Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Methotrexate 10 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains methotrexate 10mg.
Excipients: also includes 38.5mg lactose monohydrate per tablet.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
Scored yellow capsule shaped tablets marked 'M10' on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Methotrexate 10 mg is indicated in:

- Active rheumatoid arthritis in adult patients.
- Severe forms of psoriasis vulgaris, particularly of the plaque type, which cannot be sufficiently treated with conventional therapy such as phototherapy and PUVA, and severe psoriatic arthritis.

4.2 Posology and method of administration

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

The prescriber should ensure that patients or their carers will be able to comply with the once weekly regimen.

Important warning about the dosage of methotrexate

In the treatment of psoriasis and rheumatoid arthritis, methotrexate **must only be taken 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.

Posology
For doses not realisable/practicable with this strength, another strength of this medicinal product is available.

It is recommended to specify a certain day of the week as "the day for taking Methotrexate" on the prescription

This medicine should be taken once a week. Do not exceed the weekly dose of this medicine due to toxicity hazards in psoriasis and rheumatoid arthritis. The prescriber should specify the day of intake on the prescription.

Rheumatoid arthritis

Adults
The usual dose is 7.5 – 15 mg once weekly. The schedule may be adjusted gradually to achieve an optimal response but should not exceed a total weekly dose of 20 mg. Once the desired therapeutic result has been achieved, dose should be reduced gradually to the lowest possible effective maintenance dose.

Psoriasis and Psoriatic Arthritis

Adults

Before starting treatment it is advisable to give the patient a test dose of 2.5–5.0 mg to exclude unexpected toxic effects. If, one week later, appropriate laboratory tests are normal, treatment may be initiated.

The usual dose is 7.5 - 15 mg taken once weekly, starting with a low dose and increasing as necessary. As necessary, the total weekly dose can be increased up to 25 mg.

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

Once the desired therapeutic result has been achieved, dose should be reduced gradually to the lowest possible effective maintenance dose.
The patient should be fully informed of the risks involved and the clinician should pay particular attention to the appearance of 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:

Patients with 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 1. 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.

Patients with impaired hepatic function
Methotrexate should be administered with great caution, if at all, to patients with significant current or previous liver disease, especially when caused by alcohol. Methotrexate is contraindicated if bilirubin values are >5 mg/dl (85.5 micromole/l) (see section 4.3 and 4.4).

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
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.

Paediatric population
Methotrexate is not recommended for children under 3 years as insufficient data on efficacy and safety is available for this population.

Method of administration
Methotrexate 10 mg is for oral administration.

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).
- Liver disease including fibrosis, cirrhosis, recent or active hepatitis.
- Alcohol abuse.

- Renal insufficiency (creatinine clearance less than 30 ml/min., see section 4.2).
- Pre-existing blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anaemia.
- Serious, acute or chronic infections such as tuberculosis and HIV.
- Patients with overt or laboratory evidence of immunodeficiency syndrome(s)
- Stomatitis
- 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 (including early signs and symptoms of toxicity) and the recommended safety measures. Patients should be informed that they must notify the doctor immediately if any symptoms of an overdose occur and that the symptoms of the overdose need to be monitored (including regular laboratory tests).

It should be emphasized to the patient treated for rheumatoid arthritis and psoriasis that the recommended dose must be taken 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 therapy in patients with impaired renal function should be undertaken with extreme caution and should be monitored by renal function tests and urinalyses, and at reduced doses, because impairment of renal function will decrease methotrexate elimination

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 (see sections 4.2 and
4.3).

Treatment with moderately high and high doses of methotrexate 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.

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.

Doses exceeding 20 mg week can be associated with a substantial increase in toxicity, especially bone marrow depression.

Because of the delayed excretion of methotrexate in patients with impaired kidney function, they should be treated with particular caution and only with low doses of methotrexate (see sections 4.2 and 4.3).

Methotrexate should be used only with great caution, if at all, in patients who have a significant liver disease, particularly if this is/was alcohol-related (see sections 4.2 and 4.3).

Methotrexate should be used with extreme caution in patients with haematological depression, renal impairment, peptic ulcer, ulcerative colitis, ulcerative stomatitis, diarrhoea, debility, and in the elderly and young children.

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

Methotrexate-induced lung diseases such as pneumonitis can occur acutely and at any time during treatment, are not always completely reversible and have already been observed at all doses (including low doses of 7.5 mg/week).

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

Teratogenicity – Reproductive risk: Methotrexate causes embryotoxicity, abortion and fetal 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 (to exclude infection and tumours) 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: Particular attention should be paid to the onset of liver toxicity. Treatment should not be initiated or should be discontinued if there are any abnormalities in liver function tests or liver biopsies, or if these develop during therapy. Such abnormalities should return to normal within two weeks; after which, treatment may be resumed at the discretion of the physician.

In patients with rheumatoid arthritis, the timing on when to perform a liver biopsy has not been established either in terms of a cumulative methotrexate dose or duration of therapy.

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

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

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

· **Renal function** should be monitored by renal function tests and urinalysis (see also
4.2 and 4.3): As methotrexate is eliminated mainly by renal route, increased serum concentrations are to be expected in the case of renal insufficiency, which may result in severe undesirable effects.

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

methotrexate. High doses may cause the precipitation of methotrexate or its metabolites in the renal tubules. Treatment with moderately high and high doses of methotrexate should not be initiated at urinary pH values of less than 7. A high fluid throughput and alkalinization of the
urine by oral or intravenous administration of sodium bicarbonate or acetazolamide is recommended as a preventive measure. Alkalinisation of the urine must be tested by repeat pH monitoring (value greater than o requal to 6.8) for at least the first 24 hours after the administration of methotrexate is started.

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.

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

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

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

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

Pleuropulmonary manifestations of rheumatoid arthritis have been reported in the literature. In patients with rheumatoid arthritis, the physician should be specifically alerted to the potential for potentially serious methotrexate-induced adverse effects in the pulmonary system that may occur acutely at any time during therapy and are not always fully reversible. Patients should be advised to contact their physicians immediately should they develop a cough or dyspnoea.

· 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/history 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) or treatment should be withdrawn when appropriate.

· **Diarrhoea and ulcerative stomatitis** can be toxic effects and require interruption of therapy, otherwise haemorrhagic enteritis and death from intestinal perforation may occur. Use in patients with active gastrointestinal ulcer disease is contraindicated. Following the occurrence of heamatemesis, black coloured stools or blood in the stools, treatment must be discontinued.

In addition, other conditions leading to dehydration such as emesis can increase the toxicity of methotrexate due to the elevated levels of the active substance. In these cases use of methotrexate should be interrupted until symptoms cease. It is important to determine any increase in active substance levels within 48 hours of therapy, otherwise irreversible methotrexate toxicity may occur.

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

· In patients with rheumatoid arthritis or psoriasis, folic acid or folinic acid supplementation may reduce methotrexate toxicity, such as gastrointestinal symptoms, stomatitis, alopecia and elevated liver enzymes.
· It is recommended to check levels of vitamin B12 prior to initiating folic acid supplementation, particularly in adults aged over 50 years, as folic acid intake may mask a vitamin B12 deficiency.
· Skin toxicity: Due to risk of phototoxicity the patients must avoid **sun light and solarium.** Lesions of **psoriasis** may be aggravated by concomitant exposure to ultraviolet radiation.
· Radiation induced dermatitis and sun-burn can reappear under methotrexate therapy (recall-reaction). Psoriatic lesions can exacerbate during UV-irradiation and simultaneous administration of methotrexate.
· Severe, occasionally fatal, dermatologic reactions, including toxic epidermal necrolysis (Lyell's syndrome) or Stevens-Johnson syndrome have been reported after single or multiple doses of methotrexate.

Use caution when administering high-dose methotrexate to patients receiving proton pump inhibitor (PPI) therapy. 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 coadministered with PPIs, but was not observed when methotrexate was coadministered with ranitidine. However, no formal drug interaction studies of methotrexate with ranitidine have been conducted.

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

Patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interactions

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).

Non-steroidal anti-inflammatory drugs (NSAIDs) should not be administered prior to, or concomitantly with, high-dose methotrexate as fatal methotrexate toxicity has been reported.

In animal experiments, 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. Existing data suggest that etretinate is formed from acitretin after ingestion of alcoholic beverages. However, the formation of etretinate without concurrent alcohol intake cannot be excluded. Serum levels of methotrexate may be increased by etretinate and severe hepatitis has been reported following concurrent use

Patients taking potentially hepatotoxic or hematotoxic 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.

Concomitant use of other drugs with nephrotoxic potential should be avoided.

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

However, concomitant administration of levetiracetam and methotrexate has been reported to decrease methotrexate clearance, resulting in increased/prolonged blood methotrexate concentration to potentially toxic levels. Blood methotrexate and levetiracetam levels should be carefully monitored in patients treated concomitantly with the two drugs.

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

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

Antibiotics, like 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, chloramphenicol, pyrimethamine), the risk of pronounced haematopoietic disorders during methotrexate therapy must be considered.

Administration of additional haematotoxic medicinal products (e.g. metamizole) increases the probability of severe haematoxic effects of methotrexate.

Concomitant administration of drugs that cause folate deficiency (e.g. sulfonamides, trimethoprim/sulfamethoxazole [co-trimoxazole]) may lead to increased methotrexate toxicity including acute megaloblastic pancytopenia in rare instances. 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 or other products, which contain folic acid or derivatives, may impair methotrexate efficacy.

Methotrexate should be used with caution in patients taking drugs with an antifolate potential, including nitrous oxide.

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

Colestyramine can increase the non-renal elimination of methotrexate by interrupting the enterohepatic circulation.

Concomitant administration of proton-pump inhibitors like omeprazole or pantoprazole can lead to interactions (see section 4.4): In combination with pantoprazole, inhibited renal elimination of the 7-hydroxymethotrexate metabolite, 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 under concomitant methotrexate administration. Excessive consumption of caffeine- or theophylline-containing beverages (coffee, caffeine-containing beverages, black tea) should be avoided during methotrexate therapy, since the efficacy of methotrexate may be reduced due to possible interaction between methotrexate and methylxanthines at adenosine receptors.

The combined use of methotrexate and leflunomide may increase the risk for pancytopenia. Methotrexate leads to increased plasma levels of mercaptopurines. Therefore, the combination of these may require dosage adjustment. Particularly in the case of orthopaedic surgery where susceptibility to infection is high, a combination of methotrexate with immune- modulating agents must be used with caution.

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

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

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

be carried out (see section 4.3). Radiotherapy during use of methotrexate can increase the risk of soft tissue or bone necrosis. Cyclosporine may potentiate methotrexate efficacy and toxicity. There is a risk of excessive immunosuppression with risk of lymphoproliferation when the combination is used.

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

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

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

As methotrexate can be genotoxic, all women who wish to become pregnant are advised to consult a genetic counselling centre, if possible, already 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 6 months after cessation of methotrexate. Men should not donate semen during therapy or for 6 months following discontinuation of methotrexate.

Women who are planning to become pregnant are advised to consult a genetic counselling centre, if possible, prior to therapy.

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.

Most serious adverse reactions of methotrexate include bone marrow suppression, pulmonary toxicity, hepatotoxicity, renal toxicity, neurotoxicity, thromboembolic events, anaphylactic shock and Stevens-Johnson syndrome.

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.

	Very common	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations*					Sepsis, opportunistic infections (maybe fatal in some cases), infections caused by the cytomegalovirus	Infection susceptibility increased
Neoplasms benign,			Individual cases of lymphoma, which abated			

malignant and unspecified (incl. cysts and polyps)			in a number of cases once methotrexate treatment had been discontinued. In a recent study, it was not possible to establish that methotrexate therapy increases the incidence of lymphomas			
Blood and lymphatic system disorders *		Leukocytopenia, thrombo-cytopenia, anaemia	Pancytopenia, agranulocytosis, haematopoietic disorders.	Megaloblastic anaemia	Severe courses of bone marrow depression, aplastic anaemia. Lymphaden-opathy, lymphopro-liferative disorders$^{\alpha}$ (partly reversible), eosinophilia and neutropenia	Haemorrhage , abnormal (usually "megaloblastic") red cell Morphology
Metabolism and nutrition disorders						Diabetes and other metabolic disorders
Immune system disorders*					Immuno-suppression hypogamma-globulinaemia	Anaphylactic reactions
Psychiatric disorders				Mood alterations	Insomnia Psychoses	
Nervous system disorders *		Headache, fatigue, drowsiness	Vertigo, confusion, depression, seizures, leuko-encephalopathy/encephalopathy	Severely impaired vision, mood alterations	Pain, muscular asthenia or paresthesia, hypoaesthesia, changes in sense of taste (metallic taste), meningism (paralysis, vomiting), acute aseptic meningitis, cerebral oedema, dysarthria, tinnitus	Dizziness, blurred vision. Low dose: Transient subtle cognitive dysfunction, unusual cranial sensations. High-dose: Aphasia, paresis, hemiparesis
Eye disorders				Visual disturbances	Conjunctivitis, retinopathy	Eye irritation
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, respiratory paralysis	Pneumocystis carinii/ jiroveci pneumonia, shortness of breath, chronic obstructive pulmonary disease. Infections including pneumonia have also been observed. Pleural effusion.	Acute pulmonary oedema (after oral use), syndrome consisting of pleuritic pain and pleural thickening (following high doses), reactivation of inactive chronic infection, epistaxis, pulmonary alveolar haemorrhage
Gastro-inte	Loss of	Diarrhoea	Gastrointestinal ulcers and	Enteritis,	Haematemes	

stinal disorders*	appetite, nausea, vomiting, abdominal pain, inflammation and ulcerations of the mucous membrane of mouth and throat (especially during the first 24-48 hours after administration of methotrexate). Stomatitis, dyspepsia	(especially during the first 24-48 hours after administration of methotrexate).	bleeding.	melaena. Gingivitis, malabsorption	is, 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).	Acute liver atrophy, necrosis or death (usually following chronic administration)
Skin and subcutaneous tissue disorders		Exanthema, erythema, itching.	Urticaria, photosensibility, enhanced pigmentation of the skin, hair loss, increase of rheumatic nodules, herpes zoster, painful lesions of psoriatic plaque; severe toxic reactions: vasculitis, herpetiform eruption of the skin, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome).	Increased pigmentary changes of nails, acne, petechiae, ecchymoses, erythema multiforme, cutaneous erythematous eruptions, onycholysis	Acute paronychia, furunculosis, telangiectasia Furthermore, nocardiosis, histoplasma and Cryptococcus mycosis and disseminated herpes simplex have been reported. Allergic vasculitis, hidradenitis.	Recall phenomenon has been reported in both radiation and solar damaged skin, skin exfoliation, dermatitis exfoliative.
Musculo-sk			Arthralgia, myalgia,	Stress fracture.		Osteonecrosis

eletal and connective tissue disorders			osteoporosis.			of jaw (secondary to lymphoproliferative disorders).
Renal and urinary disorders			Inflammation and ulceration of the urinary bladder (possibly with haematuria), dysuria.	Oliguria, anuria, renal failure and uraemia (usually in high doses).	Proteinuria.	Nephropathy, disturbed micturition, electrolyte disturbance
Reproductive system and breast disorders			Inflammation and ulceration of the vagina.		Loss of libido, impotence, oligospermia, impaired menstruation, vaginal discharge, infertility.	Amenorrhoea (during and for a short period after cessation of therapy)
General disorders and administration site conditions			Severe allergic reactions progressing to anaphylactic shock.		Fever, impaired wound healing.	Malaise, chills, sudden death, oedema.

[α] Lymphoma/Lymphoproliferative disorders: there have been reports of individual cases of lymphoma and other lymphoproliferative disorders which subsided in a number of cases once treatment with methotrexate had been discontinued.

Reporting of suspected adversereactions
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
Toxicity of methotrexate mainly affects the haematopoietic and gastrointestinal systems. Symptoms include leukocytopenia, thrombocytopenia, anaemia, pancytopenia, neutropenia,
bone marrow depression, mucositis, stomatitis, oral ulceration, nausea, vomiting, gastrointestinal ulceration and gastrointestinal bleeding. Some patients showed no signs of overdose.

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.

There are reports of death due to sepsis, septic shock, renal failure

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

In cases of accidental overdose, a dose of calcium folinate equal to or higher than the offending dose of methotrexate should be administered intravenously or intramuscularly within one hour and dosing continued until the serum levels of methotrexate are below 10-7 mol/l. Other supporting therapy such as a blood transfusion and renal dialysis may be required.

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: L04AX03

Mechanism of action
Methotrexate is a folic acid antagonist which belongs to the class of cytotoxic agents known as antimetabolites. It acts by the competitive inhibition of the enzyme dihydrofolate reductase and thus inhibits DNA synthesis.

5.2 Pharmacokinetic properties

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

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

Elimination
Excretion takes place, mainly in unchanged form, primarily renal via glomerular filtration and active secretion in the proximal tubule. 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
Animal carcinogenicity studies have demonstrated methotrexate to be free of carcinogenic potential. 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.

Reproductive toxicology
Teratogenic effects have been identified in four species (rats, mice, rabbits, cats). In rhesus monkeys, no malformations comparable to humans occurred.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Lactose monohydrate
Pre gelatinised starch
Polysorbate 80
Microcrystalline cellulose
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Keep the tablet container in the outer carton in order to protect from light.

6.5 Nature and contents of container

White polyethylene bottle with high density polyethylene screw closure containing 100 tablets.

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

Women who are pregnant, planning to be or breast- feeding should not handle methotrexate.

Parents, care givers and patients should be advised to keep methotrexate out of the reach of children, preferably in a locked cupboard.

Accidental ingestion can be lethal for children.

Anyone handling methotre xate should wash their hands after administering a dose. To decrease the risk of exposure, parents and care givers should wear disposable gloves when handling methotrexate.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 21 September 2006

10 DATE OF REVISION OF THE TEXT

September 2020