1. NAME OF THE MEDICINAL PRODUCT

Ebetrexat 10 mg/ml

solution for injection in a pre–filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution contains 10 mg methotrexate (as methotrexate disodium).

The medicinal product contains 3.8 mg/ml sodium (0.16mmol/ml sodium).

1 pre–filled syringe of 0.75 ml contains 7.5 mg methotrexate.
1 pre–filled syringe of 1 ml contains 10 mg methotrexate.
1 pre–filled syringe of 1.5 ml contains 15 mg methotrexate.
1 pre–filled syringe of 2 ml contains 20 mg methotrexate.

For a full list of excipients, see section 6.1, "List of Excipients".

3. PHARMACEUTICAL FORM

Solution for injection, pre–filled syringe.
Clear, yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ebetrexat is indicated for the treatment of:

- Active rheumatoid arthritis in adult patients where treatment with disease modifying antirheumatic drugs (DMARDs) is indicated.
- Polyarthritic forms of severe, active juvenile idiopathic arthritis (JIA) when the response to nonsteroidal anti–inflammatory drugs (NSAIDs) has been inadequate.
- Severe forms of psoriasis vulgaris, particularly of the plaque type, which cannot be sufficiently treated with conventional therapy such as phototherapy, PUVA, and retinoids, and severe psoriatic arthritis.

4.2 Posology and method of administration

Ebetrexat should only be prescribed by physicians with experience in the various properties of the medicinal product and its mode of action. Ebetrexat is injected once weekly.
It is recommended to specify a certain day of the week as "day for injection".
Dose reduction should be considered in elderly patients due to reduced liver and kidney function as well as lower folate reserves which occurs with increased age.

The administration should routinely be done by health professionals. If the clinical situation permits the treating physician can, in selected cases, delegate the administration to the patient her/himself. In these cases, detailed administration instructions from the physician are obligate.

The solution is to be visually inspected prior to use.
Only clear solutions practically free from particles should be used.

Any contact of methotrexate with skin and mucosa is to be avoided! In case of contamination, the affected parts are to be rinsed immediately with plenty of water! See section 6.6.

Dosage in patients with rheumatoid arthritis:
The recommended initial dose is 7.5 mg of methotrexate once weekly, administered subcutaneously, intramuscularly or intravenously. Depending on the individual activity of disease and patient tolerability, the initial dose may be increased gradually in increments of 2.5 mg per week. A weekly dose of 25 mg should not be exceeded. However, doses exceeding 20 mg/week can be associated with significant increase in toxicity, especially bone marrow suppression. Response to treatment can be expected after approximately 4 – 8 weeks. Once the desired therapeutic result has been achieved, dosage should be reduced gradually to the lowest possible effective maintenance dose.

Dosage in children and adolescents with polyarthritic forms of juvenile idiopathic arthritis
The recommended dose is 10–15 mg/m² body surface area (BSA)/week. In therapy–refractory cases the weekly dosage may be increased up to 20 mg/m² body surface area/week. However, an increased monitoring frequency is indicated if the dose is increased.
Due to limited data availability about intravenous use in children and adolescents, parenteral administration is limited to subcutaneous and intramuscular injection.
Patients with JIA should always be referred to a rheumatology unit specializing in the treatment of children/adolescents.

Use in children < 3 years of age is not recommended as insufficient data on efficacy and safety are available for this population. (see section 4.4)

Dosage in patients with severe forms of psoriasis and psoriatic arthritis:
It is recommended that a test dose of 5 – 10 mg be parenterally administered one week prior to initiation of therapy, in order to detect idiosyncratic adverse effects. The recommended initial dose is 7.5 mg methotrexate once weekly, administered subcutaneously, intramuscularly or intravenously. The dose should be increased as necessary but should not exceed a maximum weekly dose of 30 mg of methotrexate. Response to treatment can generally be expected after approximately 2 – 6 weeks. Once the desired therapeutic result has been achieved, dosage should be reduced gradually to the lowest possible effective maintenance dose.

Patients with impaired renal function:
Ebetrexat should be used with caution in patients with impaired renal function. Dosage should be adjusted as follows:

Creatinine clearance (ml/min)	
>50	100%
20 – 50	50%
<20	Ebetrexat 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).

Duration and method of administration:
The medicinal product is for single use only.
Ebetrexat solution for injection can be injected via the intramuscular, intravenous or subcutaneous route.

In adults, intravenous administration should be given as a bolus injection.
Please also refer to section 6.6.

The overall duration of treatment is decided by the doctor.

Ebetrexat treatment of rheumatoid arthritis, juvenile idiopathic arthritis, severe psoriasis vulgaris and psoriatic arthritis represents long–term treatment.

Rheumatoid arthritis
Treatment response in patients with rheumatoid arthritis can be expected after 4–8 weeks. Symptoms may return after treatment discontinuation.

Severe forms of psoriasis vulgaris and psoriatic arthritis
Response to treatment can generally be expected after 2–6 weeks. Depending on the clinical picture and the changes of laboratory parameters, the therapy is then continued or discontinued.

Note:
When switching from oral use to parenteral use, a reduction in the dose may be required, due to the variable bioavailability of methotrexate after oral administration.

Folic acid or folinic acid supplementation may be considered in accordance with current therapeutic guidelines.

4.3 Contraindications

Ebetrexat is contraindicated in:

- hypersensitivity to methotrexate or to any of the excipients,
- liver insufficiency (see also section 4.2),
- alcohol abuse,
- renal insufficiency (creatinine clearance < 20 ml/min, see also section 4.2),
- pre–existing blood dyscrasias, 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 also section 4.6),
- concurrent vaccination with live vaccines.

4.4 Special warnings and precautions for use

Patients must be clearly advised that the therapy is to be administered once a week, and not every day.
Patients receiving therapy should be appropriately monitored, so that signs of possible toxic effects or adverse reactions can be recognised and assessed without delay. Hence, methotrexate should be only administered by – or under the supervision of – doctors whose knowledge and experience include the use of antimetabolite therapy. Due to the risk of severe or even fatal toxic reactions, the patient should be thoroughly informed by the doctor about the risks and 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:

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.

1. Examination of the oral cavity and throat for mucosal changes.
2. 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.
3. 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. In rheumatological indications, there is no evidence to support use of liver biopsies in monitoring hepatotoxicity. For psoriasis patients the need of a liver biopsy prior to and during therapy is controversial. 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 Interaction with other medicinal products and other forms of interaction). 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.
4. 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.
5. 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 dosages.
6. 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.
7. 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.
8. 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).

Radiation induced dermatitis and sun-burn can reappear under methotrexate therapy (recall-reaction). Psoriatic lesions can exacerbate during UV-irradiation and simultaneous administration of methotrexate.

This medicinal product contains less than 1 mmol sodium per dose and is i.e. essentially „sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

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 Ebetrexat.

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

Oral antibiotics such as tetracyclines, chloramphenicol and non-absorbable broad-spectrum antibiotics may reduce intestinal methotrexate absorption or interfere with the enterohepatic circulation, due to inhibition of the intestinal flora or suppression of bacterial metabolism.

Under (pre-)treatment with substances that may have adverse effects on the bone marrow (e.g. sulphonamides, trimethoprim-sulphamethoxazole, chloramphenicol, pyrimethamine), the possibility of marked haematopoietic disorders should be considered.

Co-administration of medications which cause folate deficiency (e.g. sulphonamides, trimethoprim-sulphamethoxazole) can lead to increased methotrexate toxicity. Particular caution should therefore also be exercised in the presence of 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.

A rise in the toxicity of methotrexate is generally not anticipated when Ebetrexat is used concomitantly with other antirheumatic agents (e.g. gold compounds, penicillamine, hydroxychloroquine, sulfasalazine, azathioprine, cyclosporin).

Co-administration of proton-pump inhibitors such as omeprazole or pantoprazole can lead to interactions: Concomitant administration of methotrexate and omeprazole has led to a delay in the renal elimination of methotrexate. In combination with pantoprazole, inhibited renal elimination of the 7-hydroxymethotrexate metabolite, 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 beverages containing caffeine or theophylline (coffee, soft drinks containing caffeine, 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 and 4.4).

4.6 Pregnancy and lactation

Ebetrexat is contraindicated during pregnancy (see section 4.3 Contraindications). In animal studies, methotrexate has shown reproductive toxicity, especially during the first trimester (see 5.3). Methotrexate has been shown to have a teratogenic effect in humans; it has been reported to cause foetal 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 extremity-related). When methotrexate was 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 Ebetrexat 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 counselling 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. Ebetrexat 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 Ebetrexat 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 in the following 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.

Subcutaneous methotrexate application indicates a good local tolerability. Up to now, only mild skin reactions have been observed, and their number decreases during treatment.

	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
Metabolism and nutrition disorders					
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
Ear and labyrinth disorders					
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/ pneumonitisand 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, Ebetrexat 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 during the first 24–48 hours after administration of Ebetrexat). Stomatitis, dyspepsia	Diarrhoea (especially during the first 24–48 hours after administration of Ebetrexat).	Gastrointestinal ulcers and bleeding.	Enteritis, melaena Gingivitis, malabsorption	Haematemesis, toxic megacolon
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
Investigations					
Reproductive system and breast disorders			Inflammation and ulceration of the vagina		Loss of libido, impotence, oligospermia, impaired menstruation, vaginal discharge, infertility

4.9 Overdose

a) Symptoms of overdose

The adverse toxic effects of methotrexate mainly affect the haematopoietic and gastrointestinal system.

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.

b) Treatment of overdose

Calcium folinate is the specific antidote for neutralising the adverse toxic effects of methotrexate.

In the event of accidental overdosage, a dose of calcium folinate equal to or higher than the offending dose of methotrexate should be administered intravenously or intramuscularly within 1 hour, and dosing continued until serum levels of methotrexate are below 10^{-7} mol/L.

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

In patients with rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriasis arthritis or psoriasis vulgaris, administration of folic or folinic acid may reduce methotrexate toxicity (gastrointestinal symptoms, inflammation of oral mucosa, hair loss and increase of liver enzymes), see section 4.5. Prior to using folic acid products, monitoring of vitamin B12 levels is recommended, since folic acid may mask an existing vitamin B12 deficiency, particularly in adults over 50 years of age.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other immunosuppressants; Folic acid analogues

ATC code: **L04AX03;** L01BA01

Methotrexate is a folic acid antagonist which, as an antimetabolite, belongs to the class of cytotoxic substances. It acts by competitively inhibiting the dihydrofolate reductase enzyme, thereby inhibiting DNA synthesis. As yet, it has not been clarified whether the efficacy of methotrexate – in the treatment of psoriasis, psoriasis arthritis and chronic polyarthritis – is due to an anti-inflammatory or immunosuppressive effect, or to which extent a methotrexate-induced increase in extracellular adenosine concentrations contribute to these effects.

5.2 Pharmacokinetic properties

After oral application, methotrexate is absorbed from the gastrointestinal tract. When administered in low doses (7.5 mg/m2 to 80 mg/m2 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 distribution, it accumulates mainly in the liver, kidneys and spleen in the form of polyglutamates, which may be retained for weeks or months. When administered in small doses, methotrexate passes into the liquor in minimal amounts; under high doses (300 mg/kg body weight), concentrations between 4 and 7 µg/ml have been measured in the liquor. The mean terminal half-life is 6 – 7 hours and shows considerable variation (3 – 17 hours). In patients with a third distribution space (pleural effusion, ascites), the half-life can be up to 4 times longer.

Approximately 10% of the administered methotrexate dose is hepatically metabolised. The main metabolite is 7-hydroxymethotrexate.

Excretion mainly occurs in unchanged form via the kidneys, by glomerular filtration and active secretion in the proximal tubule.

Approximately 5 – 20% of methotrexate and 1 – 5% of 7-hydroxymethotrexate is excreted via the biliary route. There is marked enterohepatic circulation.

Elimination is significantly prolonged in cases of impaired renal function. It is not yet known whether excretion is impaired in patients with reduced hepatic function.

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 chloride

Sodium hydroxide for pH adjustment

Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years

The product has to be used immediately after opening. See section 6.6.

6.4 Special precautions for storage

Do not store above 25°C.

Do not freeze.

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

6.5 Nature and contents of container

Ebetrexat is available in pre-filled syringes of colourless glass (type I according to Ph. Eur.) with a capacity of 1.25 ml, 2.25 ml or 3.00 ml, an elastomeric tip cap and an elastomeric plunger stopper.

Each box contains 1, 4 or 5 pre-filled syringes with 0.75 ml, 1.0 ml, 1.5 ml and 2.0 ml solution for injection, single-use injection needles and alcohol pads.

6.6 Special precautions for disposal and other handling

The manner of handling and disposal must be consistent with the handling and disposal of other cytotoxic preparations, in accordance with national requirements. Pregnant healthcare personnel should not handle Ebetrexat and/or administer it.

For single use only. Any unused solution should be discarded.

Any unused product or waste material should be disposed of in accordance with local requirements for cytotoxic agents.

7. MANUFACTURER

EBEWE Pharma Ges.m.b.H. Nfg.KG

A-4866 Unterach, Austria

8. DATE OF REVISION OF THE TEXT

February 2009

Ebewe PHARMA