

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT

**Methotrexate 25 mg/ml solution for injection**

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

<b>concentration</b>	<b>size</b>	<b>amount per vial</b>
25 mg methotrexate per ml (2.5%)	2.0 ml	50 mg
25 mg methotrexate per ml (2.5%)	20 ml	500 mg
25 mg methotrexate per ml (2.5%)	40 ml	1.000 mg
25 mg methotrexate per ml (2.5%)	200 ml	5.000 mg

One vial with 2 ml contains 50 mg methotrexate.

One vial with 20 ml contains 500 mg methotrexate.

One vial with 40 ml contains 1.000 mg methotrexate.

One vial with 200 ml contains 5.000 mg methotrexate.

For a full list of excipients, see section 6.1.

### 3. PHARMACEUTICAL FORM

Solution for injection

Vials containing a clear yellowish solution

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

Methotrexate 25 mg/ml solution for injection may be used for the following indications:

- Severe, generalised psoriasis vulgaris resistant to therapy, including psoriatic arthritis.
- Acute lymphocytic leukaemias (ALL).
- Prophylaxis and treatment of meningeal leukaemia (intrathecal administration).
- Non-Hodgkin's lymphomas.
- Cancer of the ovary.
- Head and neck cancer.
- Breast cancer.
- Choriocarcinoma and similar trophoblastic diseases.
- Cancer of the cervix.
- Bronchogenic carcinoma.
- Osteosarcoma.
- Mycosis fungoides.
- Cancer of the bladder.

## 4.2 Posology and method of administration

**Note: Methotrexate 25 mg/ml solution for injection (5000 mg/200 ml, 1000 mg/40 ml and 500 mg/20 ml) are hypertonic presentations and therefore not suitable for intrathecal and intraventricular use.**

Since methotrexate is predominately eliminated renally, in patients with impaired creatinine clearance, delayed elimination is to be expected, which can lead to severe side effects. In patients with impaired renal function, the dose regimens must be adjusted according to the creatinine clearance and serum methotrexate concentrations. Renal function can be adversely affected by the application of methotrexate.

Doses are usually based on the patient's body weight or body surface area. Total doses greater than 100 mg are usually given by intravenous infusion.

High doses may cause the precipitation of methotrexate or its metabolites in the renal tubules. A high fluid throughput and alkalinisation 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/ $\mu$ l, thrombocytes 50,000 to 100,000/ $\mu$ l). 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 alkalinisation 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.

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

Methotrexate 25 mg/ml solution for injection 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 <sup>2</sup>
Medium-dose therapy	Single dose between 100 mg/m <sup>2</sup> and 1,000 mg/m <sup>2</sup>
High-dose therapy	Single dose above 1,000 mg/m <sup>2</sup>
For methotrexate doses exceeding approx. 100 mg/m <sup>2</sup> 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.

### **Adults and children**

#### **Severe, generalised psoriasis vulgaris resistant to therapy, including psoriatic arthritis**

Psoriatic arthritis: The recommended initial dosage is 7.5 mg methotrexate once weekly intravenously or intramuscularly. According to the activity of the disease, the initial dose can be increased step by step with 2.5 mg methotrexate. A weekly dose of 20 mg methotrexate should not be exceeded. After reaching the desired therapy results, the dosage should be decreased step by step to the lowest effective maintenance dose if possible.

Psoriasis: The recommended initial dosage is 5-10 mg and maximum dose 25 mg methotrexate once weekly intravenously or intramuscularly. The initial dosage can be increased step by step until an optimal therapy result is reached but a weekly dose of 25 mg should not be exceeded. After reaching the desired therapy results, the dosage should be decreased step by step to the lowest effective maintenance dose if possible.

### **Acute lymphocytic leukaemias (ALL)**

In low doses, methotrexate is applied within the scope of complex therapy protocols for maintaining remission in children and adults with acute lymphocytic leukaemias. Normal single doses lie within the range of 20-40 mg/m<sup>2</sup> methotrexate. The maintenance dose for ALL is 15-30 mg/m<sup>2</sup> once or twice weekly.

### **Prophylaxis and treatment of meningeal leukaemia (intrathecal administration)**

Note: For the 50 mg/2 ml presentation only!

Some patients with leukaemia are subject to leukaemic invasions of the central nervous system and the CSF (= cerebrospinal fluid) should be examined in all leukaemia patients.

Passage of methotrexate from blood to the cerebrospinal fluid is minimal and for adequate therapy the drug should be administered intrathecally.

Methotrexate may be given in a prophylactic regimen in all cases of lymphocytic leukaemia. Methotrexate is administered by intrathecal injection in doses of 200-500 microgram/kg bodyweight. The administration is at intervals of 2 to 5 days and is usually repeated until the cell count of cerebrospinal fluid returns to normal. At this point one additional dose is advised. Alternatively, methotrexate 12 mg/m<sup>2</sup> can be given once weekly for 2 weeks, and then once monthly. Large doses may cause convulsions and untoward side effects may occur as with any intrathecal injection, and are commonly neurological in character.

### **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/m<sup>2</sup> 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/m<sup>2</sup> as an intravenous infusion.

### **Cancer of the ovary**

Single doses of 40-1,000 mg/m<sup>2</sup> have been reported. One reported polychemotherapy (low-dose methotrexate) regimen includes methotrexate (40 mg/m<sup>2</sup> intravenously on days 1 and 8), altretamine (150 mg/day orally for 14 days), cyclophosphamide (150 mg/day orally for 14 days), and 5-fluorouracil (600 mg/m<sup>2</sup> intravenously on days 1 and 8), repetition every 28 days. High-dose regimens include 1,000 mg/m<sup>2</sup> as an intravenous infusion every 4 weeks.

### **Head and neck cancer**

Intravenous infusions of 240-1,080 mg/m<sup>2</sup> with calcium folinate rescue have been used both as preoperative adjuvant therapy and in the treatment of advanced 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/m<sup>2</sup> intravenously on the first and eighth days of the cycle. Methotrexate, in intravenous doses of 10-60 mg/m<sup>2</sup>, is also commonly included in cyclic combination regimes with other cytotoxic drugs in the treatment of advanced breast cancer.

**Choriocarcinoma and similar trophoblastic diseases (e.g., hydatidiform mole and chorioadenoma destruens)**

15-30 mg/m<sup>2</sup> 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.

**Cancer of the cervix**

5 mg/m<sup>2</sup> intravenously for five days (single doses of 3-20 mg/m<sup>2</sup> are reported). One reported polychemotherapy regimen includes methotrexate (30 mg/m<sup>2</sup> intravenously on days 1, 15, and 22), vinblastine (3 mg/m<sup>2</sup> intravenously on days 2, 15, and 22), doxorubicin (30 mg/m<sup>2</sup> intravenously on day 2), and cisplatin (70 mg/m<sup>2</sup> intravenously on day 2), repetition every 28 days.

**Bronchogenic carcinoma**

Intravenous infusions of 20-100 mg/m<sup>2</sup> of methotrexate has been included in cyclical combination regimens for the treatment of advanced tumours. High doses with calcium folinate rescue have also been employed as the sole treatment.

**Osteosarcoma**

Effective adjuvant chemotherapy requires the administration of several cytotoxic chemotherapeutic drugs. Methotrexate is used in high doses (8,000-12,000 mg/m<sup>2</sup>) once weekly. Calcium folinate rescue is necessary. Methotrexate has also been used as the sole treatment in metastatic cases of osteosarcoma.

**Mycosis fungoides**

50 mg once weekly or 25 mg 2 times weekly intramuscularly. Dose levels of the drug and adjustment of dose regimen by reduction or cessation of the drug are guided by patient response and haematologic monitoring.

**Cancer of the bladder**

Intravenous injections or infusions of methotrexate in doses of up to 100 mg every one or two weeks have been used in the treatment of bladder cancer with promising results, varying from symptomatic relief only to complete though unsustained regression.

**Elderly**

Methotrexate should be used with extreme caution in elderly patients. A reduction in dosage should be considered.

Methotrexate can be applied in the form of an intravenous, intramuscular, intraventricular, intra-arterial or intrathecal injection as well as an intravenous infusion. Within the scope of therapy with high doses, methotrexate is administered as a continuous intravenous infusion (glucose, isotonic saline). The duration of treatment is determined by the attending physician, taking the therapy protocol and individual therapy situation into consideration.

**4.3 Contraindications**

Methotrexate 25 mg/ml solution for injection is contraindicated in patients with hypersensitivity to methotrexate, pronounced renal and hepatic insufficiency, pronounced functional impairment of the haematopoietic system such as anaemia, leucopenia, and/or thrombocytopenia (e.g., following prior radio- or chemotherapy), bone marrow suppression, active infections, overt or laboratory evidence of immunodeficiency syndrome(s), and in pregnant or breast feeding patients.

#### 4.4 Special warnings and precautions for use

Strict monitoring is necessary in patients with pulmonary dysfunction. Especially strict monitoring of the patient is indicated following prior radiotherapy (especially of the pelvis), functional impairment of the haematopoietic system (e.g., following prior radio- or chemotherapy), impaired general condition as well as advanced age and in very young children.

A chest X-ray has to be performed as a routine examination prior to administration of methotrexate. In addition, before administration of methotrexate, the following check-up examinations and safety precautions are recommended. Renal and hepatic function tests have to exclude the possibility of renal insufficiency or liver damage. Furthermore, a complete blood picture has to be taken. Urinalysis should be performed as part of the prior and follow-up examinations. During therapy, the following examinations have to be performed:

Monitoring of the serum concentration of methotrexate as a factor of the dosage for the therapy protocol used.
Regular check-ups of the oral cavity and the pharynx for changes in the mucus membranes. Ulceration mainly precedes a decrease in the number of leukocytes and/or thrombocytes.
Regular leucocyte and thrombocyte counts have to be taken.
A complete blood picture has to be taken regularly.
Regular testing of hepatic and renal function, especially in the case of high-dose methotrexate therapy should be performed. Creatinine, urea, and electrolytes have to be checked on days 2 and 3 to identify any threatening impairment of methotrexate elimination at an early stage.
In the case of long-term therapy, if deemed necessary, bone marrow biopsies have to be taken.
Preparations for a possible blood transfusion should be made.

Laboratory analysis should be repeated at least every 2 months in the course of treatment with methotrexate.

Liver biopsy should be considered after cumulative doses of methotrexate >1.5 g, if hepatic impairment is suspected.

Follow-up examinations also apply to patients receiving intrathecal methotrexate.

In addition, skin and mucus membrane contact with methotrexate should be avoided.

In the case of high-dose methotrexate therapy as well as inadvertently administered overdosage with methotrexate, calcium folinate is indicated to diminish the toxicity and counteract the effects of methotrexate.

Methotrexate should be used with extreme caution in patients with ulcers of the mouth, peptic ulcer, ulcerative colitis, ascites, and/or pleural effusion. Patients with pleural effusions or ascites should have these drained before treatment, or treatment should be withdrawn.

Special care is also required in the treatment of patients with mild to moderate renal or hepatic impairment, and in patients with diarrhoea.

Concomitant use of other medicinal products with nephrotoxic and hepatotoxic potential (incl. alcohol) should be avoided.

Concomitant use of NSAIDs (non-steroidal anti-inflammatory drugs) and cotrimoxazole (trimethoprim) should be avoided (see also section 4.5).

Methotrexate has some immunosuppressive activity and immunological responses to concurrent vaccination may be decreased. The immunosuppressive effect of methotrexate should be taken into account when immune responses of patients are important or essential.

When methotrexate is combined with radiotherapy soft tissue necrosis and osteonecrosis may occur.

Necessary actions have to be taken in case of a drop in white cell count or platelet count (i.e. immediate withdrawal of methotrexate), liver function abnormalities (suspension of therapy for at least two weeks), renal impairment (adjustment of dose), diarrhoea and ulcerative stomatitis (interruption of therapy).

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.

Methotrexate affects gametogenesis during the period of its administration and may result in decreased fertility which is thought to be reversible on discontinuation of therapy. Conception should be avoided during the period of methotrexate administration and for at least 6 months thereafter. Patients and their partners should be advised to this effect.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

Salicylates, amidopyrine derivatives, phenylbutazone, diphenylhydantoin (phenytoin), barbiturates, tranquillisers, tetracyclines, sulphonamides, doxorubicin, probenecid, and p-aminobenzoic acid, antidiabetic agents and diuretics displace methotrexate bound to the plasma protein and can increase its toxicity.

Penicillins (e.g., amoxicillin, carbenicillin, mezlocillin) can reduce the renal clearance of methotrexate in some cases, so that increased serum concentrations of methotrexate with concomitant haematological and gastrointestinal toxicity can occur.

Non-steroidal anti-inflammatory agents (e.g., indomethacin, ibuprofen) should not be administered prior to or concomitantly with high-dose methotrexate therapy used for the treatment of osteosarcoma, for example. Concomitant administration of some non-steroidal anti-inflammatory agents with methotrexate has been reported to elevate and prolong serum methotrexate levels, resulting in deaths from severe haematological and gastrointestinal toxicity.

Salicylate, non-steroidal anti-inflammatory agents, p-aminohippuric acid, probenecid, penicillin, and sulphonamide can reduce the tubular secretion of methotrexate and, especially within the low-dose range of methotrexate, increase its toxicity.

In the case of pre-treatment with medicinal products exhibiting myelosuppressive or immunosuppressive effects (e.g., cytostatics, sulphonamides, chloramphenicol, diphenylhydantoin, amidopyrine derivatives), it is possible to observe enhancement of bone marrow toxicity and immunosuppression.

Sequential use of methotrexate and 5-fluorouracil may result in synergistic enhancement of cytotoxic effects.

In the presence of an existing folic acid deficiency, the toxicity of methotrexate is increased, the efficacy of therapy can be impaired by tetrahydrofolic acid preparations. Vitamin preparations containing folic acid may alter the response to methotrexate ("over-rescue").

The application of pyrimethamine and cotrimoxazole (trimethoprim) in combination with methotrexate can cause acute megaloblastic pancytopenia, probably due to additive inhibition of the dihydrofolic acid reductase.

Methotrexate may increase the bioavailability of mercaptopurine by interference with first-pass metabolism.

Cholestyramine can increase the nonrenal elimination of methotrexate by interrupting the enterohepatic circulation.

The application of procarbazine during high-dose methotrexate therapy increases the risk of impairment of renal function.

Patients receiving concomitant therapy with methotrexate and acitretin or other retinoids should be monitored closely for any possible increased risk of hepatotoxicity.

In patients receiving methotrexate therapy, treated for a cutaneous herpes zoster with adrenocortical steroids, in isolated cases, disseminated herpes zoster manifested.

Concomitant application of methotrexate and theophylline can reduce theophylline clearance.

Care should be taken when erythrocyte concentrates are administered concomitantly with methotrexate. In patients infused with methotrexate over 24 hours and who subsequently received blood transfusions, increased toxicity was observed, caused by prolonged high serum concentrations of methotrexate.

The use of nitrous oxide-based anaesthetics intensifies the effect of methotrexate on folic acid metabolism and leads to severe unpredictable myelosuppression and stomatitis. This can be reduced by the administration of calcium folinate.

Concomitant application of L-asparaginase is antagonistic towards the effects of methotrexate.

Concomitant use of other medicinal products with nephrotoxic and hepatotoxic potential (incl. alcohol) should be avoided.

#### **4.6 Pregnancy and lactation**

Methotrexate is a human teratogen which causes a variety of malformations. It causes chromosomal aberrations in bone marrow cells in humans. Methotrexate must not be administered during pregnancy as the drug can cause foetal death. Women must not become pregnant during treatment with methotrexate. The drug may only be used in the event of the potential benefit outweighing the risk to the foetus.

Conception during and for up to six months after methotrexate therapy should be avoided.

Methotrexate can cause genetic damage. Although patients who had previously received methotrexate have conceived and born normal children, both men and

women should avoid conception during and immediately following methotrexate therapy so that normal reproduction of germinal cells may be re-established.

Since methotrexate is excreted in the breast milk, treatment must not be carried out during lactation, or breast feeding should be stopped, to avoid serious adverse drug reactions in breast-fed infants.

Fertility may be (temporarily) decreased as a result of methotrexate therapy due to defective oogenesis / spermatogenesis, transient oligospermia, or menstrual dysfunction.

#### **4.7 Effects on ability to drive and use machines**

Not known.

#### **4.8 Undesirable effects**

##### **General remarks**

The most common undesirable effects are ulcerative stomatitis, leucopenia, nausea, and abdominal discomfort.

With respect to treatment of rheumatoid arthritis with methotrexate adverse reactions with DMARDs frequently occur and may be life-threatening. All patients require careful monitoring to avoid severe toxicity. Patients who relapse during treatment with one DMARD may gain benefit when a different one is substituted. Treatment with more than one DMARD in various regimens is being tried but there is little evidence available to assess benefit. A meta-analysis of 5 different combinations of DMARDs demonstrated that although efficacy might be greater than single DMARDs, toxicity was also increased.

Methotrexate has the potential for serious, sometimes fatal toxicity. The toxic effects may be related in frequency and severity to the dose or frequency of administration but have been seen at all doses. Because the toxic reactions can occur at any time during therapy, the patients have to be observed closely and must be informed of early signs and symptoms of toxicity.

The major toxic effects of methotrexate refer to normal, rapidly proliferating tissues, particularly the bone marrow and lining of the gastrointestinal tract. Myelosuppression and mucositis are the predominant dose-limiting toxic effects of methotrexate. The severity of these reactions depends on the dose, mode and duration of application of methotrexate. Mucositis generally appears about 3 to 7 days after methotrexate application, leucopenia and thrombocytopenia follow a few days later. In patients with unimpaired elimination mechanisms, myelosuppression and mucositis are generally reversible within 14 to 28 days. Concomitant treatment and the underlying disease make it very difficult to attribute an observed side effect specifically to methotrexate.

##### **Haematological effects**

Myelosuppression and leucopenia, thrombocytopenia, anaemia up to pancytopenia, hypogammaglobulinaemia, eosinophilia, haemorrhages, haematoma, and septicaemia, and abnormal (megaloblastic) red cell morphology have been reported.

##### **Gastrointestinal disturbances**

Therapy with methotrexate may cause inflammation of the oral and pharyngeal mucus membranes, e.g., gingivitis, glossitis, pharyngitis, stomatitis, enteritis as well

as ulcerations. Furthermore, anorexia, nausea, vomiting, diarrhoea, haemorrhagic gastroenteritis, melaena, pancreatitis and ulceration accompanied by bleeding and susceptibility to perforation, malabsorption, and toxic megacolon have been reported.

When stomatitis or diarrhoea occur, therapy with methotrexate should be discontinued due to the danger of haemorrhagic enteritis or perforation or dehydration. The drug must be used with caution in patients with peptic ulcer disease or ulcerative colitis.

### **Urogenital tract**

Therapy with methotrexate at high doses especially can lead to renal failure with oliguria / anuria and an increase in the creatinine concentration.

In addition, impairment of renal function, azotaemia, cystitis, haematuria, defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, infertility, abortion, and foetal defects, dysuria, vaginitis, and vaginal ulcers may occur.

### **Hepatotoxicity**

Acute hepatotoxicity caused by methotrexate may manifest as elevations in liver enzymes (transaminases, alkaline phosphatase) and bilirubin. In addition, after long-term methotrexate therapy hepatotoxicity may occur and manifest as hepatic (periportal) fibrosis, cirrhosis, hepatitis, acute hepatic necrosis, fatty degeneration of the liver or other histologic changes in the liver which may sometimes be fatal.

### **Respiratory effects**

Upper respiratory infection has been reported. Pulmonary toxicity, which can progress rapidly and is potentially fatal, can be observed in patients treated with methotrexate. Severe reactions such as acute or chronic interstitial pneumonitis (nonspecific / interstitial accompanied by eosinophilia) and pulmonary fibrosis (rare) may occur even at low dosages of 7.5 mg per week.

Acute pulmonary oedema and the development of a "syndrome consisting of pleuritic pain and pleural thickening" following high doses have been reported.

### **Dermatologic reactions and integumentary appendages**

Severe, occasionally fatal, cutaneous or sensitivity reactions (e.g., toxic epidermic necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, skin necrosis, erythema multiforme, vasculitis and extensive herpetiform skin eruptions) may occur after the administration of methotrexate and recovery ensured mostly after discontinuation of the therapy.

Furthermore, exanthema, erythema, pruritus, urticaria, folliculitis, photosensitivity, pigmentary changes, telangiectasia, acne, furunculosis, petechia, ecchymoses, (acute desquamative) dermatitis, and an increase in rheumatic nodules have been reported. Alopecia occurs occasionally (reversible after several months). With concomitant UV therapy psoriatic lesions can worsen. Hyperpigmentation of the nails, acute paronychia and onycholysis can occur. Radiation dermatitis and sunburn may be "recalled" by the use of methotrexate.

### **Effects following intrathecal administration**

After intrathecal administration of methotrexate, acute chemical arachnoiditis (manifested as headache, back pain, nuchal rigidity, and/or fever), subacute myelopathy (manifested as paraparesis, paraplegia), Guillain-Barré syndrome, chronic leucoencephalopathy (which may be progressive or even fatal) and increased CSF pressure may occur. The leucoencephalopathy may manifest as ventricular

enlargement, confusion, tremor, irritability, somnolence, ataxia, dementia, nausea, vomiting, fever, and occasionally seizures or coma, spasticity and death.

### **Central nervous system effects and sensory organs**

Following intrathecal application, usually in combination with prior cranial radiotherapy, or after high-dose parenteral application with or without prior cranial radiotherapy leucoencephalopathy may also occur as well as a significant intellectual deficit. Discontinuance of methotrexate did not always result in a complete recovery.

Furthermore, headache, drowsiness, aphasia, hemiparesis, paresis, convulsions, vertigo, vomiting, psychoses, pain, myasthenia, paraesthesia, and cerebral oedema, may occur. After low doses of methotrexate subtle cognitive dysfunction, mood alterations, or unusual cranial sensations have occasionally been reported.

Ophthalmic reactions (sometime severe) include periorbital oedema, blepharitis, conjunctivitis, epiphora, photophobia, and impairment of vision.

### **Other side effects**

Other rare reactions related to or attributed to the use of methotrexate can be anaphylactic reactions, nodulosis, loss of libido / impotence, chills, fever without any detectable pathogen, immunosuppression, decreased resistance to infection, abnormal tissue cell changes, metabolic disorders, hyperuricaemia (due to cell destruction and hepatic and renal damage), diabetes, osteoporosis, including aseptic necrosis of the femoral head, arthralgia, myalgia, malaise and undue fatigue, gynaecomastia, tinnitus, sweating, in rare cases pericarditis, pericardial effusion, hypotension, thromboembolic complications (e.g. thrombophlebitis, pulmonary embolism, arterial, cerebral, deep vein or retinal vein thrombosis), pericardial tamponade, and even sudden death.

There have been reports on the manifestation of lymphomas which were, in some cases, reversible after discontinuing methotrexate therapy. In a recent study, no increased incidence in the manifestation of lymphomas during the course of methotrexate treatment could be detected. Furthermore, the potential of methotrexate to produce other cancers in humans has been evaluated in several studies, but the results do not confirm a cancerogenic risk.

Sometimes fatal opportunistic infections (pneumocystis carinii pneumonia, norcardiosis, histoplasmosis, cryptococcosis, herpes zoster, herpes simplex hepatitis, disseminated herpes simplex) have been reported.

Due to the immunosuppressive action of methotrexate, the drug should be used with extreme caution in patients with an active infection or in the presence of debility and is usually contraindicated in patients with overt or laboratory evidence of immunodeficiency syndromes. Immunisation may be ineffective during methotrexate therapy and immunisation with live virus vaccines is generally not recommended. Hypogammaglobulinaemia has been reported. There have been reports of disseminated vaccinia infections. Cytostatics can reduce antibody formation following an influenza vaccination.

In rare cases, following intrathecal administration, a tumour lysis syndrome has been observed.

It has been suggested that children with Down's syndrome are less able to tolerate methotrexate therapy.

In cases of acute lymphocytic leukaemia, methotrexate can cause pain in the left epigastric region (inflammation of the episplenic region due to destruction of the leukaemic cells).

Furthermore, osteopathy may occur. Several authors reported this effect in patients (adults and children) treated with methotrexate for rheumatoid arthritis, acute lymphocytic leukaemia, osteosarcoma.

#### 4.9 Overdose

In the case of high-dose methotrexate therapy as well as inadvertently administered overdose with methotrexate, calcium folinate is indicated to diminish the toxicity and counteract the effects of methotrexate. As there are no generally valid standard recommendations for the dosage and mode of application of calcium folinate as an antidote to massive-dose methotrexate therapy at higher dosage, the following dose recommendations are given as examples. Dosage guidelines are presented below. In cases of massive overdose with methotrexate, hydration and alkaline diuresis may be necessary to prevent the precipitation of methotrexate and/or its metabolites in the renal tubules. Neither haemodialysis nor peritoneal dialysis have been shown to improve methotrexate elimination.

Calcium folinate dosage regimens vary depending upon the dose of methotrexate administered. In general, it should be administered at a dosage of 15 mg (approximately 10 mg/m<sup>2</sup>) every 6 hours for 10 doses either parenterally by intramuscular injection, bolus intravenous injection or intravenous infusion. Where overdose of methotrexate is suspected, the dose should be equal to or higher than the offending dose of methotrexate and should be administered within the first hour. The following dose recommendations are given as examples.

serum methotrexate level 24-30 hours	dosage	duration
less than 1.5x10 <sup>-6</sup> mol/l to 1x10 <sup>-8</sup> mol/l	10-15 mg/m <sup>2</sup> every 6 hours	48 hours
1.5 to 5.0x10 <sup>-6</sup> mol/l	30 mg/m <sup>2</sup> every 6 hours	until level is less than 5x10 <sup>-8</sup> mol/l
more than 5.0x10 <sup>-6</sup> mol/l	60-100 mg/m <sup>2</sup> every 6 hours	until level is less than 5x10 <sup>-8</sup> mol/l

Intrathecal overdose (exceeding 100 mg) results in severe neurotoxicity, which occurs as prompt burning or numbness in the lower extremities, stupor, agitation, seizures, and / or respiratory insufficiency, and in some cases brain damage or fatal necrotising leucoencephalopathy. Intensive systemic support, high-dose systemic calcium folinate, alkaline diuresis, and rapid CSF drainage and ventriculolumbar perfusion are necessary.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

ATC-Code: L01 BA 01 (Antineoplastic and immunosuppressive drugs, cytostatics, antimetabolites).

Methotrexate is an antimetabolite antineoplastic agent that inhibits folate metabolism due to its effects on dihydrofolate reductase and thus diminishes reduced folate pools, which are essential cofactors, particularly for DNA synthesis, but also for

purine and protein synthesis. Furthermore, the drug has immunosuppressive and anti-inflammatory effects.

## 5.2 Pharmacokinetic properties

Methotrexate is completely available systemically after intravenous, intramuscular or intrathecal administration. Peak serum concentrations are reached within 0.5 to 2 hours following intravenous or intramuscular administration. Conventional doses of methotrexate of 25-100 mg/m<sup>2</sup> result in peak plasma concentrations of 1-10×10<sup>-6</sup> M. High-dose infusion regimens using 1,500 mg/m<sup>2</sup> or greater yield peak levels of 1-10×10<sup>-4</sup> M.

The drug is actively transported across cell membranes and is bound as polyglutamate conjugates. The drug is widely distributed into body tissues with the highest concentrations in the kidneys, gallbladder, spleen, liver, skin, colon and small intestine. The drug may remain in the body for several months, particularly in the liver. As the drug penetrates ascitic fluid and effusions, these spaces may act as depots. After intravenous administration the initial volume of distribution is approximately 0.18 l/kg (18 % of the body weight) and the steady-state volume of distribution is approximately 0.4 to 0.8 l/kg, which correspond to 40 % to 80 % of the body weight.

The drug undergoes hepatic and intracellular metabolism to polyglutamated forms, which can be converted back to methotrexate by hydrolase enzymes. Small amounts of these active metabolites may be converted to 7-hydroxymethotrexate. The accumulation of this metabolite may become substantial following the administration of high doses. The clearance of methotrexate from the serum is reported to be triphasic and the terminal elimination half-life is within a range of 3-10 hours for patients receiving methotrexate for rheumatoid arthritis, psoriasis or who have received low-dose methotrexate antineoplastic therapy. In patients receiving high-dose methotrexate, the elimination half-life is within the range between 8 and 15 hours. The drug is eliminated primarily in the urine by glomerular filtration and active tubular secretion. After intravenous administration about 80-90% is excreted within the urine as unchanged drug within 24 hours. Biliary excretion is limited to about 10 % and small amounts (up to 10 %) can also be detected in the faeces (enterohepatic circulation). The clearance rates of methotrexate vary widely and are generally decreased at higher dosages and dependent on the route of administration. Drug clearance from plasma under conditions of normal renal function is 103 ml/min/m<sup>2</sup>.

Delayed drug clearance has been reported to be one of the major reasons for methotrexate toxicity. Excretion is impaired and accumulation occurs more rapidly in patients with impaired renal function, pleural effusions, or those with other "third-space" compartments (e.g., ascites).

Approximately 50 % of the drug is bound to serum proteins and laboratory studies demonstrate that the drug may be displaced from plasma albumin by various compounds, including sulphonamides, salicylates, tetracyclines, chloramphenicol, and phenytoin.

Methotrexate crosses the placental barrier and is distributed into breast milk. The drug does not reach therapeutic concentrations in the cerebrospinal fluid (CSF) after parenteral administration of low doses. High CSF concentrations can be attained after intrathecal administration. After the administration of extremely high doses (15,000 to 30,000 mg/m<sup>2</sup>) CSF concentrations can be attained, which correspond to CSF concentrations after intrathecal administration. Following intrathecal application there is a significant passage into the systemic circulation. Intrathecal administration is

associated with delayed elimination of methotrexate from the body due to slow release from the CSF (terminal elimination half-life 52-78 hours).

### **5.3 Preclinical safety data**

There are no preclinical data of relevance to the prescriber other than those already provided in other sections of this SPC.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Sodium hydroxide (pH adjustment)  
sodium chloride  
water for injections

### **6.2 Incompatibilities**

Incompatibility data are available for the following drugs and the product may not be mixed with these: chlorpromazine hydrochloride, cytarabine, droperidol, fluorouracil, fludarabine, heparin sodium, idarubicine, metoclopramide hydrochloride, prednisolone sodium phosphate, promethazine, and ranitidine hydrochloride. The product is incompatible with strong oxidants and strong acids.

### **6.3 Shelf-life**

The shelf-life is 2 years.

This medicinal product should not be used after the expiry date.

For single dose use only. Discard any unused solution immediately and safely after initial use.

After dilution – Chemical and physical in-use stability has been demonstrated in glucose (5 %) and sodium chloride (0.9 %) solutions for 24 hours at room temperature without special light protection.

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.

After dilution – see 6.3.

### **6.5 Nature and contents of container**

Type I clear glass vial with chlorobutyl rubber stopper and aluminium flip-off seal.

Original pack containing 1 vial of 2 ml  
Original pack containing 5 vials of 2 ml each  
Original pack containing 10 vials of 2 ml each  
  
Original pack containing 1 vial of 20 ml  
Original pack containing 5 vials of 20 ml each  
Original pack containing 10 vials of 20 ml each  
Original pack containing 1 vial of 40 ml  
Original pack containing 5 vials of 40 ml each  
  
Original pack containing 1 vial of 200 ml

Not all pack sizes may be marketed.

## **6.6 Special precautions for disposal**

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

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, for example.

Pregnant staff should avoid handling antineoplastic agents.

## **7. MARKETING AUTHORISATION HOLDER**

hameln pharmaceuticals ltd  
Gloucester  
UK

**8. MARKETING AUTHORISATION NUMBER(S)**

PL 01502/0077

**9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION**

22/09/2006

**10. DATE OF REVISION OF THE TEXT**

30/12/2010