1. Name of the medical product!

**Methotrexat “Ebewe”**

2. Composition

1 ampoule of 1ml contains 5mg methotrexate as active ingredient.
1 vial of 1ml contains 5mg methotrexate as active ingredient.
1 ampoule of 1ml contains 10mg methotrexate as active ingredient.
1 vial of 1ml contains 10mg methotrexate as active ingredient.
1 ampoule of 1ml contains 50mg methotrexate as active ingredient.
1 vial of 5ml contains 50mg methotrexate as active ingredient.
1 ampoule of 10ml contains 500mg methotrexate as active ingredient.
1 vial of 5ml contains 500mg methotrexate as active ingredient.
1 ampoule of 10ml contains 1000mg methotrexate as active ingredient.
1 vial of 10ml contains 1000mg methotrexate as active ingredient.
1 vial of 50ml contains 5000mg methotrexate as active ingredient.

3. Drug form

Solution for injection and infusion.
Concentrate for solution for infusion.

4. Clinical particulars

4.1 indications

Malignant tumours and haemoblastoses such as acute lymphatic leukaemia, non-Hodgkin’s lymphoma, CNS tumours, pulmonary carcinoma, cervix carcinoma, advanced urothelial cell and gastric carcinoma, mammary carcinoma, chorion epithelioma, ovarian carcinoma, tumoura of the head and neck, bronchial carcinoma, testicular tumours, osteosarcoma, leukaemic meningoencephalomyelopathy, refractory psoriasis vulgaris.

Only indicated in the symptomatic control of severe, recalcitrant, disabling psoriasis which is not adequately responsive no other forms of therapy but only when the diagnosis has been established and the need for therapy has been confirmed by dermatologic consultation; autoimmunopathies (eg rheumatoid arthritis).

High Dose Methotrexate Therapy (HDMTX): indicated for certain defined clinical situations as in osteosarcoma and subgroups of non-Hodgkin’s lymphoma, with subsequent calciumfolinate (citrovorum factor) rescue therapy.

4.2 Dosage and Route of administration

Dosage

Malignant tumours and haemoblastoses:

In a polychemotherapy of malignant tumours or haemoblastoses the dosage of methotrexate has to be adjusted according to the indication and is made individually under control of the general condition and the blood count of the patient. The administered dose in conventional low dose methotrexate therapy (single dose lower than 100mg/m$^2$), medium dose MTX therapy (single dose 100mg/m$^2$-1000mg/m$^2$) and high dose MTX therapy (single dose higher than 1000mg/m$^2$) depends on the respective therapy scheme.

The following dosage instructions are only guidelines.

Conventional methotrexate therapy—no calciumfolinate rescue required:
15—20mg/m² (IV); twice weekly
30—50mg/m² (IV); once weekly
15mg/m²/day (IV; IM); 5 days; repetition after 2—3 weeks.

Medium high dose methotrexate therapy:
50-150mg/m² (IV injection); no calcium folinate rescue; repetition after 2-3 weeks
240mg/m² (IV infusion over 24 hours); calcium folinate rescue required; repetition after 4-7 days
0.5-1.0g/m² (IV infusion over 36-42 hours); calcium folinate rescue required; repetition after 2-3 weeks.

High dose methotrexate therapy - calcium folinate rescue required:
1-12g/m² (IV 1-6 hours); repetition after 1-3 weeks

For intrathecal or intraventricular methotrexate therapy a maximum dose of 15mg/m² is administered.
In the intrathecal application 0.2-0.5mg/kg or 8-12mg/m² methotrexate is administered every 2-3 days, after disappearance of the symptoms weekly, later in monthly intervals until the liquor level is normalised. A 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 dosage should be reduced correspondingly if required.
In severe, generalised, therapy-resistant psoriasis vulgaris including arthritis psoriatica and other autoimmune rheumatologies generally 10—25mg methotrexate are administered parenterally in weekly intervals. Dosage is adjusted according to the general condition of the patient.
In therapy-resistant rheumatoid arthritis generally 5—15mg methotrexate are administered initially intramuscularly as massive dose therapy once weekly. Dosage can be increased by 5mg to a maximum of 26mg weekly.

Route of administration
Methotrexat "Ebewe" 5mg, 10mg and 50mg can be administered intramuscularly, intravenously (as bolus injection or infusion, intra-arterial, intrathecally and intravascularly.
Methotrexat "Ebewe" 500mg, 1000mg and 5000mg - concentrate for infusion preparation are to be diluted with standard infusion solution before administration according to therapy schemata and duration of the infusion. This dilution is carried out with glucose solution or Ringer lactate or physiological saline solution.
Generally 1—2% methotrexate concentrations are administered (in osteosarcoma higher concentrations are also described in the literature).
For these methotrexate invasion solutions the stability was tested at room temperature over 24 hours both under light exposure and protected from light.
Please change the infusion bottle if longer infusion times are required. Dosages higher than 100mg/m² are generally administered as IV infusion. Partially it can be administered IV as initial dose (as bolus).
Use only fresh prepared and clear solutions. For single use only.
Avoid contact with skin or mucosa.

4.3 Contraindications
-hypersensitivity to one of the components of the drug
-severe liver and renal impairments (serum creatinine >2mg% contraindication, serum creatinine 1.5 - 2mg% dose reduction to 25%)
-abuse of alcohol
-diseases of the haematopoietic system (bone marrow hypoplasia, leucopenia,
thrombocytopenia, anaemia)
-existing infections
-ulcera of the oral cavity and the gastro-intestinal tract
-fresh operation wounds
Particular care is to be taken in impaired activity of the bone marrow after an intensive radiotherapy, chemotherapy and/or longer pretreatment with drugs causing bone marrow impairment (eg sulphonamide, chloramphenicol, pyrazole derivatives, indomethacin, diphenylhydantoin); further in impaired general condition of the patient as well as in children and aged patients.
In the therapy of rheumatoid arthritis or psoriasis vulgaris methotrexate should not be administered in case of previous severe lung diseases.
If a “third space” is present as a reserve compartment in which MTX can accumulate (eg ascites, pleural effusion, seroma in the region of operation wounds) an intensified and prolonged action or toxicity of MTX is to be reckoned with.
Pregnancy and lactation period are a strict contraindication. A strict contraception must be guaranteed before, during and after a methotrexate therapy, for both male and female patients.

4.4 Warnings and precautionary measures
Therapy with methotrexate should only be carried out by qualified physicians experienced in the field of (antineoplastic) chemotherapy and only in hospital departments.
Particular care is to be taken in simultaneous administration of methotrexate and non-steroidal antiphlogistics Severe side effects and also deaths (after high methotrexate doses) have been reported.
Alcohol is to be avoided, even in low doses.
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 tonic reactions.
Plasma concentrations of methotrexate
- higher than 1-2 times 10\(^{-5}\) mol/l (24 hours after beginning of methotrexate administration)
- twice 10\(^{-6}\) mol (48 hours after beginning of methotrexate administration)
- 10\(^{-7}\) mol/l (72 hours after beginning of methotrexate administration)
show an increased intoxication risk (myelosuppression, mucositis) and require a tong-lasting and high dose calcimfolinate rescue therapy. In impaired renal functions methotrexate dosage has to be reduced coo-respondingly. In high dose methotrexate therapy the creatinine clearance should be at least 75% of the normal value (50ml/min/m\(^2\) resp 90ml/min).
A medium dose methotrexate therapy (>100mg/m\(^2\)) should not be carried out if the creatinine clearance is reduced below 50% of the normal value (<35ml/min/m\(^2\) resp <60ml/min) unless in daily determination of carom creatinine, methotrexate concentration end calciumfolinate rescue until the methotrexate serum concentration decreases below 10-7 mol/l. During convensional methotrexate therapy a dose reduction of 50% is recommended if the serum creatinine values are 1.2-2mg/dl, and stopping of therapy is recommended if the serum creatinine values are over 2mg/dl.
Prerequisites for a medium or high dose methotrexate therapy:
adequate availability of calciumfolinate for subsequent rescue therapy
opportunity for rapid determination of MTX serum levels
opportunities for haemodialysis
- supply of autologous bone marrow conserves, blood conserves, leucocyte and thrombocyte concentrates.

Check-ups and safety measures:
Exclusion of renal and liver function disturbances, disturbances of the haematopoietic system (renal and liver function tests, complete blood count).
Before treatment of rheumatoid arthritis with methotrexate in hepatic diseases a liver biopsy should be carried out.
A gravidity must be excluded.

For prevention of intrarenal precipitation of MTX resp its metabolites and for prophylaxis and therapy of a cell nucleus dependent disintegration of hyperuricaetmia a forced hydration and alkalinisation of the urine (eg by infusion of a NaHCO₃ solution, 20-25 mmol/l in an amount of 3l/m²/24 hours) 24 hours before and up to 24 hours after methotrexate administration is required.

If necessary 150-220mg/m²/day acetazolamid (Diamox) resp 8mg/kg/day allopurinol can be used. A medium and high dose methotrexate therapy must not be started when urinary pH-values are below 7.0. Urinary alkalinisation must be controlled at least during the first 24 hours after beginning of methotrexate administration by repeated controls of the pH-values (≥6.8).

Methotrexate serum level must determined immediately after therapy stopping as well as after 24, 48 and 72 hours. Signs of toxicity and the adjustment of calciumfolinate therapy can he determined according to the serum values.

During intrathecal administration systemic side affects may also appear.
A careful clinical examination of the patients particularly inspection of the oral cavity, pharynx and larynx for changes of the mucosa. regular control of the leucocytes and thrombocytes (daily up to 3 times weekly), complete blood count (once weekly), renal and liver functions should be made. 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 a therapy stop and a corresponding antibiotic therapy is required. In severe cases of myelosuppression the transfusion of blood, leucocyte and throwbocyte concentrates may be necessary.

4.5 Drug interactions
Several drugs may cause interactions (mainly pharmacokinetic) during simultaneous administration of methotrexate.

The activity of methotrexate is increased by:
Inhibition of the renal elimination (secretion) of methotrexate, eg non-steroidal antiphlogistic agents, salicylates, sulphonamides, probenecid, cephalothin, penicillin, carbenicillin. ticarcillin, para-aminohippuric acid. Usually drugs which are involved in the active tubular secretion impair the elimination of methotrexate and therefore cause an increased plasma concentration.

The displacement of she methotrexate which is bound to plasma proteins lends to a higher free concentration in the plasma, eg salicylates, sulfisoxazole, sulfurazola, doxorubicin. bleomycin, cyclophosphamide, phenytoin, barbiturates, tranquilizers, tetracyclines, chloramphenicol, p-aminobenzoic acid, oral antidiabetics (eg chlorpropamide, amidopyrine derivatives).

Increase of the intracellular accumulation of methotrexate and methotrexate polyglutamates, eg vincaalkaloids, epipodophyllotoxines, probenecid.
The activity of methotrexate decreased by:
Inhibition of the intracellular uptake of methotrexate (corticosteroids, L-asparaginase, bleomycin, penicillin); increase of the dihydrofolate reductasa concentration (trimeterene) or increase of the intracellular purine concentration (allopurinol); vitamin preparations which contain folic acid or its derivatives (especially folinic acid). Because of an increased hepatotoxic risk drugs with known hepatotoxicity should not be administered simultaneously.
Drugs with folic acid antagonist activity (eg trimethoprim) can increase the toxicity of methotrexate.
The myelosuppressive activity can increase due to long-lasting pretreatment with myelosuppmsaive substances (eg sulphonamide, chloramphenicol, pyrazole derivatives, indomethacin, diphenylhydantoin)
Methotrexate can improve the activity of coumarin- like oral anticoagulants (the prothrombin time is prolonged due to a reduced decomposition of coumarin
During simultaneous parenteral administration of acyclovir and intrathecal administration of methotrexate neurologic disturbances cannot be excluded.
Methotrexate may impair the immunotogic 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 immunosuppressive therapy of the disease and other factors the restoration of the normal reaction ability to vaccine administration can last 3-12 months. Patients with leucaemia should receive life vaccines after remission at least 3 months after the last methotrexate administration.

4.6 Pregnancy and lactation
Methotrexate has been shown to be teratogenic; it has been reported to cause foetal death and/or congenital abnormalities. Therefore, it is not recommended in women of childbearing potential unless the benefits can be expected to outweigh the considered risks. If this drug is used during pregnancy for antineoplastic indications, or if the patient becomes pregnant while taking this drug, the patient should be appraised of the potential hazard to the foetus.

4.7 Effects on ability to drive and use machines
The ability of patients to drive or operate machinery my be impaired.

4.5 Side effects
Even if the therapeutic plan la correctly carried cut, aide effects are to be expected, especially in tissues with high proliferation rate. Frequency and severity of side effects are generally dose dependent and clearly correlate with the lowering at the urinary pH-value. Since MIX in mainly excreted renally, if signs of disturbed renal excretion are present, severe signs of toxicity are to be reckoned with due to raised serum levels of MTX. The most frequent side effects are nausea and vomiting, difficulty in swallowing, stomatitis, pharyngitis, leucopenia and thrombocytopenia.

Haematopoietic system:
Primary bone marrow depression (with a maximum 7—10 days after iv short term infusion or bolus, regeneration approx after one week). A severe haematotoxicity leads to a transient hypo- up to aplastic condition with
leucopenia, thrombocytopenia, anaemia and hypogammaglobulinaemia (rarely in intermittent massive-dose treatment). Bleeding and septicaemia can appear.

Gastro-intestinal tract:
Changes in the gastro-intestinal tract appear approx 2-7 days after a high-dose methotrexate therapy with symptoms of erythema and/or ulcerations of the oral cavity, the pharynx and the gastro-intestinal tract (mucositis). Furthermore anorexia, nausea and vomiting can appear. Gastro-intestinal ulcerations can lead to bleeding, perforation and toxic megacolon.

Urogenital tract:
A nephrotoxic activity like oliguria, anuria, electrolyte disturbances due to a precipitation of methotrexate resp its metabolites or metabolic disturbances of the tubuli cells may appear. An increase of serum creatinine and a decrease of the creatinine clearance, cystitis, mucosa of the bladder with haematuria are first signs at nephrotoxicity. Disturbances of oogenesis and spermatogenesis, temporary oligospermia, loss of libido, importance, menstrual disturbances, fertility disturbances, abortion and teratogenesis were described.

Liver:
In high dose methotrexate therapy a transient increase of serum transaminase, alkaline phosphatase and rarely hyperbilirubinaemia may appear. During a long term therapy an acute liver distrophy, periportal fibrosis, liver metamorphosis and cirrhosis were observed. During intermittent massive-dose treatment with subsequent calciumfolinate rescue the mentioned side effects do not appear anymore.

Lungs:
A methotrexate pneumonitis (granuloma and infiltrations) and lung fibrosis are rare. First symptoms are cough, tachypnoea and dyspnoea.

Central nervous system:
High does iv methotrexate therapy:
Acute neurotoxicity (within 24 hours) with dizziness, lethargy, confusion, somnolence, coma which can lead to death and rarely spasms. The symptoms are transient and appear probably due to a cerebral oedema which disappears quickly after systemic administration of cortisone. Subacute neurotoxicity (after 9-13 days) with stroke-like signs as aphasia, haemiparesis, paraplegia and spasms in few patients (mostly after several therapy cycles, but reversible). Retarded neurotoxicity (months to years after methotrexate administration) manifesting in an encephalopathy (spasms, quadriplegia, ataxia and dementia).

Intrathecal methotrexate therapy:
Acute neurotoxicity (within 12 hours) caused by an acute arachnoiditis (chemical meningitis, toxic syndrome) with headache, nausea, vomiting and meningism. The symptoms usually disappear after 1—2 days but may also disappear after 1 week or later, Subacute neurotoxicity (within some days at weeks after starting methotrexate therapy) due to a myelopathy or an encephalopathy with mainly myokinetic disturbances (paraplegia) which are
mostly reversible after stopping methotrexate therapy. Retarded neurotoxicity in manifested in a leucencephalopathy.

Skin:
Erythema, exanthema, pruritus, photosensitvity, alopecias, telangiectasias, dyschromia: ecchymosea, acne, furunculosis. Severe toxic manifestations like vasculitis, severe harpetiform skin eruptions and Lyell syndrome may appear. Psoriatic lesions can increase by simultaneous UV radiation therapy.

Other side effects:
Allergic reactions (up to anaphylactic shock, fever, chills, impaired resistance to infections, immunosuppression, osteoporosis, metabolic disorders (diabetes mellitus, hyperuricaemia). During treatment with methotrexate in acute lymphatic leucaemia complaints in the left epigastrium can appear )episplenitis by destruction of the leucaemic cells).

4.9 overdose
Calcium folitnate is the antidote for neutralising the immediate toxic effects of methotrexate on the haemopoietic system. it may be administered orally, intramuscularly or by en intravenous bolus iniection or intusion, In cases of accidental overdosage, a dose of calcium folinste equal to or higher than the offending done of methosrexate should be administered within one hour and doing continued until the serum levele ot methoirexete are below 10’M, Other supporting therapy such as abroad transiunion and renal dialysis may be required.

5. pharmaceutics t properties
5.1 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 (FH₂) to tetrahydrofolic acid (FH₄). 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 FH₄ 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 in 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 at methotrexate can be neutralised with the administration of folic acid (as calciumfolinate, Falinic acid is metabolised intracellularly through N5 methyl tetrahydrofolic acid into tetrahydrofolic acid and N5.10 methylen tetrahydrofolic acid and causes a filling of the intracellular pool of reduced folate derivatives avoiding the inhibition of the dihydrofolate reductase by methotrexate.
5.2. Pharmacokinetics
In high dose methotrexate therapy plasma concentrations of 10^{-3} mol/l were reached immediately after infusion. After iv application of methotrexate the extracellular distribution is very fast; in the total water content of the body the distribution is in a volume of approx 76% of the body weight. With parenteral application therapeutic insufficient concentrations are reached in the liquor due to an impaired crossing of the blood-brain-barrier. High concentrations can be reached by intrathecal application if required.
After iv administration a triphasic pathway in assumed for the plasma concentrations of methotrexate with medium half-life times of 0.75, 3.49 and 26.99 hours whereby there are wide fluctuations in the third phase (6—69 hours). After the administration of methotrexate as IV bolus injection or short term infusion 80—95% of methotrexate a renally eliminated unchanged within 24—30 hours with normal renal function. Particularly with impaired renal function but also with gastrointestinal obstruction (ileus) and if a “third space” is present an a reserve compartment in which MTX can accumulate (eg ascites and/or pleural effusions), the total clearance is reduced and an intensified and prolonged action an MTX is to be reckoned with. After intrathecal methotrexate administration a slow resorption in the plasma compartment occurs and leads to possible prolonged toxic plasmatic concentrations, 7-hydroxy methotrexate and 2,4-diamino-N^{10} methylpteroin acid (DAMPA) were found as metabolites in plasma and urine, Methotrexate, 7-hydroxy methotrexate and DAMPA are slightly soluble in acid urine', therefore a corresponding hydration and alkalinisation of the urine are absolutely required during high dose methotrexate Therapy to avoid acute renal insufficiency due to internal application.
Methothrexate is bound to serum protein in a rate of 50-70%.

6. Pharmaceutical particulars

6.1. Incompatibilities
Known incompatibilities include strong oxidants and acids, Immediate precipitation or turbidity results when combined with chlorpromazine hydrochloride, droperidol, idarubicine, metoclopramide hydrochloride, heparin solution, prednisolone sodium phosphate and promethazine hydrochloride.

6.2 Storage
Store at room temperature not over 25°C, away from light.
Keep in a safe place out of the reach of children

6.3. Presentation and packs
Methotrexate “Ebewe” 5mg: 10 ampoules of 1ml,
Methotrexate “Ebewe” 5mg: 1 vial of 1ml,
Methotrexate “Ebewe” 10mg: 10 ampoules of 1ml,
Methotrexate “Ebewe” 10mg: 1 vial of 1ml,
Methotrexate “Ebewe” 50mg: 5 ampoules of 5ml,
Methotrexate “Ebewe” 50mg: 1 vial of 5ml,
Methotrexate “Ebewe” 500mg: 5 ampoules of 5ml,
Methotrexate “Ebewe” 500mg: 1 vial of 5ml,
Methotrexate “Ebewe” 1000mg: 1 ampoules of 10ml,
Methotrexate “Ebewe” 1000mg: 1 vial of 10ml,
Methotrexate “Ebewe” 5000mg: 1 vial of 50m1.

Calciumfolinat “Ebewe” is available for the rescue therapy and as antidote.

6.4 Instruction for handling staff

Parenteral methotrexate preparations do not contain an antimicrobial preservative. Any unused injection should be discarded.

Perenteral methotrexate preparations are stable for 24 hours when diluted with the following intravenous infusion fluids: 0.9% sodium chloride; glucose; sodium chloride and glucose; compound sodium chloride (Ringers Injection); compound sodium lactate (Lactated Ringera injection).

Other drugs should not be mixed with methotrexate in the same infusion container. Handling of cytotoxic drugs: cytotoxic drugs should only be handled by trained personnel in a designated area.

The work surface should be covered with disposable plastic-packed absorbent paper.

Protective gloves and goggles should be worn to avoid the drug accidentally coming into contact with the skin or eyes.

Methotrexate is not vesicant and should not cause harm if it comes in contact with the skin, it should, of course, be washed off with water immediately. Any transient stinging may be treated with bland cream. If there is any danger of systemic absorption of significant quantities of methotrexate by any route, calciumfolinate cover should be given.

Cytotoxic preparations should not be handled by pregnant staff.

Any spillage or waste material may be disposed of by incineration, We do not make any specific recommendations with regards to the temperature of the incinerator.

7. Manufacturer

EBEWE Arzneimittel Ges.m.b.H., A-4866 Unterach, Austria. Europe