SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Methotrexate 100 mg/ml concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 mg methotrexate.

5 ml of solution contains 500 mg methotrexate.

10 ml of solution contains 1000 mg methotrexate.

50 ml of solution contains 5000 mg methotrexate.

Excipients with known effect:

10.60 mg/ml (0.461 mmol/ml) sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion

Clear, yellow solution with pH 7.0 to 9.0.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Acute lymphocytic leukaemia, Non-Hodgkin's lymphomas, osteogenic sarcoma, adjuvant and in advance disease of breast cancer, metastatic or recurrent head and neck cancer, choriocarcinoma and similar trophoblastic diseases, advanced cancer of urinary bladder.

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 **incorrectly calculated** doses. Health care professionals and patients should be fully informed about toxic effects.

Methotrexate 100mg/ml is hypertonic and must not be administered intrathecally.

Treatment should be initiated by or occur in consultation with a doctor with significant experience in cytostatic treatment.

Methotrexate can be administered intramuscularly, intravenously or intra-arterial. Methotrexate 100mg/ml is hypertonic and must not be administered intrathecally. The dosage is generally calculated per m^2 body surface area or body weight. Doses of over 100 mg methotrexate always require subsequent administration of folinic acid (See calcium folinate rescue).

The application and dosage recommendation for the administration of methotrexate for different indications varies considerably. Some common dosages which have been used in different indications are given below. None of these dosages 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 Current published protocols should be consulted for dosages and the method and sequence of administration.

For instructions on dilution of the medicinal product before administration, see section 6.6.

Posology:

Methotrexate can be given as convention low dose therapy, intermediate dose therapy and high dose therapy.

Conventional low dose therapy: 15-50 mg/m^2 body surface area per week intravenously or intramuscularly in one or more doses. 40-60 mg/m^2 body surface area (for head and neck cancer) once weekly as intravenous bolus injection.

Intermediate dose therapy: Between 100 mg/m^2 to 1000 mg/m^2 body surface area in single dose. In advanced squamous epithelial and bladder cancer, intermediate doses of methotrexate up to 100-200 mg/m^2 can be used (See calcium folinate rescue).

High dose therapy: In several malignant diseases, including malignant lymphoma, acute lymphatic leukaemia, osteogenic sarcoma and metastatic choriocarcinoma, doses of 1000 mg methotrexate or more per m^2 body surface area may be used, administered over a 24-hour period. High dose methotrexate therapy has to be followed by calcium folinate rescue therapy
(further refer to therapy protocols, see calcium folinate rescue).

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 $\geq$7.0 by oral or intravenous administration of sodium bicarbonate or acetazolamide is recommended as per individual therapy protocols as a preventive measure or current guidelines to be followed to achieve the desired urine pH.

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/microlitre, thrombocytes 50,000 to 100,000/microliter). 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
Since the calcium folinate rescue dosage regimen depends heavily on the posology and method of the intermediate or high-dose methotrexate administration, the methotrexate protocol will dictate the dosage regimen of calcium folinate rescue. Therefore, it is best to refer to the applied intermediate or high dose methotrexate protocol for posology and method of administration of calcium folinate.

In addition to calcium folinate administration, measures to ensure the prompt excretion of methotrexate (maintenance of high urine output and alkalinisation of urine) are integral parts of the calcium folinate rescue 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.

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.

Adults

Acute lymphocytic leukaemias (ALL)
In low doses, methotrexate is applied within the scope of complex therapy protocols for maintaining remission in adults with acute lymphocytic leukaemias. Normal single doses lie within the range of 20-40 mg/m^2 methotrexate. The maintenance dose for ALL is 15-30 mg/m^2 once or twice weekly.
Other examples:

- 3.3 mg/m^2 in combination with other cytostatic agent once daily for 4-6 week.
- 2.5 mg/kg every week.
- High dose regimen between 1 to 12 g/m^2 (i.v. 1-6 h) repeated every 1-3 weeks.
- 20 mg/m^2 in combination with other cytostatic agents once week.

Breast cancer
Cyclic combination with cyclophosphamide, methotrexate and fluorouracil has been used as adjuvant treatment to radical mastectomy in primary breast cancer with positive axillary lymph nodes. The dose of methotrexate is 40 mg/m^2 intravenously on the first and eighth days of the cycle. The treatment is repeated at 3 week intervals. Methotrexate, in intravenous doses of 10-60 mg/m^2, could be included in cyclic combination regimes with other cytotoxic drugs in the treatment of advanced breast cancer.

Osteosarcoma
Effective adjuvant chemotherapy requires the administration of several cytotoxic chemotherapeutic drugs. In addition to high dose methotrexate with calcium folinate rescue, doxorubicin, cisplatin and a combination of bleomycin, cyclophosphamide and dactinomycin (BCD) can be given. Methotrexate is used in high doses (8,000-12,000 mg/m^2) once weekly. If dose is insufficient to reach real serum concentration of 10^{-3} mol/L at the end of infusion, dose can be increased to 15 g/m^2 for subsequent treatment. Calcium folinate rescue is necessary. Methotrexate has also been used as the sole treatment in metastatic cases of osteosarcoma.

Special populations:

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

Patient with impaired renal function
Methotrexate should be used with caution in patients having impaired renal function. The dose regimens must be adjusted according to the creatinine clearance and serum methotrexate concentrations.

- If creatinine clearance (ml/min) is >50, 100% MTX dose can be given
- If creatinine clearance (ml/min) is 20-50, 50% of MTX dose can be given
- If creatinine clearance (ml/min) is <20,MTX should not be given

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) (see section 4.3). In the event of a constant increase in liver related enzymes, consideration should be given to reducing the dose or discontinuing therapy.

Patients with pathologic fluid accumulation
Methotrexate is eliminated slowly from collections of fluid (e.g. pleural effusion, ascites). This results in a prolonged terminal half-life and unexpected toxicity. In patients with significant collections of fluid, drainage of the fluid before treatment is started and monitoring of plasma methotrexate levels are recommended

Paediatric population
Methotrexate should be used with caution in paediatric patients. Treatment should follow currently published therapy protocols for children (see section 4.4).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Sever liver impairment (see section 4.2).
- Alcohol abuse.
- Severe renal impairment (creatinine clearance below 20 mL/min, see section 4.2).
- Pre-existing blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anemia.
- Serious, acute or chronic infections such as tuberculosis and HIV.
- Ulcers of the oral cavity and known active gastrointestinal ulcer disease.
- Breast-feeding (see section 4.6)
- Concurrent vaccination with live vaccines.

4.4 Special warnings and precautions for use

Fatal toxicity in association with intravenous administration due to dose miscalculation has been reported. Particular caution should be exercised when calculating the dose (see 4.2 posology and administration).

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 risk of severe toxic reactions (which can be fatal), methotrexate must only be used in life-threatening neoplastic diseases. Deaths have been reported during treatment of malignancies with methotrexate. The doctor should inform the patient of the risks of treatment and the patient should be monitored constantly by the doctor.

Use caution when administering high-dose methotrexate to patients receiving proton pump inhibitor (PPI) therapy (see section 4.5). Case reports and published population pharmacokinetic studies suggest that concomitant use of some PPIs, such as omeprazole, esomeprazole and pantoprazole, with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate, possibly leading to methotrexate toxicities. In two of these cases, delayed methotrexate elimination was observed when high-dose methotrexate was co-administered with PPIs, but was not observed when methotrexate was co-administered with ranitidine. However, no formal drug interaction studies of methotrexate with ranitidine have been conducted. Concomitant use of proton pump inhibitors (PPIs) and high dose methotrexate should be avoided, especially in patients with renal impairment.

Cases of neurological side effects ranging from headache to paralysis, coma and stroke-like episodes have been reported, primarily in children and adolescents receiving concomitant medication with cytarabine.

Fertility
Methotrexate has been reported to cause impairment of fertility, oligospermia, menstrual dysfunction and amenorrhoea in humans during and for a short period after the discontinuation of treatment, 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 age (see section 4.6). In non-oncologic indications, 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.

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.

Tumour lysis syndrome
Like other cytotoxic agents, methotrexate can induce tumour lysis syndrome in patients with rapidly growing tumours. Appropriate supportive treatment and pharmacological measures can prevent or alleviate such complications.

Methotrexate and NSAIDs
Unexpected severe (including fatal) myelosuppression, aplastic anaemia and gastrointestinal toxicity have been reported in connection with concomitant treatment with methotrexate (usually at a high dose) and non-steroidal anti-inflammatory agents (NSAIDs) (see section 4.5 interaction with other medicinal products and other forms of interaction).

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 UV rays should be avoided unless medically indicated. Patients should use adequate sun-protection to protect themselves from intense sunlight.

Concomitant methotrexate treatment and radiotherapy can increase the risk of soft tissue necrosis and osteonecrosis.

Intravenous administration of methotrexate can result in acute encephalitis and acute encephalopathy, possibly with a fatal outcome.

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

If stomatitis, diarrhoea, haematemesis or black stool occurs, therapy with methotrexate should be discontinued due to the danger of haemorrhagic enteritis or death from intestinal perforation or dehydration (see section 4.8 undesirable side effects).

Conditions in which there is folic acid deficiency can increase the risk of methotrexate toxicity.

In high dose treatment, methotrexate must not be mixed with solutions which contain preservatives (see also 6.6).

Solutions of methotrexate which contain the preservative benzyl alcohol are not recommended for use in infants. Gasping syndrome with fatal outcome has been reported in infants following intravenous treatment with solutions containing the preservative benzyl alcohol. Symptoms include rapid onset of respiratory problems, hypotension, bradycardia and cardiovascular collapse.

Infection or immunological conditions
Methotrexate must be used with great care in connection with active infection and is usually contraindicated in patients with manifest suppression of the immune response or where immunodeficiency is demonstrated by laboratory tests.
Pneumonia (which in certain cases can lead to respiratory failure) can occur. Potentially fatal opportunistic infections including *Pneumocystis jirovecii* pneumonia can occur in association with methotrexate treatment. When a patient exhibits pulmonary symptoms, the possibility of *Pneumocystis jirovecii* pneumonia should be considered (see section 4.8).

Immunisation
Methotrexate may interfere with results of immunological tests. Immunisation after a vaccination may be less effective in association with methotrexate treatment. Particularly caution should be excercised in the presence of inactive, chronic infections (e.g herpes zoster, tuberculosis, hepatitis B or C) due to possible activation. Immunisation with live viruses is not normally recommended.

Monitoring treatment
Patients who start treatment with methotrexate must be carefully monitored so that toxic effects can be detected immediately. Analysis before treatment must include a full blood count with differential and platelet count, liver enzymes, tests for hepatitis B and C infections, renal function test and chest x-ray. Toxic effects of methotrexate can occur even at low doses and it is therefore important to monitor treated patients carefully. Most undesirable effects are reversible if detected early.
After initiation of treatment or when there is change in the dose, or during periods with an increased risk of elevated methotrexate levels (e.g. in dehydration), monitoring should be performed.

Bone marrow biopsy must be performed as necessary.

Serum methotrexate level monitoring can significantly reduce methotrexate toxicity and routine monitoring of serum methotrexate level is necessary depending on dosage or therapy protocol.

Leucopenia and thrombocytopenia occur usually 4 -14 days after administration of methotrexate. In rare cases recurrence of leucopenia may occur 12 - 21 days after administration of methotrexate. Methotrexate therapy should only be continued if the benefit outweighs the risk of severe myelosuppression (see section 4.2).

Haematopoietic suppression: 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, trimetoprim/co-trimoxazole and cytarabine), 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 doctor. Further research is needed to establish whether serial liver chemistry tests or propeptide of type III collagen can detect hepatotoxicity sufficiently. This assessment should differentiate between patients without any risk factors and patients with risk factors, e.g. excessive prior alcohol consumption, persistent elevation of liver enzymes, history of liver disease, family history of hereditary liver disorders, diabetes mellitus, obesity and previous contact with hepatotoxic drugs or chemicals and prolonged methotrexate treatment or cumulative doses of 1.5 g or more.
Screening for liver-related enzymes in serum: A transient rise in transaminase levels to twice or three times the upper limit for 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.

Insulin-dependent diabetes
Patients suffering from insulin-dependent diabetes should be carefully monitored because liver cirrhosis and an increase in transaminase can occur.

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.

Malignant lymphomas may occur in patients receiving low-dose methotrexate; in which case, methotrexate must be discontinued. If lymphomas should fail to regress spontaneously, initiation of cytotoxic therapy is required.

Renal function: methotrexate treatment in patients with impaired renal function should be monitored via renal function tests and urinalysis, since impaired renal function reduces the elimination of methotrexate, which may result in severe adverse reactions.

In cases of possible renal impairment (e.g. in elderly patients), close monitoring of renal function is required. This is 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 disorder. Dehydration may also potentiate the toxicity of methotrexate. Alkalinisation of the urine and increase a high diuresis is recommended.

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) , thoracic pain 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.

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.

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 doses.

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

High dose treatment: There have also been reports of leukoencephalopathy following high-dose intravenous methotrexate, with prior cranial radiation.

Although methotrexate has been reported to cause chromosomal damage to animal somatic cells and bone marrow cells in humans, these effects are transient and reversible. In patients treated with methotrexate, evidence is insufficient to permit conclusive evaluation of any increased risk of neoplasia.

Paediatric population
Methotrexate should be used with caution in paediatric patients. Treatment should follow currently published therapy protocols for paediatric population. Serious neurotoxicity, frequently manifested as generalised or focal seizures has been reported with unexpectedly increased frequency among paediatric patients with acute lymphoblastic leukaemia who were treated with intermediate-dose intravenous methotrexate (1 g/m^2). Symptomatic patients were commonly noted to have leukoencephalopathy and/or microangiopathic calcifications on diagnostic imaging studies.

Elderly
Because of deterioration in liver and kidney function as well as reduced folic acid reserves, relatively low doses should be considered in elderly patients. These patients must be closely monitored for early signs of toxicity.

Sodium
This medicinal product contains 194 mg sodium per maximum recommended daily dose, equivalent to 9.7% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

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).

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

Under (pre-)treatment with substances that may have adverse reactions affecting the bone marrow (e.g. sulfonamides, trimethoprim/sulfamethoxazole (co-trimoxazole), 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.

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 vaccination 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).

Non-steroidal anti-inflammatory drugs (NSAIDs).
NSAID preparations must not be given prior to or concomitantly with the high doses of methotrexate used in the treatment of conditions such as osteosarcoma. Concomitant administration of NSAIDs and methotrexate at high doses has reportedly elevated and prolonged serum methotrexate levels, resulting in deaths from severe haematological and gastrointestinal toxicity. NSAID preparations and salicylates have reportedly reduced the tubular secretion of methotrexate in animal models and may increase its toxicity by increasing methotrexate levels. Concomitant treatment with NSAIDs and low doses of methotrexate must therefore be administered with caution.

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

Leflunomide
Methotrexate in combination with leflunomide may increase risk of pancytopenia and interstitial pneumonitis.

Probenecid
Renal tubular transport is diminished by probenecid, and its use together with methotrexate must be avoided.

Oral antibiotics
Oral antibiotics such as tetracycline, chloramphenicol and non-absorbable broad-spectrum antibiotics may decrease intestinal absorption of methotrexate or interfere with the enterohepatic circulation by inhibiting bowel flora and hence the metabolism of methotrexate by bacteria. In isolated cases, trimethoprim/sulfamethoxazole has reportedly increased myelosuppression in patients treated with methotrexate, probably due to reduced tubular secretion and/or an additive antifolate effect.

Antibiotics, like penicillins, 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.

Chemotherapeutic products
An increase in renal toxicity can be observed when high doses of methotrexate are given in combination with potentially nephrotoxic chemotherapeutic agents (e.g. cisplatin).

Radiotherapy
Concurrent methotrexate and radiotherapy can increase the risk of soft tissue necrosis and osteonecrosis.

Cytarabine
Concomitant therapy with cytarabine and methotrexate can increase the risk of severe neurological side effects ranging from headache to paralysis, coma and stroke-like episodes.

Hepatotoxic products
The risk of increased hepatotoxicity when methotrexate is administered concurrently with other heptatotoxic products has not been studied. Hepatotoxicity has however been reported in such cases. Patients receiving concomitant treatment with drugs with a known hepatotoxic effect (e.g. leflunomide, azathioprine, sulfasalazine, retinoids) must be carefully monitored for signs of any increase in hepatotoxicity.

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

Haematotoxic products
Administration of additional haematotoxic medicinal products increases the likelihood of severe haematotoxic adverse reactions to methotrexate. Concurrent administration of metamizole and methotrexate can increase the haematotoxic effect of methotrexate, especially in elderly patients. Therefore, coadministration should be avoided.

Theophylline
Methotrexate can reduce clearance of theophylline. Theophylline levels must therefore be monitored during concomitant treatment with methotrexate.

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.

Mercaptopurine
Methotrexate increases plasma content of mercaptopurine. The combination of methotrexate and mercaptopurine can therefore require dose adjustment.

Drugs with high plasma protein binding
Methotrexate is partially bound to serum albumin. Other highly bound drugs such as salicylates, phenylbutazone, phenytoin , barbiturates, tranquillisers, oral

contraceptives, tetracyclines, amidopyrine derivatives, sulfonamides, hypoglycaemics, diuretics, acidic anti-inflammatory agents and p-aminobenzoic acid can increase the toxicity of methotrexate by means of displacement and thus increase bioavailability (indirect dose increase).

Furosemide
Concomitant administration of furosemide and methotrexate can result in increased levels of methotrexate due to competitive inhibition of tubular secretion.

Vitamins
Vitamin preparations containing folic acid or its derivatives can cause a reduced response to systemically administered methotrexate, however conditions in which there is a deficiency of folic acid can increase the risk of methotrexate toxicity.

Proton pump inhibitors
Literature data indicate that co-administration of proton pump inhibitors and methotrexate, especially at high dose, may result in elevated and prolonged plasma levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicity. 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.

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. If pregnancy occurs during treatment with methotrexate and up to six months thereafter, medical advice should be given regarding the risk of harmful effects on the child associated with treatment and ultrasonography examinations should be performed to confirm normal foetal development. In animal studies, methotrexate has shown reproductive toxicity, especially during the first trimester (see section 5.3).

Methotrexate has been shown to be teratogenic to humans; it has been reported to cause foetal death, miscarriages and/or congenital abnormalities (e.g. craniofacial, cardiovascular, central nervous system and extremity-related).

Methotrexate is a powerful human teratogen, with an increased risk of spontaneous abortions, intrauterine growth restriction and congenital malformations in case of exposure during pregnancy.
• Spontaneous abortions have been reported in 42.5% of pregnant women exposed to low-dose methotrexate treatment (less than 30 mg/week), compared to a reported rate of 22.5% in disease-matched patients treated with drugs other than methotrexate.

• Major birth defects occurred in 6.6% of live births in women exposed to low-dose methotrexate treatment (less than 30 mg/week) during pregnancy, compared to approximately 4% of live births in in disease-matched patients treated with drugs other than methotrexate.

Insufficient data is available for methotrexate exposure during pregnancy higher than 30 mg/week, but higher rates of spontaneous abortions and congenital malformations are expected, in particular at doses commonly used in oncologic indications

When methotrexate was discontinued prior to conception, normal pregnancies have been reported.

When used in oncological indications, methotrexate should not be administered during pregnancy in particular during the first trimester of pregnancy. In each individual case the benefit of treatment must be weighed up against the possible risk to the foetus. If the drug is used during pregnancy or if the patient becomes pregnant while taking methotrexate, the patient should be informed of the potential risk to the foetus.

Breastfeeding:
Methotrexate passes into breast milk in quantities such that there is a risk to the child even at therapeutic doses. Breast feeding must therefore be discontinued prior to treatment with methotrexate (see section 4.3).

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. In oncologic indications, women who are planning to become pregnant are advised to consult a genetic counselling centre, if possible, prior to therapy and men should seek advice about the possibility of sperm preservation before starting therapy as methotrexate can be genotoxic at higher doses (see section 4.4).

4.7 Effects on ability to drive and use machines

Since fatigue and dizziness can occur as an undesirable effect, ability to react and judgement can be impaired, which should be taken into account for example when driving or carrying out work involving a high degree of precision.

4.8 Undesirable effects

Conventional and high dose therapy
The frequency and degree of severity of undesirable effects depends on the dose administered, the duration of exposure and method of administration, but side effects have been seen at all doses and can occur at any time during treatment. Most undesirable effects are reversible when detected at an early stage. When severe reactions occur, the dose should be reduced or treatment discontinued and appropriate measures initiated (see section 4.9). If treatment with methotrexate is resumed, this should be done with caution after adequate consideration of the further need for the drug. Increased vigilance with regard to any recurrence of toxicity is required.
The most frequently reported undesirable effects include ulcerative stomatitis, leukopenia, nausea and bloating. Other frequently reported undesirable effects are feeling unwell, unusual tiredness, chills and fever, dizziness, reduced resistance to infections. Treatment with folinic acid during high dose therapy can counteract or alleviate a number of undesirable effects. Temporary discontinuation of therapy is recommended if there are signs of leukopenia.

Organ system class	**Very common** (≥1/10)	**Common** (≥1/100 to <1/10)	**Uncommon** (≥1/1,000 to <1/100)	**Rare** (≥1/10,000 to <1/1,000)	**Very rare** (<1/10,000)	**Not known** (Cannot be estimated from the available data)
Infections and infestations		*Herpes zoster*			Sepsis, Opportunistic infections (may be fatal in some cases), infections caused by the cytomegaly virus	
Cardiac disorders				Pericardial effusion, pericarditis, pericardial tamponade		
Blood and lymphatic system disorders		leukocypenia, thrombocytopenia and anaemia	Pancytopenia, agranulocytosis, haematopoietic disorders	Megaloblastic anaemia	Severe courses of bone marrow depression,aplastic anaemia. Lymphadenopathy, eosinophilia and neutropenia, Lymphoproliferative disorders	Haemorrhage, haematoma
Immune system disorders			Anaphylactoid reactions, allergicvasculitis		Immunosuppression, hypogammaglobulinaemia	
Metabolism and nutrition disorders				Diabetes mellitus		
Psychiatric disorders					Insomnia, cognitive dysfunction	psycosis
Nervous system disorders		Headache, fatigue, drowsiness	Vertigo, confusion, depression, seizures, convulsion,	Severely impaired vision, mood alterations, paresis,	Pain, muscular asthenia or paresthesia of the extremities, myasthenia,	

			encephalopathy,	speech impairment incl. dysarthria and aphasia, myelopathy	changes in sense of taste (metallic taste), meningism (paralysis, vomiting), acute aseptic meningitis	
Eye disorders				visual disturbances, blurred vision	Conjunctivitis, Retinopathy, transient blindness/loss of vision, periorbital oedema, blepharitis, epiphora, photophobia	
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.		Tumour lysis syndrome	
Vascular disorders			Vasculitis	hypotension, thromboembolic events reactions (incl. arterial thrombosis, cerebral thrombosis, thrombophlebitis, deep vein thrombosis, retinal vein thrombosis, pulmonary embolism)		Cerebral oedema, petechie
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,	Pulmonary fibrosis	Pharyngitis, apnoea, bronchial asthma	Pneumocystis jirovecii pneumonia, shortness of breath, chronic obstructive pulmonary disease. Infections including pneumonia have also been observed. Pleural effusion	Acute pulmonary oedema

		methotrexate treatment must be discontinued immediately and infections (including pneumonia) must be excluded.				
Gastrointestinal disorders	Loss of appetite, nausea, vomiting, abdominal pain, inflammation and ulcerations of the mucous membrane of mouth and throat (especially during the first 24-48 hours after administration of methotrexate). Stomatitis, dyspepsia	Diarrhoea (especially during the first 24-48 hours after administration of methotrexate)	gastrointestinal bleeding and ulcers, pancreatitis	Gingivitis, Enteritis, melaena (bloody stools), malabsorption	Haematemesis (vomiting blood), toxic megacolon	
Hepato-biliary disorders	Increase in liver-related enzymes (ALAT, ASAT, alkaline phosphatase and bilirubin).		Development of liver fattening, fibrosis and cirrhosis (occurs frequently despite regularly monitored, normal values of liver enzymes); diabetic metabolism; drop of serum albumin.	Acute hepatitis, and hepatotoxicity	Reactivation of chronic hepatitis, acute liver degeneration. Furthermore, herpes simplex hepatitis and liver insufficiency have been observed (also see the notes regarding liver biopsy in section 4.4).	Metabolic disorder
Skin and subcutaneous tissue disorders		Exanthema, erythema, itching	urticaria, 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,	Increased pigmentary changes of nails, acne, petechiae, ecchymoses, erythema multiforme, cutaneous erythematous eruptions.	Furunculosis, teleangiectasis, acute paronychia, Furthermore, nocardiosis, histoplasma and cryptococcus mycosis and disseminated herpes simplex have been reported. Allergic vasculitis, hidradenitis	Skin exfoliation / dermatitis exfoliative, skin necrosis

			Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyells syndrome), photosensitivity reactions			
Musculoskeletal system, connective tissue and bone disorders			Osteoporosis, Arthralgia, myalgia	Stress fracture		Osteonecrosis of jaw (secondary to lympho-proliferative disorders)
Renal and urinary disorders			Inflammation and ulceration of the urinary bladder (possibly with haematuria), dysuria.	Renal failure, oliguria, anuria, azotaemia, hyperuricaemia, elevated serum creatinine and urea level	Proteinuria	
Reproductive system and breast disorders			Inflammation and ulceration of the vagina		Loss of libido, impotence, oligospermia, impaired menstruation,, vaginal discharge, infertility, gynaecomastia	
General disorders and administration site conditions			Severe allergic reactions progressing to anaphylactic shock;		Fever, impaired wound healing	

The following undesirable effects have also been reported, but their frequency has not been established: Pneumocystis jirovecii pneumonia (including reversible cases), foetal death, damage to the foetus, abortion.

Systemic organ toxicity

Lymphoma
Malignant lymphoma which can go into remission after discontinuation of the treatment with methotrexate can occur in patients on low dose therapy, and may not therefore require any cytotoxic treatment. Methotrexate should be discontinued first and appropriate treatment initiated if the lymphoma does not regress.

Haematological
Methotrexate can suppress haematopoiesis and cause anaemia, aplastic anaemia, pancytopenia, leukopenia, neutropenia and/or thrombocytopenia. Methotrexate must be administered with caution to patients with malignancies and underlying factors affecting haematopoiesis. When treating neoplastic conditions, treatment with methotrexate should only be given provided the potential benefits outweigh the risk of myelosuppression.

Lungs

Lung disease caused by methotrexate, including acute or chronic interstitial pneumonitis, is a potentially dangerous complication, which can occur at any time during the course of treatment. This undesirable effect has been reported at low doses and is not always totally reversible. Deaths have been reported. Signs of pulmonary involvement or symptoms such as dry non-productive cough, fever, chest pains, dyspnoea, hypoxemia and infiltrate on x-ray of the lungs, or non-specific pneumonitis which occurs in connection with methotrexate therapy, may indicate potentially serious damage and requires discontinuation of treatment and careful investigation. Lung changes can occur at all doses. The possibility of infection (including pneumonia) must be excluded.

Gastrointestinal
If vomiting, diarrhoea or stomatitis occur, with resulting dehydration, methotrexate therapy must be discontinued until the patient has recovered. Haemorrhagic enteritis and deaths caused by intestinal perforation can occur. Methotrexate must be used with great caution in patients with peptic ulcers or ulcerative colitis. Stomatitis can be prevented or alleviated by folinic acid mouthwashes.

Liver
Methotrexate involves a potential risk of acute hepatitis and chronic (fibrosis and cirrhosis) hepatotoxicity. Chronic toxicity is potentially fatal and occurs commonly after long-term use (in general after 2 years or more) and after a total cumulative dose greater than 1.5 g. In studies of psoriasis patients hepatotoxicity was seen to be proportional to the cumulative dose and was potentiated by alcoholism, overweight, diabetes and age.
Transient deterioration in liver enzyme values is frequently seen after methotrexate treatment and does not usually necessitate adjustment of treatment. Existing abnormal liver values and/or reduction in serum albumin can indicate severe hepatotoxicity. Methotrexate has caused reactivation of hepatitis B infections and exacerbation of hepatitis C infections, in some cases with fatal outcome. Some cases of hepatitis B reactivation have occurred following discontinuation of methotrexate. Clinical and laboratory tests should be performed to investigate any occurrence of liver disease in patients with prior hepatitis B or C infections. Based on these investigations, treatment with methotrexate may prove unsuitable for certain patients.
In the event of impaired liver function, the undesirable effects of methotrexate (in particular stomatitis) can be exacerbated.

Kidneys
Methotrexate can cause kidney damage which can result in acute renal failure. Renal function can be exacerbated following high dose therapy to such an extent that the excretion of methotrexate is inhibited, as a result of which systemic methotrexate toxicity can occur. In order to prevent renal failure, alkalinisation of the urine and adequate fluid intake (at least 3 l/day) are recommended. Measurement of serum methotrexate and renal function is recommended.

Skin
Serious, in some cases fatal skin reactions, including toxic epidermal necrolysis (Lyell’s syndrome), Stevens-Johnson syndrome and erythema multiforme have been reported within a few days of oral, intramuscular or intravenous treatment with methotrexate in single or repeat doses. Radiation dermatitis and sunburn can be accentuated during use of methotrexate.

CNS
There are reports of leukoencephalopathy after intravenous treatment with methotrexate in patients who have undergone craniospinal radiotherapy. Severe

neurotoxicity, often manifested as generalised or focal seizures have been reported with an unexpected increase in frequency in children with acute lymphoblastic leukaemia treated with a moderately high dose of intravenous methotrexate (1 g/m^2). Symptomatic patients frequently had leukoencephalopathy and/or microangiopathic calcifications in x-ray investigations.

Chronic leukoencephalopathy has also been reported in patients treated with repeated high doses of methotrexate together with folinic acid, even without concomitant cranial radiotherapy. Discontinuation of the methotrexate therapy did not always result in full recovery. Leukoencephalopathy has also been reported in patients treated with methotrexate tablets.

One transient acute neurological syndrome has been observed in patients undergoing high dose therapy. Manifestations of this neurological syndrome can include abnormal behaviour, focal sensorimotor symptoms including transient blindness, and abnormal reflexes. The exact cause is unclear.

Intrathecal therapy
The subacute neurotoxicity is usually reversible after discontinuing methotrexate.

Organ system class	**Common (>1/100)**
Central and peripheral nervous system disorders	Headache, chemical arachnoiditis, subacute neurotoxicity, necrotising demyelinating leukoencephalopathy
Gastrointestinal disorders	Nausea and vomiting
General disorders and administration site conditions	Fever

Chemical arachnoiditis, which can occur a few hours after intrathecal administration of methotrexate is characterised by headache, back pain, stiff neck, vomiting, fever, meningism and pleocytosis in the cerebrospinal fluid similar to that in bacterial meningitis. Arachnoiditis generally disappears within a few days.

Subacute neurotoxicity, common after frequently repeated intrathecal administration, mainly affects the motor functions in the brain or spinal cord. Paraparesis/paraplegia, with involvement of one or more spinal nerve roots, tetraplegia, cerebellar dysfunction, cranial nerve paralysis and epileptic seizures can occur.

Necrotising demyelinating leukoencephalopathy can occur several months or years after starting intrathecal therapy. The condition is characterised by progressive neurological deterioration with insidious onset, confusion, irritability and somnolence. Ultimately severe dementia, dysarthria, ataxia, spasticity, seizures and coma can occur. The condition can be fatal. Leukoencephalopathy occurs primarily in patients who have received large quantities of intrathecal methotrexate in combination with cranial radiotherapy and/or systemically administered methotrexate.
Signs of neurotoxicity (meningeal inflammation, transient or permanent paresis, encephalopathy) must be followed up after intrathecal administration of methotrexate.

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 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

Experience of overdose with the product has in general been associated with oral and intrathecal treatment, although overdose in association with intravenous and intramuscular administration has also been reported.

Reports of oral overdose have often been due to accidental daily instead of weekly ingestion. Commonly reported symptoms following oral overdose include the symptoms and signs seen at pharmacological doses, in particular haematological and gastrointestinal reactions such as leukopenia, thrombocytopenia, anaemia, pancytopenia, neutropenia, myelosuppression, mucositis, stomatitis, oral ulceration, nausea, vomiting, gastrointestinal ulceration, gastrointestinal bleeding. In certain cases no symptoms were reported. There are reports of deaths associated with overdose. In these cases there were also reports of conditions involving sepsis or septic shock, renal failure and aplastic anaemia.

The most common symptoms of intrathecal overdose are CNS symptoms including headache, nausea and vomiting, seizures or convulsions and acute toxic encephalopathy. In certain cases, no symptoms were reported. There have been reports of deaths following intrathecal overdose. In these cases there were also reports of cerebellar herniation accompanying elevated intracranial pressure and toxic encephalopathy.

Recommended treatment

Antidote therapy: Folinic acid should be given parenterally at a dose at least the size of the methotrexate dose and should wherever possible be administered within an hour. Folinic acid is indicated to minimise toxicity and counter the effect of methotrexate overdose. Folinic acid treatment should be initiated as soon as possible. The longer the interval between the administration of methotrexate and the initiation of folinic acid, the less the effect of folinic acid in suppressing the toxic effect. Monitoring of serum methotrexate concentrations is necessary to be able to determine the optimum dose of folinic acid and the length of the treatment.

In the event of a major overdose, hydration and alkalinisation of the urine may be required to prevent precipitation of methotrexate and/or its metabolites in the renal tubules. Neither standard haemodialysis nor peritoneal dialysis have been shown to increase the elimination of methotrexate. Acute intermittent haemodialysis with the use of highly permeable dialyser may be attempted for methotrexate intoxication.

Intrathecal overdose may require intensive systemic supportive measures such as systemic administration of high doses of folinic acid, alkaline diuresis, acute CSF drainage and ventricular lumbar perfusion.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Folic acid analogues
ATC code: L01BA01

Mechanism of action:
Methotrexate is a folic acid antagonist with a cytostatic effect. Methotrexate inhibits the conversion of folic acid to tetrahydrofolic acid since the compound has a greater affinity for the enzyme dihydrofolate reductase than the natural substrate folic acid. As a result, DNA synthesis and new cell formation are inhibited. Methotrexate is s-phase specific.

Clinical efficacy and safety:
Actively proliferating tissues such as malignant cells, bone marrow, foetal cells, epithelium and buccal and intestinal mucosa are generally most susceptible to methotrexate.

5.2 Pharmacokinetic properties

Absorption:
Following intravenous administration, peak serum concentrations of methotrexate are reached after approx. 0.5 – 1 hour. There is wide inter-individual and intra-individual variation, especially with repeated doses. Subcutaneous, intravenous and intramuscular administration demonstrated similar bioavailability.

Distribution:
About half of the absorbed methotrexate is bound to plasma proteins, but binding is reversible, and methotrexate is easily diffused into the cells with the highest concentrations reached in the liver, spleen and kidneys in the form of polyglutamate can be found which can be retained for few weeks or months. Methotrexate also passes to a lesser degree into cerebrospinal fluid.

Biotransformation:
The half-life is approx. 3 to 10 hours with low dose therapy and approx. 8 to 15 hours with high dose therapy. 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 through the placental barrier in rats and monkeys.

Elimination:
Elimination from plasma is triphasic and the majority of the methotrexate is excreted unchanged in urine within 24 hours. Excretion takes place, mainly in unchanged form, primarily renal via glomerular filtration and active secretion in the proximal tubules. Approximately 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 those in humans occurred.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide, Water for Injections-

6.2 Incompatibilities

Owing to the absence of compatibility studies, this medicine should not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

Unopened vials - 2 years
Vial after first opening – Use immediately after opening.

After dilution
Chemical and physical stability of the diluted solution have been demonstrated in glucose solution (5%) and sodium chloride solution (0.9%) at concentrations of 5mg/ml and 20mg/ml for 36 hours at 20-25°C and 35 days at 2-8°C. Diluted product is stable in both diluents at both concentrations for 36 hours at 20-25°C and 35 days at 2-8°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and condition prior to use are the responsibility of the user and would not longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled validated aseptic condition.

6.4 Special precautions for storage

Do not store above 30°C.

For storage conditions after dilution, see section 6.3.

6.5 Nature and contents of container

5 ml: 5 ml Type I clear tubular glass vial, sealed with a grey butyl rubber stopper and aluminium flip-off royal blue seal.
10 ml: 10 ml Type I clear tubular glass vial, sealed with a grey butyl rubber stopper and aluminium flip-off orange seal.
50 ml: 50 ml Type I clear tubular glass vial, sealed with a grey butyl rubber stopper and aluminium flip-off yellow seal.

Pack size: 1 vial in carton for 5 ml, 10 ml and 50 ml pack size.
5 vials in a carton for 5 ml, 10 ml & 50 ml pack size

Not all the pack size may be marketed.

6.6 Special precautions for disposal

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

Methotrexate 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 solution 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).

Pregnant healthcare personnel should not handle and/or administer Methotrexate injection.

Methotrexate should not come into contact with the skin or mucosa. In the event of contamination, the affected area must be irrigated immediately with copious quantities of water at least ten minutes.

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

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

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Limited Sage House

319 Pinner Road

North Harrow

Middlesex

HA1 4HF

United Kingdom

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