.

Special warnings and precautions apply to the following areas:

Infections. Methotrexate therapy has immunosuppressive activity which can potentially lead to serious or even fatal infections. Signs/symptoms of infection should be carefully observed and aggressive antibiotic therapy may be necessary.

Gastrointestinal toxicity. 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. Chronic (fibrosis and cirrhosis) liver toxicity may occur following prolonged (2 years or longer) treatment and high cumulative drug doses. Although liver biopsy is currently believed to be the only reliable measure of methotrexate-induced hepatotoxicity, liver function tests should be repeated periodically during the treatment period. 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.

Pulmonary toxicity. Methotrexate has a potential for causing lung toxicity and patients should be closely monitored for pulmonary signs/symptoms (e.g. dry, unproductive cough). If such manifestations occur, the treatment should be discontinued and appropriate supportive therapy instituted.

Neurotoxicity. Systemic high-doses or intrathecal administration 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. 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 metabolites can be reduced by adequate oral hydration and urine alkalinization (methotrexate is a weak acid and tends to precipitate at urine pH below 6.0). Renal function tests should be performed periodically.

High-dose therapy. Administration of folinic acid (calcium folinate) is mandatory in high-dose methotrexate therapy. The administration of folinic acid, hydration and urine alkalinization should be carried out with constant monitoring of the toxic effects and the elimination of methotrexate.

Interaction with Other Medicaments and Other Forms of Interaction

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, gastro-intestinal and pulmonary toxicity.

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

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

Severe, and in some cases fatal, aggravation of methotrexate toxicity has been reported when concomitantly administered with various *non-steroidal anti-inflammatory drugs* (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. Despite the risks, methotrexate and NSAIDs are frequently prescribed together in the treatment of rheumatoid arthritis: with special caution, and appropriate monitoring low dosages (7.5 to 15 mg/week) in combination need not be contraindicated.

The concurrent use of *pyrimethamine* or *trimethoprim* may increase the toxic effects of methotrexate because of 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 receiving methotrexate.

The administration of *L-asparaginase* has been reported to antagonize the effect of Methotrexate.

An increased risk of hepatotoxicity has been reported when methotrexate and *etretinate* are given concurrently.

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 *PUVA therapy* (methoxalen and ultraviolet light).

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.

Pregnancy and Lactation

Abortion, foetal death and/or congenital abnormalities have occurred in pregnant women receiving methotrexate. If the drug is administered during pregnancy or if the patient becomes pregnant while receiving methotrexate, information on the potential hazard to the foetus should be provided.

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.

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.

Effects on the Ability to Drive and Use Machines

There have been no reports explicitly relating to effects of methotrexate treatment on the ability to drive or use machines. However, on the basis of reported adverse reactions, the drug is presumed to be potentially dangerous.

Undesirable 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 gastro-intestinal tract. Ulcerations of the oral mucosa are usually the earliest signs of toxicity. The most common adverse reactions include stomatitis, leucopenia, 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.

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

Hematologic Effects. Bone marrow depression (leukopenia, neutropenia, thrombocytopenia and anemia) is expected following methotrexate therapy. The nadir of circulating leukocytes, neutrophils and platelets usually occurs between 5 and 13 days after an IV bolus dose (with recovery between 14 to 28 days). 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 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, 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 gastro-intestinal tract, intestinal perforation, abdominal distress, anorexia. Methotrexate administration has been associated with acute and chronic hepatotoxicity. Alteration of liver function tests (increases in transaminases and LDH levels) is commonly reported but usually resolve within one month after cessation of therapy (REF). 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. Erythematous rashes, urticaria and pruritus have been reported following methotrexate administration. Anaphylactic reactions and skin ulceration/necrosis consistent with toxic epidermal necrolysis have also been reported. Dermatitis, acne/furunculosis/fulliculitis, vasculitis, petechiae, ecchymoses, teleangiectasia, 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.

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).

CNS Effects. Neurotoxicity is reported in patients receiving intrathecal or high-doses of methotrexate. Chemical arachnoiditis is manifested by headache, back pain, nuchal rigidity. A subacute form of toxicity may be characterised by varying degrees of paresis. Paraplegia and increased CSF pressure have also been reported. A delayed syndrome, occurring months to years after treatment, is characterised by necrotising leukoencephalopathy. The syndrome may begin insidiously and progress to confusion, stupor, seizures, ataxia and dementia. 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. Cognitive impairment has been recorded in children who received intrathecal methotrexate together with cranial irradiation.

Urogenital and Reproductive Effects. Renal failure, azotemia, cystitis, haematuria may occur. Defective oogenesis or spermatogenesis, transient oligospermia, urogenital dysfunction, vaginal discharge, infertility, abortion and foetal defects 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 fever and chills, malaise, fatigue, headache, dizziness, drowsiness, tinnitus, blurred vision and eye discomfort. Metabolic changes, precipitating diabetes and osteoporotic effects including aseptic necrosis of the femoral head have also been reported.

Overdosage

Acute overdosage with methotrexate will result in severe myelosuppression and gastrointestinal toxicity, with anorexia, progressive weight loss and bloody diarrhea. Folinic acid (calcium folinate, Leucovorin rescue) is a potent agent for neutralising the immediate toxic effect of inadvertently administered overdoses of methotrexate. Folinic acid administration should start as soon as possible, preferably within the first hour, at dosage equal to or greater than the methotrexate dose.

In case of massive overdosage, hydration and urinary alkalinization may be necessary to prevent the precipitation of the drug and/or its metabolites in the renal tubules.

Inadvertent intrathecal overdosage can be managed by a repeat lumbar puncture performed immediately once the overdosage is recognised and the CSF allowed to drain to gravity. If the dose exceeds 100 mg, prompt neurosurgical intervention with ventriculolumbar perfusion following immediate CSF drainage should be considered; continuous CSF drainage or multiple CSF exchanges may also be considered but are likely not to be as effective.

Pharmacological Properties

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.

Pharmacokinetic Properties

Absorption. Rapid and complete absorption is achieved following intramuscular administration and peak serum levels are reached within 0.5-2 hrs. Low oral doses (up to 25 - 30 mg/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 achievable following oral administration are slightly lower than those detected after intramuscular injection; these peak values 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 or 8 to 15 hrs after high-dose parenteral therapy. 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. Up to 92% of a single dose is excreted unchanged in the urine within 24 hrs following IV administration followed by excretion of 1-2% of the retained dose daily. Small amounts are excreted in the faeces, probably via the bile.

The pattern of elimination, however, varies considerably according to the dosage and route of administration. 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.

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 hemolymphopoietic system, G.I. tract, lung, liver, kidney, testes, and skin. The tolerance of mice to chronic methotrexate doses increased with age.

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.

Pharmaceutical Particulars

List of Excipients

2.5 mg and 10 mg tablet

Lactose

Maize starch

Pregelatinized starch

Polysorbate 80

Microcrystalline cellulose

Magnesium stearate

2.5 mg/ml and 25 mg/ml solution for injection

Sodium chloride

Sodium hydroxide

Incompatibilities

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

Shelf Life

2.5 mg and 10 mg tablets: 5 years

2.5 mg/ml and 25 mg/ml injection solution: 2 years

Special Precaution for Storage

Methotrexate tablets as well as vials containing the injectable solution should be protected from light and stored below 25°C.

Storage of solutions diluted in 0.9% sodium chloride injection in polyvinyl chloride bags is reported to show little photodegradation; storage under normal lighting results in little change in drug concentration over 24 hrs with a decrease of up to 12% by 48 hrs. Loss is greatest from unprotected polybutadiene tubing, with almost 80% drug loss in 48 hrs.

Instructions for Use/Handling

Protective measures The following protective recommendations are given due to the toxic nature of this substance:

- personnel should be trained in good technique for reconstitution and handling
- pregnant staff should be excluded from working with this drug
- personnel handling injectable methotrexate should wear protective clothing: goggles, gowns, and disposable gloves and masks
- a designated area should be defined for reconstitution (preferably under a laminar flow system). The work surface should be protected by disposable, plastic backed, absorbent paper
- all items used for reconstitution, administration or cleaning, including gloves, should be placed in high risk, waste-disposal bags for high temperature incineration
- accidental contact with the skin or eyes should be treated immediately by copious lavage with water, or sodium bicarbonate solution; medical attention should be sought.

Package Quantities

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

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

Medicine Classification

Prescription Medicine

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