SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ebetrex 20 mg/ml solution for injection, pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml solution for injection contains 20 mg methotrexate (as 21.94mg methotrexate disodium).
Each pre-filled syringe of 0.375 ml solution for injection contains 7.5 mg methotrexate.
Each pre-filled syringe of 0.5 ml solution for injection contains 10 mg methotrexate.
Each pre-filled syringe of 0.625 ml solution for injection contains 12.5 mg methotrexate.
Each pre-filled syringe of 0.75 ml solution for injection contains 15 mg methotrexate.
Each pre-filled syringe of 0.875 ml solution for injection contains 17.5 mg methotrexate.
Each pre-filled syringe of 1 ml solution for injection contains 20 mg methotrexate.
Each pre-filled syringe of 1.125 ml solution for injection contains 22.5 mg methotrexate.
Each pre-filled syringe of 1.25 ml solution for injection contains 25 mg methotrexate.
Each pre-filled syringe of 1.375 ml solution for injection contains 27.5 mg methotrexate.
Each pre-filled syringe of 1.5 ml solution for injection contains 30 mg methotrexate.

Excipients with known effect:
Each ml solution for injection contains 0.18 mmol/ml sodium (4.13 mg/ml sodium).

3 PHARMACEUTICAL FORM

Solution for injection
Clear, yellowish solution for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Active rheumatoid arthritis in adult patients
- Polyarthritic forms of severe, active juvenile idiopathic arthritis (JIA) when the response to nonsteroidal anti-inflammatory drugs (NSAIDs) has been inadequate.
- Severe recalcitrant disabling psoriasis, which is not adequately responsive to other forms of therapy such as phototherapy, PUVA, and retinoids, and severe psoriatic arthritis in adult patients.

4.2 Posology and method of administration

Important warning about the dosage of Ebetrex:
In the treatment of rheumatoid arthritis, juvenile idiopathic arthritis (JIA) and psoriasis, methotrexate **must only be used once a week.**
Dosage errors in the use of Ebetrex can result in serious adverse reactions, including death. Please read this section of the summary of product characteristics very carefully.

Ebetrex should only be prescribed by physicians with expertise in the use of methotrexate and a full understanding of the risks of methotrexate therapy.
Ebetrex is injected once weekly.
It must be explicitly pointed out to the patient that Ebetrex is applied **only once a week.**
It is recommended to specify a certain day of the week as “day for injection”.

Patients must be educated and trained in the proper injection technique when self-administering methotrexate. The first injection of Methotrexate should be performed under direct medical supervision.

Dose 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. A weekly dose of 25 mg should in general 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, dose should be reduced gradually to the lowest possible effective maintenance dose.

Dose in children and adolescents below 16 years 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 dose may be increased up to 20mg/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.

Dose in patients with severe forms of psoriasis vulgaris 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 is to be increased gradually but should not, in general, exceed a weekly dose of 25 mg of methotrexate. Doses exceeding 20 mg per week can be associated with significant increase in toxicity, especially bone marrow suppression. Response to treatment can generally be expected after approximately 2 – 6 weeks. Once the desired therapeutic result has been achieved, dose should be reduced gradually to the lowest possible effective maintenance dose.
The dose should be increased as necessary but should in general not exceed the maximum recommended weekly dose of 25 mg. In a few exceptional cases a higher dose might be clinically justified, but should not exceed a maximum weekly dose of 30 mg of methotrexate as toxicity will markedly increase.

Renal impairment and Hepatic impairment:
Ebetrex should be used with caution in patients with impaired renal function. Dose should be adjusted as follows:

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

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) see Section 4.3.

Elderly
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.

Use in patient with a third distribution space (pleural effusions, ascitis):
As the half-life of Methotrexate can be prolonged to 4 times the normal length in patients who possess a third distribution space dose reduction or, in some cases, discontinuation of methotrexate administration may be required (see section 5.2 and 4.4).

Duration and method of administration:
The medicinal product is for single use only.

Ebetrex solution for injection can be injected via the intramuscular, intravenous or subcutaneous route (in children and adolescents only subcutaneous or intramuscular). 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.

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.

Ebetrex 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

Ebetrex is contraindicated in:

- hypersensitivity to methotrexate or to any of the excipients listed in section 6.1,
- severe hepatic impairment, if serum if bilirubin is > 5 mg/dl (85.5 µmol/l) (see also section 4.2),
- alcohol abuse,
- severe renal impairment (creatinine clearance less than< 20 ml/min.), or serum creatinine values above 2 mg/dl (see also sections 4.2 and 4.4),
- pre-existing blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia or significant anaemia,
- Immunodeficiency,
- serious, acute or chronic infections such as tuberculosis and HIV,
- stomatitis, ulcers of the oral cavity and known active gastrointestinal ulcer disease,
- pregnancy and breast-feeding (see 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.
Incorrect intake of methotrexate can lead to severe, including potentially lethal, side effects. Health personal and patients should be clearly instructed.

Particularly in elderly patients fatal outcomes have been reported with **accidentally daily administration** of the weekly dose.

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).

Renal function
In the presence of risk factors, such as – even borderline – impaired renal function, concomitant administration of non-steroidal antiphlogistics is not recommended (increased toxicity possible).

In patients with impaired renal function methotrexate therapy should only be performed with increased caution and lower doses due to delayed methotrexate elimination (see section 4.2).

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 such as impaired renal function up to renal failure. In connection with the administration of non-steroidal anti-inflammatory drugs, severe side effects including deaths have been reported.

During therapy with methotrexate, exacerbation of renal function may develop with an increase in certain laboratory values (creatinine, urea and uric acid in serum).

Gastrointestinal toxicity
Conditions leading to dehydration (emesis, diarrhoea, stomatitis) may also potentiate the toxicity of methotrexate due to elevated agent levels. In these cases use of methotrexate should be interrupted until the symptoms cease.

Methotrexate and pleural effusion/ascites
In patients with pathological accumulation of liquid in body cavities (“third space”), such as ascites or pleural effusions, the plasma elimination half-life of methotrexate is prolonged resulting in unexpected toxicity.

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

Increased caution should generally be exercised in patients with insulin-dependent diabetes mellitus as well as pulmonary function impairment.

Infection or immunological conditions
On account of its possible effect on the immune system, methotrexate can falsify vaccinal and test results (immunological procedures to record the immune reaction).

Vaccination with live vaccines should therefore be avoided in patients on methotrexate therapy. There are reports on disseminated cowpox infections after smallpox vaccinations of patients on methotrexate therapy.

Methotrexate induced reactivation of hepatitis B infection or worsening of hepatitis C infections, with fatal outcome in some cases. Some cases of hepatitis B reactivation occurred after discontinuation of methotrexate. To evaluate clinically pre-existing liver disease in patients with previous hepatitis B or C infection, clinical and laboratory tests should be carried out. As a result, methotrexate treatment may prove to be unsuitable for some patients.

Furthermore, in the presence of an inactive, chronic infection such as herpes zoster or tuberculosis special caution is required on account of a possible activation

During methotrexate therapy, opportunistic infection can occur including pneumocystis carinii pneumonia, which may take a lethal course.

Pulmonary toxicity
Pulmonary complications, pleural effusion, alveolitis or pneumonitis with symptoms such as general malaise, dry irritating cough, dyspnoea up to dyspnoea at rest, cough, thoracic pain, fever, hypoxaemia and infiltrates in the thoracic x-ray occurring during methotrexate treatment may be signs of a possibly dangerous damage with possible lethal outcome.

Pulmonary diseases induced by methotrexate, like pneumonitis, can occur acutely at any time of therapy, were not always completely reversible and have been reported already at all doses (inclusive low doses of 7.5 mg/week).

If these complications are suspected, treatment with methotrexate is to be discontinued immediately and differentiation compared to infections (including pneumonia) necessary.

In addition, pulmonary alveolar haemorrhage has been reported with methotrexate used in rheumatologic and related indications. This event may also be associated with vasculitis and other comorbidities. Prompt investigations should be considered when pulmonary alveolar haemorrhage is suspected to confirm the diagnosis.

Skin toxicity
Severe, occasionally fatal allergic skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome) occurred.

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.

Occasionally malignant lymphomas may occur in patients receiving low-dose methotrexate; which regressed in some cases after discontinuation of methotrexate therapy. If lymphomas should fail to regress spontaneously, initiation of cytotoxic therapy is required. An increased incidence of lymphoma under methotrexate treatment could not be found in a recent study.

Intravenous administration of methotrexate may result in acute encephalitis (inflammation of the brain) and acute encephalopathy (abnormal brain change) with fatal outcome.

Progressive multifocal leukoencephalopathy (PML)
Cases of progressive multifocal leukoencephalopathy (PML) have been reported in patients receiving methotrexate, mostly in combination with other immunosuppressive medication. PML can be fatal and should be considered in the differential diagnosis in immunosuppressed patients with new onset or worsening neurological symptoms.

Use in the elderly
Particularly elderly patients, fatal outcomes have been reported with accidentally daily administration of the weekly dose. Furthermore, particularly elderly patients should be examined in short intervals for early signs of toxicity. The methotrexate dose should the adapted due to the higher age and reduced liver and kidney function (see section 4.2).

Paediatric population
In children and adolescents methotrexate should be introduced and monitored only by specialists with sufficient experience in the diagnosis and treatment of the existing disorder concerned.

Fertility and reproduction

Fertility
Methotrexate has been reported to cause oligospermia, menstrual dysfunction and amenorrhoea in humans, during and for a short period after cessation of therapy, and to cause impaired fertility, affecting spermatogenesis and oogenesis during the period of its administration - effects that appear to be reversible on discontinuing therapy.

Teratogenicity – Reproductive risk

Methotrexate causes embryotoxicity, abortion and foetal defects in humans. Therefore the possible risks of effects on reproduction, pregnancy loss and congenital malformations should be discussed with female patients of childbearing potential (see section 4.6). The absence of pregnancy must be confirmed before Ebetrex is used. If women of a sexually mature age are treated, effective contraception must be performed during treatment and for at least six months after.

For contraception advice for men see section 4.6.

Recommended examinations and safety measures:

Patients must be closely monitored during treatment with methotrexate, so that symptoms of intoxication can be noticed promptly.

Before initiating therapy

- Complete blood count with differential blood count and platelets
- liver enzymes (ALT [GPT], AST [GOT], bilirubin,
- serum albumin
- if necessary chest X-ray
- renal function tests (if necessary with creatinine clearance).
- hepatitis serology (A, B, C)
- if necessary tuberculosis exclusion

During therapy (in the first two weeks weekly, then every two weeks for the next month; afterwards, depending on leukocyte count and stability of the patient at least once monthly during the next six months and at least every three months thereafter): Increased monitoring frequency should also be considered when increasing the dose or agent levels are elevated (e.g.due to dehydration, increased toxicity of methotrexate).

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

2. Complete blood count with differential blood count and platelets.

3. Liver function tests

   Treatment should not be initiated or should be discontinued if there are persistent or significant abnormalities in liver function tests, other non-invasive investigations of hepatic fibrosis, or liver biopsies.

   Temporary increases in transaminases to two or three times the upper limit of normal have been reported in patients at a frequency of 13-20 %. Persistent elevation of liver enzymes and/or decrease in serum albumin may be indicative for severe hepatotoxicity. In the event of a persistent increase in liver enzymes, consideration should be given to reducing the dose or discontinuing therapy.

   Histological changes, fibrosis and more rarely liver cirrhosis may not be preceded by abnormal liver function tests. There are instances in cirrhosis where transaminases are normal. Therefore, non-invasive diagnostic methods for monitoring of liver condition should be considered, in addition to liver function tests. Liver biopsy should be considered on an individual basis taking into account the patient’s comorbidities, medical history and the risks related to biopsy. Risk factors for hepatotoxicity include 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.

   Additional hepatotoxic medicinal products should not be given during treatment with methotrexate unless clearly necessary. Alcohol consumption

should be avoided (see sections 4.3 and 4.5). Closer monitoring of liver enzymes should be undertaken in patients concomitantly taking other hepatotoxic medicinal products.

Increased caution should be exercised in patients with insulin-dependent diabetes mellitus, as during methotrexate therapy, liver cirrhosis developed in isolated cases without any elevation of transaminases.

4. Monitoring of renal function/creatinine values in serum
   If serum creatinine is increased, the dose should be reduced. In serum creatinine values above 2 mg/dl, no treatment with methotrexate should be done.

   In case of borderline renal function (e.g. in higher age) monitoring should be performed more frequently (closely). This applies particularly if additional medicines are given which impair the excretion of methotrexate, cause nephrotoxicity (e.g. non-steroidal anti-inflammatory drugs) or potentially can lead to haematopoietic disorders.

5. Questioning the patient with regard to possible pulmonary dysfunctions, if necessary lung function test.

Notes
Due to the risk of severe or even fatal toxic reactions, the patients should be thoroughly informed by the doctor about the risks (including early signs and symptoms of toxicity) and recommended safety measures. They are to be informed about the necessity to immediately consult the physician if symptoms of intoxication occur as well as about the subsequent necessary monitoring of symptoms of intoxication (including regular laboratory tests).
Doses exceeding 20 mg/week can be associated with significant increase in toxicity, especially bone marrow suppression.

Special note
Skin and mucosal contacts with methotrexate are to be avoided. In the case of contamination, the parts concerned should be rinsed with plenty of water.

This medicinal product contains less than 1 mmol (23 mg) sodium per dose and is i.e. essentially “sodium-free”.

Photosensitivity
Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking methotrexate (see section 4.8). Exposure to intense sunlight or to UV rays should be avoided. Patients should use a sun- protection product with a high protection factor.

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 low-dose methotrexate therapy but only under close medical supervision.

A concomitant administration of proton-pump inhibitors (omeprazole, pantoprazole, lansoprazole) can lead to delayed or inhibited renal elimination of methotrexate and can result in elevated plasma levels of methotrexate with clinical signs and symptoms of methotrexate toxicity. In patients with impaired renal function care has to be taken.

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 Ebetrex.

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 penicillins, glycopeptides, sulfonamides 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.
The tubular renal secretion is reduced by ciprofloxacin. Use of methotrexate with this medicinal product should be monitored carefully.

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 Ebetrex is used concomitantly with other antirheumatic agents (e.g. gold compounds, penicillamine, hydroxychloroquine, sulfasalazine, azathioprine, cyclosporin).

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 dose adjustment.

The use of nitrous oxide potentiates the effect of methotrexate on folate, yielding increased toxicity such as severe unpredictable myelosuppression and stomatitis. Whilst this effect can be reduced by administering calcium folinate, the concomitant use of nitrous oxide and methotrexate should be avoided.

During methotrexate therapy concurrent vaccination with live vaccines must not be carried out (see section 4.3 and 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
Methotrexate is contraindicated during pregnancy in non-oncological indications (see section 4.3). If pregnancy occurs during treatment with methotrexate and up to six months thereafter, medical advice should be given regarding the risk of harmful effects on the child associated with treatment and ultrasonography examinations should be performed to confirm normal foetal development.
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 foetal death, miscarriages and/or congenital abnormalities (e.g. craniofacial, cardiovascular, central nervous system and extremity-related).

Methotrexate is a powerful human teratogen, with an increased risk of spontaneous abortions, intrauterine growth restriction and congenital malformations in case of exposure during pregnancy.

- Spontaneous abortions have been reported in 42.5% of pregnant women exposed to low-dose methotrexate treatment (less than 30 mg/week), compared to a reported rate of 22.5% in disease-matched patients treated with drugs other than methotrexate.
- Major birth defects occurred in 6.6% of live births in women exposed to low-dose methotrexate treatment (less than 30 mg/week) during pregnancy, compared to approximately 4% of live births in in disease-matched patients treated with drugs other than methotrexate.

Insufficient data is available for methotrexate exposure during pregnancy higher than 30 mg/week, but higher rates of spontaneous abortions and congenital malformations are expected.
When methotrexate was discontinued prior to conception, normal pregnancies have been reported.
Women of childbearing potential /Contraception in females
Women must not get pregnant during methotrexate therapy, and effective contraception must be used during treatment with methotrexate and at least 6 months thereafter (see section 4.4). Prior to initiating therapy, women of childbearing potential must be informed of the risk of malformations associated with methotrexate and any existing pregnancy must be excluded with certainty by taking appropriate measures, e.g. a pregnancy test. During treatment pregnancy tests should be repeated as clinically required (e.g. after any gap of contraception). Female patients of reproductive potential must be counselled regarding pregnancy prevention and planning.
Contraception in males
It is not known if methotrexate is present in semen. Methotrexate has been shown to be genotoxic in animal studies, such that the risk of genotoxic effects on sperm cells cannot completely be excluded. Limited clinical evidence does not indicate an increased risk of malformations or miscarriage following paternal exposure to low-dose methotrexate (less than 30 mg/week). For higher doses, there is insufficient data to estimate the risks of malformations or miscarriage following paternal exposure. As precautionary measures, sexually active male patients or their female partners are recommended to use reliable contraception during treatment of the male patient and for at least 3 months after cessation of methotrexate. Men should not donate semen during therapy or for 3 months following discontinuation of methotrexate.

Breast-feeding
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.

Fertility
Methotrexate affects spermatogenesis and oogenesis and may decrease fertility. In humans, methotrexate has been reported to cause oligospermia, menstrual dysfunction and amenorrhoea. These effects appear to be reversible after discontinuation of therapy in most cases.

4.7 Effects on ability to drive and use machines

As, during use of methotrexate, central-nervous adverse reactions, such as fatigue and vertigo can occur the ability to drive and/or operate machinery can be impaired in isolated cases (see section 4.8). This applies to an increased extent in conjunction with alcohol.

4.8 Undesirable effects

Occurrence and severity of undesirable effects depend on dose level and frequency of Ebetrex 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, dose 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 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 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:

	Very common	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations			Herpes zoster	Sepsis	Herpes simplex, hepatitis	opportunistic infections (may be fatal in some cases), lethal sepsis, histoplasma and cryptococcus mycosis nocardiosis, disseminated herpes simplex, infections caused by the cytomegaly virus including

	Very common	Common	Uncommon	Rare	Very rare	Not known
						pneumonia, reactivation of a hepatitis B infection and worsening of a hepatitis C infection.
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			Individual cases of lymphoma[1],			
Blood and lymphatic system disorders		Leukocytopenia thrombocyto-penia, anaemia	Pancytopenia, agranulocytosis, haematopoietic disorders	Megaloblastic anaemia	Severe courses of bone marrow depression, aplastic anaemia. lymphoproliferative disorders (see "description" below)	Lymphadenopathy, eosinophilia and neutropenia[2].
Immune system disorders			Severe allergic reactions up to anaphylactic shock		Hypogammaglobulinaemia	Immunosuppression, fever[3]), allergic vasculitis
Metabolism and nutrition disorders			Diabetes mellitus			
Psychiatric disorders			Depression	Mood fluctuations, transient perception disorders		
Nervous system disorders		Headache, fatigue, drowsiness, paraesthesia	Hemiparesis, vertigo, confusion, seizures, leukoencephalopathy/encephalopathy (in parenteral	Paresis, speech disorders including dysarthria and aphasia	Pain, myasthenia in the extremities, dysgeusia (metallic taste), acute aseptic meningitis, meningism (paralysis,	

	Very common	Common	Uncommon	Rare	Very rare	Not known
			administration)		vomiting), paraesthesia/ hypoaesthesia	
Eye disorders				Severe visual disturbances (blurred or cloudy vision), severe dysopia of unknown aetiology	Conjunctivitis,	
Cardiac disorders				Hypotension	Pericarditis, pericardial effusion, pericardial tamponade	
Vascular disorders			Vasculitis (as severe toxic symptom)	thromboembolic events[4]		
Respiratory, thoracic and mediastinal disorders		Pulmonary complications due to interstitial alveolitis/pneumonitis and related deaths[5]	Pulmonary fibrosis, pleural effusion	Pharyngitis, respiratory arrest	Pneumocystis carinii pneumonia chronic obstructive pulmonary disease. asthma bronchiale	Pulmonary alveolar haemorrhage
Gastrointestinal disorders[6*]	Loss of appetite, nausea, vomiting, abdominal pain, inflammation and ulcerations of the mucous membrane of mouth and throat[7]	Diarrhoea[7]	Gastrointestinal ulcers and bleeding, pancreatitis	Enteritis, melaena Gingivitis,	Haematemesis,	Noninfectious peritonitis
Hepato-biliary disorders	Increase in liver-related		Development of liver fattening,	Acute hepatitis and hepatotoxicit	Acute liver necrosis	liver insufficiency

	Very common	Common	Uncommon	Rare	Very rare	Not known
	enzymes (ALAT [GPT], ASAT [GOT], alkaline phosphatase and bilirubin).		fibrosis and cirrhosis[8] drop of serum albumin.	y		
Skin and subcutaneous tissue disorders		Exanthema, erythema, itching	Urticaria, photosensibility, enhanced pigmentation of the skin, hair loss, nodulosis, painful lesions of psoriatic plaque severe toxic reactions: herpetiform eruption of the skin, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome).	Increased pigmentary changes of nails, onycholysis, acne, petechiae, ecchymoses, erythema multiforme, cutaneous erythematous eruptions.	acute paronychia, furunculosis, telangiectasia, photosensitivity	Disturbed wound healing, skin exfoliation / dermatitis exfoliative
Musculoskeletal and conjunctive tissue disorders			Arthralgia, myalgia, osteoporosis	Stress fracture		Osteonecrosis of jaw (secondary to lymphoproliferative disorders)
Renal and urinary disorders			Inflammation and ulceration of the urinary bladder (possibly with haematuria), dysuria.	azotaemia	Proteinuria	

	Very common	Common	Uncommon	Rare	Very rare	Not known
Pregnancy, puerperium and perinatal conditions			Foetal malformations	Abortion	Foetal death	
Reproductive system and breast disorders			Inflammation and ulceration of the vagina	Oligospermia, menstruation disorders, which however regress at the end of treatment	Disturbed ovogenesis, spermatogenesis, loss of libido, impotence, vaginal discharge, infertility	
General disorders and administration site conditions			After intramuscular use of methotrexate, local adverse reactions (burning sensation) or damage (sterile formation of abscess, destruction of fatty tissue) can occur at the site of injection.		Fever[9]	Injection site necrosis, oedema

[1] abated in a number of cases once methotrexate treatment had been discontinued.
[2] First signs for these life-threatening complications may be: fever, sore throat, ulcerations of oral mucosa, flu-like complaints, strong exhaustion, epistaxis and dermatorrhagia. Use of methotrexate should be interrupted immediately if the number of blood cells significantly declines.

[3] requires clarification of bacterial or mycotic septicaemia!

[4] including arterial and cerebral thrombosis, thrombophlebitis, deep vein thrombosis, retinal vein thrombosis, pulmonary embolism).

[5] independent of dose and duration of methotrexate treatment.

[6] If diarrhoea or ulcerations occur in the oral and pharyngeal area, interruption of treatment may be necessary due to the risk of gastrointestinal perforation or haemorrhagic enteritis.

[7] especially during the first 24-48 hours after administration of Ebetrex

[8] occurs frequently despite regularly monitored, normal values of liver enzymes

[9] Subcutaneous administration of methotrexate shows good local tolerance. Only mild local skin reactions, the number of which decreased in the course of treatment, have been observed so far.

Description of selected adverse reactions

Lymphoma/Lymphoproliferative disorders: there have been reports of individual cases of lymphoma and other lymphoproliferative disorders which subsided in a number of cases once treatment with methotrexate had been discontinued.

Adverse reactions that were observed with usually higher doses of methotrexate in oncology include:
Uncommon: Severe nephropathy, renal failure
Very rare: Unusual cranial sensation, transient blindness/loss of sight

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in Google play or Apple App store.

4.9 Overdose

a) Symptoms of overdose
Post-marketing experience has shown that methotrexate overdose generally occurred after oral use, but also after intravenous or intramuscular use. In the reports regarding oral overdose, the weekly dose was inadvertently taken daily (as total dose or divided into several single doses). The symptoms following oral overdose 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 as a result of an overdose . In these cases sepsis, septic shock, renal failure and aplastic anaemia have also been reported.

b) Treatment of overdose
Calcium folinate is the specific antidote for neutralising the adverse toxic effects of methotrexate.

If leukocytes decline at low methotrexate dosage, e.g. 6-12 mg calcium folinate may be injected intravenously or intramuscularly as soon as possible, followed by several times (at least 4 times) the same dose at 3-6-hour intervals.

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 B_{12} levels is recommended, since folic acid may mask an existing vitamin B_{12} deficiency, particularly in adults over 50 years of age.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and immunomodulating Agents; Immunosuppressants, Other immunosuppressants, ATC-code: L04AX03
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/m2 to 80mg/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 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 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

For storage conditions after first opening of the medicinal product, see section 6.3.

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

Do not store above 25°C

6.5 Nature and contents of container

Ebetrex is available in pre-filled syringes with a capacity of 1.25ml (for filling volumes of 0.375 ml, 0.5 ml, 0.625ml, 0.75 ml and 0.875 ml), 2.25 ml(for filling volumes of 1 ml, 1.125ml, 1.25 ml and 1.375 ml) and 3.0 ml (for filling volumes of 1.5 ml) of colourless glass (type I according Ph.Eur), an elastomeric tip cap and an elastomeric plunger stopper.

Each carton box contains 1 pre-filled syringe with 0.375ml, 0.5ml, 0.625ml, 0.75ml, 0.875ml, 1ml, 1.125ml, 1.25ml, 1.375ml or 1.5ml solution for injection, single-use injection needles without or with security cannula and alcohol pads.

Multipacks containing 4, 5, 6, 12 or 30 pre-filled syringes (1 pre-filled syringe per carton box).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Handling and disposal must be consistent with that of other cytotoxic preparations in accordance with local requirements. Pregnant health care personnel should not handle and/or administer Ebetrex.

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 MARKETING AUTHORISATION HOLDER

Sandoz Limited
Park View, Riverside Way
Watchmoor Park
Camberley, Surrey
GU15 3YL
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 04416/1599

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29/04/2009

10 DATE OF REVISION OF THE TEXT

14/03/2024