METHOTREXAT "EBEWE" 10 mg/ml and 100 mg/ml

solution for injection & infusion

Composition

1 vial of 5 ml contains: 50 mg methotrexate
1 vial of 5 ml contains: 500 mg methotrexate
1 vial of 10 ml contains: 1000 mg methotrexate
1 vial of 50 ml contains: 5000 mg methotrexate

Clinical Particulars

Indications

Antineoplastic Chemotherapy: Treatment of gestational choriocarcinoma, chorioadenoma destruens and hydatidiform mole. Palliation of acute lymphocytic leukemia. In the treatment and prophylaxis of meningeal leukemia. Greatest effect has been observed in palliation of acute lymphoblastic (stem cell) leukemias in children. In combination with other anticancer agents, methotrexate may be used for the induction of remission, but is most commonly used in maintenance of induced remissions. Methotrexate may be used alone or in combination with other antineoplastics in the management of breast cancer, epidermoid cancers of the head and neck, lung cancer (particularly squamous cell and small cell types), bladder cancer and osteogenic cancer. Methotrexate is effective in the treatment of the advanced stages (III and IV, Peters' Staging System) of lymphosarcoma, particularly in children, and in advanced cases of mycosis fungoides.

Psoriasis: Because of the high risk attending its use, methotrexate is indicated only in the symptomatic control of severe recalcitrant, disabling psoriasis which is not adequately responsive to other forms of therapy, and only when the diagnosis has been established, as by biopsy and/or after dermatological consultation.

Rheumatoid Arthritis: Methotrexate can be used in the treatment of selected adults with severe rheumatoid arthritis, only when the diagnosis has been well-established according to rheumatological standards, with inadequate response to other forms of antirheumatic therapy, including full dose NSAIDs and usually a trial of at least one or more disease-modifying antirheumatic drugs.

Dosage and Administration

Dosage

Malignant tumors and hemoblastoses:

In polychemotherapy of malignant tumors and hemoblastoses the dosage of methotrexate has to be adjusted according to the indication, general condition and the blood counts of the patient. The administered dose in conventional low-dose MTX therapy (single dose lower than 100 mg/m^2), medium-dose MTX therapy (single dose 100 mg/m^2–1000 mg/m^2) and high-dose MTX therapy (single dose higher than 1000 mg/m^2) depends on the respective therapy protocol.
The following dosage instructions are only guidelines:

Conventional dose of methotrexate therapy – no calcium folinate rescue required:
15–20 mg/m^2 IV - twice weekly
30–50 mg/m^2 IV - once weekly
15 mg/m^2/day IV/IM - given at 2–3 weeks intervals

Intermediate dose of methotrexate therapy:
50–150 mg/m^2 IV injection; no calcium folinate rescue required, given at 2–3 weeks intervals
240 mg/m^2 IV infusion over 24 h; calcium folinate rescue required, given at 4–7 days intervals
500–1000 mg/m^2 IV infusion over 36–42 h; calcium folinate rescue required, given at 2–3 weeks intervals

High-dose methotrexate therapy – calcium folinate rescue required:
1–12 gm/m^2 IV over 1–6 hours, given at 1–3 weeks intervals

For intrathecal or intraventricular methotrexate therapy a maximum dose of 15 mg/m^2 is administered.
Intrathecal route of administration: 0.2–0.5 mg/kg or 8–12 mg/m^2 methotrexate is administered every 2–3 days, after disappearance of the symptoms at weekly intervals, and subsequently at monthly intervals until CSF findings return to normal. Prophylactic intrathecal instillation should be carried out every 6–8 weeks.
In patients with impaired renal function the therapy risk should be carefully considered and the dosage should be reduced correspondingly if required.

In severe, generalized, therapy-resistant psoriasis vulgaris including psoriatic arthritis and other autoimmunopathies:
Generally 10–25 mg methotrexate administered parenterally at weekly intervals. Dosage should be adjusted according to the general condition of the patient.

In therapy-resistant rheumatoid arthritis:
Generally 5–15 mg methotrexate administered IM initially, as a massive-dose therapy once weekly. Dosage can be increased by 5 mg weekly, to a maximum of 25 mg weekly.

Method of Administration

Methotrexat "EBEWE" 50 mg can be administered IM, IV (as bolus injection or infusion), intra-arterially, intrathecally and intraventricularly.

Methotrexat "EBEWE" 500 mg, 1000 mg and 5000 mg – concentrate for infusion has to be diluted with standard solutions for infusions before administration according to therapy protocol and duration of infusion. Use 5% glucose solution, Ringer's lactate or physiological saline solution.

Generally 1–2% methotrexate solution is administered (in osteosarcoma higher concentrations are described in the literature).

These methotrexate solutions for infusion are stable at room temperature over 24 hours when exposed to light or protected from light. If longer infusion period is required, the infusion bags/bottle should be changed.

Dosages higher than 100 mg/m^2 are generally administered as IV infusion.

Use only clear and freshly prepared solutions.

Avoid contact with skin or mucosa.

For single use only!

Contraindications

- Known hypersensitivity to any component of the drug
- Severe hepatic and renal impairment (serum creatinine > 2 mg%: contraindication; serum creatinine 1.5–2 mg%: dose to be reduced to 25% of the stated dose)
- Alcoholism
- Diseases of the hematopoietic system (bone marrow hypoplasia, leucopenia, thrombocytopenia, anemia)
- Existing infections
- Ulcers of the oral cavity and gastrointestinal tract
- Fresh surgical wounds
- Pregnancy and lactation (use of reliable method of contraception is mandatory before, during and after methotrexate therapy both in men and women.)

Particular care should be taken in impairment of bone marrow after an intensive radiotherapy, chemotherapy and/or prolonged pretreatment with drugs impairing bone marrow (sulphonamides, chloramphenicol, pyrazole derivatives, indomethacin, diphenylhydantoin); patients with poor general health, children and the elderly.

Methotrexate should not be used for the treatment of rheumatoid arthritis or psoriasis vulgaris in patients with pre-existing severe lung disease.

Caution should be exercised in patients with third space fluid collections (ascites, pleural effusion, seroma at site of operative wounds), since excretion of methotrexate may be reduced resulting in increase of toxicity.

Warnings and Precautions

Methotrexate should be administered only under the supervision of a qualified physician experienced in the use of antineoplastic therapy.

Special care should be taken when methotrexate is co-administered with non-steroidal anti-inflammatory drugs (NSAIDs).

Severe side effects including fatalities (after high doses of methotrexate) have been reported.

Consumption of alcohol even in low doses should be avoided.

The patient should be informed about possible risks (side effects). Contraindications and precautions for use must be strictly observed because of possible severe (under particular circumstances lethal) toxic reactions.

Plasma concentration of methotrexate

- Higher than 1–2 times 10^{-5} mol/l (24 hours after initiating methotrexate therapy)
- Twice 10^{-6} mol/l (48 hours after initiating methotrexate therapy)
- 10^{-7} mol/l (72 hours after initiating methotrexate therapy)

indicate an increased risk of intoxication (myelosuppression, mucositis) and require a long-lasting and high dose of calcium folinate rescue therapy.

In patients with impaired renal functions methotrexate dosage has to be reduced accordingly.

In the case of high dose of methotrexate the creatinine clearance should be at least 75% of the normal value (50 ml/min/m^2 resp. 90 ml/min).

An intermediate dose of methotrexate (> 100 mg/m^2) should not be prescribed if the creatinine clearance is reduced below 50% of the normal value (< 35 ml/min/m^2 resp. < 60 ml/min), unless daily determination of serum creatinine, methotrexate levels and calcium folinate rescue performed till the methotrexate levels decrease below 10^{-7} mol/l.

During the conventional dose of methotrexate a dose reduction of 50% is recommended if the serum creatinine values are 1.2–2 mg/dl and cessation of therapy is recommended if serum creatinine values exceed 2 mg/dl.

Prerequisites for a medium or high-dose methotrexate administration:
- Adequate availability of calcium folinate for subsequent rescue therapy
- Rapid determination of methotrexate serum levels
- Availability of hemodialysis
- Autologous bone marrow or blood supplies, leukocytes and platelet concentrates

Pretreatment examinations and safety precautions:
- Exclusion of renal and liver impairment and disturbances of the hemopoietic system (renal and liver function tests, complete blood counts).
- Before treatment of rheumatoid arthritis with methotrexate in patients with hepatic disease a liver biopsy should be performed.
- Pregnancy should be excluded.

For prevention of intrarenal precipitation of methotrexate or its metabolites and for prophylaxis and treatment of hyperuricemia resulting from destruction of the cell nucleus, forced hydration and alkalization of the urine (by infusion of $NaHCO_3$ solution, 20–25 mmol/l in an amount of 3 l/m^2/24 hours) 24 hours before and up to 24 hours after methotrexate administration is required.
If necessary 150–220 mg/m^2/day acetazolamide or allopurinol: 8 mg/kg/day can be used.
An intermediate and high-dose methotrexate therapy should not be initiated when urinary pH values are below 7.0. The alkaline status of the urine must be controlled at least during the first 24 h after initiation of methotrexate administration (pH value ≥ 6.8).
Monitoring of methotrexate serum levels is mandatory immediately after cessation of methotrexate administration, as well as 24 h, 48 h and 72 h afterwards. On the basis of methotrexate serum levels, the occurrence of signs of toxicity can be inferred and the calcium folinate dosage can be adjusted.
During the intrathecal administration systemic side effects may occur.
A careful clinical examination of the patients, particularly inspection of the oral cavity, pharynx and larynx for changes in mucosa, regular monitoring of leucocytes and thrombocytes (daily up to 3 times weekly), complete blood count (once weekly), renal and liver functions should be performed.
During long-term or high-dosage therapy, bone marrow biopsies may be necessary.
In severe leucopenia the risk of an infection should be borne in mind. In case of infection, therapy should be stopped and appropriate antibiotic therapy should be instituted. In severe cases of myelosuppression the transfusion of blood, leucocytes and thrombocytes may be necessary.

Drug Interactions

Several drugs may cause interactions (mainly pharmacokinetic) during concomitant administration of methotrexate.

The activity of methotrexate is increased by:
Inhibition of the renal excretion of methotrexate with non-steroidal anti-inflammatory drugs, salicylates, sulphonamides, probenecid, cephalothin, penicillin, carbenicillin, ticarcillin, para-aminohippuric acid.
Drugs which are involved in the active tubular secretion impair the elimination of methotrexate and therefore cause an increased plasma concentration.
The displacement of the methotrexate which is bound to plasma proteins leads to a higher free concentration in the plasma, e.g. with salicylates, sulfisoxazole, sulfafurazole, doxorubicin, bleomycin, cyclophosphamide, phenytoin, barbiturates, tranquilizers, tetracyclines, chloramphenicol, p-aminobenzoic acid, oral antidiabetics (chlorpropamide, amidopyrine derivatives), diuretics.
Increase of the intracellular accumulation of methotrexate and methotrexate polyglutamates, e.g. with vinca alkaloids, epipodophyllotoxins, probenecid.

The activity of methotrexate is decreased by:
Inhibition of the intracellular uptake of methotrexate (corticosteroids, L-asparaginase, bleomycin, penicillin); increase of the dihydrofolate reductase concentration (triamterene) or increase of the intracellular purine concentration (allopurinol); vitamin preparations which contain folic acid or its derivatives (especially folinic acid).

Drugs with known hepatotoxicity should not be administered concomitantly with methotrexate due to increased risk of hepatoxicity.
Drugs with folic acid antagonist activity (pyrimethamine, trimethoprim) may increase the toxicity of methotrexate.

The myelosuppressive activity can increase due to long-lasting pretreatment with myelosuppressive substances (e.g. sulphonamide, chloramphenicol, pyrazole derivatives, indomethacin, and diphenylhydantoin).
Methotrexate can enhance the activity of coumarin-like oral anticoagulants (the prothrombin time is prolonged due to a reduced decomposition of coumarin derivatives).
During simultaneous parenteral administration of acyclovir and intrathecal administration of methotrexate, neurological disorders can not be excluded.
Methotrexate may impair the immunologic reaction to vaccinations and may lead to severe complications. Therefore vaccinations should not be carried out during methotrexate therapy.
According to the type and intensity of the myelosuppressive therapy of the disease and other factors the ability to respond normally to vaccination may take 3–12 months. Leukemia patients in remission should not be vaccinated with live vaccines at least 3 months after the last dose of methotrexate.
The use of nitrous oxide anesthesia potentiates the effect of methotrexate on folate metabolism, yielding severe unpredictable myelosuppression and stomatitis. This effect can be reduced by the use of folinic acid rescue.
Amiodarone administration to patients receiving methotrexate treatment for psoriasis has induced ulcerated skin lesions.
An increased risk of hepatotoxicity has been reported when methotrexate and etretinate are given concurrently.

Pregnancy and Lactation

Methotrexate is a teratogenic drug; abortion, fetal death and/or congenital abnormalities have been reported. Therefore, it is not recommended in women of childbearing potential unless the potential benefits can be expected to outweigh the risks. If the drug is used during pregnancy for antineoplastic indications, or if the patient becomes pregnant while taking this drug, the patient should be informed on the potential hazard to the fetus.
For the management of psoriasis or rheumatoid arthritis, methotrexate therapy in women should be started immediately following a menstrual period.
Appropriate measures should be taken in men or women to avoid conception during and for at least 6 months following cessation of methotrexate therapy.

Effects on the Ability to Drive and Use Machines

The ability of patients to drive or operate machinery may be impaired.

Adverse Effects

Many side effects of methotrexate therapy are unavoidable being due to the pharmacological actions of the drug. However, these adverse effects are generally reversible if detected early. The major toxic effects of methotrexate occur in normal, rapidly proliferating tissues, particularly 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 difficulty in swallowing, ulcerative stomatitis, pharyngitis, leucopenia, thrombocytopenia, nausea, vomiting 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 appear to be dose-related.

Other side effects can be classified as follows:

Skin and Hypersensitivity Reactions: Erythema, exanthema, pruritis, photosensitivity, alopecia, telangiectasias, dyschromia, ecchymosis, acne, furunculosis. Severe toxic manifestations like vasculitis, severe herpetiform skin eruptions and Lyell's syndrome may appear. Psoriatic lesions can increase by simultaneous UV radiation therapy.

Blood: Bone marrow depression, leucopenia, neutropenia, thrombocytopenia, anemia and hypogammaglobulinemia 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, septicemia and hemorrhage from various sites may be expected.
Megaloblastic anemia 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 anemia.

Alimentary System: Gingivitis, glossitis, pharyngitis, stomatitis, anorexia, vomiting, diarrhea, hematemesis, melena, 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, azotemia, cystitis, hematuria, defective oogenesis or spermatogenesis, transient oligospermia, urogenital/menstrual dysfunction, vaginal discharge, infertility, abortion, fetal 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), dyspnea, 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, Guillain-Barré 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, nucal rigidity. A subacute form of toxicity may be characterized by varying degrees of paresis. Paraplegia and increased CSF pressure have also been reported. A delayed syndrome, occurring months to years after treatment, is characterized by necrotizing 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.

Carcinogenicity: Cytotoxic drugs have been reported to be associated with an increased risk of development of secondary tumors 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.

Overdose

Calcium folinate is the antidote for neutralizing the immediate toxic effects of methotrexate on the hematopoietic system. When large doses or overdoses are given, calcium folinate may be administered by intravenous infusion in doses up to 75 mg within 12 hours, followed by 12 mg intramuscularly every 6 hours for 4 doses. When average doses of methotrexate appear to have an adverse effect, 6–12 mg of calcium folinate may be given intramuscularly every 6 hours for 4 doses. In general, where overdosage is suspected, the dose of calcium folinate should be equal to or higher than the offending dose of methotrexate and should be administered as soon as possible; preferably within the first hour and certainly within 4 hours after which it may not be effective.
Other supporting therapy such as blood transfusion and renal dialysis may be required.
Effective clearance of methotrexate has been reported with acute, intermittent hemodialysis using a high-flux dialyser.

Pharmaceutical Properties

Properties and Efficacy

Methotrexate is a folic acid antagonist with cytotoxic activity belonging to the group of antimetabolites. Methotrexate acts mainly in the S-phase of the cell division. It inhibits competitively dihydrofolate reductase and the reduction of dihydrofolic acid (FH_2) to tetrahydrofolic acid (FH_4).
Activated reduced folate derivatives are necessary for the transmission of C1 units and the synthesis of pyrimidine, purine and amino acids. Therefore methotrexate induces an inhibition of the DNA, RNA and protein synthesis through the intracellular decrease of FH_4 and activated reduced folate derivatives.
The cytotoxic activity of methotrexate correlates *in vitro* with the inhibition of the DNA synthesis.
Rapidly proliferating tissues like malignant cells, bone marrow, fetal cells, skin epithelium and mucosa are generally more sensitive to methotrexate. The cell proliferation is accelerated in malignomas and methotrexate can therefore influence persistently the malignant growth without causing irreversible damage to the normal tissue. In psoriasis cell proliferation of the epithelium as compared to normal skin is increased. This difference in the cell proliferation rate is the reason for the use of methotrexate in severe recalcitrant disabling psoriasis and arthritis psoriatica. The activity of methotrexate can be neutralized with the administration of folinic acid (as calcium folinate). Folinic acid is metabolized intracellularly through N_5-methyl-tetrahydrofolic acid into tetrahydrofolic acid and $N_{5,10}$-methylen-tetrahydrofolic acid and causes filling of the intracellular pool of reduced folate derivatives avoiding the inhibition of the dihydrofolate reductase by methotrexate.

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