Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Methotrexate 1 g/10 ml Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 mg of methotrexate as methotrexate sodium which is formed *in situ*.

Each 10ml vial contains 1 g of methotrexate as methotrexate sodium which is formed in situ.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection. (Injection)
A clear yellow/orange aqueous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Methotrexate is indicated in the treatment of neoplastic disease, such as trophoblastic neoplasms and leukaemia, and the symptomatic treatment of severe recalcitrant disabling psoriasis which is not adequately responsive to other forms of treatment.

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

4.2 Posology and method of administration

Posology
Methotrexate should only be prescribed by physicians with expertise in the use of methotrexate and a full understanding of the risks of methotrexate therapy.

Important warnings about the dosage of Methotrexate

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

In the treatment of psoriasis methotrexate **must only be used once a week**. Dosage errors in the use of methotrexate can result in serious adverse reactions, including death. Please read this section of the summary of product characteristics very carefully.

Methotrexate Injection 1 g/10 ml and 5 g/50 ml can be given intramuscularly, intravenously and intraarterially.

Note: Methotrexate Injection 1g/10ml and 5g/50ml are hypertonic and must not be administered intrathecally.

The dose is usually calculated per m^2 body surface area (BSA).

Methotrexate 1 g/10 ml Injection should only be used by physicians with experience in antimetabolite chemotherapy and the other indication ranges. It is useful to categorise the treatment with methotrexate according to the following regimen.

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

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

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

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

Before beginning combination therapy involving high-dose methotrexate the leukocyte and thrombocyte count should exceed the respective minimum values (leukocytes 1,000 to 1,500/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 therapy should be performed after high-dose treatment with methotrexate.

Calcium folinate rescue
Calcium folinate rescue is necessary when methotrexate is given at doses exceeding 100 mg/m2 BSA.

As a rule, the first dose of Calcium folinate is 15 mg (6-12 mg/m^2) to be given 12-24 hours (24 hours at the latest) after the beginning of methotrexate infusion. The same dose is given every 6 hours throughout a period of 72 hours. After several parenteral doses treatment can be switched to the oral form.

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

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

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

The following regimens are only examples.

Acute lymphatic leukaemia
- 3.3 mg/m^2 in combination with other cytostatic agents once daily for 4-6 weeks.
- 2.5 mg/kg every two weeks.
- 30 mg/m^2/week maintenance therapy.
- 20 mg/m^2 in combination with other cytostatic agents once weekly.

In children:
Doses between 1,000 to 5,000 mg/m^2 BSA i.v. have been used sequentially (with subsequent folinic acid administration) for consolidation of remission and maintenance treatment. Oral treatment with doses up to 20 mg/m^2/week is used together with intravenous administration and intrathecal CNS prophylaxis as maintenance treatment.

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

Choriocarcinoma and similar trophoblastic diseases (e.g., hydatidiform mole and chorioadenoma destruens)
15-30 mg/m^2 intramuscularly for five days. Usually such courses may be repeated 3 to 5 times as required, with rest periods of one or more weeks interposed between the courses, until any manifesting toxic symptoms subside.

Non-Hodgkin's lymphomas
Stages I or II of Burkitt's lymphoma have been treated with methotrexate (orally). Stage III lymphomas and lymphosarcomas may respond to methotrexate given in doses of 0.625-2.5 mg/kg body weight daily as part of polychemotherapy, and 90-900 mg/m^2 as an intravenous infusion, followed by administration of calcium folinate.

In Non-Hodgkin's lymphomas in children, methotrexate is used according to the phase of the disease and the histological type within the scope of various polychemotherapies at the appropriate doses. Dosage range for therapy with methotrexate at medium or high dosage: single doses from 300-5,000 mg/m^2 as an intravenous infusion.

Head and neck cancer
Monotherapy: 40-60 mg/m^2 can be given once weekly as intravenous bolus injection.
Intravenous infusions of 240-1,080 mg/m^2 with calcium folinate rescue have been used in the treatment of metastatic or recurrent tumours. Intra-arterial infusions of methotrexate have also been used.

Breast cancer
Prolonged cyclic combination with cyclophosphamide, methotrexate and fluorouracil has given good results when used as adjuvant treatment to radical mastectomy in primary breast cancer with positive axillary lymph nodes. The dose of methotrexate is 40 mg/m^2 intravenously on the first and eighth days of the cycle. Methotrexate, in intravenous doses of 10-60 mg/m^2, is also commonly included in cyclic combination regimes with other cytotoxic drugs in the treatment of advanced breast cancer.

Osteosarcoma
Effective combination chemotherapy requires administration of several cytotoxic chemotherapeutics. In addition to high-dose methotrexate with calcium folinate rescue, doxorubicin, cisplatin, and a combination of bleomycin, cyclophosphamide and dactinomycin (BCD) can be given. The starting dose for high-dose methotrexate treatment is 12 g/m^2. If this dose is insufficient to reach peak serum concentrations of 10^{-3}mol/l at the end of the infusion, the dose can be increased to 15 g/m^2 for the subsequent treatments. If the patient vomits or cannot tolerate oral treatment, calcium folinate is given i.v. or i.m.

Non Neoplastic Indications:
Adults

Psoriasis Chemotherapy
Cases of severe uncontrolled psoriasis, unresponsive to conventional therapy, have responded to weekly single, oral, I.M. or I.V. doses of 10-25mg per week, and adjusted according to the patient's response. An initial test one week prior to initiation of therapy is recommended to detect any idiosyncrasy. A suggested dose range is 5-10mg parentally.

The prescriber should specify the day of intake on the prescription.

The patient should be fully informed of the risks involved and the clinician should pay particular attention to the appearance of the liver toxicity by carrying out liver function tests before starting Methotrexate treatment, and repeating these at 2 to 4

month intervals during therapy. The aim of therapy should be to reduce the dose to the lowest possible level with the longest possible rest period. The use of Methotrexate may permit the return to conventional topical therapy which should be encouraged.

Special populations:

Impaired renal function
Methotrexate is excreted to a significant extent by the kidneys, and therefore should be used with caution in patients with impaired renal function (see sections 4.3 and 4.4). The health care provider may need to adjust the dose to prevent accumulation of drug. The table below provided recommended starting doses in renally impaired patients; dosing may need further adjustment due to wide intersubject pK variability:

Table 1a. Dose adjustments for methotrexate doses <100 mg/m^2 in patients with renal impairment		
Creatinine Clearance (ml/min)		**% of dose to Administer**
>60		100
30-59		50
<30		Methotrexate must not be administered.
Table 1 b. Dose adjustments for methotrexate doses >100 mg/m^2 in patients with renal impairment		
Creatinine Clearance (ml/min)	**% of dose to Administer**	
>80	100	
= ~80	75	
= ~60	63	
<60	Methotrexate must not be administered.	

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 micromole/l) (see section 4.3).

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

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

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Liver insufficiency (see section 4.2).
- Alcohol abuse.
- Renal insufficiency (creatinine clearance less than 30 ml/min) for methotrexate doses <100 mg/m2, and moderate renal impairment (creatinine clearance less than 60 ml/min) for methotrexate doses >100 mg/m2 (see section 4.2).
- Pre-existing blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anaemia.
- Serious, acute or chronic infections such as tuberculosis and HIV.
- Ulcers of the oral cavity and known active gastrointestinal ulcer disease.
- Pregnancy, breast-feeding (see section 4.6).
- Concurrent vaccination with live vaccines.

4.4 Special warnings and precautions for use

Patients undergoing therapy should be subject to appropriate supervision so that signs of possible toxic effects or adverse reactions may be detected and evaluated with minimal delay. Therefore methotrexate should only be administered by, or under the supervision of physicians whose knowledge and experience includes the use of antimetabolite therapy. Because of the possibility of severe or even fatal toxic reactions, the patient should be fully informed of the risks involved and the recommended safety measures.

It should be emphasized to the patient treated for psoriasis that the recommended dose must be used only once a week. The prescriber should specify the day of intake on the prescription. Patients should be instructed on the importance of adhering to the once-weekly intakes, and that mistaken daily use of the recommended dose has led to fatal toxicity (see sections 4.2 and 4.9).

Methotrexate should be used with extreme caution in the presence of debility, in the elderly and in very young children.

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.

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.
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.

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

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), 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.

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

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

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

- **Liver function tests:** Treatment should not be initiated or should be discontinued if there are persistent or significant abnormalities in liver function tests, other non-invasive investigations of hepatic fibrosis, or liver biopsies.

Temporary increases in transaminases to two or three times the upper limit of normal have been reported in patients at a frequency of 13-20 %. Persistent elevation of liver enzymes and/or decrease in serum albumin may be indicative for severe hepatotoxicity. In the event of a persistent increase in liver enzymes, consideration should be given to reducing the dose or discontinuing therapy.

Histological changes, fibrosis and more rarely liver cirrhosis may not be preceded by abnormal liver function tests. There are instances in cirrhosis where transaminases are normal. Therefore, non-invasive diagnostic methods for monitoring of liver condition should be considered, in addition to liver function tests. Liver biopsy should be considered on an individual basis taking into account the patient's comorbidities, medical history and the risks related to biopsy. Risk factors for hepatotoxicity include excessive prior alcohol consumption, persistent elevation of liver enzymes, history of liver disease, family history of hereditary liver disorders, diabetes mellitus, obesity and previous contact with hepatotoxic drugs or chemicals and prolonged methotrexate treatment.

Additional hepatotoxic medicinal products should not be given during treatment with methotrexate unless clearly necessary. Alcohol consumption should be avoided (see sections 4.3 and 4.5). Closer monitoring of liver enzymes should be undertaken in patients concomitantly taking other hepatotoxic medicinal products.

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

- **Renal function** Methotrexate therapy in patients with impaired renal function should be undertaken with extreme caution because impairment of renal function will decrease methotrexate elimination.

Renal function should be monitored by renal function tests and urinalyses. If serum creatinine levels are increased, the dose should be reduced. If creatinine clearance is less than 30 ml/min, treatment with methotrexate should not be given. If creatinine clearance is less than 60 ml/min, methotrexate doses >100 mg/m2 not be given (see section 4.2 and 4.3).

Treatment with methotrexate doses of >100 mg/m2 should not be initiated at urinary pH values of less than 7.0. Alkalinisation of the urine must be tested by repeated pH monitoring (value greater than or equal to 6.8) for at least the first 24 hours after the administration of methotrexate is started.

Methotrexate may cause renal damage that may lead to acute renal failure. Close attention to renal function including adequate hydration, urine alkalinization, and measurement of serum methotrexate and renal function are recommended.

As methotrexate is eliminated mainly via the kidneys, increased concentrations are to be expected in the presence of renal impairment, which may result in severe adverse reactions.

If there is the possibility of renal impairment (e.g. in elderly subjects), monitoring should take place at shorter intervals. This applies in particular when medicinal products that affect the elimination of methotrexate, or that cause kidney damage (e.g. NSAIDs) or that can potentially lead to impairment of haematopoiesis, are administered concomitantly.

If risk factors such as renal function disorders, including mild renal impairment, are present, combined administration with NSAIDs is not recommended. Dehydration may also intensify the toxicity of methotrexate.

Concomitant use of proton pump inhibitors (PPIs) and high dose methotrexate should be avoided, especially in patients with renal impairment.

- **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. Pulmonary toxicity and pulmonary lesions (see section 4.8) can occur acutely at any time and at all dosages during therapy.

- Methotrexate may, due to its effect on the **immune system**, impair the response to vaccination and interfere with the results of immunological tests. Particular caution is also needed in the presence of inactive, chronic infections (e.g. herpes zoster, tuberculosis, hepatitis B or C) due to possible activation. Concurrent vaccination using live vaccines should not be carried out.
- **Malignant lymphomas** may occur in patients receiving low dose methotrexate, in which case therapy must be discontinued. Failure of the lymphoma to show signs of spontaneous regression requires the initiation of cytotoxic therapy.
- **Pleural effusions and ascites** should be drained prior to initiation of methotrexate treatment (see section 4.2).
- **Diarrhoea and ulcerative stomatitis** can be toxic effects and require interruption of therapy, otherwise haemorrhagic enteritis and death from intestinal perforation may occur.
- Vitamin preparations or other products containing **folic acid, folinic acid** or their derivatives may decrease the effectiveness of methotrexate.
- Skin toxicity: Due to risk of phototoxicity the patients must avoid **sunlight and solarium.**

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

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.

Methotrexate given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.

Lesions of psoriasis may be aggravated by concomitant exposure to ultraviolet radiation.

The combined use of methotrexate and leflunomide may increase the risk for pancytopenia and interstitial pneumonitis.

Excipient information
Methotrexate 1g/10 ml Injection contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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

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

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

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

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.

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

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. On the other hand, concomitant administration of folinic acid containing drugs or of vitamin preparations, which contain folic acid or derivatives, may impair methotrexate efficacy.

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

Though the combination of methotrexate and sulphasalazine may enhance methotrexate efficacy by sulphasalazine-related inhibition of folic acid synthesis and thus may lead to an increased risk of side effects, these were only observed in single patients within several trials. Methotrexate may reduce theophylline clearance. Therefore, theophylline blood levels should be monitored during concomitant methotrexate administration. Excessive consumption of caffeine- or theophylline-containing beverages (coffee, caffeine-containing beverages, black tea) should be avoided during methotrexate therapy, since the efficacy of methotrexate may be reduced due to possible interaction between methotrexate and methylxanthines at adenosine receptors.

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

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

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

On account of its possible effect on the immune system, methotrexate can falsify 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).

There is evidence of pharmacodynamic interaction between methotrexate and cytarabine leading to encephalopathy (see section 4.4)

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 cases 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.

4.6 Fertility, pregnancy and lactation

Pregnancy:
Methotrexate is contraindicated during pregnancy with non-oncological indications, including psoriasis or rheumatoid arthritis (see section 4.3).

In women of child-bearing age, any existing pregnancy must be excluded with certainty by taking appropriate measures, e.g. a pregnancy test, prior to initiating therapy. Women must not get pregnant during methotrexate therapy and patients of a sexually mature age must use effective contraception during treatment with methotrexate and at least 6 months thereafter (see section 4.4). If, nevertheless, pregnancy occurs during this period, medical advice should be given regarding the risk of harmful effects on the child associated with treatment.

As methotrexate can be genotoxic, all women who wish to become pregnant are advised to consult a genetic counselling centre, if possible, prior to therapy, and men should seek advice about the possibility of sperm preservation before starting therapy.

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.

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

Breast-feeding:

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

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

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.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Occurrence and severity of undesirable effects depend on dosage level and frequency of methotrexate administration. However, as severe adverse reactions may occur even at lower doses, it is indispensable that the doctor monitors patients regularly at short intervals.

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

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

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

The following adverse reactions may occur:

	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not Known**
Infections and infestations					Sepsis, opportunistic infections (maybe fatal in some cases), infections	Neutropenic sepsis

					caused by the cytomegalovirus	
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)			Individual cases of lymphoma, which abated in a number of cases once methotrexate treatment had been discontinued. In a recent study, it was not possible to establish that methotrexate therapy increases the incidence of lymphomas			
Blood and lymphatic system disorders		Leukopenia, thrombo-cyto penia, anaemia	Pancytopenia, agranulocytosis, haematopoietic disorders.	Megaloblastic anaemia	Severe courses of bone marrow depression, aplastic anaemia. Lymphaden-opathy, lymphopro-liferative disorders (partly reversible), eosinophilia and neutropenia	Haemorrhage, septicaemia
Immune system disorders					Immuno-suppression, hypogamma-globulinaemia	Anaphylactic Reactions
Metabolism and nutrition disorders						Metabolic disorders
Psychiatric disorders					Insomnia	
Nervous system disorders		Headache, fatigue, drowsiness	Vertigo, confusion, depression, seizures, leuko-encephalopathy/encephalopathy	Severely impaired vision, mood alterations	Pain, muscular asthenia or paraesthesia, hypoaesthesia, changes in sense of taste (metallic taste),meningism (paralysis, vomiting), acute aseptic meningitis	Posterior reversible encephalopathy syndrome (paediatric patients), aphasia, blurred vision, hemiparesis, dizziness.
Eye disorders				Visual disturbances	Conjunctivitis,	

					retinopathy	
Ear and labyrinth disorders						Tinnitus
Cardiac disorders				Pericarditis, pericardial effusion, pericardial tamponade		
Vascular disorders				Hypotension, thrombo-embolic events (including arterial and cerebral thrombosis, thrombo-phlebitis, deep vein thrombosis, retinal vein thrombosis, pulmonary embolism).		
Respiratory, thoracic and mediastinal disorders		Pulmonary complications due to interstitial alveolitis/-pneumonitis and related deaths (independent of dose and duration of methotrexate treatment). Typical symptoms may be: general illness; dry, irritating cough; shortness of breath progressing to rest dyspnoea, chest pain, fever. If such complications are suspected, methotrexate treatment must be discontinued immediately and infections (including pneumonia) must be excluded.	Pulmonary fibrosis	Pharyngitis, apnoea, bronchial asthma	Pneumocystis carinii pneumonia, shortness of breath, chronic obstructive pulmonary disease. Infections including pneumonia have also been observed. Pleural effusion.	Pulmonary oedema, acute pulmonary oedema. Syndrome consisting of pleuritic pain and pleural thickening following high doses. Pulmonary alveolar haemorrhage.*

Gastro-intestinal 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 ulcers and bleeding.	Enteritis, melaena. Gingivitis, malabsorption	Haematemesis, toxic megacolon	Pancreatitis
Hepatobiliary disorders	Increase in liver-related enzymes (ALAT, ASAT, alkaline phosphatase and bilirubin).		Development of liver fattening, fibrosis and cirrhosis (occurs frequently despite regularly monitored, normal values of liver enzymes); diabetic metabolism; drop of serum albumin.	Acute hepatitis and hepatotoxicity.	Reactivation of chronic hepatitis, acute liver degeneration. Furthermore, herpes simplex hepatitis and liver insufficiency have been observed (also see the notes regarding liver biopsy in section 4.4).	Hepatic necrosis Death
Skin and subcutaneous tissue disorders		Exanthema, erythema, itching.	Urticaria, photosensibility, enhanced pigmentation of the skin, hair loss, increase of rheumatic nodules, herpes zoster, painful lesions of psoriatic plaques; severe toxic reactions: vasculitis, herpetiform eruption of the skin, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome).	Increased pigmentary changes of nails, acne, petechiae, ecchymoses, erythema multiforme, cutaneous erythematous eruptions.	Acute paronychia, furunculosis, telangiectasia Furthermore, nocardiosis, histoplasma and cryptococcus mycosis and disseminated herpes simplex have been reported. Allergic vasculitis,	Recall phenomenon has been reported in both radiation and solar damaged skin, skin exfoliation, dermatitis exfoliative.

					hidradenitis.	
Musculo-skeletal and connective tissue disorders			Arthralgia, myalgia, osteoporosis.	Stress fracture.		Osteonecrosis of jaw (secondary to lymphoproliferative disorders).
Pregnancy, puerperium and perinatal conditions						Abortion, foetal defects
Renal and urinary disorders			Inflammation and ulceration of the urinary bladder (possibly with haematuria), dysuria.	Renal failure, oliguria, anuria, azotaemia.	Proteinuria.	
Reproductive system and breast disorders			Inflammation and ulceration of the vagina.		Loss of libido, impotence, oligospermia, impaired menstruation, vaginal discharge, infertility.	Defective oogenesis or spermatogenesis
General disorders and administration site conditions			Severe allergic reactions progressing to anaphylactic shock.		Fever, impaired wound healing.	Malaise, chills, sudden death, oedema, abnormal changes in tissue cells, injection sitereaction, injection site necrosis

*(has been reported for methotrexate used in rheumatologic and related indications)

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 HPRA Pharmacovigilance. Website: www.hpra.ie.

4.9 Overdose

Symptoms of overdose
In post-marketing experience, overdose with methotrexate has generally occurred with oral and intrathecal administration, although intravenous and intramuscular overdose has also been reported.

Cases of overdose have been reported, sometimes fatal, due to erroneous daily intake instead of weekly intake of oral methotrexate. In these cases, symptoms that have been commonly reported are hematological and gastrointestinal reactions. For example, leukopenia, thrombocytopenia, anemia, pancytopenia, bone marrow suppression, mucositis, stomatitis, oral ulceration, nausea, vomiting, gastrointestinal ulceration, gastrointestinal bleeding. In some cases, no symptoms were reported. There have been reports of death following chronic overdose in the self-administered dosage for rheumatoid arthritis and psoriasis (see sections 4.2 and 4.4). In these cases, events such as sepsis or septic shock, renal failure, and aplastic anaemia were also reported.

In cases of accidental overdose, a dose of calcium folinate equal to or higher than the offending dose of methotrexate should be administered intravenously or intramuscularly within one hour and dosing continued until the serum levels of methotrexate are below
10^{-7} mol/l.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
Antimetabolites, Folic acid analogues, ATC-code: L01BA01
Mechanism of action
Methotrexate is a folic acid antagonist which belongs to the class of cytotoxic agents known as antimetabolites. It acts by the competitive inhibition of the enzyme dihydrofolate reductase and thus inhibits DNA synthesis.

5.2 Pharmacokinetic properties

Distribution
Subcutaneous, intravenous and intramuscular administration demonstrated similar bioavailability. Approximately 50 % of methotrexate is bound to serum proteins. Upon being distributed into body tissues, high concentrations can be found particularly in liver, kidneys and spleen in form of polyglutamates, which can be retained for weeks or months. When administered in small doses, methotrexate passes into the liquor in minimal amounts; with high doses (300 mg/kg body weight), concentrations between 4 and 7 microgram/ml have been measured in the liquor.

Biotransformation
Average terminal half-life is 6-7 hours and demonstrates considerable variation (3-17 hours). Half-life may be prolonged to 4 times the normal length in patients with third spaces (pleural effusion, ascites). Approximately 10 % of the administered methotrexate is metabolised intrahepatically. The major metabolite is 7-hydroxymethotrexate. Methotrexate passes through the placental barrier in rats and monkeys.

Elimination
Excretion takes place, mainly in unchanged form, primarily renal via glomerular filtration and active secretion in the proximal 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

Immediate precipitation or turbidity results when combined with certain concentrations of Droperidol, Heparin Sodium, Metaclopramide Hydrochloride, Ranitidine Hydrochloride in syringe.
This medicinal product must not be mixed with other medicinal products, except those in section 6.6.

6.3 Shelf life

As packaged for sale – 30 months.

Vials after first opening: use immediately.

After dilution – Chemical and physical in-use stability has been demonstrated in dextrose 5% and sodium chloride 0.9 % infusion solutions for 30 days at 4°C.

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 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

As packaged for sale –
Do not store above 25°C. Do not freeze. 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

Conventional or Onco-Tain Type 1 glass vial containing 10ml solution for injection with rubber stopper, aluminium seal and plastic 'flip-off' tops. Packs containing 1 vial.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

As with other potentially toxic agents, caution should be exercised when handling and preparing solutions of methotrexate.

Guidelines for the safe handling and disposal of antineoplastic agents
Preparation
Local guidelines on safe preparation and handling should be consulted.

Cytotoxic agents should only be prepared and handled by personnel trained in the safe handling of such preparations. Pregnant personnel should not handle cytotoxic agents.

All personnel involved with handling cytotoxic agents should be adequately protected with appropriate personal protective equipment, including protective disposable gloves, eye shield, mask and long-sleeved gown. Preparation and manipulation of solutions should be performed in a designated handling area. It is forbidden to smoke, eat or drink in this area.

Contamination
In the event of skin contact, thoroughly wash the affected area with soap and water, taking care not to abrade the skin. A bland cream may be used to treat transient stinging of the skin.

In the event of contact with the eyes, irrigate with copious amounts of water or sodium chloride 0.9%. Seek medical evaluation.

In the event of spillage, trained personnel wearing appropriate personal protective equipment should remove the maximum amount of material by use of a cytotoxic drug spill kit or designated absorbent materials. The area should be rinsed with copious amounts of water. All contaminated cleaning materials should be disposed of as described below.

Disposal
All contaminated waste materials (including sharps, containers, absorbent materials, unused solutions) should be placed in a designated sealed and labelled impervious waste disposal bag or rigid waste container, and incinerated in accordance with local procedures for destruction of hazardous waste.

Instructions for preparation
From a microbiological and chemical point of view, the solution should be diluted immediately with dextrose 5% or sodium chloride 0.9% infusion solutions.

Inspect visually prior to use. Only clear solutions without particles should be used. This medicinal product is for single use only. Any unused solution should be discarded immediately after use.

Compatibility: It is not recommended to mix methotrexate with other drugs (see section 6.2).

Administration: For instructions on administration see section 4.2.

7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland
9 Riverwalk
National Digital Park
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0822/206/006

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09 March 1988
Date of last renewal: 21 September 2006

10 DATE OF REVISION OF THE TEXT

April 2024