

DBL[®] METHOTREXATE INJECTION AND TABLETS

Name of medicine

Methotrexate BP

Presentation

DBL[®] Methotrexate Injection is a sterile solution of Methotrexate BP in Water for Injections BP. Sodium chloride is included for isotonicity except in the 1 g/10 mL vial. DBL[®] Methotrexate Injection is preservative-free. DBL[®] Methotrexate Injection has a pH of 7.5 to 9.0. DBL[®] Methotrexate Tablets contain 2.5 mg of Methotrexate BP. The 2.5 mg tablets are unscored.

Uses

Actions

Methotrexate is an antimetabolite and an analogue of folic acid. It enters the cells via an active transport system for reduced folates and, due to a relatively irreversible binding, exerts its cytotoxic effect by competitively inhibiting the enzyme dihydrofolate reductase which catalyses the conversion of folic acid to tetrahydrofolate. This interferes with the synthesis of thymidylic acid and purines which in turn inhibits DNA synthesis and cell reproduction and to a lesser extent protein and RNA synthesis.

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. Methotrexate 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.

Methotrexate acts specifically on the S-phase of the cell cycle. Tissues with a high cellular proliferation rate such as neoplastic tissue, bone marrow, epithelial cells or foetal cells seem to be the most susceptible. Methotrexate is used for this reason in the treatment of psoriasis, where the rate of production of epithelial cells of the skin is much higher than that of normal cells.

Pharmacokinetics

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 inter-individual 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.

Indications

Antineoplastic chemotherapy

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

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

High dose therapy

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

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

Psoriasis chemotherapy

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

Rheumatoid arthritis chemotherapy

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

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

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

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

Dosage and administration

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

(a) Antineoplastic chemotherapy

Oral administration of methotrexate in tablet form is often preferred since absorption is rapid and effective serum levels are obtained. It is recommended that oral methotrexate should be taken on an empty stomach.

Methotrexate may be administered by intramuscular, intravenous, intra-arterial or intrathecal injection. Non-isotonic solutions of DBL[®] Methotrexate Injection should not be administered intrathecally.

A guideline of a ratio of 1:30 is given for the conversion of mg/kg body weight to mg/m² body surface area. The conversion factor varies between 1:20 and 1:40 depending on age and body build.

Trophoblastic neoplasms

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

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

Breast carcinoma

Prolonged cyclic combination chemotherapy with cyclophosphamide, methotrexate and fluorouracil has given good results when used as adjuvant treatment to radical mastectomy in primary breast cancer with positive axillary lymph nodes. Methotrexate dosage was 40 mg/m² intravenously on the first and eighth days.

Leukaemia

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

Methotrexate in doses of 3.3 mg/m² orally in combination with prednisolone 60 mg/m² daily has been given for induction of remission of lymphoblastic leukaemia. When remission and general clinical improvement have been attained, a maintenance dosage of methotrexate 30 mg/m² orally or IM twice weekly may be given. This treatment is expected to produce remission in 50% of patients treated, usually within 4 to 6 weeks.

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

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

Meningeal leukaemia

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

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

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

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

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

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

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

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

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

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

Lymphomas

The usual dosage of methotrexate for the treatment of stage I or II of Burkitt's lymphoma is 10 to 25 mg per day orally for 4 to 8 days. In stage III methotrexate is commonly given concomitantly with other antineoplastic agents. In all stages, several courses of drug therapy are usually administered interposed with 7 to 10 day rest periods.

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.

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

Mycosis fungoides

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

Methotrexate has also been given IM in doses of 50 mg once weekly or 25 mg twice weekly.

Methotrexate appears to produce clinical remissions in 50% of the cases treated.

High-dosage therapy

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

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

(b) Psoriasis chemotherapy

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

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

There are three commonly used general types of dosage schedules:

- (1) weekly oral or parenteral intermittent large doses;
- (2) divided dose intermittent oral schedule over a 36 hour period;
- (3) daily oral with a rest period.

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

Recommended dose schedules for a 70kg adult are:

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

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

(c) Rheumatoid arthritis chemotherapy

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

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

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

All schedules should be continually tailored to the individual patient. An initial test dose may be given prior to the regular dosing schedule to detect any extreme sensitivity to adverse effects. Complete blood count with platelets should be evaluated seven to ten days later.

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

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

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

Contraindications

Known hypersensitivity to methotrexate and severe renal impairment are contraindications.

In the treatment of psoriasis, methotrexate is contraindicated in pregnant women and in patients with poor nutritional status, severe hepatic disorders or in those with pre-existing blood dyscrasias (such as bone marrow hypoplasia, leucopenia, thrombocytopenia or anaemia).

The presence of liver impairment, alcoholism, serious infections, peptic ulcer disease or ulcerative colitis warrant extreme caution in using methotrexate for antineoplastic therapy while they represent contraindications for its use in patients with psoriasis.

Methotrexate is also contraindicated in patients with recent exposure to, recent or existing chicken-pox or Herpes Zoster, and in patients with immunodeficiency.

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

Radiotherapy to the central nervous system should not be given concurrently with intrathecal methotrexate.

Warnings and precautions

Methotrexate should be used only by physicians experienced with antimetabolite chemotherapy and thus familiar with its various characteristics and its established clinical usage.

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 informed of the risks of toxic or fatal reactions and be under appropriate supervision, so that any signs or symptoms of such reactions may be detected as early as possible. Most adverse reactions are reversible and, when they do occur, dosage should be reduced or discontinued and appropriate corrective measures taken.

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.

The following laboratory tests should be carried out prior to, during and after termination of therapy: haemogram, haematocrit, urinalysis, renal function, liver function and chest x-ray. During therapy for 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.

Deaths have been reported with the use of methotrexate in psoriasis and it should therefore be used only in severe disabling psoriasis not responsive to other types of therapy.

Extreme caution should be taken if using methotrexate in the presence of infection, in patients with peptic ulcer, ulcerative colitis, debility and in the young or the elderly. Methotrexate should be used with caution, if at all, in patients who have pre-existing bone marrow aplasia, leucopenia, thrombocytopenia or anaemia (see Contraindications).

Hepatotoxicity: At high or prolonged doses, methotrexate may be hepatotoxic. Concomitant use of other hepatotoxic agents (including alcohol) should be avoided and liver function should be monitored. 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 preexisting 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.

Renal function: Renal function should be monitored as, although methotrexate is not nephrotoxic, it is excreted principally via the kidneys. If there is significant renal impairment, medicine dosage should be reduced or discontinued as methotrexate accumulates and is nephrotoxic. 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 alkalinisation (methotrexate is a weak acid and tends to precipitate at urine pH below 6.0). Renal function tests should be performed periodically.

Infections: Methotrexate may cause bone marrow depression, anaemia, leucopenia and thrombocytopenia which can potentially lead to serious or even fatal infections and bleeding. This may occur suddenly and on an apparently safe dosage. Signs/symptoms of infection should be carefully observed and aggressive antibiotic therapy may be necessary. Any drop in blood cell count warrants ceasing the agent and administering appropriate therapy. If severe bone marrow depression occurs, blood or platelet transfusions may be required.

Gastrointestinal toxicity: Methotrexate therapy should be discontinued if severe and recurrent vomiting, diarrhoea or ulcerative stomatitis occur, as haemorrhagic enteritis and death from intestinal perforation may ensue.

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.

High Dose Therapy

Use of high dose methotrexate followed by leucovorin rescue should only be carried out by qualified specialists and in hospitals where the necessary expertise and resources are available. Large doses should not be used in any cases where excretion is likely to be impaired or where there is a third-space reservoir such as ascites or large pleural effusion. Adequate renal excretion is important as the greatest danger is renal toxicity due to precipitation of the agent in the renal tubules.

Administration of folinic acid (calcium folinate) is mandatory in high-dose methotrexate therapy. Constant monitoring of the toxic effects, renal function and serum levels is necessary to determine the need for extended leucovorin administration. The urine should be alkalinised and the urine volume increased to prevent renal precipitation in acidic urine.

Pregnancy and Lactation

Category D: Abortion, foetal death and/or congenital abnormalities have been reported. Pregnant psoriatic patients should not receive 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.

Methotrexate is not recommended in women of child bearing potential unless the potential benefits can be expected to outweigh the risks. Pregnancy should be excluded and the patient 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 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.

Other

Carcinogenicity And Mutagenicity

Anti-metabolites have been shown to be carcinogenic in animals, and may be associated with an increased risk of development of secondary carcinomas in humans, although the risk appears to be less than with alkylating agents.

There is evidence that methotrexate causes chromosomal damage to animal somatic cells and human bone marrow cells.

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 commonly reported adverse effects are ulcerative 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.

Other reported adverse effects include malaise, undue fatigue, chills and fever, dizziness, decreased resistance to infection, tinnitus, blurred vision and eye discomfort. The incidence and severity of side effects appears to be dose related.

Other side effects can be classified as follows:

Skin and hypersensitivity reactions: Erythematous rashes, pruritis, urticaria, dermatitis, photosensitivity, skin depigmentation/hyperpigmentation, vasculitis, petechiae, ecchymosis, telangiectasia, acne and furunculosis/folliculitis have been reported following methotrexate administration. Anaphylactic reactions and skin ulceration/necrosis consistent with toxic epidermal necrolysis have also been reported. Burning and erythema may appear in psoriatic areas for 1-2 days following each dose and this may be aggravated by concomitant exposure to ultraviolet radiation. Alopecia may occur and requires several months for regrowth.

Blood: Bone marrow depression, leucopenia, neutropenia, pancytopenia, thrombocytopenia, anaemia and hypogammaglobulinaemia are 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, septicaemia 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.

Alimentary System: Gingivitis, glossitis pharyngitis, stomatitis, anorexia, vomiting, diarrhoea, haematemesis, melaena, gastrointestinal ulceration and bleeding, enteritis, intestinal perforation, abdominal distress and anorexia may occur. Methotrexate administration has been associated with acute and chronic hepatotoxicity: acute liver atrophy, necrosis, fatty metamorphosis, periportal fibrosis or hepatic cirrhosis. Alteration of liver function tests (increases in transaminases and LDH levels) is commonly reported but usually resolves within one month 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.

Urogenital System: Renal failure, azotaemia, cystitis, haematuria, defective oogenesis or spermatogenesis, transient oligospermia, urogenital/menstrual dysfunction, vaginal discharge, infertility, abortion, foetal defects, severe nephropathy have been reported.

Pulmonary System: Interstitial pneumonitis, interstitial fibrosis, reversible eosinophilic pulmonary infiltrates may occur. Deaths have been reported and chronic interstitial obstructive pulmonary disease has occasionally occurred. 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).

Central Nervous System: Headaches, drowsiness, blurred vision, aphasia, hemiparesis and convulsions have occurred. Convulsions, paresis, Guillan-Barre Syndrome and increased cerebrospinal fluid pressures have followed intrathecal administration. 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.

Ophthalmic: conjunctivitis, eye discomfort, blurred vision and serious visual changes of unknown aetiology have been reported in patients receiving methotrexate.

Infections: There have been case reports of sometimes fatal opportunistic infections in patients receiving methotrexate therapy for neoplastic and non-neoplastic diseases. Pneumonia (in some cases leading to respiratory failure) may occur. *Pneumocystis carinii* pneumonia was the most common infection. Other reported infections include nocardiosis, histoplasmosis, cryptococcosis, *Herpes Zoster*, *H.simplex* hepatitis, and disseminated *H.simplex*.

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.

Other reactions related to methotrexate use include pneumonitis, metabolic changes, precipitation of diabetes, osteoporotic effects, including aseptic necrosis of the femoral head, abnormal changes in tissue cells and even sudden death.

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, 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 *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 contra-indicated.

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

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 folic 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.

Other Forms of Interactions

Assay for folate: Methotrexate may inhibit the organism used in the assay and interfere with detection of folic acid deficiency.

Isocitric acid dehydrogenase (ICD) concentrations may be increased, indicating hepatotoxicity.

Serum aspartate aminotransferase (AST [SGOT]) concentrations may be increased transiently during high-dose therapy.

Uric acid concentrations in blood and urine may be increased.

Overdosage

Acute overdosage with methotrexate will result in severe myelosuppression and gastrointestinal toxicity. Symptoms of fatal intoxication are anorexia, progressive weight loss, bloody diarrhoea, leucopenia, depression and coma.

Leucovorin (folic acid) is a potent agent for neutralising the immediate toxic effects of methotrexate on the haematopoietic system. In general, when overdosage is suspected, the dose of leucovorin should be equal to or higher than the offending dose of methotrexate and should be given as soon as possible, preferably within the first hours after which time it is much less effective. Leucovorin may be administered by IV infusion in doses of up to 75 mg within 12 hours, followed by 12 mg IM every six hours for four doses. 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.

When average doses of methotrexate appear to have an adverse effect, 6-12 mg of leucovorin may be given IM every six hours for four doses.

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.

Pharmaceutical precautions

Instructions for Use/Handling

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

- personnel should be trained in good handling technique,
- pregnant staff should be excluded from working with this drug,
- personnel handling injectable methotrexate should wear protective clothing including goggles, gowns and disposable gloves and masks,
- a designated area should be assigned for preparation (preferably under a laminar flow system), with the work surface protected by disposable, plastic-backed, absorbent paper,
- all items used for 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.

Stability

The liquid vials are preservative-free and should therefore be used once only and discarded.

Methotrexate Injection, when diluted to a concentration of 1 mg/mL with sodium chloride 0.9% injection, glucose 5% injection, Hartmann's Injection, Ringer's Injection and 5% glucose in 0.9% sodium chloride injection, retains its potency for 24 hours when stored at room temperature in the presence and absence of fluorescent light.

However, because of microbiological contamination hazards, infusion of the admixed solutions should commence as soon as possible after preparation, and in any case, should be completed within 24 hours. Storage of admixed solutions should be at 2 to 8°C.

Incompatibilities

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

Special Precautions for Storage

DBL[®] Methotrexate Injection should be stored below 25°C and protected from light.

DBL[®] Methotrexate Tablets should be stored below 30°C.

Medicine classification

Prescription Medicine.

Package quantities

Methotrexate Injection

Strength	Pack
5 mg/2 mL	5 x 2 mL vials
50 mg/2 mL	5 x 2 mL vials
100 mg/4 mL	5 x 4 mL vials
500 mg/20 mL	1 x 20 mL vials
1 g/10 mL	1 x 10 mL vials
1 g/10 mL	1 x 10 mL ONCO-VIAL [®]

Methotrexate Tablets

Strength	Pack
2.5 mg	1 x 30 tabs

Further information

Methotrexate is 4-amino-4-deoxy-10-methyl-pteroyl-glutamic acid. Its chemical formula is $C_{20}H_{22}N_8O_5$ and it has a molecular weight of 454.4.

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.

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