Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Methotrexate 25 mg/ml Solution for Injection/Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 25 mg methotrexate.

One vial with 2 ml contains 50 mg methotrexate.
One vial with 4 ml contains 100 mg methotrexate.
One vial with 10 ml contains 250 mg methotrexate.
One vial with 40 ml contains 1000 mg methotrexate.

For the full list of excipients, see section 6.1

Methotrexate 25 mg/ml contains 0.21 mmol (4.945 mg) sodium per ml.

3 PHARMACEUTICAL FORM

Solution for injection/infusion

Clear yellow solution

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Methotrexate 25 mg/ml solution for injection/infusion is used alone or in combination with other anticancer agents in the treatment of:

- Acute lymphocytic leukaemias
- Intermediate or high degree Non-Hodgkin's lymphomas in adults
- Non-Hodgkin’s lymphomas in paediatric patients
- Metastatic or recurrent head and neck cancer
- Adjuvant treatment of breast cancer after tumour resection or mastectomy
- Advanced breast cancer
- Choriocarcinoma and other trophoblastic tumours (in monotherapy in patients at low risk or in combination therapy in patients at high risk)
- Adjuvant and neoadjuvant therapy of osteosarcoma

4.2 Posology and method of administration

WARNINGS
The **dose must be adjusted carefully** depending on the body surface area if methotrexate is used for the treatment of **tumour diseases**. Fatal cases of intoxication have been reported after administration of **incorrect calculated** doses.

Methotrexate can be given intramuscularly, intravenously, intraarterially and intrathecally.

The dose is usually calculated per m² body surface area (BSA).

Methotrexate 25 mg/ml solution for injection or infusion should only be applied by physicians with experience in antimetabolite chemotherapy and the other indication ranges. It is useful to separate the treatment with methotrexate

according to the following regimen.

Low-dose therapy	Single dose under 100 mg/m^2
Medium-dose therapy	Single dose between 100 mg/m^2 and 1,000 mg/m^2
High-dose therapy	Single dose above 1,000 mg/m^2
For methotrexate doses exceeding approx. 100 mg/m^2 as a single dose, the methotrexate treatment must be followed by application of calcium folinate (see calcium folinate rescue).	

The application and dosage recommendations for the administration of methotrexate (low-dose therapy, mostly as part of polychemotherapy) for different indications varies considerably. Some common dosages and therapy protocols, which have proved to be efficacious in the therapy of the disorder in each case, are given below. Furthermore, several different polychemotherapies involving methotrexate have proved efficacious for the various indications for high-dose methotrexate therapy. None of these therapy protocols can currently be described as standard therapy. Since the application and dosage recommendations for therapy with methotrexate at high and low dosages vary, only the most commonly used guidelines are given, and should be considered as examples. High-dose methotrexate therapy should only be carried out if the creatinine concentration is within the normal range. If there is evidence to indicate impairment of renal function (e.g., marked side effects from prior therapy with methotrexate or impairment of urine flow), the creatinine clearance must be determined. Current published protocols should be consulted for dosages and the method and sequence of administration.

Methotrexate can be used at very high doses (> 1 g) in certain neoplastic conditions. Disease states that have been successfully treated with high-dose methotrexate either alone or in combination with other cytostatics are acute lymphatic leukaemia, osteogenic sarcoma and certain solid tumours. High-dose therapy is usually given as an infusion over 24 h.

High doses may cause the precipitation of methotrexate or its metabolites in the renal tubules. A high fluid throughput and alkalisation of the urine to pH 6.5-7.0 by oral or intravenous administration of sodium bicarbonate (e.g., 5 times 625 mg tablets every three hours) or acetazolamide (e.g., 500 mg orally four times a day) is recommended as a preventive measure.

Before beginning combination therapy involving high-dose methotrexate the leukocyte and thrombocyte count should exceed the respective minimum values (leukocytes 1,000 to 1,500/µl, thrombocytes 50,000 to 100,000/µl). When applying high-dose methotrexate therapy, the serum methotrexate concentration must be checked at regular intervals. The sampling times and the maximum values for toxic serum methotrexate concentrations which require measures such as an increase in the calcium folinate dose or the intravenous fluid supply can be taken from the individual therapy protocols. As a prophylactic measure against nephrotoxic effects, when conducting a course of therapy involving high-dose methotrexate an intravenous fluid supply and alkalisation of the urine is necessary. Urine flow and the pH value of the urine should be monitored during the methotrexate infusion. Calcium folinate rescue therapy should be performed after high-dose treatment with methotrexate.

Calcium folinate rescue
Calcium folinate rescue is necessary when methotrexate is given at doses exceeding 100 mg/m² BSA.
As a rule, the first dose of Calcium folinate is 15 mg (6-12 mg/m²) to be given 12-24 hours (24 hours at the latest) after the beginning of methotrexate infusion. The same dose is given every 6 hours throughout a period of 72 hours. After several parenteral doses treatment can be switched to the oral form.

Forty-eight hours after the start of the methotrexate-infusion, the residual methotrexate-level should be measured. If the residual methotrexate-level is >0.5 µmol/l, an intensification of the rescue regime might be necessary.

In addition to calcium folinate administration, the prompt excretion of methotrexate has to be assured by
- maintenance of high urine output (adequate hydration)
- alkalinisation of urine (e.g. with sodium bicarbonate 8.4%)

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

The following regimens are only examples.

Acute lymphatic leukaemia
- 3.3 mg/m² in combination with other cytostatic agents once daily for 4-6 weeks.
- 2.5 mg/kg every two weeks.
- 30 mg/m²/week maintenance therapy.
- 20 mg/m² in combination with other cytostatic agents once weekly.

In children:
Doses between 1,000 to 5,000 mg/m² BSA i.v. have been used sequentially (with subsequent leucovorin administration) for consolidation of remission and maintenance treatment. Oral treatment with doses up to 20 mg/m²/week is used together with intravenous administration and intrathecal CNS prophylaxis as maintenance treatment.

In adults:
Maintenance treatment with the sequential POMP combination and intrathecal CNS prophylaxis with methotrexate is customary. On relapse, high-dose methotrexate can be tried.

Choriocarcinoma and similar trophoblastic diseases (e.g., hydatidiform mole and chorioadenoma destruens)
15-30 mg/m2 intramuscularly for five days. Usually such courses may be repeated 3 to 5 times as required, with rest periods of one or more weeks interposed between the courses, until any manifesting toxic symptoms subside.

Non-Hodgkin's lymphomas
Stages I or II of Burkitt's lymphoma have been treated with methotrexate (orally). Stage III lymphomas and lymphosarcomas may respond to methotrexate given in doses of 0.625-2.5 mg/kg body weight daily as part of polychemotherapy, and 90-900 mg/m² as an intravenous infusion, followed by administration of calcium folinate.

In Non-Hodgkin's lymphomas in children, methotrexate is applied according to the phase of the disease and the histological type within the scope of various polychemotherapies at the appropriate doses. Dosage range for therapy with methotrexate at medium or high dosage: single doses from 300-5,000 mg/m² as an intravenous infusion.

Head and neck cancer
Monotherapy: 40-60 mg/m² can be given once weekly as intravenous bolus injection.
Intravenous infusions of 240-1,080 mg/m² with calcium folinate rescue have been used in the treatment of metastatic or recurrent tumours. Intra-arterial infusions of methotrexate have also been used.

Breast cancer
Prolonged cyclic combination with cyclophosphamide, methotrexate and fluorouracil has given good results when used as adjuvant treatment to radical mastectomy in primary breast cancer with positive axillary lymph nodes. The dose of methotrexate is 40 mg/m² intravenously on the first and eighth days of the cycle. Methotrexate, in intravenous doses of 10-60 mg/m², is also commonly included in cyclic combination regimes with other cytotoxic drugs in the treatment of advanced breast cancer.

Osteosarcoma
Effective combination chemotherapy requires the administration of several cytotoxic chemotherapeutics.
In addition to high-dose methotrexate with calcium folinate rescue, doxorubicin, cisplatin, and a combination of bleomycin, cyclophosphamide and dactinomycin (BCD) can be given. The starting dose for high-dose methotrexate treatment is 12 g/m². If this dose is insufficient to reach peak serum concentrations of 10-3M at the end of the infusion, the dose can be increased to 15 g/m² for the subsequent treatments. If the patient vomits or cannot tolerate oral treatment, calcium folinate is given i.v. or i.m.

Special population:

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

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

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) (see section 4.3).

Patients with pathologic fluid accumulation
Methotrexate elimination is reduced in patients with pathologic fluid accumulation (third space fluids) such as ascites or pleural effusions that may lead to prolonged methotrexate plasma elimination half-life and unexpected toxicity. Pleural effusions and ascites should be drained prior to initiation of methotrexate treatment. Methotrexate dose should be reduced according to the serum methotrexate concentrations.

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

Method of administration
Precautions to be taken before handling or administering the medicinal product, see section 6.6.

4.3 Contraindications

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- liver insufficiency (see section 4.2).
- alcohol abuse.
- renal insufficiency (creatinine clearance < 20 ml/min, see section 4.2).
- pre-existing blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia or significant anaemia.
- serious, acute or chronic infections such as tuberculosis and HIV.
- ulcers of the oral cavity and known active gastrointestinal ulcer disease.
- pregnancy, breast-feeding (see section 4.6).
- concurrent vaccination with live vaccines.

4.4 Special warnings and precautions for use

Patients undergoing therapy should be subject to appropriate supervision so that signs of possible toxic effects or adverse reactions may be detected and evaluated with minimal delay. Therefore methotrexate should only be administered by, or under the supervision of, physicians whose knowledge and experience includes the use of antimetabolite therapy. Because of the possibility of severe or even fatal toxic reactions, the patient should be fully informed of the risks involved and the recommended safety measures.
However doses exceeding 20 mg/week can be associated with significant increase in toxicity, especially bone marrow suppression.

Methotrexate has been reported to cause impairment of fertility, oligospermia, menstrual dysfunction and amenorrhoea in humans, during and for a short period after cessation of therapy. In addition, methotrexate causes embryotoxicity, abortion and foetal defects in humans. Therefore the possible risks of effects on reproduction should be discussed with patients of childbearing potential (see section 4.6).

Recommended examinations and safety measures:

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

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

- Examination of the mouth and throat for **mucosal changes**.

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

- **Liver function** tests:

Particular attention should be paid to the onset of liver toxicity. Treatment should not be initiated or should be discontinued if there are any abnormalities in liver function tests or liver biopsies, or if these develop during therapy. Such abnormalities should return to normal within two weeks; after which, treatment may be resumed at the discretion of the physician.

Further research is needed to establish whether serial liver chemistry tests or propeptide of type III collagen can detect hepatotoxicity sufficiently. This assessment should differentiate between patients without any risk factors and patients with risk factors, e.g. excessive prior alcohol consumption, persistent elevation of liver enzymes, history of liver disease, family history of hereditary liver disorders, diabetes mellitus, obesity and previous contact with hepatotoxic drugs or chemicals and prolonged methotrexate treatment or cumulative doses of 1.5 g or more.

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

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

- **Renal function** should be monitored by renal function tests and urinalysis (see also 4.2 and 4.3):

As methotrexate is eliminated mainly by renal route, increased serum concentrations are to be expected in the cases of renal insufficiency, which may result in severe undesirable reactions.

In cases of possible renal impairment (e.g. in elderly patients), closer monitoring is required. This particularly applies to the co-administration of medicinal products which affect methotrexate excretion, cause kidney damage (e.g. non-steroidal anti-inflammatory drugs) or which can potentially lead to haematopoietic disorders. Dehydration may also potentiate the toxicity of methotrexate.
Alkalising the urine and increase a high diuresis is recommended, especially in high dose treatement.

- **Respiratory system:** Acute or chronic interstitial pneumonitis, often associated with blood eosinophilia, may occur and deaths have been reported. Symptoms typically include dyspnoea, cough (especially a dry non-productive cough) and fever for which patients should be monitored at each follow-up visit. Patients should be informed of the risk of pneumonitis and advised to contact their doctor immediately should they develop persistent cough or dyspnoea.

Methotrexate should be withdrawn from patients with pulmonary symptoms and a thorough investigation (including chest x-ray) should be made to exclude infection. If methotrexate induced lung disease is suspected, treatment with corticosteroids should be initiated and treatment with methotrexate should not be restarted.

Pulmonary symptoms require a quick diagnosis and discontinuation of methotrexate therapy. Pneumonitis can occur at all dosages.

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

- **Malignant lymphomas** may occur in patients receiving low-dose methotrexate, in which case, therapy must be discontinued. Failure of the lymphoma to show signs of spontaneous regression requires the initiation of cytotoxic therapy.

- **Pleural effusions and ascites** should be drained prior to initiation of methotrexate treatment (see section 4.2).

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

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

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

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

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

This medicinal product contains 0.21 mmol (4.945 mg) sodium per ml. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

Patients taking potentially hepatotoxic medicinal products during methotrexate therapy (e.g. leflunomide, azathioprine, sulphasalazine, and retinoids) should be closely monitored for possibly increased hepatotoxicity. Alcohol consumption

should be avoided during treatment with methotrexate.

Be aware of pharmacokinetic interactions between methotrexate, anticonvulsant drugs (reduced methotrexate blood levels), and 5- fluorouracil (increased t½ of 5-fluorouracil).

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

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

Antibiotics, like penicillines, glycopeptides, sulfonamides, ciprofloxacin and cefalotin can, in individual cases, reduce the renal clearance of methotrexate, so that increased serum concentrations of methotrexate with simultaneous haematological and gastro-intestinal toxicity may occur.

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

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

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

Under concomitant administration of Methotrexate 25 mg/ml and basic treatments (e.g. gold compounds, penicillamine, hydroxychloroquine, sulfasalazine, azathioprine, cyclosporine), increased toxic effects of methotrexate are generally not be expected.

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

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

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

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

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

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

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy:
Methotrexate is contraindicated during pregnancy (see section 4.3). In animal studies, methotrexate has shown reproductive toxicity (see section 5.3). Methotrexate has been shown to be teratogenic to humans; it has been reported to cause fetal death and/or congenital abnormalities. Exposure of a limited number of pregnant women (42) resulted in an increased incidence (1:14) of malformations (cranial, cardiovascular and extremital). If methotrexate is discontinued prior to conception, normal pregnancies have been reported.

In women of child-bearing age, any existing pregnancy must be excluded with certainty by taking appropriate measures, e.g. a pregnancy test, prior to initiating therapy. Women must not get pregnant during methotrexate therapy and patients of a sexually mature age (women and men) must use effective contraception during treatment with methotrexate and at least 6 months thereafter (see section 4.4). If, nevertheless, pregnancy occurs during this period, medical advice should be given regarding the risk of harmful effects on the child associated with treatment.
As methotrexate can be genotoxic, all women who wish to become pregnant are advised to consult a genetic councelling centre, if possible, already prior to therapy, and men should seek advice about the possibility of sperm preservation before starting therapy.

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

Fertility:
Animal studies show that methotrexate impairs fertility.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Occurrence and severity of undesirable effects depend on dosage level and frequency of methotrexate administration. However, as severe adverse reactions may occur even at lower doses, it is indispensable that the doctor monitors patients regularly at short intervals. Most undesirable effects are reversible if recognised early. If such adverse reactions occur, dosage should be reduced or therapy be interrupted and appropriate countermeasures should be taken (see section 4.9).

Methotrexate therapy should only be resumed with caution, under close assessment of the necessity for treatment and with increased alertness for possible reoccurrence of toxicity.

Frequencies in this table are defined using the following convention: very common (≥ 1/10), common (≥ 1/100 < 1/10), uncommon (≥ 1/1,000 < 1/100), rare (≥ 1/10,000 < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data). Further details are given following this table.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The following adverse reactions may occur:
After intramuscular methotrexate administration, local adverse reactions (burning sensation) or damage (formation of

sterile abscess, destruction of fatty tissue) may occasionally occur at the injection site.

	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**
Infections and infestations					Sepsis, opportunistic infections (may be fatal in some cases), infections caused by the cytomegaly virus
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			Individual cases of lymphoma, which abated in a number of cases once methotrexate treatment had been discontinued. In a recent study, it was not possible to establish that methotrexate therapy increases the incidence of lymphomas		
Blood and lymphatic system disorders		Leukocytopenia, thrombocytopenia, anaemia	Pancytopenia, agranulocytosis, haematopoietic disorders.	Megaloblastic anaemia	Severe courses of bone marrow depression, aplastic anaemia. Lymphadenopathy, lymphoproliferative disorders (partly reversible), eosinophilia and neutropenia
Immune system disorders					Immunosuppression hypogammaglobulinaemia
Psychiatric disorders					Insomnia
Nervous system disorders		Headache, fatigue, drowsiness	Vertigo, confusion, depression, seizures, leukoencephalopathy/ encephalopathy	Severely impaired vision, mood alterations	Pain, muscular asthenia or paresthesia of the extremities, changes in sense of taste (metallic taste), meningism (paralysis, vomiting), acute aseptic meningitis
Eye disorders				Visual disturbances	Conjunctivitis, retinopathy
Cardiac disorders				Pericarditis, pericardial effusion, pericardial tamponade	
Vascular disorders				Hypotension, thromboembolic events (including arterial and cerebral thrombosis, thrombophlebitis, deep vein thrombosis, retinal vein thrombosis, pulmonary embolism).	
Respiratory, thoracic and mediastinal disorders		Pulmonary complications due to interstitial alveolitis/-pneumonitis and related deaths (independent of dose and duration of methotrexate treatment). Typical symptoms may be: general illness; dry, irritating cough; shortness of breath progressing to rest dyspnoea, chest pain, fever. If such complications are suspected, methotrexate treatment must be discontinued immediately and infections (including pneumonia) must be excluded.	Pulmonary fibrosis	Pharyngitis, apnoea, bronchial asthma	Pneumocystis carinii pneumonia, shortness of breath, chronic obstructive pulmonary disease. Infections including pneumonia have also been observed. Pleural effusion.
Gastrointestinal	Loss of	Diarrhoea	Gastrointestinal	Enteritis,	Haematemesis, toxic

disorders	appetite, nausea, vomiting, abdominal pain, inflammation and ulcerations of the mucous membrane of mouth and throat (especially during the first 24-48 hours after administration of methotrexate). Stomatitis, dyspepsia	(especially during the first 24-48 hours after administration of methotrexate).	ulcers and bleeding.	melaena. Gingivitis, malabsorption	megacolon
Hepatobiliary disorders	Increase in liver-related enzymes (ALAT, ASAT, alkaline phosphatase and bilirubin).		Development of liver fattening, fibrosis and cirrhosis (occurs frequently despite regularly monitored, normal values of liver enzymes); diabetic metabolism; drop of serum albumin.	Acute hepatitis and hepatotoxicity.	Reactivation of chronic hepatitis, acute liver degeneration. Furthermore, herpes simplex hepatitis and liver insufficiency have been observed (also see the notes regarding liver biopsy in section 4.4).
Skin and subcutaneous tissue disorders		Exanthema, erythema, itching.	Urticaria, photosensibility, enhanced pigmentation of the skin, hair loss, increase of rheumatic nodules, herpes zoster, painful lesions of psoriatic plaque; severe toxic reactions: vasculitis, herpetiform eruption of the skin, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome).	Increased pigmentary changes of nails, acne, petechiae, ecchymoses, erythema multiforme, cutaneous erythematous eruptions.	Acute paronychia, furunculosis, telangiectasia Furthermore, nocardiosis, histoplasma and cryptococcus mycosis and disseminated herpes simplex have been reported. Allergic vasculitis, hidradenitis.
Musculoskeletal and connective tissue disorders			Arthralgia, myalgia, osteoporosis.	Stress fracture.	
Renal and urinary disorders			Inflammation and ulceration of the urinary bladder (possibly with haematuria), dysuria.	Renal failure, oliguria, anuria, azotaemia.	Proteinuria.
Reproductive system and breast disorders			Inflammation and ulceration of the vagina.		Loss of libido, impotence, oligospermia, impaired menstruation, vaginal discharge, infertility.
General disorders and administration site conditions			Severe allergic reactions progressing to anaphylactic shock.		Fever, impaired wound healing.

4.9 Overdose

Symptoms of overdose
Toxicity of methotrexate mainly affects the haematopoietic and gastrointestinal systems.
Symptoms include leukocytopenia, thrombocytopenia, anaemia, pancytopenia, neutropenia, bone marrow depression, mucositis, stomatitis, oral ulceration, nausea, vomiting, gastrointestinal ulceration and gastrointestinal bleeding. Some patients showed no signs of overdose.
There are reports of death due to sepsis, septic shock, renal failure and aplastic anaemia.

Therapeutic measures in case of overdose
Calcium folinate is the specific antidote for neutralising the toxic undesirable effects of methotrexate.

In cases of accidental overdose, a dose of calcium folinate equal to or higher than the offending dose of methotrexate should be administered intravenously or intramuscularly within 1 hour, and dosing continued until serum levels of

methotrexate are below 10^{-7} mol/L.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action
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.

5.2 Pharmacokinetic properties

Distribution
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 (300 mg/kg body weight), concentrations between 4 and 7 µg/ml have been measured in the liquor.

Biotransformation
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.
Methotrexate passes the placental barrier in rats and monkeys.

Elimination
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.

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

Hydrochloric acid (pH adjustment)
Sodium hydroxide (pH adjustment)
Sodium chloride
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

The shelf-life is 18 months.

Chemical and physical in-use stability after dilution has been demonstrated in glucose (5 %) and sodium chloride (0.9 %) solutions for 24 hours at room temperature and for 30 days at 2°C-8°C, if protected from light.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

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

For storage of the product after dilution see Section 6.3.

6.5 Nature and contents of container

2, 4, 10 or 40 ml solution in Type I clear glass vial with bromobutyl rubber stopper and aluminium flip-off seal.

Each pack contains 5 vials of 2 ml solution.
Each pack contains 5 vials of 4 ml solution.
Each pack contains 5 vials of 10 ml solution.
Each pack contains 1 vial of 40 ml solution.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Methotrexate 25 mg/ml solution for injection/infusion may be further diluted with an appropriate preservative-free medium such as glucose solution (5 %) or sodium chloride solution (0.9 %) to an in-use concentration of 2 mg/ml.

With respect to the handling the following general recommendations should be considered: The product should be used and administered only by trained personnel; the mixing of the solutions should take place in designated areas, designed to protect personnel and the environment (e.g. safety cabins); protective clothing should be worn (including gloves, eye protection, and masks if necessary).

The product is for single use only. Discard any unused solution immediately after initial use. Waste should be disposed of carefully in suitable separate containers, clearly labelled as to their contents (as the patient’s body fluids and excreta may also contain appreciable amounts of antineoplastic agents and it has been suggested that they, and material such as bed linen contaminated with them, should also be treated as hazardous waste). Any unused product or waste should be

disposed of in accordance with local requirements by incineration. For example, chemical destruction methods (oxidation with e.g., potassium permanganate and sulphuric acid or aqueous alkaline potassium permanganate or sodium hypochlorite) have also been used.

Adequate procedures should be in place for accidental contamination due to spillage; staff exposure to antineoplastic agents should be recorded and monitored.

If a cytotoxic drug should contaminate the skin it should be washed off immediately using copious amounts of running water for at least ten minutes. For example, if eyes are sprayed with cytotoxic material they should be rinsed immediately with copious amounts of water and bathed with sterile sodium chloride solution for at least ten minutes.

Pregnant staff should avoid handling antineoplastic agents.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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