Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Methotrexate Ebewe 100mg/ml Concentrate for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of concentrate contains 100 mg methotrexate
Each vial with 5 ml of concentrate contains 500 mg methotrexate
Each vial with 10 ml of concentrate contains 1000 mg methotrexate
Each vial with 50 ml of concentrate contains 5000 mg methotrexate

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Clear, dark yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Methotrexate is indicated in the treatment of different malignant diseases such as acute lymphatic leukaemia (ALL), breast cancer and osteosarcoma.

4.2 Posology and method of administration

Treatment with methotrexate should be initiated by or in consultation with a doctor with considerable experience of cytostatic treatment.

Methotrexate 100 mg/ml is given intravenously.
Methotrexate 100 mg/ml concentrate for infusion is not suitable for intrathecal, intramuscular or intraarterial administration, as an extreme dilution would be necessary. For these purposes a preparation with lower concentration should be used

High-dose treatment:
Methotrexate can be used at very high doses (> 1 g) in certain neoplastic conditions. Disease states that have been successfully treated with high-dose methotrexate either alone or in combination with other cytostatics are acute lymphatic leukaemia, osteogenic sarcoma and certain solid tumours. High-dose therapy is usually given as an infusion over 24 h.
The dose is usually calculated per m^2 body surface.
Calcium folinate rescue is necessary when methotrexate is given at doses exceeding 500 mg/m2 body surface and has to be considered with doses of 100 mg – 500 mg/m2 body surface.
As a rule, the first dose of Calcium folinate is 15 mg (6-12 mg/m^2) to be given 12-24 hours (24 hours at the latest) after the beginning of methotrexate infusion. The same dose is given every 6 hours throughout a period of 72 hours. After several parenteral doses treatment can be switched to the oral form.
Forty-eight hours after the start of the methotrexate-infusion, the residual methotrexate-level should be measured. If the residual methotrexate-level is > 0.5 µmol/l, an intensification of the rescue regime might be necessary.
In addition to calcium folinate administration, the prompt excretion of methotrexate has to be assured by

- maintenance of high urine output (adequate hydration)
- alkalinisation of urine (e.g. with sodium bicarbonate 8.4%)

Renal function should be monitored through daily measurements of serum creatinine.
For more detailed information, please refer to the Summary of Product Characteristics of Calcium Folinate.
If signs of leukopenia appear, temporary interruption of methotrexate is advisable.

The following regimens are only examples.

Acute lymphatic leukaemia:

- 3.3 mg/m^2 in combination with other cytostatic agents once daily for 4-6 weeks.
- 2.5 mg/kg every two weeks.
- 30 mg/m^2/week maintenance therapy.
- High-dose regimen between 1 and 12 g/m^2 (i.v. 1-6 h) repeated every 1-3 weeks.
- 20 mg/m^2 in combination with other cytostatic agents once weekly.

In children:

- Doses of up to 8000 mg/m^2 i.v. have been used sequentially (with subsequent leucovorin administration) for consolidation of remission and maintenance treatment. Oral treatment with doses up to 20 mg/m2/week is used together with intravenous administration and intrathecal CNS prophylaxis (see below) as maintenance treatment.

In adults:

- Maintenance treatment with the sequential POMP combination and intrathecal CNS prophylaxis (see below) with methotrexate is customary. On relapse, high-dose methotrexate can be tried.

Breast cancer:

- 40 mg/m^2 i.v. in combination with other cytostatic agents on day 1, or 1 and 3, or 1 and 8, or 3 x per year.
- Methotrexate forms part of CMF regimen, in which the methotrexate dose is usually 40 mg i.v. on days 1 and 8. The treatment is repeated at 3-week intervals.

Osteosarcoma:
Effective combination chemotherapy requires administration of several cytotoxic chemotherapeutics. In addition to high-dose methotrexate with calcium folinate rescue, doxorubicin, cisplatin, and a combination of bleomycin, cyclophosphamide and dactinomycin (BCD) can be given. The starting dose for high-dose methotrexate treatment is 12 g/m^2. If this dose is insufficient to reach peak serum concentrations of 10-3M at the end of the infusion, the dose can be increased to 15 g/m^2 for the subsequent treatments. If the patient vomits or cannot tolerate oral treatment, calcium folinate is given i.v. or i.m.

Patients with impaired renal function:
Methotrexate should be used with caution in patients with impaired renal function. The dose should be adjusted as follows:

% of dose that should be administered Creatinine clearance (ml/min)
>50 100%
20 – 50 50%
<20 methotrexate must not be used.

Patients with impaired hepatic function:
Methotrexate should be administered with great caution, if at all, to patients with significant current or previous liver disease, especially when caused by alcohol. Methotrexate is contraindicated if bilirubin values are >5 mg/dl (85.5 µmol/L).

Elderly
Dose reduction should be considered in elderly patients due to reduced liver and kidney function as well as lower folate reserves which occur with increased age.

4.3 Contraindications

- Hypersensitivity to methotrexate or to any of the excipients.
- Liver insufficiency (see section 4.2).
- Alcohol abuse.
- Renal insufficiency (creatinine clearance less than 20 ml/min., see section 4.2)
- Pre-existing blood dycrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anaemia.
- Serious, acute or chronic infections such as tuberculosis and HIV.
- Ulcers of the oral cavity and known active gastrointestinal ulcer disease.
- Pregnancy, breast-feeding (see section 4.6).
- Concurrent vaccination with live vaccines.

4.4 Special warnings and precautions for use

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. Therefore methotrexate should only be administered by, or under the supervision of, physicians whose knowledge and experience includes the use of antimetabolite therapy. Because of the possibility of severe or even fatal toxic reactions, the patient should be fully informed of the risks involved and the recommended safety measures. However, doses exceeding 20 mg/week can be associated with significant increase in toxicity, especially bone marrow suppression.

Methotrexate has been reported to cause impairment of fertility, oligospermia, menstrual dysfunction and amenorrhoea in humans, during and for a short period after cessation of therapy. 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 childbearing potential (see section 4.6).

Recommended examinations and safety measures:

Before initiating therapy or upon resuming therapy after a rest period:
Complete blood count with differential blood count and platelets, liver enzymes, bilirubin, serum albumin, chest X-ray and renal function tests. If clinically indicated, exclude tuberculosis and hepatitis.

During therapy (at least once monthly during the first six months and at least every three months thereafter):
Increased monitoring frequency should also be considered when increasing the dose.

- Examination of the oral cavity and throat for mucosal changes.

- Complete blood count with differential blood count and platelets. Haematopoietic suppression induced by methotrexate may occur abruptly and at apparently safe doses. In the event of any significant drop in leukocytes or platelets, treatment must be discontinued immediately and appropriate supportive therapy instituted. Patients must be instructed to report all signs and symptoms suggestive of infection. In patients concomitantly taking haematotoxic medications (e.g. leflunomide), the blood count and platelets should be closely monitored.

- *Liver function tests:* Particular attention should be paid to the onset of liver toxicity. Treatment should not be initiated or should be discontinued if there are any abnormalities in liver function tests or liver biopsies, or if these develop during therapy. Such abnormalities should return to normal within two weeks; after which, treatment may be resumed at the discretion of the doctor. Further research is needed to establish whether serial liver chemistry tests or propeptide of type III collagen can detect hepatotoxicity sufficiently. This assessment should differentiate between patients without any risk factors and patients with risk factors, e.g. excessive prior alcohol consumption, persistent elevation of liver enzymes, history of liver disease, family history of hereditary liver disorders, diabetes mellitus, obesity and previous contact with hepatotoxic drugs or chemicals and prolonged methotrexate treatment or cumulative doses of 1.5 g or more.

  Screening for liver-related enzymes in serum: A transient rise in transaminase levels to twice or three times the upper limit of normal has been reported, with a frequency of 13 - 20%. In the event of a constant increase in liver-related enzymes, consideration should be given to reducing the dose or discontinuing therapy.

  Due to the potentially toxic effect on the liver, additional hepatotoxic medications should not be given during treatment with methotrexate *unless clearly necessary* and alcohol consumption should be avoided or greatly reduced (see section 4.5). Closer monitoring of liver enzymes should be undertaken in patients concomitantly taking other hepatotoxic medications (e.g. leflunomide). The same should also be taken into consideration if haematotoxic medications are co-administered.

- *Renal function* should be monitored via renal function tests and urinalysis.
  As methotrexate is predominantly excreted via the renal route, increased concentrations can be expected in cases of renal impairment, which may result in severe adverse reactions.
  In cases of possible renal impairment (e.g. in elderly patients), closer monitoring is required. This particularly applies to the co-administration of medicinal products which affect methotrexate excretion, cause kidney damage

(e.g. non-steroidal anti-inflammatory drugs) or which can potentially lead to haematopoietic disorders. Dehydration may also potentiate the toxicity of methotrexate.
Alkalising the urine and increase a high diuresis is recommended.

- *Respiratory system:* Acute or chronic interstitial pneumonitis, often associated with blood eosinophilia, may occur and deaths have been reported. Symptoms typically include dyspnoea, cough (especially a dry non-productive cough) and fever for which patients should be monitored at each follow-up visit. Patients should be informed of the risk of pneumonitis and advised to contact their doctor immediately should they develop persistent cough or dyspnoea.
  Methotrexate should be withdrawn from patients with pulmonary symptoms and a thorough investigation (including chest x-ray) should be made to exclude infection. If methotrexate induced lung disease is suspected treatment with corticosteroids should be initiated and treatment with methotrexate should not be restarted.
  Pulmonary symptoms require a quick diagnosis and discontinuation of methotrexate therapy. Pneumonitis can occur at all doses.

- Methotrexate may, due to its effect on the immune system, impair the response to vaccinations and interfere with the result of immunological tests. Particular caution should be exercised in the presence of inactive, chronic infections (e.g. herpes zoster, tuberculosis, hepatitis B or C), due to possible activation. Concurrent vaccination using live vaccines must not be carried out.

- Malignant lymphomas may occur in patients receiving low-dose methotrexate; in which case, methotrexate must be discontinued. If lymphomas should fail to regress spontaneously, initiation of cytotoxic therapy is required.

- Pleural effusions and ascites should be drained prior to initiation of methotrexate treatment.

- Diarrhoea and ulcerative stomatitis can be toxic effects and require interruption of therapy, otherwise haemorrhagic enteritis and death from intestinal perforation may occur.

- Vitamin preparations or other products containing folic acid, folinic acid or their derivatives may decrease the effectiveness of methotrexate.

- Use in children < 3 years of age is not recommended as insufficient data on efficacy and safety are available for this population. (see section 4.2).

- *Skin toxicity:* Due to the risk of phototoxicity, the patient must avoid sunlight and solarium

- *High dose treatment:* During high dose treatment, folinic acid should be given concomitantly. The serum concentration of methotrexate is a valuable indicator for how long the folinic acid treatment should be continued. Forty-eight hours after the start of the methotrexate-infusion, the residual methotrexate-level should be measured. If the residual methotrexate-level is < 0.5 µmol/l, no additional treatment with folinic acid is necessary.

This medicine contains less than 1 mmol (23 mg sodium) per ml, i.e. it is essentially sodium free.

4.5 Interaction with other medicinal products and other forms of interaction

Methotrexate is normally used in combination with other cytostatics. Additive toxicity can be expected during combination chemotherapy with medicines with the same pharmacological effect, especially regarding bone marrow inhibition, renal, gastrointestinal and pulmonary toxicity (see section 4.4).

In animal experiments non-steroidal anti-inflammatory drugs (NSAIDs) including salicylic acid caused reduction of tubular methotrexate secretion and consequently increased its toxic effects. However, in clinical studies, where NSAIDs and salicylic acid were given as concomitant medication to patients with rheumatoid arthritis, no increase of adverse reactions was observed. Treatment of rheumatoid arthritis with such drugs can be continued during methotrexate therapy but only under close medical supervision.

Regular alcohol consumption and administration of additional hepatotoxic medicinal products increase the probability of hepatotoxic effects of methotrexate.

Patients taking potentially hepatotoxic medicinal products during methotrexate therapy (e.g. leflunomide, azathioprine, sulphasalazine, and retinoids) should be closely monitored for possibly increased hepatotoxicity. Alcohol consumption should be avoided during treatment with methotrexate.
Be aware of pharmacokinetic interactions between methotrexate, anticonvulsant drugs (reduced methotrexate blood levels), and 5- fluorouracil (increased t½ of 5-fluorouracil).

Salicylates, phenylbutazone, phenytoin, barbiturates, tranquillisers, oral contraceptives, tetracyclines, amidopyrine derivatives, sulfonamides and p-aminobenzoic acid displace methotrexate from serum albumin binding and thus increase bioavailability (indirect dose increase).

Probenecid and mild organic acids may also reduce tubular methotrexate secretion, and thus cause indirect dose elevations, too.

Antibiotics, like penicillines, glycopeptides, sulfonamides, ciprofloxacin and cefalotin can, in individual cases, reduce the renal clearance of methotrexate, so that increased serum concentrations of methotrexate with simultaneous haematological and gastro-intestinal toxicity may occur.
Oral antibiotics like tetracyclines, chloramphenicol and non-absorbable broad-spectrum antibiotics may reduce intestinal methotrexate absorption or interfere with enterohepatic circulation by inhibition of the intestinal flora or suppression of the bacterial metabolism.

Under (pre-)treatment with substances that may have adverse reactions affecting the bone marrow (e.g. sulfonamides, trimethoprim/sulfamethoxazole, chloramphenicol, pyrimethamine), the risk of pronounced haematopoietic disorders during methotrexate therapy must be considered.

Concomitant administration of drugs that cause folate deficiency (e.g. sulfonamides, trimethoprim/sulfamethoxazole) may lead to increased methotrexate toxicity. Therefore, particular caution must be exercised in patients with existing folic acid deficiency. On the other hand, concomitant administration of folinic acid containing drugs or of vitamin preparations, which contain folic acid or derivatives, may impair methotrexate efficacy.

Under concomitant administration of methotrexate and basic treatments (e.g. gold compounds, penicillamine, hydroxychloroquine, sulphasalazine, azathioprine, cyclosporine), increased toxic effects of methotrexate are generally not to be expected.

Proton-pump inhibitors
Concomitant administration of proton-pump inhibitors like omeprazole or pantoprazole can lead to interactions:
Concomitant administration of methotrexate and omeprazole has led to delayed renal elimination of methotrexate. In combination with pantoprazole inhibited renal elimination of the metabolite 7-hydroxymethotrexate with myalgia and shivering was reported in one case.

Though the combination of methotrexate and sulfasalazine may enhance methotrexate efficacy by sulfasalazine related inhibition of folic acid synthesis, and thus may lead to an increased risk of side effects, these were only observed in single patients within several trials.

Methotrexate may reduce theophylline clearance. Therefore, theophylline blood levels should be monitored under concomitant methotrexate administration.

Excessive consumption of caffeine- or theophylline-containing beverages (coffee, caffeine-containing beverages, black tea) should be avoided during methotrexate therapy, since the efficacy of methotrexate may be reduced due to possible interaction between methotrexate and methylxanthines at adenosine receptors.

The combined use of methotrexate and leflunomide may increase the risk for pancytopenia. Methotrexate leads to increased plasma levels of mercaptopurines. Therefore, the combination of these may require dosage adjustment.

Particularly in the case of orthopaedic surgery where susceptibility to infection is high, a combination of methotrexate with immune-modulating agents must be used with caution.

Delayed methotrexate clearance should be considered in combination with other cytostatic agents

On account of its possible effect on the immune system, methotrexate can falsify vaccinal and test results (immunological procedures to record the immune reaction). During methotrexate therapy concurrent vaccination with live vaccines must not be carried out (see section 4.3).

4.6 Fertility, pregnancy and lactation

Pregnancy:
Methotrexate is contraindicated during pregnancy (see section 4.3). In animal studies, methotrexate has shown reproductive toxicity, especially during the first trimester (see section 5.3). Methotrexate has been shown to be teratogenic to humans; it has been reported to cause fetal death and/or congenital abnormalities. Exposure of a limited number of pregnant women (42) resulted in an increased incidence (1:14) of malformations (cranial, cardiovascular and extremital). If methotrexate is discontinued prior to conception, normal pregnancies have been reported.
In women of child-bearing age, any existing pregnancy must be excluded with certainty by taking appropriate measures, e.g. a pregnancy test, prior to initiating therapy. Women must not get pregnant during methotrexate therapy and patients of a sexually mature age (women and men) must use effective contraception during treatment with methotrexate and at least 6 months thereafter (see section 4.4). If, nevertheless, pregnancy occurs during this period, medical advice should be given regarding the risk of harmful effects on the child associated with treatment.
As methotrexate can be genotoxic, all women who wish to become pregnant are advised to consult a genetic councelling centre, if possible, already prior to therapy, and men should seek advice about the possibility of sperm preservation before starting therapy.

Lactation:
As methotrexate passes into breast milk and may cause toxicity in nursing infants, treatment is contraindicated during the lactation period (see section 4.3). If use during the lactation period should become necessary, breast-feeding is to be stopped prior to treatment.

4.7 Effects on ability to drive and use machines

CNS symptoms, such as fatigue and confusion, can occur during treatment. Methotrexate has minor or moderate influence on the ability to drive and use machines

4.8 Undesirable effects

Occurrence and severity of undesirable effects depend on dosage level and frequency of methotrexate administration. However, as severe adverse reactions may occur even at lower doses, it is indispensable that the doctor monitors patients regularly at short intervals.

Most undesirable effects are reversible if recognised early. If such adverse reactions occur, dosage should be reduced or therapy be interrupted and appropriate countermeasures should be taken (see section 4.9). Methotrexate therapy should only be resumed with caution, under close assessment of the necessity for treatment and with increased alertness for possible reoccurrence of toxicity.

Frequencies in this table are defined using the following convention: very common (≥ 1/10) common (≥ 1/100 < 1/10), uncommon (≥ 1/1,000 < 1/100), rare (≥ 1/10,000 < 1/1,000), very rare (< 1/10,000) , not known (cannot be estimated from the available data).
Further details are given following this table.
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness

The following adverse reactions may occur:

After intramuscular methotrexate administration, local adverse reactions (burning sensation) or damage (formation of sterile abscess, destruction of fatty tissue) may occasionally occur at the injection site.

	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**
Infections and infestations*					Sepsis, opportunistic infections (may be fatal in some cases), infections caused by the cytomegaly virus
Cardiac disorders				Pericarditis, pericardial effusion, pericardial tamponade	
Blood and lymphatic system disorders *		Leukocytopenia, thrombocytopenia, anaemia	Pancytopenia, agranulocytosis, haematopoietic disorders.	Megaloblastic anaemia	Severe courses of bone marrow depression, aplastic anaemia. Lymphadenopathy, lymphoproliferative disorders (partly reversible), eosinophilia and neutropenia
Immune system disorders*					Immunosuppression hypogammaglobulinaemia
Psychiatric disorders					insomnia
Nervous system disorders *		Headache, fatigue, drowsiness	Vertigo, confusion, depression, seizures	Severely impaired vision, mood alterations	Pain, muscular asthenia or paresthesia of the extremities, changes in sense of taste (metallic taste), meningism (paralysis, vomiting), acute aseptic meningitis
Eye disorders				Visual disturbances	Conjunctivitis, retinopathy
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			individual cases of lymphoma, which abated in a number of cases once methotrexate treatment had been discontinued. In a recent study, it was not possible to establish that methotrexate therapy increases the		

			incidence of lymphomas		
Vascular disorders				hypotension, thromboembolic events (including arterial and cerebral thrombosis, thrombophlebitis, deep vein thrombosis, retinal vein thrombosis, pulmonary embolism).	

Respiratory, thoracic and mediastinal disorders		Pulmonary complications due to interstitial alveolitis/pneumonitis and related deaths (independent of dose and duration of methotrexate treatment). Typical symptoms may be: general illness; dry, irritating cough; shortness of breath progressing to rest dyspnoea, chest pain, fever. If such complications are suspected, methotrexate treatment must be discontinued immediately and infections (including pneumonia) must be excluded.	Pulmonary fibrosis	Pharyngitis, apnoea, bronchial asthma	Pneumocystis carinii pneumonia, shortness of breath, chronic obstructive pulmonary disease. Infections including pneumonia have also been observed. Pleural effusion
Gastrointestinal disorders*	Loss of appetite, nausea, vomiting, abdominal pain, inflammation and ulcerations of the mucous membrane of mouth and throat (especially	Diarrhoea (especially during the first 24-48 hours after administration of methotrexate).	Gastrointestinal ulcers and bleeding.	Enteritis, melaena Gingivitis, malabsorption	Haematemesis, toxic megacolon

	during the first 24-48 hours after administration of methotrexate). Stomatitis, dyspepsia				
Hepato-biliary disorders	Increase in liver-related enzymes (ALAT, ASAT, alkaline phosphatase and bilirubin).		Development of liver fattening, fibrosis and cirrhosis (occurs frequently despite regularly monitored, normal values of liver enzymes); diabetic metabolism; drop of serum albumin.	Acute hepatitis and hepatotoxicity	Reactivation of chronic hepatitis, acute liver degeneration. Furthermore, herpes simplex hepatitis and liver insufficiency have been observed (also see the notes regarding liver biopsy in section 4.4).

Skin and subcutaneous tissue disorders		Exanthema, erythema, itching	Urticaria, photosensibility, enhanced pigmentation of the skin, hair loss, increase of rheumatic nodules, herpes zoster, painful lesions of psoriatic plaque; severe toxic reactions: vasculitis, herpetiform eruption of the skin, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome).	increased pigmentary changes of nails, acne, petechiae, ecchymoses, erythema multiforme, cutaneous erythematous eruptions.	acute paronychia, furunculosis, telangiectasia Furthermore, nocardiosis, histoplasma and cryptococcus mycosis and disseminated herpes simplex have been reported. Allergic vasculitis, hidradenitis
Musculoskeletal system, connective tissue and bone disorders			Arthralgia, myalgia, osteoporosis	Stress fracture	
Renal and urinary disorders			Inflammation and ulceration of the urinary bladder (possibly with haematuria), dysuria.	Renal failure, oliguria, anuria, azotaemia	Proteinuria

General disorders and administration site conditions			Severe allergic reactions progressing to anaphylactic shock;		Fever, impaired wound healing
Reproductive system and breast disorders			Inflammation and ulceration of the vagina		Loss of libido, impotence, oligospermia, impaired menstruation, vaginal discharge, infertility

4.9 Overdose

Symptoms:
Toxicity of methotrexate mainly affects the haematopoietic and gastrointestinal systems. Symptoms include leukocytopenia, thrombocytopenia, anaemia, pancytopenia, neutropenia, bone marrow depression, mucositis, stomatitis, oral ulceration, nausea, vomiting, gastrointestinal ulceration and gastrointestinal bleeding. Some patients showed no signs of overdose.

There are reports of death due to sepsis, septic shock, renal failure and aplastic anaemia.

Treatment:
Calcium folinate is the specific antidote for neutralising the toxic undesirable effects of methotrexate.

In cases of accidental overdose, a dose of calcium folinate equal to or higher than the offending dose of methotrexate should be administered intravenously or intramuscularly within one hour and dosing continued until the serum levels of methotrexate are below 10-7 mol/l.

In cases of massive overdose, hydration and urinary alkalisation may be necessary to prevent precipitation of methotrexate and/or its metabolites in the renal tubules. Neither haemodialysis nor peritoneal dialysis has been shown to improve methotrexate elimination. Effective clearance of methotrexate has been reported with acute, intermittent haemodialysis using a high flux dialyser.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
Antimetabolites, Folic acid analoges, ATC-code: L01BA01

Methotrexate is a folic acid antagonist which belongs to the class of cytotoxic agents known as antimetabolites. It acts by the competitive inhibition of the enzyme dihydrofolate reductase and thus inhibits DNA synthesis. It has not yet been clarified, as to whether the efficacy of methotrexate, in the management of psoriasis, psoriasis arthritis and chronic polyarthritis, is due to an anti-inflammatory or immunosuppressive effect and to which extent a methotrexate-induced increase in extracellular adenosine concentration at inflamed sites contributes to these effects.

5.2 Pharmacokinetic properties

After oral application, methotrexate is absorbed from the gastrointestinal tract. When administered in low doses (7.5mg/m^2 to 80mg/m^2 body surface area), methotrexate has a mean bioavailability of approximately 70%, although considerable inter- and intra-subject variations are possible (25-100%). Plasma peak concentrations are attained within 1-2 hours. Subcutaneous, intravenous and intramuscular administration demonstrated similar bioavailability. Approximately 50% of methotrexate is bound to serum proteins. Upon being distributed into body tissues, high concentrations particularly in liver, kidneys and spleen in form of polyglutamates can be found, which can be retained for weeks or months. When administered in small doses, methotrexate passes into the liquor in minimal amounts; under high doses (300mg/kg body weight), concentrations between 4 and 7 µg/ml have been measured in the liquor. Average terminal half-life is 6-7 hours and demonstrates considerable variation (3-17 hours). Half-life may be prolonged to 4 times the normal length in patients with third spaces (pleural effusion, ascites). Approximately 10% of the administered methotrexate is metabolised intrahepatically. The major metabolite is 7-hydroxymethotrexate.
Excretion takes place, mainly in unchanged form, primarily renal via glomerular filtration and active secretion in the proximal tubulus. Approx. 5-20% of methotrexate and 1-5% of 7-hydroxymethotrexate are eliminated via the bile. Pronounced enterohepatic blood flow exists.
In case of renal insufficiency, elimination is delayed significantly. Impaired elimination in presence of hepatic insufficiency is not known.
Methotrexate passes the placental barrier in rats and monkeys.

5.3 Preclinical safety data

Chronic toxicity
Chronic toxicity studies in mice, rats and dogs showed toxic effects in the form of gastrointestinal lesions, myelosuppression and hepatotoxicity.
Mutagenic and carcinogenic potential
Long-term studies in rats, mice and hamsters did not show any evidence of a tumorigenic potential of methotrexate. Methotrexate induces gene and chromosome mutations both in vitro and in vivo. A mutagenic effect is suspected in humans.
Reproductive toxicology
Teratogenic effects have been identified in four species (rats, mice, rabbits, cats). In rhesus monkeys, no malformations comparable to humans occurred.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide
Water for injection.

6.2 Incompatibilities

Strong oxidants and acids. Precipitation or formation of a cloudy solution has been seen during combinations with chlorpromazine hydrochloride, droperidol, idarubicin, methoclopramide hydrochloride, heparin solution, prednisolone sodium phosphate and promethazine hydrochloride.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years.
After opening 24 hours.
Chemical and physical stability have been demonstrated for 24 hours. From a microbiological point of view the product must be used immediately. If the product is not used immediately, the use of other storage conditions is the responsibility of the user.

6.4 Special precautions for storage

Store in the original package in order to protect from light.

Do not store above 25°C.

For storage conditions of the diluted medicinal product, see section 6.3

6.5 Nature and contents of container

1 or 5 Vials:
5 ml vials: clear glass (Ph.Eur. Type I)
10 ml vials: clear glass (Ph.Eur. Type I)
50 ml vials: clear glass (Ph.Eur. Type I)

Fluoropolymer coated chlorobutyl stopper

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Parenteral methotrexate preparations do not contain antimicrobial preservatives. Unused solutions must therefore be discarded.

Parenteral methotrexate preparations can be prepared with the following intravenous solutions for infusion: 0.9% sodium chloride, 5% glucose, 10% glucose and ringer-lactat.
Other pharmaceuticals should not be mixed with Methotrexate in the same infusion container.

Handling of cytostatics:
Cytostatics handling should only be carried out by specially trained staff and should only take place in locations fitted for this purpose. Work surfaces should be covered by plastified absorbant paper, which can be discarded after use.

Protective gloves and glasses should be used in order to avoid potential contact with skin or eyes.

Methotrexate is not blister forming and should therefore not cause damage to skin. If the compound should get in contact with the skin, the skin should still be rinsed immediately with water, however. Transient stinging can be treated with a mild cream. If there is a danger that larger quantities of methotrexate have been absorbed (regardless of absorption method), treatment with leucovorin should be carried out.
Cytostatics should not be handled by pregnant staff.

Waste material should be destroyed according to hospital standard procedures applicable to cytotoxic agents with due regard to current laws related to the disposal of hazardous waste.

7 MARKETING AUTHORISATION HOLDER

Ebewe Pharma Ges m.b.H. Nfg. KG
Mondseestrasse 11
A-4866 Unterach
Austria

8 MARKETING AUTHORISATION NUMBER

PA 789/20/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 6th May 2011

10 DATE OF REVISION OF THE TEXT

September 2011