SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ebetrex 10 mg/ml solution for injection in pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml solution contains 10 mg of methotrexate (as 10.97 mg of methotrexate disodium).
Each pre-filled syringe of 0.75 ml contains 7.5 mg of methotrexate.
Each pre-filled syringe of 1 ml contains 10 mg of methotrexate.
Each pre-filled syringe of 1.5 ml contains 15 mg of methotrexate.
Each pre-filled syringe of 2 ml contains 20 mg of methotrexate.

Excipient(s) with known effect
Each ml solution for injection contains 0.16 mmol (3.8 mg) of sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection in pre-filled syringes.
Clear, yellow solution free of particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Active rheumatoid arthritis in adult patients
- Polyarthritic forms of severe, active juvenile idiopathic arthritis (JIA) (children > 3 years) 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 dosing of Ebetrex:
In the treatment of rheumatoid arthritis, active juvenile idiopathic arthritis (JIA) and psoriasis Ebetrex (methotrexate) **must only be used once a week.** Dosage errors in the use of Ebetrex (methotrexate) can result in serious adverse reactions, including death.
Please read this paragraph 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 administered **only once a week.**
The prescriber should specify the day of intake on the prescription.

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.

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

Dose in patients with rheumatoid arthritis:
It is recommended that a test dose is parenterally administered one week prior to initiation of therapy, in order to detect idiosyncratic adverse effects.
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. Alternatively a higher starting dose can be used. The average weekly dose is 15mg - 20mg Methotrexate. 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, dose should be reduced gradually to the lowest possible effective maintenance dose.
Symptoms might re-occur after stopping the treatment,

Paediatric population
Dose in children (> 3 years) 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 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. (see section 4.4)

Dose in patients with severe forms of psoriasis vulgaris and psoriatic arthritis:
Recommended initial dose (relative to an average adult of 70 kg body weight):
A single test dose of 2.5-5 mg is recommended for the assessment of toxicity. With unchanged laboratory parameters 1 week later continuation with approx. 7.5 mg. The dose is gradually increased (in increments of 5-7.5 mg per week) while monitoring the laboratory parameters until an optimal treatment result is achieved. A weekly dose of 25 mg methotrexate should generally not be exceeded.
Once the desired outcome has been achieved, the dose should, as far as possible, be gradually reduced to the lowest maintenance dose still effective in the individual patient.
Response to therapy generally occurs after 4-8 weeks. Thereafter, the therapy is continued or discontinued according to the clinical picture and laboratory parameter changes.

Patients with impaired renal function:
Ebetrex should be used with caution in patients with impaired renal function. The following table lists recommended baseline doses for patients with impaired renal function; due to pronounced inter-individual pharmacokinetic variability, further dose adjustment may be necessary.

Creatinine clearance (ml / min)	**% of the stated standard dose**
> 80	100
~ 60-80	~ 63-75
<60	Use of alternative therapy

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 occurs with increased age.

Use in patient with a third distribution space (pleural effusions, ascites):
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 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 the active substance or to any of the excipients listed in section 6.1,
- Severe hepatic impairment
- Increased consumption of alcohol (alcohol-dependent or other chronical hepatic diseases)
- Severe renal dysfunctions (creatinine clearance < 60 ml/min, see also section 4.2)
- Pre-existing dysfunctions of the haematopoietic system

- Immunodeficiency,
- Severe and/or existing active infections
- Stomatitis, ulcers of the gastrointestinal tract
- Pregnancy and breast-feeding (see also section 4.6).

4.4 Special warnings and precautions for use

Special warnings

The prescriber should specify the day of intake on the prescription.
The prescriber should make sure patients understand that methotrexate should only be taken once a week.
Patients should be instructed on the importance of adhering to the once-weekly intakes.
The patient should be strongly advised that the recommended dose is administered weekly and that accidental daily administration of the recommended dose resulted in fatal toxicities (see also section 4.2 and 4.9). Especially in the elderly, deaths were reported following the **accidental daily use of the weekly dose**.
Methotrexate should only be prescribed by physicians who have sufficient experience in treating the disease with methotrexate.

Fertility and reproduction

Fertility

Methotrexate has been reported to cause oligospermia, menstrual dysfunction and amenorrhoea in humans during and for a short period after the discontinuation of treatment 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 malformations in humans. Therefore, the possible 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 methotrexate is used. If women of a sexually mature age are treated, effective contraception must be used during treatment and for at least six months after.

For contraception advice for men see section 4.6.

Toxicity

Psoriasis

Due to the possibility of severe toxic reactions (which can be fatal), methotrexate should only be used in patients with psoriasis with severe persistent disabling disease that does not provide adequate answers to other treatment.

Patients undergoing methotrexate therapy should be closely monitored so that signs of possible toxic effects or adverse reactions may be detected and evaluated with minimal delay.

Patients must be informed about the possible benefit and the risks (including early signs and symptoms of toxicity) of methotrexate therapy. Furthermore, they are to be informed about the necessity to immediately consult the physician if symptoms of intoxication occur and informed about the subsequently necessary monitoring of the symptoms of intoxication (including laboratory tests).

Withdrawal of methotrexate does not always lead to complete remission of adverse reactions.

Methotrexate is eliminated slowly from **pathological accumulations of liquid in body cavities** ("third space"), such as ascites or pleural effusions, which results in prolongation of the plasma elimination half-life and unexpected toxicity. Pleural effusions and ascites should be drained prior to initiation of methotrexate treatment.

Haematopoietic system
Methotrexate can suppress haematopoiesis, causing anaemia, aplastic anaemia, pancytopenia, leukopenia, neutropenia, and/or thrombocytopenia. First signs of life-threatening complications may be: fever, sore throat, ulcerations of oral mucosa, influenza-like complaints, strong exhaustion, epistaxis and dermatorrhagia.
Particularly during long-term therapy in geriatric patients **megaloblastic anaemia** has been reported.

Hepatic function
On account of its potential **hepatotoxic** effect it is recommended not to consume any additional hepatotoxic medicinal products or medicinal products considered to be hepatotoxic and to refrain from alcohol resp. to minimise alcohol consumption during therapy with methotrexate.

Methotrexate may provoke a potential risk of acute **hepatitis** and chronic potentially fatal **hepatotoxicity** (fibrosis and cirrhosis), however typically occurring only after prolonged use. Acute increases of liver enzymes are frequently observed. These are usually transient and asymptomatic and are no signs of subsequent liver diseases.

Chronic toxicity usually occurred after prolonged use (generally after 2 years or more) and after a total cumulative dose greater than 1.5 g. In studies in psoriatic patients it was found that hepatotoxicity is associated with the total cumulative dose and toxicity is enhanced by alcohol abuse, obesity, diabetes, and advanced age. Liver biopsies performed after prolonged use have often shown histological alterations; also reporting of fibroses and cirrhosis.

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.

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

Renal function

Because methotrexate is excreted primarily via the kidneys, increased, longer-lasting serum concentrations are expected with impaired kidney function, which can result in serious adverse reactions.

In patients with renal impairment (e.g. elderly patients), due to delayed methotrexate elimination in these patients, methotrexate should be used with extreme caution and low doses should be used (see section 4.2).

When risk factors such as renal dysfunctions, including mild renal impairment, are present, co-administration with non-steroidal anti-inflammatory drugs is not recommended.
Therapy with methotrexate may cause deterioration of renal function with an increase in certain laboratory values (creatinine, urea, serum uric acid) that may result in **acute renal failure** with oliguria/anuria. This is probably attributable to precipitation of methotrexate and its metabolites in the renal tubuli.

Gastrointestinal toxicity
Conditions leading to dehydration such as emesis, diarrhoea, stomatitis can increase toxicity of methotrexate due to elevated methotrexate levels. In these cases, supportive therapy should be initiated and use of methotrexate should be interrupted until the symptoms cease.

If **ulcerative stomatitis** or **diarrhoea**, **haematemesis, black discolouration of stool** or **blood in stool** occur, therapy is to be interrupted, as otherwise haemorrhagic enteritis and death due to intestinal perforation may occur.

Immune system
On account of its possible effect on the immune system, methotrexate can falsify vaccinal and test results (immunological procedures to record the immune reaction). Vaccinations during methotrexate therapy can be ineffective.

Due to the increased risk of infection, **vaccines containing live vaccines** should not be used during therapy with methotrexate.

Pulmonary function

Special caution is required in patients with **impaired pulmonary function.**

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

Lung biopsies provided different findings (e.g. interstitial oedema, mononuclear infiltrates or non-caseating granulomas).

On suspicion of these complications, treatment with methotrexate must be discontinued immediately and a thorough investigation excluding infections and tumours is required.
Pulmonary diseases induced by methotrexate can occur at any time of therapy, were not always completely reversible and have been reported at low doses of 7.5 mg/week.

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.

Potentially fatal **opportunistic infections**, including *pneumocystis-jirovecii* pneumonia, may occur during treatment with methotrexate. In patients presenting with pulmonary symptoms *pneumocystis-jirovecii* pneumonia must be taken into consideration.

Skin and subcutaneous tissue disorders
Serious, occasionally fatal skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome) were reported after single or continuous administration of methotrexate.

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.

Neoplasms
The **occurrence of malignant lymphomas** has uncommonly been reported during use of low-dosed methotrexate; they subsided in some cases after the cessation of methotrexate therapy. If lymphomas occur, methotrexate therapy should therefore be stopped first and only if the lymphoma does not subside, appropriate therapy should be initiated.

Nervous system

Intravenous administration of methotrexate may result in **acute encephalitis** and **acute encephalopathy** with fatal outcome.
There are reports of **leukoencephalopathy** in patients receiving oral methotrexate.

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.

Folic acid supplementation
Folate deficiency can increase methotrexate toxicity (see section 4.5).

The use of folic acid or folinic acid may reduce the toxicity of methotrexate (gastrointestinal symptoms, stomatitis, alopecia and increase in liver enzymes).
Before taking folic acid preparations, it is advisable to check the vitamin B12 levels, as folate intake can mask a vitamin B12 deficiency, especially in adults over the age of 50 years.

Recommended examinations and safety measures:
Patients should be closely monitored during methotrexate treatment including adequate hydration, alkalisation of urine, determination of serum methotrexate level and renal function in order to detect symptoms of intoxication quickly.

Before initiating therapy
- Complete blood count with differential blood count,
- Liver enzymes (ALT [GPT], AST [GOT]), bilirubin,
- Serum albumin,
- Chest X-ray if necessary
- Lung function test if necessary
- Renal function tests (if necessary with creatinine clearance),
- If clinically indicated, exclude tuberculosis
- Hepatitis serology (A, B, C).

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 approx. monthly):
Increased monitoring frequency should also be considered when increasing the dose or levels of the active substance 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.
   The use of methotrexate should be stopped immediately if there is a significantly reduced number of blood cells.

3. Monitoring of liver-related enzymes in serum
   Transient increases in transaminases to the two-to threefold standard are stated with a frequency of 13-20% of the patients. This is usually no reason for a change in the treatment regimen. Persistent anomalies of liver-related enzymes and/or decrease in serum albumin may be indicative for severe hepatotoxicity.

   Enzyme diagnostics does not allow any reliable prediction of the development of a morphologically detectable hepatotoxicity, i.e. even in case of normal transaminases, hepatic fibrosis only histologically identifiable or, more rarely, also hepatocirrhosis may be present.

   If the elevation in liver-related enzymes persists, dose reduction or further breaks of treatment should be considered. In patients with persistent hepatic impairment, methotrexate should always be discontinued. For severest forms of psoriasis, see also point 4 “Liver biopsy”.

4. Liver biopsy
   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.

5. Monitoring of renal function/creatinine values in serum
   Renal function should be monitored via renal function tests and urinalysis. If serum creatinine is increased, the dose should be reduced. In serum creatinine values above 2 mg/dl and with serum creatinine clearance rate of less than 60 ml/min, no treatment with methotrexate should be done.

   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.

6. Assessment of respiratory system
   Questioning the patient with regard to possible pulmonary dysfunctions, if necessary lung function test in case pulmonary disease (e.g. interstitial pneumonia) is suspected particularly if relevant reference values exist from the first examination.

More frequent check-ups may become necessary

- During the initial phase of treatment
- When the dose is changed
- During episodes of a higher risk of elevated methotrexate blood levels (e.g. dehydration, impaired renal function, additional or elevated dose of medicinal products administered concomitantly, such as nonsteroidal anti-inflammatory drugs).

Use in the elderly
Elderly patients should be examined in short intervals for early signs of toxicity. The methotrexate dose should be adapted due to the higher age and reduced liver and kidney function (see section 4.2)

Children and adolescents
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

This medicinal product contains less than 1 mmol (23 mg) sodium per dose, that is to say 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

The use of nitrous oxide base 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.

L-asparaginase antagonises the effects of methotrexate during concomitant administration with methotrexate.

In animal experiments non-steroidal anti-inflammatory drugs (NSAIDs) including salicylic acid caused reduction of tubular methotrexate secretion and consequently increased its toxic effects. Therefore, these medicinal products and low-dosed methotrexate should be used concurrently only with caution. Serious side effects, including deaths, including unexpectedly strong bone marrow suppression, aplastic anaemia and gastrointestinal toxicity have been reported with concomitant use of NSAIDs and, particularly high dose methotrexate.
In the presence of risk factors, e.g. borderline renal function, the concurrent use of NSAIDs and methotrexate is not recommended.

Combined use of methotrexate with DMARDs (e.g. gold salts, penicillamine, hydroxychloroquine, sulfasalazine, azathioprine, ciclosporin) has not been studied and an increase in methotrexate toxicity cannot be ruled out.
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.

Hepatotoxicity of methotrexate can be increased during regular consumption of alcohol or administration of other hepatotoxic medicinal products, e.g. **azathioprine, leflunomide, retinoids**, **sulfasalazine.** Patients who take hepatotoxic medicinal products in addition should be closely monitored. Alcohol consumption should be avoided during methotrexate treatment.

The following medicinal products can increase bioavailability of methotrexate (indirect dose increase) and raise its toxicity due to **displacement of methotrexate from the plasma protein binding**: amidopyrine derivatives, para-aminobenzoic acid, barbiturates, doxorubicin, oral contraceptives, phenylbutazone, phenytoin, probenecid, salicylates, sulphonamides, tetracyclines, tranquillisers, sulfonylureas, penicillins, pristinamycin and chloramphenicol. Concomitant use of methotrexate should therefore be carefully monitored.

The following medicinal products can cause a **reduction in tubular secretion** and consequently increased toxicity of methotrexate, particularly in the low dose range: paraaminohippuric acid, non-steroidal anti-inflammatory medicinal products, probenecid, salicylates, sulphonamides and other weak organic acids may reduce tubular methotrexate secretion, and thus also cause

indirect dose elevations. Concomitant use of methotrexate should therefore be monitored carefully
Penicillins and sulfonamides 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 medicinal products that may have adverse effects on the bone marrow (e.g. amidopyrine derivatives, chloramphenicol, phenytoin, pyrimethamine, sulphonamides, trimethoprim-sulphamethoxazole,cytostatics), the possibility of marked haematopoietic disorders due to therapy with methotrexate 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 medicinal products or of vitamin preparations, which contain folic acid or derivatives**, may affect methotrexate efficacy.

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.

Cases of bone marrow suppression and decreased folate levels have been described in the concomitant administration of **triamterene** and methotrexate.

Amiodarone has resulted in ulcerating skin lesions in patients receiving methotrexate for psoriasis therapy.

Some patients with psoriasis have reported skin cancer with methotrexate and **PUVA therapy**.

Radiotherapy during use of methotrexate can increase the risk of soft tissue or bone necrosis.
During methotrexate therapy concurrent **vaccination with live vaccines** must not be carried out (see section 4.4).

Concomitant administration of **levetiracetam** and methotrexate has been reported to decrease methotrexate clearance, resulting in increased/prolonged blood methotrexate concentration to potentially toxic levels. Blood methotrexate and levetiracetam levels should be carefully monitored in patients treated concomitantly with the two medicinal products.

4.6 Fertility, pregnancy and lactation

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.

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 medicinal products other than methotrexate.
- Serious 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.

Breastfeeding
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

Incidence and severity of undesirable effects usually depend on dose level and frequency of methotrexate administration. As severe adverse reactions may occur even at lower doses and at any time during therapy, it is indispensable that the doctor monitors patients regularly at short intervals.
Most undesirable effects are reversible if recognised early. However, some of the severe adverse reactions named below may result in sudden death in very rare cases. If such adverse reactions occur, dose should be reduced or therapy be interrupted depending on severity and intensity, 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.

The adverse reactions most commonly reported are thrombocytopenia, leukopenia, headache, vertigo, cough, loss of appetite, diarrhoea, abdominal pain, nausea, vomiting, ulcerative stomatitis (particularly within the first 24-48 hours after administration of methotrexate), increase in liver enzymes and bilirubin, alopecia, lowered creatinine clearance, fatigue and malaise-

Ulcerative stomatitis is usually the first sign 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 (frequency cannot be estimated from the available data).

	Very common	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations		Herpes zoster	Opportunistic infections (may be fatal in some cases)	Sepsis (including fatal)	Herpes simplex, hepatitis, histoplasmosis, cryptococcosis, cytomegalovirus infection (including pneumonia), disseminated herpes simplex, nocardiosis, *pneumocystis-jirovecii* pneumonia*	Pneumonia, reactivation of a hepatitis B infection and worsening of a hepatitis C infection.
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)			Malignant lymphomas *			Skin cancer (see also section 4.5)
Blood and lymphatic system disorders	Thrombocytopenia, leukopenia	Anaemia, pancytopenia, myelosuppression, agranulocytosis		Megaloblastic anaemia	Aplastic anaemia, eosinophilia, neutropenia, lymphadenopathy (partly reversible), lymphoproliferative disorders (see “description”	

	Very common	Common	Uncommon	Rare	Very rare	Not known
					below).	
Immune system disorders			Allergic reactions, up to anaphylactic shock, immunosuppression		Hypogammaglobulinaemia	
Metabolism and nutrition disorders			Diabetes mellitus			
Psychiatric disorders			Depression	Mood fluctuations, transient perception disorders		
Nervous system disorders	Headache, vertigo	Drowsiness, paraesthesia	Hemiparesis, confusion, seizures, leukoencephalopathy/ encephalopathy*	Paresis, speech disorders including dysarthria and aphasia	Pain and myasthenia in the extremities, dysgeusia (metallic taste), acute aseptic meningitis, meningism (paralysis, vomiting), cranial nerve syndrome, Paraesthesia/ hypoaesthesia	Neurotoxicity, arachnoiditis, paraplegia, stupor, ataxia, dementia, increase in the pressure of cerebrospinal fluid
Eye disorders		Conjunctivitis		Visual disturbances, (partly severe), retinal vein thrombosis	Periorbital oedema, blepharitis, epiphora, photophobia, transient blindness, loss of vision	Retinopathy
Cardiac disorders					Pericarditis, pericardial effusion, pericardial tamponade	
Vascular disorders			Vasculitis, allergic vasculitis.	Hypotension, thromboembolic events (including arterial and cerebral thrombosis, thrombophlebitis, deep vein		

	Very common	Common	Uncommon	Rare	Very rare	Not known
				thrombosis),		
Respiratory, thoracic and mediastinal disorders	Cough	Pulmonary complications due to interstitial alveolitis/pneumonitis and related deaths (independent of dose and duration of methotrexate treatment).	Pulmonary fibrosis, pleural effusion	Pharyngitis, respiratory arrest, pulmonary embolism	Chronic interstitial pulmonary disease, asthma, bronchiale-like reactions with cough, dyspnoea, pathological findings in pulmonary function test.	Hypoxia, Pulmonary alveolar haemorrhage
Gastrointestinal disorders	Loss of appetite, diarrhoea (particularly within the first 24 – 48 hours after administration of methotrexate) 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 methotrexate).		Gastrointestinal ulcers and haemorrhages, pancreatitis	Enteritis, melaena gingivitis,	Haematemesis	Non-infectious peritonitis, toxic megacolon, intestinal perforation, glossitis.
Hepato-biliary disorders (see also the notes regarding liver biopsy in section 4.4)	Increase in liver-related enzymes (ALAT [GPT], ASAT [GOT], alkaline phosphatase and bilirubin).		Hepatotoxicity, hepatic steatosis, chronic hepatic fibrosis and hepatocirrhosis, drop of serum albumin.	Acute hepatitis	Acute liver necrosis, acute liver degeneration, hepatic failure	
Skin and subcutaneous tissue	Alopecia	Exanthema, erythema, pruritus,	As severe toxic phenomena:	Acne, petechiae, ecchymoses,	Acute paronychia, furunculosis,	Drug reaction with eosinophilia

	Very common	Common	Uncommon	Rare	Very rare	Not known
disorders		photosensitivity skin ulceration	herpetiform eruption of the skin, Stevens-Johnson syndrome* toxic epidermal necrolysis (Lyell's syndrome)*, urticaria, enhanced pigmentation of the skin, nodulosis, disturbed wound healing, painful lesions of psoriatic plaque	erythema multiforme, cutaneous erythematous eruptions, increased pigmentary changes of nails, onycholysis.	telangiectasia, photosensitivity	and systemic symptoms (DRESS) dermatitis. skin exfoliation / dermatitis exfoliative
Musculoskeletal system, connective tissue and bone disorders			Arthralgia, myalgia, osteoporosis	Stress fracture		Osteonecrosis, osteonecrosis of jaw (secondary to lymphoproliferative disorders)
Renal and urinary disorders	Decreased creatinine clearance		Nephropathy, renal failure, cystitis with ulceration (possibly with haematuria), voiding disorder, dysuria, oliguria, anuria.	Hyperuricaemia, elevated urea and creatinine serum concentrations, azotaemia.	Haematuria, proteinuria	
Pregnancy, puerperium and perinatal conditions			Foetal malformations	Abortion	Foetal death	
Reproductive system and breast disorders			Inflammation and ulceration of the vagina	Transient oligospermia, transient menstruati	Disturbed ovogenesis/ spermatogenesis*, infertility*, cycle	Urogenitory dysfunction

	Very common	Common	Uncommon	Rare	Very rare	Not known
				on disorders	disturbances, loss of libido, impotence, gynaecomastia, vaginal discharge	
General disorders and administration site conditions	Asthenia		Pyrexia			Chest pain, chills, injection site necrosis, oedema

* For serious undesirable effects, see section 4.4.

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.

When methotrexate is given by the intramuscular route, local undesirable effects (burning sensation) or damage (formation of sterile abscess, destruction of fatty tissue) at the site of injection can occur uncommonly. Subcutaneous application of methotrexate is locally well tolerated. Only mild local skin reactions were observed, decreasing during therapy.

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. website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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 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.

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

If leukocytes decline at low methotrexate dose, 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.
With increasing time interval between methotrexate calcium folinate use, the efficacy of calcium folinate decreases. For determining the optimum dose and duration of the calcium folinate use, the monitoring of the methotrexate serum levels is required.

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.
If the intoxication is caused by considerably delayed elimination (methotrexate serum levels) e.g. as a result of acute renal insufficiency, haemodialysis and/or haemoperfusion may be taken into consideration. Effective methotrexate clearance has been reported with acute, intermittent haemodialysis using a high-flux dialyser.

Neither standard haemodialysis nor peritoneal dialysis has been shown to improve methotrexate elimination.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Other immunosuppressants;
ATC code: L04AX03

Methotrexate belongs as Folic acid analogue in the series of antimetabolites. It is partly taken via an active transport system for reduced folic acid in the cell and firmly bound there. Methotrexate competitively inhibits the enzyme dihydrofolate reductase and thus inhibits DNA and RNA synthesis. So far, it is not clear whether the efficacy of methotrexate in rheumatoid arthritis is due to an antiphlogistic or immunosuppressive effect. Dihydrofolate must be reduced to tetrahydrofolate by this enzyme before it can be used as a carrier for C1 groups in the synthesis of purine nucleotides and thymidylates. Therefore, methotrexate causes an accumulation of cellular folates and inhibits DNA synthesis, DNA repair and cell replication. The thymidylate synthesis is inhibited by extracellular concentrations of free methotrexate from 10-8 mol / l and the purine synthesis from 10-7 mol / l. The affinity of dihydrofolate reductase to methotrexate is significantly greater than its affinity for folic acid or dihydrofolic acid, so that even large amounts of folic acid given at the same of methotrexate do not reverse the effects of methotrexate. In addition, methotrexate appears to cause an increase in intracellular deoxyadenosine

triphosphate, which is believed to inhibit ribonucleotide reduction and polynucleotide ligase, an enzyme involved in DNA synthesis and repair. Actively proliferating tissues such as malignant cells, bone marrow, fetal cells, oral and intestinal mucosa, spermatogonia and bladder cells are generally more sensitive to this effect of methotrexate.
In psoriasis, the production rate of epithelial cells of the skin is greatly increased over normal skin. This differential proliferation rate forms the basis for the use of methotrexate to control the psoriatic process.

5.2 Pharmacokinetic properties

Absorption
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.
After intramuscular administration, methotrexate is rapidly and completely absorbed. Maximum serum levels are reached within 0.25-2 h.

Distribution
After intravenous administration, the initial volume of distribution is about 0.18 l / kg (18% of body weight) and under steady-state conditions about 0.4-0.8 l / kg (40-80% of body weight). Methotrexate competes with reduced folates for active carrier-mediated cell membrane transport. At serum concentrations of over 100 μmol / l, passive diffusion becomes the main route of transport, through which effective intracellular concentrations can be achieved. Approximately 50% of methotrexate is bound to serum proteins. Methotrexate reaches the highest concentrations in the kidney, gall bladder, spleen, liver, skin and in the large and small intestine. Methotrexate slowly passes into the so-called "third space" (pleural effusions and ascites) and is released from this delayed (which may lead to a possible increase in toxicity!). Methotrexate passes into the CSF only in minimal quantities at low doses, At high doses (300 mg / kg body weight), concentrations between 4 and 7 μg / ml were measured in the CSF.
Low levels of methotrexate were found in saliva and in breast milk, and it also passes through the placental barrier.

Biotransformation
At low doses, methotrexate does not appear to undergo significant metabolism. After high doses, methotrexate is metabolised intrahepatically to 7-hydroxymethotrexate and 2,4-diamino-10-methylpteroic acid as well as intracellularly to methotrexate polyglutamates, which can be re-formed by hydrolase enzymes into methotrexate. The polyglutamate metabolites are inhibitors of dihydrofolate reductase and thymidylate synthetase. Small amounts of methotrexate polyglutamates may remain in the tissue for a longer time. The retention and prolonged action of these active metabolites vary between different cells, tissues and tumors.
The terminal half-life is approximately 3-10 hours when doses of methotrexate [≤ 30 mg / m2 KOF (body surface area)] are used. In the high-dose therapy, the terminal half-life is 8-15 hours.
Pediatric patients receiving methotrexate for JIA (3.75-26.2 mg / m2 KOF) had a terminal half-life of 0.9-2.3 hours.

Elimination
The elimination of methotrexate is mainly renal by glomerular filtration and active secretion in the proximal tubule and depends on the dosage and type of application. After intravenous administration, 80-90% of the administered dose is excreted unchanged in the urine within 24 hours. Biliary elimination is limited to a maximum of 10% of the administered dose. Methotrexate is subject to a pronounced enterohepatic circulation, so that a maximum of 10% of the administered dose is excreted via the faeces.
Following intravenous administration, methotrexate is eliminated after a few minutes of distribution during a second 12-24 hour phase with a plasma half life of 2-3 hours and during a third phase with a plasma half life of 12-24 hours. If renal function is impaired, delayed elimination may be expected, which may result in severe side effects. A good correlation was found between methotrexate clearance and endogenous creatinine clearance. Total methotrexate clearance averages 12 l / h, but varies widely and is generally decreased at higher doses. Delayed elimination is one of the main causes of the toxicity of methotrexate.
Limitations of excretion in impaired liver function are currently unknown.

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

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.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER(S)

PL 04416/1600

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/02/2025

10 DATE OF REVISION OF THE TEXT

21/02/2025