METHOTREXATE SODIUM

Methotrexate

CDS

AfME markets using same as LPD: Kenya

1. NAME OF THE MEDICINAL PRODUCT

Methotrexate

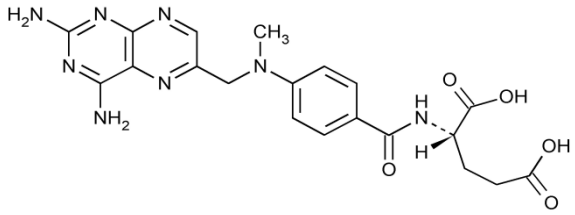
2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Chemical Name

N-[4-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-L-glutamic acid

Structure

Molecular Formula



$C_{20}H_{22}N_8O_5$

Molecular weight: 454.45

Methotrexate Sodium is a yellow to orange-brown crystalline powder, containing not more than 12% water.

Practically insoluble in water, alcohol, chloroform, and ether; dissolves in dilute solutions of mineral acids and of alkali hydroxides and carbonates.

Methotrexate is available as:

- Oral tablets containing 2.5 mg of methotrexate sodium

3. PHARMACEUTICAL FORM

Tablets

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Methotrexate is a cytotoxic drug used for antineoplastic chemotherapy and in certain nonmalignant conditions.

<u>Oncological indications</u>

Methotrexate is indicated for the treatment of the following solid tumors and hematologic malignancies:

- Choriocarcinoma (gestational trophoblastic neoplasm)
- Chorioadenoma destruens
- Hydatidiform mole

- Acute lymphoblastic leukemia
- Breast cancer
- Cervical cancer
- Ovarian carcinoma
- Testicular carcinoma
- Bladder cancer (locally advanced/metastatic)
- Epidermoid cancers (squamous cell carcinoma) of head and neck
- Mycosis fungoides (cutaneous T cell lymphoma)
- Lung cancer
- Non-Hodgkin's lymphoma
- Meningeal lymphoma
- Histiocytic and lymphatic lymphoma, Burkitt's lymphoma
- Osteosarcoma

Other diseases

- Psoriasis
- Rheumatoid arthritis including Polyarticular-course Juvenile Rheumatoid Arthritis (JRA)

4.2. Posology and method of administration

Oral dosage forms of methotrexate should not be split or crushed but should be taken whole.

Table 1. Neoplastic diseases

Dose (mg/m^2)	Route	Frequency	Folinic acid Rescue
Conventional Dose			
15 – 20	Orally	Twice per week	-
30 – 50	Orally	Weekly	-

Mycosis fungoides (cutaneous T cell lymphoma)

Therapy with methotrexate as a single agent appears to produce clinical responses in up to 50% of patients treated. Dosing in early stages is usually 5 to 50 mg once weekly. Dose reduction or cessation is guided by patient response and hematologic monitoring. Methotrexate has also been administered twice weekly in doses ranging from 15 to 37.5 mg in patients who have responded poorly to weekly therapy. Combination chemotherapy regimens that include intravenous methotrexate administered at higher doses with folinic acid rescue have been utilized in advanced stages of the disease.

Psoriasis

Weekly single oral schedule: 10 to 25 mg per week. A total weekly dose 25 mg should not ordinarily be exceeded.

Divided oral dose schedule: 2.5 to 5.0 mg every 12 hours for three doses, repeated weekly. Under these treatment conditions, dosing may be increased gradually by 2.5 mg/week, but the total weekly dosing should not ordinarily be exceeded.

Once optimal clinical response has been achieved, the dosing schedule should be reduced to the lowest possible amount of drug and the longest possible dosing interval.

Rheumatoid arthritis (RA)

1. Single oral doses of 7.5 to 20 mg once weekly.

2. Divided oral doses of 2.5 to 7.5 mg every 12 hours for three doses, repeated weekly.

A total weekly dose 20 mg should not ordinarily be exceeded. Once optimal clinical response has been achieved, dosing should be reduced to the lowest possible effective dose. The optimal duration of therapy is unknown; limited data from long term studies indicate that the initial clinical improvement is maintained for at least 2 years with continued therapy.

Use in elderly

Due to diminished hepatic and renal function as well as decreased folate stores in this population, relatively low doses (especially in RA and psoriasis indications) should be considered and these patients should be closely monitored for early signs of toxicity (see Section 4.4). See Table 3 below for reduced doses in oncology patients.

Polyarticular-course Juvenile Rheumatoid Arthritis (JRA)

The recommended starting dose is 10 mg/m^2 given once weekly.

Methotrexate doses reported in published clinical studies of pediatric patients with JRA have ranged from 4 to 17 mg/m^2/week or 0.1 to 1.1 mg/kg/week. The duration ranged from 1 month to 7.3 years. In the majority of these studies, methotrexate was administered orally; however, in some instances, it was administered intramuscularly.

Use in patients with renal impairment – dose adjustments

Methotrexate is excreted to a significant extent by the kidneys, thus in patients with renal impairment the health care provider may need to adjust the dose to prevent accumulation of drug. The table below provided recommended starting doses in renally impaired patients; dosing may need further adjustment due to wide intersubject pK variability.

Table 2. Dose adjustments in patients with renal impairment

Creatinine Clearance (ml/min)	% Standard dose to Administer
>80	Full dose
80	75
60	63
50	56

Table 2. Dose adjustments in patients with renal impairment

Creatinine Clearance (ml/min)	% Standard dose to Administer
<50	Use alternate therapy

Folate supplementation

In patients with rheumatoid arthritis, including polyarticular-course juvenile rheumatoid arthritis, or psoriasis, folic acid or folinic acid may reduce methotrexate toxicities such as gastrointestinal symptoms, stomatitis, alopecia, and elevated liver enzymes.

Before taking a folate supplement, it is advisable to check B_{12} levels, particularly in adults over the age of 50, since folate administration can mask symptoms of B_{12} deficiency.

4.3. Contraindications

- Hypersensitivity to methotrexate or any excipients in the formulation.
- Breast feeding.
- Severe renal impairment.
- Methotrexate formulations and diluents containing preservatives must not be used for intrathecal or high dose methotrexate therapy.
- ***Applies to patients with psoriasis or rheumatoid arthritis only:***
- Alcoholism, alcoholic liver disease, or other chronic liver disease.
- Overt or laboratory evidence of immunodeficiency syndromes.
- Preexisting blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anemia.
- Pregnancy.

4.4. Special warnings and precautions for use

General

Because of the possibility of serious toxic reactions (which can be fatal), methotrexate should be used only in neoplastic diseases (as indicated), or in patients with severe, recalcitrant, disabling psoriasis or rheumatoid arthritis that is not adequately responsive to other forms of therapy. The patient should be informed by the physician of the risks involved and should be under a physician's constant supervision. Refer to Section 4.4, Special Populations, Geriatric use and Pediatric use for specific warnings.

It should be emphasized to the patient treated for rheumatoid arthritis and psoriasis that the recommended dose must be taken weekly, and that mistaken daily use of the recommended dose has led to fatal toxicity (see Sections 4.2 and 4.9)

Methotrexate has been reported to cause fetal death and/or congenital anomalies. It is not recommended for the treatment of neoplastic diseases in women of childbearing potential.

Like other cytotoxic drugs, methotrexate may induce “tumor lysis syndrome” in patients with rapidly growing tumors. Appropriate supportive and pharmacologic measures may prevent or alleviate this complication.

Severe, occasionally fatal, skin reactions such as Stevens-Johnson Syndrome, toxic epidermal necrolysis (Lyell’s syndrome), have been reported following single or multiple doses of methotrexate.

Methotrexate causes hepatotoxicity, liver fibrosis, and cirrhosis, but generally only after prolonged use. Acutely, liver enzyme elevations are frequently seen. These are usually transient and asymptomatic, and do not appear predictive of subsequent hepatic disease. Liver biopsy after sustained use often shows histologic changes, and fibrosis and cirrhosis have been reported; these latter lesions may not be preceded by symptoms or abnormal liver function tests in the psoriasis population. Periodic liver biopsies are usually recommended for psoriatic patients who are under long-term treatment. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid arthritis population.

Methotrexate has caused reactivation of hepatitis B infection or worsening of hepatitis C infections, in some cases resulting in death. Some cases of hepatitis B reactivation have occurred after discontinuation of methotrexate. Clinical and laboratory evaluation should be performed to evaluate preexisting liver disease in patients with prior hepatitis B or C infections. Based on these evaluations, treatment with methotrexate may not be appropriate for some patients.

Methotrexate-induced lung disease, including acute or chronic interstitial pneumonitis and pleural effusion, may occur at any time during therapy and has been reported at low doses. It is not always fully reversible, and fatalities have been reported. Rheumatoid arthritis patients are at risk to develop rheumatoid lung disease, which is often associated with interstitial pulmonary disease. Methotrexate may exacerbate this underlying lung disease. Pulmonary symptoms (especially a dry, nonproductive cough) may require interruption of treatment and careful investigation.

Diarrhea and ulcerative stomatitis require interruption of therapy, otherwise, hemorrhagic enteritis and death from intestinal perforation may occur. Methotrexate should be used with extreme caution in the presence of peptic ulcer disease or ulcerative colitis.

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

Methotrexate exits slowly from third space compartments (e.g., pleural effusions, ascites). This results in a prolonged terminal half-life and unexpected toxicity. In patients with significant third space accumulations, it is advisable to evacuate the fluid before treatment and to monitor plasma methotrexate levels.

Methotrexate therapy in patients with impaired renal function should be undertaken with extreme caution, and at reduced doses, because impairment of renal function will decrease methotrexate elimination.

It is necessary to follow patients on methotrexate closely. Methotrexate has the potential for serious toxicity. Toxic effects may be related in frequency and severity to dose or frequency of administration, but has been seen at all doses and can occur at any time during therapy. Most

adverse reactions are reversible if detected early. When such reactions do occur, the dosing should be reduced or discontinued and appropriate corrective measures should be taken. If methotrexate therapy is reinstituted, it should be carried out with caution, with adequate consideration of further need for the drug, and with increased alertness as to possible recurrence of toxicity.

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

The use of methotrexate high-dose regimens (≥500 mg/m^2) recommended for osteosarcoma requires meticulous care (see Section 4.2 for prehydration instructions and folinic acid rescue).High dosing regimens for other neoplastic diseases are investigational and a therapeutic advantage has not been established.

Malignant lymphomas may occur in patients receiving low-dose methotrexate. These lymphomas may regress following withdrawal of methotrexate without requiring treatment.

Folate deficiency states may increase methotrexate toxicity.

Organ system toxicity

Gastrointestinal

If vomiting, diarrhea, or stomatitis occur, resulting in dehydration, supportive therapy should be instituted and methotrexate discontinuation, until recovery occurs, should be considered.

Hematologic

Methotrexate can suppress hematopoiesis and cause anemia, aplastic anemia, pancytopenia, leukopenia, neutropenia, and/or thrombocytopenia. Methotrexate should be used with caution, in patients with preexisting hematopoietic impairment (see Section 4.5). The nadir of circulating leukocytes, neutrophils and platelets usually occurs between 5 to 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 to 7 days and a second nadir after 12 to 21 days, followed by recovery. Clinical sequelae such as fever, infections and hemorrage from various sites may be expected. In the treatment of neoplastic diseases, methotrexate should be continued only if the potential benefit outweighs the risk of severe myelosuppression. In psoriasis and rheumatoid arthritis, methotrexate should be stopped immediately if there is a significant drop in blood cell counts.

Hepatic

Methotrexate has the potential for acute hepatitis and chronic (fibrosis and cirrhosis) hepatotoxicity. Chronic toxicity is potentially fatal; it generally has occurred after prolonged use (generally two years or more) and after a total cumulative dose of at least 1.5 grams. In studies in psoriatic patients, hepatotoxicity appeared to be a function of total cumulative dose and appeared to be enhanced by alcoholism, obesity, diabetes, and advanced age.

Transient abnormalities of liver parameters are observed frequently after methotrexate administration and are usually not a reason for modification of methotrexate therapy. Persistent liver abnormalities, and/or decrease of serum albumin may be indicators of serious liver toxicity.

In psoriasis, liver damage and function tests, including serum albumin and prothrombin time, should be performed several times prior to dosing. Liver function tests are often normal in developing fibrosis or cirrhosis. These lesions may be detectable only by biopsy. It is recommended to obtain a liver biopsy at: 1) before start of therapy or shortly after initiation of therapy (2 to 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 usually not a reason to avoid or discontinue methotrexate therapy, the drug should be used with caution.

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

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

Infection or immunologic states

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.

Potentially fatal opportunistic infections, including *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy. When a patient presents with pulmonary symptoms, the possibility of *Pneumocystis carinii* pneumonia should be considered.

Immunization

Vaccinations may be less immunogenic when given during methotrexate therapy. Immunization with live virus vaccines is generally not recommended.

Neurologic

There have been reports of leukoencephalopathy following intravenous administration of methotrexate to patients who have had craniospinal irradiation. Refer to Section 4.4, Special

populations, Pediatric use for specific warnings. Symptomatic patients were commonly noted to have leukoencephalopathy and/or microangiopathic calcifications on diagnostic imaging studies.

Chronic leukoencephalopathy has also been reported in patients who received repeated doses of high-dose methotrexate with folinic acid rescue even without cranial irradiation. There are also reports of leukoencephalopathy in patients who received oral methotrexate.

Discontinuation of methotrexate does not always result in complete recovery.

A transient acute neurologic syndrome has been observed in patients treated with high dosing regimens. Manifestations of this neurologic syndrome may include behavioral abnormalities, focal sensorimotor signs, including transient blindness, and abnormal reflexes. The exact cause is unknown.

After the intrathecal use of methotrexate, the central nervous system toxicity that may occur can be classified as follows: acute chemical arachnoiditis manifested by e.g., headache, back pain, nuchal rigidity, and fever; sub-acute myelopathy characterized by e.g., paraparesis/paraplegia associated with involvement with one or more spinal nerve roots; chronic leukoencephalopathy manifested by e.g., confusion, irritability, somnolence, ataxia, dementia, seizures, and coma. This central nervous system toxicity can be progressive and even fatal. There is evidence that the combined use of cranial radiation and intrathecal methotrexate increases the incidence of leukoencephalopathy. Signs of neurotoxicity (meningeal irritation, transient or permanent paresis, encephalopathy) should be monitored following intrathecal administration of methotrexate.

Intrathecal and intravenous administration of methotrexate may also result in acute encephalitis and acute encephalopathy with fatal outcome.

There have been reports of patients with periventricular CNS lymphoma who developed cerebral herniation with the administration of intrathecal methotrexate.

Cases of severe neurological adverse reactions that ranged from headache to paralysis, coma and stroke-like episodes have been reported mostly in juveniles and adolescents given intrathecal methotrexate in combination with intravenous cytarabine.

Pulmonary

Pulmonary signs and symptoms, e.g., a dry nonproductive cough, fever, cough, chest pain, dyspnea, hypoxemia, and an infiltrate on chest X-ray, or a nonspecific pneumonitis occurring during methotrexate therapy, may be indicative of a potentially dangerous lesion and require interruption of treatment and careful investigation. Methotrexate induced pneumonitis can occur at all doses. Infection (including pneumonia) needs to be excluded.

Renal

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

Concomitant use of proton pump inhibitors (PPIs) and high dose methotrexate should be avoided , especially in patients with renal impairment.

Skin

Severe, occasionally fatal, dermatologic reactions, including toxic epidermal necrolysis (Lyell's Syndrome), Stevens-Johnson syndrome, and erythema multiforme, have been reported within days of oral, intramuscular, intravenous, or intrathecal methotrexate administration.

Lesions of psoriasis may be aggravated by concomitant exposure to ultraviolet radiation. Radiation dermatitis and sunburn may be "recalled" by the use of methotrexate.

Laboratory monitoring

General

Patients undergoing methotrexate therapy should be closely monitored so that toxic effects are detected promptly.

Baseline assessment should include a complete blood count with differential and platelet counts; hepatic enzymes; hepatitis B or C infection testing, renal function tests; and a chest X-ray.

During therapy of rheumatoid arthritis and psoriasis, monitoring of the following parameters is recommended: hematology at least monthly, hepatic enzyme levels and renal function every 1 to 2 months. More frequent monitoring is usually indicated during antineoplastic therapy. During initial or change in dosing, or during periods of increased risk of elevated methotrexate blood levels (e.g., dehydration), more frequent monitoring may also be indicated.

Pulmonary function tests

Pulmonary function tests may be useful if lung disease (e.g., interstitial pneumonitis) is suspected, especially if baseline measurements are available.

Methotrexate level

Serum methotrexate level monitoring can significantly reduce toxicity and mortality by allowing the adjustment of methotrexate dosing and the implementation of appropriate rescue measures.

Patients subject to the following conditions are predisposed to developing elevated or prolonged methotrexate levels and benefit from routine monitoring of levels: e.g., pleural effusion, ascites, gastrointestinal tract obstruction, previous cisplatin therapy, dehydration, aciduria, impaired renal function.

Some patients may have delayed methotrexate clearance in the absence of these features. It is important that patients be identified within 48 hours since methotrexate toxicity may not be reversible if adequate folinic acid rescue is delayed for more than 42 to 48 hours.

The method of monitoring methotrexate concentrations varies from institution to institution. Monitoring of methotrexate concentrations should include determination of a methotrexate level at 24, 48, or 72 hours, and assessment of the rate of decline in methotrexate concentrations (to determine how long to continue folinic acid rescue).

Special populations

Pediatric use

Safety and effectiveness in pediatric patients have been established only in cancer chemotherapy and in polyarticular-course juvenile rheumatoid arthritis.

Published clinical studies evaluating the use of methotrexate in children and adolescents (i.e., patients 2 to 16 years of age) with JRA demonstrated safety comparable to that observed in adults with rheumatoid arthritis.

Overdose by intravenous and intrathecal miscalculation of dosage (particularly in juveniles) have occurred. Special attention must be given to dose calculation (see Section 4.2).

The preservative benzyl alcohol has been associated with serious adverse events, including the "gasping syndrome", and death in pediatric patients. Symptoms include a striking onset of gasping respiration, hypotension, bradycardia, and cardiovascular collapse. Although normal therapeutic doses of this product ordinarily deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the "gasping syndrome", the minimum amount of benzyl alcohol at which toxicity may occur is not known. The risk of benzyl alcohol toxicity depends on the quantity administered and the hepatic capacity to detoxify the chemical. Premature and low-birth weight infants may be more likely to develop toxicity.

Serious neurotoxicity, frequently manifested as generalized or focal seizures has been reported with unexpectedly increased frequency among pediatric patients with acute lymphoblastic leukemia who were treated with intravenous methotrexate (1 g/m^2).

Geriatric use

Fatal toxicities related to inadvertent daily rather than weekly dosing have been reported, particularly in elderly patients. It should be emphasized to the patient that the recommended dose is taken weekly for rheumatoid arthritis and psoriasis (see Section 4.2).

4.5. Interaction with other medicinal products and other forms of interaction

Chemotherapeutic agents

Enhancement of nephrotoxicity may be seen when high-dose methotrexate is administered in combination with a potentially nephrotoxic chemotherapeutic agent (e.g., cisplatin).

Cytarabine: Intrathecal methotrexate given concomitantly with IV cytarabine may increase the risk of severe neurologic adverse events such as headache, paralysis, coma and stroke-like episodes.

L-asparaginase: The administration of L-asparaginase has been reported to antagonize the effect of MTX.

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

Disease-modifying antirheumatic drug (DMARD) and Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs should not be administered prior to or concomitantly with the high doses of methotrexate such as used in the treatment of osteosarcoma. Concomitant administration of NSAIDs with high-dose methotrexate therapy has been reported to elevate and prolong serum

methotrexate levels, resulting in deaths from severe hematologic (including bone marrow suppression and aplastic anemia) and gastrointestinal toxicity. NSAIDs and salicylates have been reported to reduce the tubular secretion of methotrexate in an animal model and may enhance its toxicity by increasing methotrexate levels. Therefore, caution should be used when they are administered concomitantly with lower doses of methotrexate.

In treating rheumatoid arthritis with methotrexate, aspirin, NSAIDs, and/or low dose steroids may be continued.

The possibility of increased toxicity with concomitant use of NSAIDs including salicylates has not been fully explored. Steroids may be reduced gradually in patients who respond to methotrexate. Despite the potential interactions, studies of methotrexate in patients with rheumatoid arthritis have usually included concurrent use of constant dosing regimens of NSAIDs, without difficulty. However, the methotrexate doses used in rheumatoid arthritis (7.5 to 15 mg/week) are somewhat lower than those used in psoriasis, and larger doses could lead to unexpected toxicity. Combined use of methotrexate with gold, penicillamine, hydroxychloroquine, sulfasalazine, has not been studied and may increase the incidence of adverse effects.

Proton pump inhibitors

Co-administration of proton pump inhibitors (PPIs) with methotrexate may decrease the clearance of methotrexate causing elevated methotrexate plasma levels with clinical signs and symptoms of methotrexate toxicity. Concomitant use of PPIs and high dose methotrexate should therefore be avoided , especially in patients with renal impairment.

Antibiotics

Ciprofloxacin: Renal tubular transport is diminished by ciprofloxacin; use of methotrexate with this drug should be carefully monitored.

Penicillins and sulfonamides: Penicillins and sulfonamides may reduce the renal clearance of methotrexate; hematologic and gastrointestinal toxicity has been observed in combination with high- and low- dose methotrexate.

Oral antibiotics: Oral antibiotics, such as tetracycline, chloramphenicol, and nonabsorbable broad spectrum antibiotics, may decrease intestinal absorption of methotrexate or interfere with the enterohepatic circulation by inhibiting bowel flora and suppressing metabolism of methotrexate by bacteria.

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

Concurrent use of the anti-protozoal *pyrimethamine* may increase the toxic effects of methotrexate because of an additive antifolate effect.

Hepatotoxic agents

The potential for increased hepatotoxicity when methotrexate is administered with other hepatotoxic agents has not been evaluated. However, hepatotoxicity has been reported in such cases. Therefore, patients receiving concomitant therapy with methotrexate and other potential

hepatotoxic agents (e.g., leflunomide, azathioprine, sulfasalazine, retinoids) should be closely monitored for possible increased risk of hepatotoxicity.

Nitrous oxide anesthesia

The use of nitrous oxide anesthesia potentiates the effect of methotrexate on folate metabolism, yielding increased toxicity such as severe unpredictable myelosuppression, stomatitis and neurotoxicity with intrathecal administration. This effect can be reduced by the use of folinic acid rescue (see section 4.2).

Probenecid

Renal tubular transport is diminished by probenecid; use of methotrexate with this drug should be carefully monitored.

Vitamins

Vitamin preparations containing folic acid or its derivatives may decrease responses to systemically administered methotrexate, however, folate deficiency states may increase methotrexate toxicity.

Amiodarone

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

Drugs highly bound to plasma proteins

Methotrexate is partially bound to serum albumin, and toxicity may be increased because of displacement by other highly bound drugs, such as sulfonylureas, aminobenzoic acid, salicylates, phenylbutazone, phenytoin, sulfonamides, some antibiotics such as penicillins, tetracycline, pristinamycin, probenecid, and chloramphenicol.

Leflunomide

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

Packed red blood cells

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.

Psoralen plus ultraviolet light (PUVA) therapy

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).

Theophylline

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

Diuretics

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

4.6. Fertility, Pregnancy and Lactation

Fertility

Methotrexate has been reported to cause impairment of fertility, oligospermia and menstrual dysfunction in humans, during and for a short period after cessation of therapy.

Pregnancy

Methotrexate can cause fetal death, embryotoxicity, abortion, or teratogenic effects when administered to a pregnant woman. Methotrexate is contraindicated in pregnant patients with psoriasis or rheumatoid arthritis.

Women of childbearing potential should not be started on methotrexate until pregnancy is excluded and should be fully counseled on the serious risk to the fetus should they become pregnant while undergoing treatment. Pregnancy should be avoided if either partner is receiving methotrexate.

The optimal time interval between the cessation of methotrexate treatment of either partner and pregnancy has not been clearly established. Published literature recommendations for time intervals vary from 3 months to 1 year.

The risk of effects on reproduction should be discussed with both male and female patients taking methotrexate.

Methotrexate injection formulations containing the preservative benzyl alcohol are not recommended during pregnancy as benzyl alcohol can cross the placenta (see Section 4.4).

Lactation

Methotrexate has been detected in human breast milk and is contraindicated during breast feeding

4.7. Effects on ability to drive and use machines

Some of the effects reported in Section 4.8 (e.g., dizziness, fatigue) may have an influence on the ability to drive and use machines.

4.8. Undesirable effects

In general, the incidence and severity of adverse drug reactions are related to dose and frequency of administration. Relevant sections should be consulted when looking for information about adverse reactions with methotrexate.

The most frequently reported adverse reactions include ulcerative stomatitis, leukopenia, nausea, and abdominal distress. Other frequently reported adverse effects are malaise, undue fatigue, chills and fever, dizziness, and decreased resistance to infection. Ulcerations of the oral mucosa are usually the earliest signs of toxicity.

Other adverse reactions that have been reported with methotrexate are listed below by organ system and by frequency. In the oncology setting, concomitant treatment and the underlying disease make specific attribution of a reaction to methotrexate difficult. See Section 4.4 for specific reference to medically important and long term events including those following long term treatment or high cumulative doses (e.g., hepatic toxicity).

Frequency categories are defined as: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000), Not known (cannot be estimated from the available data).

Table 3. Adverse Reactions Table

System Organ Class	Adverse Reaction
Infections and Infestations	
Rare	Sepsis
Not known	Infections (including fatal sepsis); Pneumonia; Pneumocystis carinii pneumonia; Nocardiosis; Histoplasmosis; Cryptococcosis; Herpes zoster; H. simplex hepatitis; Disseminated H. simplex; Cytomegalovirus infection (including cytomegaloviral pneumonia); Reactivation of hepatitis B infection; Worsening of hepatitis C infection
Neoplasms Benign, Malignant, and Unspecified (including cysts and polyps)	
Uncommon	Lymphoma (including reversible lymphoma)
Very rare	Tumor lysis syndrome*
Blood and Lymphatic System Disorders	
Uncommon	Bone marrow failure; Anemia; Thrombocytopenia
Very rare	Aplastic anemia
Not known	Agranulocytosis; Pancytopenia; Leukopenia; Neutropenia; Lymphadenopathy and lymphoproliferative disorders (including reversible); Eosinophilia; Anemia megaloblastic
Immune System Disorders	
Uncommon	Anaphylactoid reactions

Table 3. Adverse Reactions Table

System Organ Class	Adverse Reaction
Very rare	Hypogammaglobulinemia
Metabolism and Nutrition Disorders	
Rare	Diabetes
Psychiatric Disorders	
Rare	Mood alterated; Transient cognitive dysfunction
Nervous System Disorders	
Common	Paresthesia
Uncommon	Hemiparesis; Encephalopathy/leukoencephalopathy*; Convulsions;* Headaches
Rare	Paresis; Dysarthria; Aphasia; Drowsiness
Very rare	Cranial nerve disorder
Not known	CSF pressure increased; Neurotoxicity; Arachnoiditis; Paraplegia; Stupor; Ataxia; Dementia; Dizziness
Eye Disorders	
Rare	Blurred vision; Serious visual changes
Very rare	Transient blindness/vision loss; Conjunctivitis
Cardiac Disorders	
Rare	Hypotension
Very rare	Pericardial effusion; Pericarditis
Vascular Disorders	
Rare	Thromboembolic events (including cerebral thrombosis, arterial thrombosis, pulmonary embolism, deep vein thrombosis, thrombophlebitis, retinal vein thrombosis)
Very rare	Vasculitis
Respiratory, Thoracic and Mediastinal disorders	
Uncommon	Interstitial pneumonitis (including fatalities); Pleural effusion
Rare	Respiratory fibrosis; Pharyngitis
Not known	Chronic interstitial pulmonary disease; Alveolitis; Dyspnea; Chest pain; Hypoxia; Cough
Gastrointestinal Disorders	
Uncommon	Pancreatitis; Decreased appetite; Vomiting; Diarrhea; Stomatitis
Rare	Gastrointestinal ulceration and bleeding; Melena; Enteritis; Gingivitis
Very rare	Hematemesis
Not known	Intestinal perforation; Noninfectious peritonitis; Glossitis; Nausea;

Table 3. Adverse Reactions Table

System Organ Class	Adverse Reaction
Hepatobiliary Disorders	
Uncommon	Liver enzyme elevations
Rare	Chronic fibrosis and cirrhosis; Acute hepatitis; Hepatotoxicity
Very rare	Decrease in serum albumin
Not known	Hepatic failure
Skin and Subcutaneous Tissue Disorders	
Uncommon	Toxic epidermal necrolysis (Lyell's syndrome); Stevens-Johnson Syndrome; Alopecia
Rare	Erythema multiforme; Erythematous rashes; Painful erosion of psoriatic plaques; Photosensitivity; Skin ulceration; Urticaria; Acne; Ecchymosis; Pigmentation disorder; Pruritus
Very rare	Furunculosis; Telangiectasia
Not known	Drug reaction with eosinophilia and systemic symptoms; Dermatitis; Petechiae
Musculoskeletal, Connective tissue and Bone disorders	
Rare	Arthralgia/myalgia; Osteoporosis; Stress fractures
Not known	Osteonecrosis
Renal and Urinary Disorders	
Uncommon	Renal failure; Nephropathy
Rare	Dysuria
Very rare	Hematuria; Azotemia; Cystitis
Not known	Proteinuria
Pregnancy, Puerperium and Perinatal Conditions	
Uncommon	Fetal defects
Rare	Abortion
Not known	Fetal death
Reproductive System and Breast Disorders	
Rare	Menstrual dysfunction
Very rare	Defective oogenesis/spermatogenesis; Impotence; Infertility; Loss of libido; Transient oligospermia; Vaginal discharge
Not known	Urogenital dysfunction
General Disorders and Administration Site Conditions	
Rare	Nodule
Very rare	Sudden death

Table 3. Adverse Reactions Table

System Organ Class	Adverse Reaction
Not known	Pyrexia; Chills; Malaise; Fatigue, Injection site reaction*; Injection site necrosis*

*parenteral only

Adverse events in JRA studies

The approximate incidences of adverse reactions reported in pediatric patients with JRA treated with oral, weekly doses of methotrexate (5 to 20 mg/m^2/wk or 0.1 to 1.1 mg/kg/wk), were as follows (virtually all patients were receiving concomitant nonsteroidal anti-inflammatory drugs, and some also were taking low doses of corticosteroids): elevated liver function tests, 14%; gastrointestinal reactions (e.g., nausea, vomiting, diarrhea), 11%; stomatitis, 2%; leukopenia, 2%; headache, 1.2%; alopecia, 0.5%; dizziness, 0.2%; and rash, 0.2%. Although there is experience with dosing up to 30 mg/m^2/wk in JRA, the published data for doses above 20 mg/m^2/wk are too limited to provide reliable estimates of adverse reaction rates.

4.9. Overdose

In post-marketing experience, overdose with methotrexate has generally occurred with oral and intrathecal administration, although intravenous and intramuscular overdose has also been reported.

Reports of oral overdose indicate accidental daily administration instead of weekly (single or divided doses). Symptoms commonly reported following oral overdose include those symptoms and signs reported at pharmacologic doses, particularly hematologic and gastrointestinal reactions. For example, leukopenia, thrombocytopenia, anemia, pancytopenia, bone marrow suppression, mucositis, stomatitis, oral ulceration, nausea, vomiting, gastrointestinal ulceration, gastrointestinal bleeding. In some cases, no symptoms were reported. There have been reports of death following chronic overdose in the self administered dosage for rheumatoid arthritis and psoriasis (see Sections 4.2 and 4.4). In these cases, events such as sepsis or septic shock, renal failure, and aplastic anemia were also reported.

Symptoms of intrathecal overdose are generally central nervous system (CNS) symptoms, including headache, nausea and vomiting, seizure or convulsion, and acute toxic encephalopathy. In some cases, no symptoms were reported. There have been reports of death following intrathecal overdose. In these cases, cerebellar herniation associated with increased intracranial pressure, and acute toxic encephalopathy has also been reported.

Recommended treatment

Folinic acid is indicated to diminish the toxicity and counteract the effect of inadvertently administered overdoses of methotrexate. Folinic acid administration should begin as promptly as possible. As the time interval between methotrexate administration and folinic acid initiation increases, the effectiveness of folinic acid in counteracting toxicity decreases. Monitoring of the serum methotrexate concentration is essential in determining the optimal dose and duration of treatment with folinic acid.

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

Accidental intrathecal overdosage may require intensive systemic support, high-dose systemic (intravenous) folinic acid, alkaline diuresis, and rapid CSF drainage and ventriculolumbar perfusion.

There are published case reports of intravenous and intrathecal carboxypeptidase G2 treatment to hasten clearance of methotrexate in cases of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1. 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 methotrexate inhibits dihydrofolic acid reductase. Dihydrofolates must be reduced to tetrahydrofolates by this enzyme before they can be utilized as carriers of one-carbon groups in the synthesis of purine nucleotides and thymidylate. Therefore, methotrexate interferes with DNA synthesis, repair, and cellular 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, fetal cells, buccal and intestinal mucosa, spermatogonia, and cells of the urinary bladder are in general more sensitive to this effect of methotrexate. Due to increased cellular proliferation methotrexate may impair malignant growth without irreversible damage to normal tissues.

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

Methotrexate in high doses, followed by folinic acid rescue, is used as a part of the treatment of patients with non-metastatic osteosarcoma. The original rationale for high-dose methotrexate therapy was based on the concept of selective rescue of normal tissues by folinic acid. More recent evidence suggests that high-dose methotrexate may also overcome methotrexate resistance caused by impaired active transport, decreased affinity of dihydrofolic acid reductase for methotrexate, increased levels of dihydrofolic acid reductase resulting from gene amplification, or decreased polyglutamation of methotrexate. The actual mechanism of action is unknown.

In the treatment of rheumatoid arthritis, the precise mechanism of action of methotrexate is unknown. Methotrexate is used as monotherapy, as well as in combination with other interventions. Methotrexate is classified as a disease modifying antirheumatic drug (DMARD) in the treatment of rheumatoid arthritis.

5.2. Pharmacokinetic properties

Absorption

Rapid and complete absorption is achieved following intramuscular administration and peak serum levels are reached within 0.25 – 2 hrs. Oral absorption appears to be dose-dependent. Peak serum levels are reached within one to five hours. At doses of 30 mg/m^2 or less, methotrexate is generally well absorbed with a mean bioavailability of about 60%. The absorption of doses greater than 80 mg/m^2 is significantly less, possibly due to a saturation effect. 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. Peak serum levels achievable following oral administration are slightly lower than those detected after intramuscular injection.

In leukemic pediatric patients, oral absorption of methotrexate also appears to be dose-dependent and has been reported to vary widely (23% to 95%). A twenty-fold difference between highest and lowest peak levels (C_{max}: 0.11 to 2.3 micromolar after a 20 mg/m^2 dose) has been reported. Significant interindividual variability has also been noted in time-to-peak concentration (T_{max} 0.67 to 4 hours after a 15 mg/m^2 dose) and fraction of dose absorbed. The absorption of doses greater than 40 mg/m^2 has been reported to be significantly less than that of lower doses.

As in leukemic pediatric patients, a wide interindividual variability in the plasma concentrations of methotrexate has been reported in pediatric patients with JRA. Following oral administration of methotrexate in doses of 6.4 to 11.2 mg/m^2/wk in pediatric patients with JRA, mean serum concentrations were 0.59 micromolar (range, 0.03 to 1.40) at 1 hour, 0.44 micromolar (range, 0.01 to 1.00) at 2 hours, and 0.29 micromolar (range, 0.06 to 0.58) at 3 hours. In pediatric patients receiving methotrexate for acute lymphocytic leukemia (6.3 to 30 mg/m^2), or for JRA (3.75 to 26.2 mg/m^2), the terminal half-life has been reported to range from 0.7 to 5.8 hours or 0.9 to 2.3 hours, respectively.

Distribution

After intravenous administration, the initial volume of distribution is approximately 0.18 L/kg (18% of body weight) and steady-state volume of distribution is approximately 0.4 to 0.8 L/kg (40% to 80% of body weight). Methotrexate competes with reduced folates for active transport across cell membranes by means of a single carrier-mediated active transport process. At serum concentrations greater than 100 micromolar, passive diffusion becomes a major pathway by which effective intracellular concentrations can be achieved. Methotrexate in serum is approximately 50% reversibly bound to protein.

Methotrexate is widely distributed into body tissues with highest concentrations in the kidneys, gallbladder, spleen, liver and skin. Methotrexate does not penetrate the blood-cerebrospinal fluid barrier in therapeutic amounts when given orally or parenterally.

High CSF concentrations of the drug may be attained by intrathecal administration.

Small amounts have been detected in saliva and breast milk. The drug crosses the placental barrier.

The drug enters slowly into third-space collections of fluid, such as pleural effusions, ascites and marked tissue edemas. In dogs, synovial fluid concentrations after oral dosing were higher in inflamed than uninflamed joints. Although salicylates did not interfere with this penetration, prior prednisone treatment reduced penetration into inflamed joints to the level of normal joints.

Metabolism

At low doses, methotrexate does not appear to undergo significant metabolism; following high dose therapy methotrexate undergoes hepatic and intracellular metabolism to polyglutamated forms that can be converted back to methotrexate by hydrolase enzymes. These polyglutamates act as inhibitors of dihydrofolate reductase and thymidylate synthetase. Small amounts of methotrexate polyglutamates may remain in tissues for extended periods. The retention and prolonged drug action of these active metabolites vary among different cells, tissues, and tumors. A small amount of metabolism to 7-hydroxymethotrexate may occur at doses commonly prescribed. Accumulation of this metabolite may become significant at the high doses used in osteogenic sarcoma. The aqueous solubility of 7-hydroxymethotrexate is 3- to 5-fold lower than the parent compound. Methotrexate is partially metabolized by intestinal flora after oral administration.

Half-life – The terminal half-life reported for methotrexate is approximately three to ten hours for patients receiving treatment for psoriasis, rheumatoid arthritis or low dose antineoplastic therapy (less than 30 mg/m^2). For patients receiving high doses of methotrexate, the terminal half-life is 8 to 15 hours.

In pediatric patients receiving methotrexate for acute lymphocytic leukemia (6.3 to 30 mg/m^2) or for JRA (3.75 to 26.2 mg/m^2), the terminal half-life has been reported to range from 0.7 to 5.8 hours or 0.9 to 2.3 hours, respectively.

Elimination

Renal excretion is the primary route of elimination and is dependent upon dosage and route of administration. With IV administration, 80% to 90% of the administered dose is excreted unchanged in the urine within 24 hours followed by excretion of 1-2% of the retain dose daily. There is limited biliary excretion amounting to 10% or less of the administered dose. Enterohepatic recirculation of methotrexate has been proposed.

Renal excretion occurs by glomerular filtration and active tubular secretion. Nonlinear elimination due to saturation of renal tubular reabsorption has been observed in psoriatic patients at doses between 7.5 and 30 mg. Impaired renal function, as well as concurrent use of drugs such as weak organic acids that also undergo tubular secretion, can markedly increase methotrexate serum levels. Excellent correlation has been reported between methotrexate clearance and endogenous creatinine clearance.

Total methotrexate clearance averages 12 L/h, but clearance rates vary widely and are generally decreased at higher doses. Delayed drug clearance has been identified as one of the major factors responsible for methotrexate toxicity. It has been postulated that the toxicity of methotrexate for normal tissues is more dependent upon the duration of exposure to the drug rather than the peak level achieved. When a patient has delayed drug elimination due to compromised renal function, a third space effusion, or other causes, methotrexate serum concentrations may remain elevated for prolonged periods.

The potential for toxicity from high dose regimens or delayed excretion is reduced by the administration of folinic acid during the final phase of methotrexate plasma elimination.

Effects of food

The bioavailability of orally administered methotrexate is not reduced by food and methotrexate may be administered without regard to meals.

5.3. Preclinical safety data

The intraperitoneal LD_{50} of methotrexate was 94 and 6to25 mg/kg for mice and rats, respectively. The oral LD_{50} 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 gastrointestinal (GI) 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, GI tract, lung, liver, kidney, testes, and skin. The tolerance of mice to chronic methotrexate doses increased with age.

Methotrexate has been evaluated in a number of animal studies for carcinogenic potential with inconclusive results. Although there is evidence that methotrexate causes chromosomal damage to animal somatic cells and human bone marrow cells, the clinical significance remains uncertain.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Maize starch, Lactose, Pregelatinised starch, Polysorbate 80, Microcrystalline

Cellulose, Magnesium stearate, Purified water.

6.2. Incompatibilities

Methotrexate has been reported to be incompatible with prednisolone sodium phosphate. Previously reported incompatibility with fluorouracil has been questioned and subsequent studies documented in the literature indicate that methotrexate and cytarabine are physically and chemically stable in intravenous admixtures over a range of concentrations and in a variety of typical vehicles. A mixture of methotrexate sodium with cytarabine and hydrocortisone sodium succinate in various infusion fluids has been reported to be visually compatible for at least 8 hours at 25°C, although precipitation did occur on storage for several days. In general, compatibility of any medicinal product admixed with methotrexate must be assured prior to patient administration. Drug-drug interactions are described in Section 4.5.

6.3. Shelf life

Protect from light.

Keep out of the sight and reach of children.

Do not use METHOTREXATE after the expiry date which is stated on the Carton/Blister/ after EXP:. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6.4. Special precautions for storage

Methotrexate tablets should be protected from light and store below 30°C.

6.6. Special precautions for disposal and other handling

Individuals who have contact with anti-cancer drugs or work in areas where these drugs are used may be exposed to these agents in air or through direct contact with contaminated objects. Potential health effects may be reduced by adherence to institutional procedures, published guidelines and local regulations for preparation, administration, transportation and disposal of hazardous drugs. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

7. FURTHER INFORMATION

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