SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Methotrexate 100 mg/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Concentration	Size	Amount per vial
100 mg methotrexate per ml (10.0%)	10 ml	1 000 mg
100 mg methotrexate per ml (10.0%)	50 ml	5 000 mg

One vial with 10 ml contains 1 000 mg methotrexate.
One vial with 50 ml contains 5 000 mg methotrexate.

Excipient with known effect
Sodium

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection
Clear orange-yellow solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Methotrexate 100 mg/ml solution for injection may be used for the following indications:

- Acute lymphocytic leukaemias (ALL)
  - in combination with other cytotoxic medicinal products
- Non-Hodgkin's lymphomas

- in combination with other cytotoxic medicinal products in adult patients with Non-Hodgkin's lymphomas of intermediate and high degree of malignancy
- -in combination with other cytotoxic medicinal products in paediatric patients

- Head and neck cancer
  - as palliative monotherapy in patients with metastatic or recurrent disease
- Breast cancer
  - in combination with other cytotoxic medicinal products in patients for adjuvant treatment after tumour resection or mastectomy and for palliative treatment in advanced disease
- Choriocarcinoma and similar trophoblastic diseases
  - as monotherapy in patients with good prognosis (low risk)
  - in combination with other cytotoxic medicinal products in patients with poor prognosis (high risk)
- Osteosarcoma
  - in combination with other cytotoxic medicinal products for adjuvant and neoadjuvant therapy
- Cancer of the bladder
  - in combination with other cytotoxic medicinal products

4.2 Posology and method of administration

Note: Methotrexate 100 mg/ml solution for injection is a hypertonic presentation and therefore not suitable for intrathecal and intraventricular use.

Methotrexate 100 mg/ml solution for injection should only be prescribed by physicians with experience in antimetabolite chemotherapy and the management of the approved indications. The treatment regimen should be decided on an individual patient basis, with reference to current treatment protocols.

Methotrexate can be applied in the form of an intravenous, intramuscular, or intra-arterial 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). Doses are usually based on the patient's body weight or body surface area (BSA). Total doses greater than 100 mg are usually given by intravenous infusion.

Pharmaceutical forms with the lowest possible strength should be used. Fatal cases of intoxication have been reported after intravenous administration of incorrectly calculated doses. Therefore, doses must be carefully calculated in all patients.

Before beginning combination therapy involving high-dose methotrexate the leukocyte and thrombocyte count should exceed the respective minimum values (leukocytes 1 000 to 1 500/µl, thrombocytes 50 000 to 100 000/µl). When applying high-dose methotrexate therapy, the serum methotrexate concentration must be checked at regular intervals. The sampling times and the maximum values for toxic serum methotrexate concentrations which require measures such as an increase in the calcium folinate dose or the intravenous fluid supply can be taken from the individual therapy protocols.

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

Skin and mucous membrane contact with methotrexate should be avoided. If methotrexate contaminates the skin it should be washed off immediately using copious amounts of running water for at least ten minutes.

For methotrexate treatment measurement of serum methotrexate level is absolutely necessary.

It is useful to separate the treatment with methotrexate according to the following regimen.

Low-dose therapy	Single dose under 100 mg/m²
Medium-dose therapy	Single dose between 100 mg/m² and 1 000 mg/m²
High-dose therapy	Single dose above 1 000 mg/m²
For methotrexate doses exceeding approx. 100 mg/m² as a single dose, the methotrexate treatment must be followed by application of calcium folinate (see calcium folinate rescue).	

High-dose methotrexate therapy (>1 000 mg/m² body surface area)
High doses may cause the precipitation of methotrexate or its metabolites in the renal tubules. A high fluid throughput and alkalisation of the urine to pH 6.5–7.0 by oral or intravenous administration of sodium bicarbonate (e.g. 5 times 625 mg tablets every three hours) or acetazolamide (e.g. 500 mg orally four times a day) is recommended as a preventative measure.

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 adverse reactions from prior therapy with methotrexate or impairment of urine flow), the creatinine clearance must be determined. Current published protocols should be consulted for posology and method and sequence of administration. High-dose methotrexate therapy has to be followed by calcium folinate rescue therapy (see also section 4.4).

Posology in patients with renal impairment
Since methotrexate is predominately eliminated renally, in patients with impaired creatinine clearance, delayed elimination is to be expected, which can lead to severe adverse reactions. 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.
Methotrexate should be used with caution in patients with impaired renal function.

The following dose adjustments have been used. Reference should be made to current published treatment protocols.

Creatinine clearance >80 ml/min:	100% of the recommended standard dose
Creatinine clearance = 80 ml/min:	75% of the recommended standard dose
Creatinine clearance = 60 ml/min:	63% of the recommended standard dose
Creatinine clearance <60 ml/min:	Use alternative therapy

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

Elderly patients

Methotrexate should be used with extreme caution in elderly patients. Elderly patients should be monitored closely for early signs of methotrexate toxicity. Dose reduction should be considered in elderly patients due to reduced liver and kidney function as well as lower folate reserves which occur with increased age. For patients above 55 years of age modified therapy protocols are used e.g. for the treatment of ALL.

Paediatric population
Methotrexate should be used with caution in the paediatric population. Standard therapy protocols should be consulted for posology and method and sequence of administration. Fatal cases of intoxication have been reported after intravenous administration of incorrectly calculated doses. Therefore, posology must be carefully calculated in the paediatric population.

For detailed information about recommended examinations and safety measures see section 4.4.

During treatment with methotrexate patients require careful monitoring to avoid severe toxicity.

The application and dose recommendation for the administration of methotrexate for different indications varies considerably. Some common doses and therapy protocols, which have proved to be efficacious in the therapy of the disorder in each case, are given below.

Current published protocols should always be consulted for posology and method and sequence of administration.

Choriocarcinoma and similar trophoblastic diseases (e.g. hydatidiform mole and chorioadenoma destruens)
The following regimens have been used. Reference should always be made to current published protocols.

Low risk patients
15–30 mg/m² intramuscularly for five days in combination with folinic acid. 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.

High risk patients
Combination therapy: Methotrexate IV as single doses of 300 mg/m² body surface area. Detailed information can be found in current published treatment protocols such as EMA/CO-protocol.

Breast cancer
Methotrexate has been used at a dose of 40 mg/m² intravenously on the first and eighth day of the cycle in combination with oral or IV cyclophosphamide and IV fluorouracil with regard to the CMF-protocol.

Head and neck cancer
Monotherapy: 40–60 mg/m² body surface area methotrexate can be given once weekly as intravenous bolus injection. Reference should always be made to current published treatment protocols.

Non-Hodgkin’s lymphomas
Methotrexate is used for the treatment of Non-Hodgkin’s lymphoma in children and adults within the scope of complex therapy protocols. Methotrexate is applied according to the phase

of the disease, age and the histological type within the scope of various polychemotherapies. Reference should always be made to current published therapy protocols.

Paediatric population
Dose range for therapy with methotrexate at medium or high dose: single doses from 300–5 000 mg/m² as an intravenous infusion. Detailed information can be found in current published therapy protocols e.g. NHL-BFM working group.

Adults (intermediate and high malignancy)
Methotrexate is used in combination therapy with prednisone, doxorubicin, cyclophosphamide, etoposide, cytarabine, bleomycin and vincristine as single dose of 120 mg/m² BSA.

In CNS localised Non-Hodgkin's lymphoma
In clinical studies an efficacious dose between 1.5 g/m²–4 g/m² IV given as single dose in mono- or combination therapy was used. Detailed information can be found in current published therapy protocols.

Acute lymphocytic leukaemias (ALL)
The following regimens have been used. Reference should always be made to current published protocols.
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/m² methotrexate.

The choice of an adequate combination therapy may be influenced by factors such as risk group, age and immunologic subgroups. For ALL of B-cell type special therapy protocols are used.

ALL in children
Usual single dose is 1 g/m²–5 g/m² BSA (during consolidation therapy).
Detailed information can be found in current published therapy protocol ALL-BFM.

ALL in adults
Usual single dose is 1.5 g/m² BSA regarding to the therapy protocol GMALL.

Cancer of the bladder
Methotrexate is used in combination therapy with vinblastine, doxorubicin and cisplatin (M-VAC regimen) at a dose of 30 mg/m² BSA.
Detailed information can be found in current published treatment protocols e.g. M-VAC.

Osteosarcoma
Effective adjuvant chemotherapy requires the administration of several cytotoxic chemotherapeutic medicinal products. Methotrexate is used intravenously in high doses (6–12 g/m²) once weekly. Calcium folinate rescue is necessary. Detailed information can be found in current published therapy protocols e.g. COSS.

4.3 Contraindications

Methotrexate 100 mg/ml solution for injection is contraindicated in the case of
- hypersensitivity to the active substance or to any of the excipients listed in section 6.1,
- liver 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,
- severe active infections,
- overt or laboratory evidence of immunodeficiency syndrome(s)
- breast-feeding (see section 4.6),
- renal insufficiency (creatinine clearance less than 60 ml/min),
- alcohol abuse,
- stomatitis, gastrointestinal ulceration.

4.4 Special warnings and precautions for use

Methotrexate 100 mg/ml solution for injection should only be prescribed by physicians with experience in antimetabolite chemotherapy and the management of the approved indications.

Because of the possibility of fatal or severe intoxication during methotrexate therapy medium or high doses should only be used in patients with life-threatening tumour diseases. Rare cases of death have been reported after methotrexate tumour therapy.

Patients undergoing methotrexate therapy should be closely monitored to prevent intoxication and to ensure fast identification of toxic adverse reactions.

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. Patients should be fully informed by the physician about risks and benefits of the therapy, of the need to inform the physician immediately if toxic signs occur and about necessary examinations and safety measures during treatment.

Discontinuation of methotrexate therapy did not always result in a complete recovery from toxic effects.

For methotrexate treatment measurement of serum methotrexate level is absolutely necessary.

Patients with pleural effusions or ascites should have these drained before treatment or treatment should be withdrawn (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 perforation or dehydration.

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

In patients with fast growing cancer a **tumour lysis syndrome** can occur.

In the case of **pre-treatment** with medicinal products exhibiting **myelosuppressive** or immunosuppressive effects (e.g. cytostatics) or prior **radiotherapy** it is possible to observe enhancement of bone marrow toxicity and immunosuppression.

Cases of severe neurological adverse reactions that ranged from headache to paralysis, coma and stroke-like episodes have been reported mostly in juveniles and adolescents given methotrexate in **combination with cytarabine.**

Unexpectedly severe (sometimes fatal) bone marrow suppression, aplastic anaemia and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high doses) along with **non-steroidal anti-inflammatory drugs** (NSAIDs). These medicinal products enhance methotrexate toxicity which may result in death from severe haematological and gastrointestinal toxicity.

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

There have been reports of leukoencephalopathy following intravenous administration of methotrexate to patients who have had **craniospinal irradiation**. Chronic **leukoencephalopathy** has also been reported in patients who received repeated doses of high-dose methotrexate with calcium folinate rescue even without cranial irradiation. Discontinuation of methotrexate does not always result in complete recovery.

<u>Progressive multifocal leukoencephalopathy (PML)</u>

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.

A transient **acute neurologic syndrome** has been observed in patients treated with high-dose regimens. Manifestations of this neurological disorder may include behavioural abnormalities, focal sensorimotor signs, including transient blindness and abnormal reflexes. The exact cause is unknown.

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).

Strict monitoring is necessary in patients with **pulmonary dysfunction**.

Pulmonary lesions, interstitial pneumonitis and alveolitis typically including symptoms such as dyspnoea, cough (especially a dry, non-productive cough), fever, chest pain, hypoxemia and infiltrate on chest X-ray may be indicative of a potentially dangerous lesion and require interruption of treatment and careful investigation. Lung biopsy showed interstitial oedema, mononuclear infiltrates or granulomas. Methotrexate should be withdrawn from patients with pulmonary symptoms and a thorough investigation should be made to exclude infection. Pulmonary lesions can occur at any time during therapy and have been reported at all doses, even doses as low as 7.5 mg/week.

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

Potentially fatal **opportunistic infections**, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy. When a patient presents with pulmonary symptoms, the possibility of *Pneumocystis carinii* should be considered.

Severe, occasionally fatal, **dermatological reactions**, including toxic epidermal necrolysis (Lyell's syndrome) or Stevens-Johnson syndrome have been reported after single or multiple doses of methotrexate.

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.

Immunisation may be ineffective during methotrexate therapy and immunisation with **live virus vaccines** is generally not recommended. There have been reports of disseminated vaccinia infections after smallpox immunisation in patients receiving methotrexate therapy. 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.

Due to the immunosuppressive action of methotrexate, the medicinal product 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**.

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.

There have been reports on the manifestation of lymphomas which were, in some cases, reversible after discontinuing methotrexate therapy. Furthermore, the potential of methotrexate to produce other cancers in humans has been evaluated in several studies, but the results do not confirm a carcinogenic risk.

Recommended examinations and safety measures

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. Baseline assessment should include a complete blood count (CBC) with differential and platelet counts, hepatic enzymes, renal function tests, hepatitis (A, B, C) serology, pulmonary function tests and tuberculosis diagnostic. 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 dose for the therapy protocol used.
- Regular check-ups of the oral cavity and the pharynx for changes in the mucous membranes. Ulceration mainly precedes a decrease in the number of leukocytes and/or thrombocytes.
- Regular leukocyte and thrombocyte counts have to be taken from daily until once weekly.
- A complete blood picture has to be taken regularly from daily until once weekly.
- 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.

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

Patients subject to the following conditions are predisposed to developing elevated or prolonged methotrexate levels e.g. pleural effusion, ascites, gastrointestinal tract obstruction, previous cisplatin therapy, dehydration, aciduria, impaired renal function. Some patients may have delayed methotrexate clearance in the absence of these features. It is important that patients be identified within 48 hours since methotrexate toxicity may not be reversible.

Calcium folinate rescue therapy should be performed after treatment with doses higher than 100 mg/m² BSA methotrexate. Calcium folinate dose depends on methotrexate dose and duration of therapy. Adequate calcium folinate rescue therapy must be initiated between 42 to 48 hours after methotrexate administration. Serum methotrexate concentrations should be measured at 24, 48 or 72 hours to determine how long to continue with calcium folinate rescue therapy. 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.

Glucarpidase rescue should be considered to reduce toxic plasma methotrexate concentration in patients with delayed methotrexate elimination or at risk of methotrexate toxicity (see section 4.9).

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).

Liver function tests

Particular attention should be paid to the onset of liver toxicity. Methotrexate may cause acute **hepatitis** and chronic fibrosis and cirrhosis (sometimes fatal). 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 medicinal products 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 of normal has been reported, with a frequency of 13–20%. In the event of a constant increase in liver-related enzymes, consideration should be given to reducing the dose or discontinuing therapy.

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

Liver lesions are only detectable by liver biopsy and not by measuring of liver enzymes. Liver biopsy should be considered after cumulative doses of methotrexate >1.5 g, if hepatic impairment is suspected.

Methotrexate may cause **reactivation of hepatitis B infection** and can worsen hepatitis C. Rare cases of hepatitis B reactivation occur after discontinuation of methotrexate therapy. Liver function tests should be evaluated for existing hepatitis B or C infections. For some infected patients alternative therapy protocol must be chosen.

Methotrexate may cause **renal damage** with oliguria, anuria and increases in creatinine levels that may lead to acute renal failure. Nephrotoxicity is due primarily to the precipitation of methotrexate and its metabolites in the renal tubules.

Renal function should be closely monitored before, during and after treatment.

Caution should be exercised if significant renal impairment is disclosed.

Methotrexate is excreted primarily by the kidneys. Its use in the presence of impaired renal function may result in accumulation of toxic amounts or even additional renal damage. A high fluid throughput and alkalinisation of the urine to pH >7.0 can reduce renal toxicity. **Urine flow and the pH value of the urine** should be monitored during the methotrexate infusion. To reduce renal toxicity intravenous fluid supply and alkalisation of the urine is necessary (pH >7).

If there is evidence to indicate **impairment of renal function** (e.g. marked adverse reactions from prior therapy with methotrexate or impairment of urine flow), the creatinine clearance must be determined. High-dose methotrexate therapy should only be carried out if the creatinine concentration is within the normal range. Since methotrexate is predominately eliminated renally, in patients with impaired creatinine clearance, delayed elimination is to be expected, which can lead to severe adverse reactions. Current published protocols should be consulted for doses and method and sequence of administration. If serum creatinine concentration is increased the dose should be reduced. If serum creatinine is above 2 mg/dl (176.8 µmol/l) alternative therapy should be chosen, especially if concomitant medicinal products are given that reduce elimination or impair renal function (e.g. NSAIDs).

Vomiting, diarrhoea or stomatitis may result in **dehydration** and that can increase toxic effects. Methotrexate treatment should be discontinued until recovery.

During initial or changing doses or during periods of increased risk of elevated methotrexate blood levels (e.g. dehydration, renal impairment, concomitant use of NSAIDs), more frequent monitoring may also be indicated.

Methotrexate should be used with extreme caution in patients with ulcerative colitis.

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).

Paediatric population

Methotrexate should be used with caution in paediatric patients. Treatment should follow currently published therapy protocols for children.

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/m²). Symptomatic patients were commonly noted to have leukoencephalopathy and/or microangiopathic calcifications on diagnostic imaging studies.

Elderly patients

Methotrexate should be used with extreme caution in elderly patients. Elderly patients should be monitored closely for early signs of methotrexate toxicity. The clinical pharmacology of methotrexate has not been well studied in elderly individuals.

Dose reduction should be considered in elderly patients due to reduced liver and kidney function as well as lower folate reserves which occur with increased age. For patients above 55 years of age modified therapy protocols are used e.g. for the treatment of ALL.

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). 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.

Sodium

10 ml vial

This medicinal product contains 115.01 mg sodium per 10 ml vial, equivalent to 5.75% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

50 ml vial

This medicinal product contains 575.04 mg sodium per 50 ml vial, equivalent to 28.75% 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

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.

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

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

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.

Sulfonamide, trimethoprim/sulfamethoxazole has been reported rarely to increase bone marrow suppression in patients receiving methotrexate, probably by decreased tubular secretion and/or an additive antifolate effect. 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”).

Patients receiving concomitant therapy with methotrexate and other potential **hepatotoxic agents** (e.g. leflunomide, azathioprine, sulfasalazine, retinoids, alcohol) should be closely monitored for 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.

Methotrexate in combination with **leflunomide** may increase the risk of pancytopenia.

Methotrexate increases the plasma levels of **mercaptopurine** by interference of first-pass metabolism. Combination of methotrexate and mercaptopurine may therefore require dose adjustment.

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. These medicinal products have been reported to reduce the tubular secretion of methotrexate in an animal model and may enhance its toxicity by increasing methotrexate levels.

Oral antibiotics such as tetracycline, chloramphenicol and nonabsorbable broad-spectrum antibiotics, may decrease intestinal absorption of methotrexate or interfere with the enterohepatic circulation by inhibiting bowel flora and suppressing metabolism of the medicinal product by bacteria.

Penicillins and sulfonamides can reduce the renal clearance of methotrexate.

After administration of low and high methotrexate doses increased serum concentrations of methotrexate with concomitant haematological and gastrointestinal toxicity can occur.

Decreased **phenytoin levels** were observed in patients with ALL which received prednisone, vincristine, mercaptopurine, high dose methotrexate and calcium folinate 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.

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

Concomitant use of **proton pump inhibitors** can lead to delayed elimination and increased serum methotrexate.

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

Concomitant application of methotrexate and **theophylline** can reduce theophylline clearance. Theophylline levels should be monitored when used concurrently with methotrexate.

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.

Salicylate, non-steroidal anti-inflammatory agents, p-aminohippuric acid, probenecid, penicillin and sulphonamide can **reduce the renal tubular secretion** of methotrexate and, especially within the low-dose range of methotrexate, increase its toxicity. Use of methotrexate with these medicinal products should be carefully monitored.

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

Concurrent administration of metamizole and methotrexate can increase the haematotoxic effect of methotrexate, especially in elderly patients. Therefore, coadministration should be avoided.

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

Concomitant use of potential nephrotoxic cytostatic agents such as cisplatin can lead to **increased nephrotoxic effects**.

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

If pregnancy occurs during treatment with methotrexate and up to six months thereafter, medical advice should be given regarding the risk of harmful effects on the child associated with treatment and ultrasonography examinations should be performed to confirm normal foetal development. In animal studies, methotrexate has shown reproductive toxicity, especially during the first trimester (see section 5.3). Methotrexate has been shown to be teratogenic to humans; it has been reported to cause foetal death, miscarriages and/or congenital abnormalities (e.g. craniofacial, cardiovascular, central nervous system and extremity-related).
Methotrexate is a powerful human teratogen, with an increased risk of spontaneous abortions, intrauterine growth restriction and congenital malformations in case of exposure during pregnancy.

- Spontaneous abortions have been reported in 42.5% of pregnant women exposed to low-dose methotrexate treatment (less than 30 mg/week), compared to a reported rate of 22.5% in disease-matched patients treated with medicinal products other than methotrexate.
- 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 disease-matched patients treated with medicinal products 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 oncological indications.
When methotrexate was discontinued prior to conception, normal pregnancies have been reported.
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 medicinal product 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 is excreted into human milk. Breastfeeding must be stopped during treatment to avoid serious adverse reactions in breast-fed infants. If use during the lactation period should become necessary, breastfeeding is to be stopped prior to treatment.

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

Central nervous symptoms such as tiredness and dizziness can occur during treatment, therefore in isolated cases methotrexate can have minor or moderate influence on the ability to drive and use machines.

4.8 Undesirable effects

Occurrence and severity of undesirable effects depend on dose level and frequency of methotrexate administration. However, as severe adverse reactions may occur even at lower doses, it is indispensable that the doctor monitors patients regularly at short intervals. Most undesirable effects are reversible if recognised early. In very rare cases severe adverse reactions mentioned below can be fatal.

If such adverse reactions occur, dose should be reduced or therapy be interrupted and appropriate countermeasures should be taken (see section 4.9). Methotrexate therapy should only be resumed with caution, under close assessment of the necessity for treatment and with increased alertness for possible reoccurrence of toxicity.

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.

The most common undesirable effects are ulcerative stomatitis, leucopenia, thrombocytopenia, nausea, vomiting, anorexia and abdominal discomfort. Especially during the first 24–48 hours after methotrexate administration decreased creatinine clearance and increase in liver enzymes (ALAT, ASAT, alkaline phosphatase, bilirubin) occur.

The following undesirable effects have been observed and reported during treatment with methotrexate with the following frequencies: 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).

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

The following adverse reactions may occur:

Infections and infestations

Common:	herpes zoster
Uncommon:	opportunistic infections (sometimes fatal), including pneumonia
Rare:	sepsis
Very rare:	nocardiosis, histoplasmosis, cryptococcosis, herpes simplex hepatitis, disseminated herpes simplex, cytomegalovirus infection, cytomegalovirus pneumonia, septicaemia

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)

Uncommon:	malignant lymphomas
Very rare:	tumour lysis syndrome

Blood and lymphatic system disorders

Very common:	leukopenia, thrombocytopenia
Common:	anaemia up to pancytopenia, myelosuppression, agranulocytosis
Rare:	megaloblastic anaemia
Very rare:	aplastic anaemia, eosinophilia, neutropenia, lymphadenopathy, lymphoproliferative disorders
Not known:	haemorrhages, haematoma

Immune system disorders

Very common:	allergic reactions, anaphylactic shock, allergic vasculitis, immunosuppression, fever
Very rare:	hypogammaglobulinaemia

Metabolism and nutrition disorders

Uncommon:	diabetes
Not known:	malabsorption, metabolic disorder

Psychiatric disorders

Uncommon:	depression
Rare:	mood alteration, transient perceptual disturbances
Not known:	psychosis

Nervous system disorders

Common:	headaches, dizziness, drowsiness
Uncommon:	convulsions, hemiparesis, leukoencephalopathy/encephalopathy, vertigo, cognitive dysfunction
Rare:	paresis, dysarthria, aphasia, myelopathy
Very rare:	unusual cranial sensations, myasthenia, paraesthesia, acute aseptic meningitis

Eye disorders

Rare:	impairment of vision, serious visual changes of not known aetiology, blurred vision

Very rare:	transient blindness/vision loss, periorbital oedema, blepharitis, conjunctivitis, epiphora, photophobia

Cardiac disorders

Rare:	hypotension
Very rare:	pericarditis, pericardial effusion, pericardial tamponade, sudden death

Vascular disorders

Uncommon:	vasculitis
Rare:	thromboembolic complications (e.g. thrombophlebitis, pulmonary embolism, arterial, cerebral, deep vein or retinal vein thrombosis)

Respiratory, thoracic and mediastinal disorders

Common:	interstitial pneumonitis, alveolitis sometimes fatal
Uncommon:	pulmonary fibrosis, pleuritic pain and pleural thickening
Rare:	pharyngitis
Very rare:	chronic interstitial obstructive pulmonary disease, asthma-like symptoms (e.g. cough, dyspnoea, impaired pulmonary function test), *pneumocystis carinii* pneumonia
Not known:	acute pulmonary oedema

Gastrointestinal disorders

Very common:	stomatitis, abdominal pain, anorexia, nausea, vomiting
Common:	diarrhoea
Uncommon:	ulcerative stomatitis, haemorrhagic gastroenteritis, pancreatitis
Rare:	enteritis, gingivitis, melena
Very rare:	haematemesis
Not known:	toxic megacolon

When stomatitis or diarrhoea occur, therapy with methotrexate should be discontinued due to the danger of haemorrhagic enteritis or perforation or dehydration.

Hepatobiliary disorders

Common:	elevated transaminases, bilirubin and alkaline phosphatase
Uncommon:	chronic cirrhosis and fibrosis, decrease in serum albumins, fatty liver
Rare:	hepatotoxicity, acute hepatitis
Very rare:	acute liver necrosis, liver failure, reactivation of chronic hepatitis
Not known:	reactivation of hepatitis B, worsening of hepatitis C

Skin and subcutaneous tissue disorders

Common:	erythema, pruritus, exanthema
Uncommon:	alopecia, Stevens-Johnson syndrome, extensive herpetiform skin eruptions, toxic epidermic necrolysis (Lyell syndrome), urticaria, photosensitivity reactions, pigmentary changes, impaired wound healing
Rare:	acne, ecchymoses, erythema multiforme, nodulosis, hyperpigmentation of the nails, onycholysis, increase in rheumatic nodules
Very rare:	acute paronychia, furunculosis, telangiectasia
Not known	skin exfoliation/dermatitis exfoliative, skin necrosis, petechiae

With concomitant UV therapy psoriatic lesions can worsen. Radiation dermatitis and sunburn may be “recalled” by the use of methotrexate.

Musculoskeletal and connective tissue disorders

Uncommon:	arthralgia, myalgia, osteoporosis
Rare:	stress fractures
Not known:	aseptic necrosis of the femoral head, osteonecrosis of jaw (secondary to lymphoproliferative disorders)

Renal and urinary disorders

Very common:	decreased creatinine clearance
Uncommon:	severe nephropathy, renal failure, cystitis, dysuria, oliguria, anuria
Rare:	hyperuricaemia, elevated serum creatinine and urea level
Very rare:	azotaemia, haematuria, proteinuria

Pregnancy, puerperium and perinatal conditions

Uncommon:	foetal defects
Rare:	abortion
Very rare:	foetal death

Reproductive system and breast disorders

Uncommon:	vaginal inflammation and ulceration
Rare:	menstrual dysfunction
Very rare:	defective oogenesis or spermatogenesis, loss of libido/impotence, transient oligospermia, vaginal discharge, gynaecomastia

Intravenous administration of methotrexate may also result in acute encephalitis and acute encephalopathy with fatal outcome.

Adverse reactions following intramuscular administration

After intramuscular administration of methotrexate, **local reactions** (burning sensation) or injuries (sterile abscesses, loss of adipose tissue) at the injection site may occur.

Reporting of suspected adverse reactions

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

4.9 Overdose

Emergency measures, symptoms and antidote

Symptoms of methotrexate overdose

Overdose with methotrexate has particularly occurred with oral administration, although intravenous, intramuscular and intrathecal overdose have also been reported. Reports of oral overdose often indicate accidental daily administration instead of weekly (single or divided doses).

Symptoms commonly reported following oral or intravenous overdose predominantly affect the haematopoietic and gastrointestinal system. For example, leucopenia, thrombocytopenia, anaemia, pancytopenia, neutropenia, bone marrow depression, mucositis, stomatitis, oral ulceration, nausea, vomiting, gastrointestinal ulceration and gastrointestinal bleeding occurred. In some cases, no symptoms were reported. There have been reports of death following overdose. In these cases, events such as sepsis or septic shock, renal failure and aplastic anaemia were also reported.

Treatment of methotrexate overdose

The antidote calcium folinate is indicated for prevention and treatment of methotrexate toxicity.

a) Prevention
Methotrexate doses equal or higher 100 mg/m² body surface area have to be followed by calcium folinate administration. Standard therapy protocols should be consulted for doses, methods and sequence of administration.

b) Therapy
Calcium folinate dose regimens vary according to the dose of methotrexate administered and the serum methotrexate levels. Reference should be made to current published protocols.

As the time interval between methotrexate administration and calcium folinate initiation increases the effectiveness of calcium folinate in counteracting toxicity decreases. Monitoring of the serum methotrexate concentration is essential in determining the optimal dose and duration of treatment with calcium folinate.
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.
If intoxication occurs as consequence of delayed elimination due to renal failure haemodialysis or haemoperfusion may be required. Effective clearance of methotrexate has been reported with acute, intermittent haemodialysis using a high flux dialyser.

Additionally, glucarpidase has been shown to reduce toxic plasma methotrexate concentration in adults and children (aged 28 days and older) with delayed methotrexate elimination or at risk of methotrexate toxicity. Glucarpidase dose varies according to the administered methotrexate dose, infusion duration and the serum methotrexate levels. The optimal time window for the administration of glucarpidase is within 48–60 hours from the start of the methotrexate infusion. For glucarpidase administration reference should be made to the current product information or published treatment protocols and respective guidelines. Concomitant calcium folinate, also known as folinic acid or leucovorin, should be administered at least 2 hours before or after glucarpidase administration.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and immunosuppressive drugs, cytostatics, antimetabolites, ATC-Code: L01 BA 01

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 co factors, particularly for DNA synthesis, but also for purine and protein synthesis. Furthermore, the medicinal product has immunosuppressive and anti-inflammatory effects.

5.2 Pharmacokinetic properties

Absorption
Methotrexate is completely available systemically after intravenous or intramuscular 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/m² result in peak plasma concentrations of $1–10\times10^{-6}$ M. High-dose infusion regimens using 1 500 mg/m² or greater yield peak levels of $1–10\times10^{-4}$ M.

Distribution
The medicinal product is actively transported across cell membranes and is bound as polyglutamate conjugates. The medicinal product is widely distributed into body tissues with the highest concentrations in the kidneys, gallbladder, spleen, liver, skin, colon and small intestine. The medicinal product may remain in the body for several months, particularly in the liver. As the medicinal product 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. In

patients with manifest meningeal leukaemia the ratio of cerebrospinal fluid (CSF) to plasma concentration increased about 10-fold. After intrathecal administration of age-dependent doses maximum liquor concentrations of 100 µmol/l have been observed.

Biotransformation
The medicinal product 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.
In paediatric patients receiving methotrexate (6.3–30 mg/m² BSA) for ALL the terminal half-life has been reported to range from 0.7–5.8 hours.

Elimination
The medicinal product 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 active substance 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 doses and dependent on the route of administration. Clearance of the medicinal product from plasma under conditions of normal renal function is 103 ml/min/m².

Delayed 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 medicinal product is bound to serum proteins and laboratory studies demonstrate that the medicinal product 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 human milk. The medicinal product 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/m²) 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)

Water for injections

6.2 Incompatibilities

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

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

The shelf life is 2 years.

After dilution: Chemical and physical in-use stability has been demonstrated in 50 mg/ml (5%) glucose solution and 9 mg/ml (0.9%) sodium chloride solution 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 in order to protect from light.

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

6.5 Nature and contents of container

10 ml or 50 ml solution in type I clear glass vial with chlorobutyl rubber stopper and aluminium flip-off seal.

Each pack contains 1 vial of 10 ml or 50 ml solution.

6.6 Special precautions for disposal

Methotrexate 100 mg/ml solution for injection may be further diluted with an appropriate preservative-free medium such as 50 mg/ml (5%) glucose solution or 9 mg/ml (0.9%) sodium chloride solution.

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

Pregnant staff should avoid handling antineoplastic agents.

7 MARKETING AUTHORISATION HOLDER

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Theaterstr. 6
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