1. TRADE NAME OF THE MEDICINAL PRODUCT

Methotrexat "Ebewe"

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1ml contains 10mg methotrexate as active ingredient.
For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection and infusion.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Cancerous conditions:
Malignant diseases, for example acute lymphatic leukaemia (ALL), non-Hodgkin's lymphoma, breast cancer, choriocarcinoma.

Non-cancerous conditions:
Treatment of rheumatoid arthritis.
Treatment of psoriasis, especially widespread psoriasis, widespread pustular psoriasis, psoriatic arthritis, or psoriatic nail disease.

4.2. Posology and method of administration

Cancerous conditions:
Adults and Children: Methotrexate may be given by intramuscular, intravenous (bolus injection or infusion) intrathecal, intra-arterial and intraventricular routes of administration. Dosages are based on the patient's body weight or surface area except in the case of intrathecal or intraventricular administration when a maximum dose of 15mg and a maximum concentration of 5mg/ml is recommended. Doses should be reduced in cases of haematological deficiency and hepatic or renal impairment. Larger doses (greater than 100mg) are usually given by intravenous infusion over periods not exceeding 24 hours. Part of the dose may be given in an initial rapid intravenous injection.
Dosage schedules vary considerably depending on the use.
Methotrexate has been used with beneficial effects in a wide variety of neoplastic diseases, alone and in combination with other cytotoxic agents, hormones, radiotherapy or surgery. Dosage schedules therefore vary considerably depending on the clinical use, particularly when more than 150mg/m² are administered, these regimens are followed by the administration of calcium folinate to rescue normal cells from toxic effects.
Dosage regimens for calcium folinate rescue vary, depending upon the dose of methotrexate administered. In general, up to 150mg are usually given in divided doses, over 12–24 hours, by intramuscular injection, bolus intravenous injection or intravenous infusion or orally, followed by 12–25mg intramuscularly, IV, or 15mg orally (one capsule), every six hours for the next 48 hours. Rescue therapy is usually started following a delay of 8 to 24 hours from the beginning of the methotrexate infusion. One capsule (15mg) of calcium folinate every six hours for 48–72 hours may be sufficient when lower doses (less than 100mg) of methotrexate have been given.
The following regimens are only examples.

Leukaemia:
- 3.3mg/m² in combination with other cytostatic agents once daily for 4–6 weeks.
- 2.5mg/kg every two weeks.
- 30mg/m²/week maintenance therapy.
- High-dose regimen between 1 and 12g/m² (i.v. 1–6 h) repeated every 1–3 weeks.
- 20mg/m² in combination with other cytostatic agents once weekly.

Non-Hodgkin-Lymphoma:
- Combination therapy varies between 500mg/m² and 2000mg/m² once weekly or in three week intervals.
- Once weekly 7500mg/m² i.v.

Breast:
- 40mg/m² i.v. in combination with other cytostatic agents on day 1, or 1 and 3, or 1 and 8, or 3 x per year.

Choriocarcinoma:
- 15–30mg daily for 5 days in therapy intervals of one week or more.

Non-cancerous conditions:
Posology:
Rheumatoid arthritis and psoriasis: The product should be used by specialists in dermatology, rheumatology and internal medicine. Methotrexate is administered orally, intramuscularly or subcutaneously.

Rheumatoid arthritis: The initial dose of 7.5mg per week is given as a single dose.

Psoriasis: The recommended initial dose is 2.5mg 3 times per week with 12 hours intervals, alternatively one single dose of 7.5mg once a week.
For both conditions, the therapeutic effect is obtained usually after 4–6 weeks or more, with the condition of the patient improving after 8–10 weeks or more. If no response has been achieved after 6 weeks and no toxic symptoms are observed, the dose can be increased stepwise by 2.5mg/week.
Usually the optimum dose per week is between 10–25mg, and the dose should not exceed 25mg/week.
Since methotrexate is a disease-modifying anti-rheumatic drug which is potentially toxic after long-term use, a balance must be struck between the induction of side effects of methotrexate therapy versus the progression of rheumatoid arthritis and severe morbidity if inadequate therapy is utilised. The dose should be adjusted according to the patient's response. If no response is obtained after 12 weeks with 25mg, methotrexate should be withdrawn. If response to methotrexate treatment is achieved, the maintenance dose should be reduced to the lowest possible effective dose. The optimal therapy duration is so far unknown but preliminary data indicate that the initially achieved effect may remain for at least 2 years with continued maintenance dose. When the treatment is withdrawn the symptoms may return within 3–6 weeks. In patients with psoriasis, the use of methotrexate may permit the return to conventional topical therapy which should be encouraged. Additionally, an initial test dose one week prior to initiation of therapy can be given to detect any idiosyncrasy.
The patient should be fully informed of the risks involved and the clinician should pay particular attention to the appearance of liver toxicity by carrying out liver function tests before starting methotrexate treatment, and repeating these at 2 to 4 month intervals during therapy. Higher doses require careful long-term monitoring for liver as well as bone marrow and lung toxicity.
Folic acid (1–2mg daily) or folinic acid (2.5–5mg once per week, 8–12 hours after methotrexate) should be administered concurrently to reduce the potential long-term toxicity of methotrexate. These doses of

folic acid respectively folinic acid (calcium folinate) do not appear to impair the therapeutic efficacy of methotrexate.
In addition, aspirin or paracetamol should be used only with caution together with methotrexate, since these combinations will often result in abnormal liver values. Liver test abnormalities are less likely with other NSAIDs.

4.3. Contra-indications

Pregnancy and lactation.
Significant hepatic dysfunction including fibrosis, cirrhosis, or hepatitis.
Significant renal dysfunction.
Blood dyscrasias including hypoplasia of the bone marrow, leukopenia thrombocytopenia, anaemia.
Active infectious disease, evidence of immuno-deficiency syndrome.
Known hypersensitivity of methotrexate.
General poor condition.

4.4. Special warnings and special precautions for use

Methotrexat may only be administered under the supervision of a physician qualified in oncology with experience in the use of antineoplastic chemotherapy.
Methotrexate should be used with extreme caution in patients with haematological depression, renal impairment, peptic ulcer, ulcerative colitis, ulcerative stomatitis, diarrhoea, poor performance status and in young children and the elderly.
Patients with pleural effusions or ascites should have these drained if appropriate before treatment or treatment should be withdrawn.
Symptoms of gastro-intestinal toxicity, usually first manifested by stomatitis, indicate interruption of therapy; otherwise haemorrhagic enteritis and death from intestinal perforation may occur if treatment is continued.
Methotrexate may cause decreased fertility, oligospermia, menstrual dysfunction and amenorrhoea. This effect appears to be reversible on discontinuing therapy. Beyond this methotrexate causes embryo toxicity and foetal defects and may cause abortion. If one of the partners is being treated with methotrexate, conception should be avoided during treatment and at least three months after cessation of treatment.
Before beginning methotrexate therapy or reinstituting methotrexate after a rest period, assessment of renal function, liver function and blood elements should be made by history, physical examination and laboratory tests. Patients undergoing therapy should be subject to appropriate supervision so that signs of possible toxic effects or adverse reactions may be detected and evaluated with minimal delay.
It is essential that the following laboratory tests are included regularly in the clinical evaluation and monitoring of patients receiving methotrexate: complete haematological analysis, urinalysis, renal function tests, liver function tests and when high doses are administered, determination of plasma levels of methotrexate.
Particular attention should be given to the appearance of liver toxicity which may occur without correlative changes in liver function tests. Treatment should not be instituted or should be discontinued if any abnormality in liver function tests or liver biopsy is present or develops during therapy. Such abnormalities should return to normal within two weeks after which treatment may be recommenced at the discretion of the physician.
Haemopoietic suppression caused by methotrexate may occur abruptly and with apparently safe dosages. Any profound drop in white-cell or platelet counts indicate immediate withdrawal of the drug and appropriate supportive therapy.
High doses may cause the precipitation of methotrexate or its metabolites in the renal tubules. A high fluid throughput and alkalinisation of the urine to pH 6.5–7.0 by oral or intravenous administration of sodium bicarbonate (5 x 625mg tablets every three hours) or acetazolamide (500mg orally four times a day) is recommended as a preventive measure.
The Rules of the National Working Environment Authority concerning handling of cytostatics should be followed.

4.5. Interactions with other Medicaments and other forms of interaction

Methotrexate has some immunosuppressive activity and therefore the immunological response to concurrent vaccination may be decreased. In addition, concomitant use of a live vaccine could cause a severe antigenic reaction.
Protein bound methotrexate may be displaced by salicylates, sulphonamides, diphenylhydantoins, tetracyclines, chloramphenicol, sulfazole, doxorubicin, cyclophosphamide and barbiturates. The higher plasma levels of unbound methotrexate may lead to increased toxicity.
Methotrexate is subject to active renal secretion. It interferes in general with other drugs subject to the same excretion-mode and this causes increased methotrexate plasma-levels.
The dose of methotrexate should be reduced when given concomitantly with probenecid.
Vinca alkaloids may increase intracellular methotrexate and methotrexate polyglutamates.
Concomitant use of drugs with nephrotoxic or hepatotoxic potential (including alcohol) should be avoided.
Vitamin preparations or oral iron preparations containing folic acid may alter the response to methotrexate.
Non-steroidal anti-inflammatory drugs may impair the renal clearance of methotrexate and lead to severe toxicity.
Concomitant administration of folate antagonists such as trimethoprim/sulphamethoxazole is reported to cause acute pancytopenia in rare cases.
Serum levels of methotrexate may be increased by etretinate and severe hepatitis has been reported following concurrent use.

4.6 Pregnancy and lactation

Methotrexate has been shown to be teratogenic. Therefore, it is not recommended in women of childbearing potential unless the benefits can be expected to outweigh the considered risks. If methotrexate 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.
Methotrexate is excreted in breast milk for which reason breast feeding is contraindicated during therapy.

4.7. Effects on ability to drive and use machines

Depending on individual susceptibility, the patient's ability to drive a vehicle or operate machinery may be impaired.

4.8. Undesirable effects

The most common adverse reactions include ulcerative stomatitis, leukopenia, nausea and abdominal distress. Although very rare, anaphylactic reactions to methotrexate have occurred. Others reported are eye irritation, malaise, undue fatigue, chills and fever, dizziness, loss of libido/impotence and decreased

resistance to infection. In general, the incidence and severity of side effects are considered to be dose-related. Adverse reactions for the various systems are as follows:

The incidence of the more frequent adverse reactions is as follows:

Common	General:	Headache, dizziness
(>1/100)	Haematological:	Leukopenia
	Gastrointestinal:	Nausea, vomiting, stomatitis diarrhoea, anorexia
	Skin:	Alopecia
	Liver:	Significant elevation of liver enzymes
	Other:	Infection
Less common	Haematological:	Epistaxis, thrombocytopenia
	Skin:	Pruritus, urticaria
	Pulmonary:	Pulmonary fibrosis, pneumonitis
	Urogenital:	Vaginal ulceration
Uncommon	General:	Impotence
(<1/1000)	CNS:	Depression, confusion
	Other:	Diminished libido, Herpes zoster

Integument: Erythematous rashes, pruritus, urticaria, photosensitivity, pigmentary changes, alopecia, eccyhmosis, telangiectasia, acne, furunculosis. Lesions of psoriasis may be aggravated by concomitant exposure to ultraviolet radiation. Skin ulceration has been reported in psoriatic patients. The recall phenomenon has been reported in both radiation and solar damaged skin.
Single cases of Stevens-Johnson-Syndrom and epidemal necrolysis have been reported.

Hematopoietic: Bone marrow depression is most frequently manifested by leukopenia, but thrombocytopenia, anaemia or any combination may occur. Infection or septicemia and haemorrhage from various sites may result. Hypogammaglobulinaemia has been reported.

Alimentary system: Mucositis (most frequently stomatitis, although gingivitis, pharyngitis and even enteritis, intestinal ulceration and bleeding) may occur. In rare cases the effect of methotrexate on the intestinal mucosa has led to malabsorption or toxic megacolon. Nausea, anorexia and vomiting and/or diarrhoea may also occur.

Hepatic: Reversible increases in transaminases occurs frequently. Hepatic toxicity resulting in significant elevations of liver enzymes, acute liver atrophy, necrosis, fatty metamorphosis, periportal fibrosis or cirrhosis or death may occur, usually following chronic administration.

Urogenital system: Renal failure and uraemia may follow methotrexate administration, usually in high doses. Vaginitis, vaginal ulcers, cystitis, haematuria and nephropathy have also been reported.

Pulmonary system: Infrequently an acute or chronic interstitial pneumonitis, often associated with blood eosinophilia, may occur and deaths have been reported. Acute pulmonary oedema has also been reported after oral and intrathecal use. Pulmonary fibrosis is rare. A syndrome consisting of pleuritic pain and pleural thickening has been reported following high doses.

Central nervous system: Headaches, drowsiness and blurred vision have occurred. Following low doses of methotrexate, transient subtle cognitive dysfunction, mood alteration or unusual cranial sensations have been reported occasionally. Aphasia, paresis, hemiparesis, and convulsions have also occurred following administration of higher doses.

Adverse reactions particularly following intrathecal administration:
Acute: chemical arachnoiditis manifested by headache, back or shoulder pain, nuchal rigidity, and fever.
Subacute: may include paresis (usually transient), paraplegia, nerve palsies and cerebellar dysfunction.
Chronic: leucoencephalopathy manifested by irritability, confusion, ataxia, spasticity, occasionally convulsions, dementia, somnolence, coma, and rarely death. There is evidence that the combined use of cranial radiation and intrathecal methotrexate increases the incidence of leucoencephalopathy.
Additional reactions related to or attributed to the use of methotrexate such as osteoporosis, abnormal (usually 'megaloblastic') red cell morphology, precipitation of diabetes, other metabolic changes and sudden death have been reported.

Carcinogenesis, mutagenesis, and impairment of fertility:
Methotrexate has been reported to cause chromosomal damage to animal somatic cells and bone marrow cells in humans, these effects are transient and reversible. In patients treated with methotrexate, this may cause an increased risk of neoplasia (Lymphoma, usually reversible), but evidence is insufficient to permit conclusive evaluation. Methotrexate has been reported to cause impairment of fertility, oligospermia, menstrual dysfunction and amenorrhoea in humans, during and for a short period after cessation.
In addition, methotrexate causes embryotoxicity, abortion and foetal defects in humans. Therefore, the possible risks of effects on reproduction should be discussed with patients of child-bearing potential.

4.9. Overdose

Calcium leucovorin is the antidote for neutralising the immediate toxic effects of methotrexate on the haemopoietic system. It may be administered orally, intramuscularly or by an intravenous bolus injection or infusion. In cases of accidental overdosage, a dose of calcium leucovorin equal to or higher than the offending dose of methotrexate should be administered within one hour and dosing continued until the serum levels of methotrexate are below 10–7M. Other supporting therapy such as a blood transfusion and renal dialysis may be required.

5. PHARMACOLOGICAL PROPERTIES

Therapeutic classification: ATC-Code L 01 BA 01

5.1. Pharmacodynamic properties

Methotrexate, a derivative of folic acid, belongs to the class of cytotoxic agents known as antimetabolites. It acts principally during the 'S' phase of cell division, by the competitive inhibition of the enzyme dihydrofolate reductase, thus preventing the reduction of dihydrofolate to tetrahydrofolate, a necessary step in the process of DNA synthesis and cellular replication. Actively proliferating tissues such as malignant cells, bone marrow, foetal cells, buccal and intestinal mucosa, and cells of the urinary bladder are generally more sensitive to the effects of methotrexate. When cellular proliferation in malignant tissues is greater than in more normal tissues, methotrexate may impair malignant growth without irreversible damage to normal tissues.

5.2. Pharmacokinetic properties

Methotrexate is generally completely absorbed from parenteral routes of administration. Peak serum concentrations following intramuscular administration are achieved in 30 to 60 minutes. After intravenous administration the initial volume of distribution is approximately 0.18L/kg (18% of body weight) and steady-

administration the initial volume of distribution is approximately 0.18L/kg (18% of body weight) and steady-state volume of distribution if approximately 0.4 to 0.8L/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% protein bound.

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 administation.

Methotrexate is reversibly bound in pleural exudates and ascites, for which reason the elimination from the organism may be remarkably delayed (see also section 4.4).

Methotrexate is metabolised predominantly to three forms; 7-hydroxy-methotrexate is produced by hepatic aldehyde oxidase, especially after high-dose infusions, although it has a 200 fold lower affinity to dihydrofolate reductase it may play a role in the cellular uptake of methotrexate, polyglutamylation and inhibition of DNA-synthesis. 2, 4-diamino-N-methylpteroic acid (DAMPA) is produced by an enteral bacterial carboxypeptidase. Following intravenous administration of methotrexate, DAMPA represented only 6% of the metabolites recovered from the urine.

Methotrexate polyglutymation results in intracellular accumulation of drug which is not at steady state with extracellular methotrexate concentration. As methotrexate and natural folates compete for the enzyme polyglutamyl synthetase, a high level of intracellular methotrexate will result in increased methotrexate polyglutymate synthesis, augmenting the cytotoxic effect of the drug.

The terminal half-life reported for methotrexate is approximately 3 to 10 hours for patients receiving treatment for psoriasis or rheumatoid arthritis or low-dose anti-neoplastic therapy (less than 30mg/m^2). For patients receiving high doses of methotrexate, the terminal half-life is 8 to 15 hours. 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. There is limited biliary excretion amounting to 10% or less of the administered dose. Enterohepatic recirculation of methotrexate has been proposed.

5.3. Preclinical safety data

Methotrexate acts mainly on proliferating tissues.

Reproductive toxicity: Methotrexate is capable of inducing teratogenic and embryolethal effects in several species at dose levels non-toxic to the mother.

Animal carcinogenicity studies have demonstrated methotrexate to be free of carcinogenic potential. Although methotrexate has been reported to cause chromosomal damage to animal somatic cells and bone marrow cells in humans, these effects are transient and reversible. In patients treated with methotrexate, evidence is insufficient to permit conclusive evaluation of any increased risk of neoplasia.

Mutagenicity: Methotrexate is genotoxic in a number of in vitro and in vivo mammalian test systems.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium chloride, sodium hydroxide and water for injections.

6.2. Incompatibilities

Strong oxidants and acids. Precipitation or formation of a turbid solution is seen in combination with chlorpromazine hydrochloride, droperidol, idarubicine, metoclopramide hydrochloride, heparin solution, prednisolone sodium phosphate and promethazine hydrochloride.

6.3. Shelf life

Expiry date is written on the carton and on the label.

6.4. Special precautions for storage

Do not store above 25°C. Keep container in the outer carton, in order to protect from light.

6.5. Nature and contents of container

Vials, colourless glass of hydrolytic class I with rubber stopper, packed in a carton.

Ampoules, brown glass of hydrolytic class I, packed in a carton.

10 ampoules containing 10mg/1ml of methotrexate, each.

5 ampoules containing 50mg/5ml of methotrexate, each.

1 vial containing 10mg/1ml of methotrexate.

1 vial containing 50mg/5ml of methotrexate.

6.6. Instruction for use/handling

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

Parenteral methotrexate preparations are stable for 24 hours when diluted with the following intravenous infusion fluids: 0.9% Sodium Chloride; Glucose; Sodium Chloride and Glucose.

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-backed 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, calcium leucovorin cover should be given.

Cytotoxic preparations should not be handled by pregnant staff.

Any spillage or waste material may be disposed of by incineration. No specific recommendations are given with regards to the temperature of the incinerator.

Handle according to guidelines for cytostatics.

7. MANUFACTURER

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A-4866 Unterach, AUSTRIA

8. DATE OF (PARTIAL) REVISION OF THE TEXT

July 2004