Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Methotrexate 2.5mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 2.5 mg methotrexate.

Excipients with known effect: 39.9 mg lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
Yellow, round, convex, uncoated tablet engraved with M 2.5 on one side, diameter 6 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Active rheumatoid arthritis in adult patients.
- Severe recalcitrant disabling psoriasis, which is not adequately responsive to other forms of therapy such as phototherapy, PUVA, and retinoids, and severe psoriatic arthritis in adult patients.

4.2 Posology and method of administration

Posology

Rheumatoid arthritis and psoriasis
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 warning about the dosage of Methotrexate

In the treatment of rheumatic diseases, psoriasis or psoriatic 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.

The prescriber should ensure that patients or their carers will be able to comply with the once weekly regimen.
The prescriber should specify the day of intake on the prescription.
For doses not realisable/practicable with this strength, another strength of this medicinal product is available.

Rheumatoid arthritis
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. Thereafter the dose should be reduced to the lowest possible effective dose which in most cases is achieved within 6 weeks.

Psoriasis
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. As necessary, the total weekly dose can be increased up to 25 mg. Thereafter the dose should be reduced to the lowest effective dose according to therapeutic response which in most cases is achieved within 4 to 8 weeks.

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.

Use in elderly
Methotrexate should be used with extreme caution in elderly patients, a dose reduction should be considered due to reduced liver and kidney function as well as lower folate reserves which occurs with increased age.

Patients with hepatic impairment
Methotrexate should be administered with great caution, if at all, to patients with significant current or previous liver disease, especially if due to alcohol (see sections 4.3 and 4.4).

Patients with renal impairment
Methotrexate should be used with caution in patients with impaired renal function (see sections 4.3 and 4.4). The dose should be adjusted as follows:

Creatinine clearance (ml/min)	Dose
≥ 60	100%
30–59	50%
< 30	Methotrexate must not be used.

Use in a patient with a third distribution space (pleural effusions, ascites)
As the half-life of methotrexate can be prolonged to 4 times the normal length in patients who possess a third distribution space dose reduction or, in some cases, discontinuation of methotrexate administration may be required.

4.3 Contraindications

- Significantly impaired hepatic function
- Significantly impaired renal function
- Pre-existing blood dycrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anaemia
- Alcoholism
- Severe acute or chronic infections and immunodeficiency syndrome
- Stomatitis, ulcers of the oral cavity and known active gastrointestinal ulcer disease
- Pregnancy and breast-feeding (see section 4.6).
- Hypersensitivity to methotrexate or to any of the excipients listed in section 6.1
- During methotrexate therapy concurrent vaccination with live vaccines must not be carried out

4.4 Special warnings and precautions for use

Dosing in the treatment of rheumatoid arthritis, psoriasis and psoriatic arthritis:
The prescriber should specify the day of intake on the prescription.
The prescriber should make sure patients understand that Methotrexate should only be taken once a week.
Patients should be instructed on the importance of adhering to the once-weekly intakes.

Warnings
Methotrexate must be used only by physicians experienced in antimetabolite chemotherapy.

Patients must be appropriately monitored during treatment so that signs of possible toxic effects or adverse reactions can be detected and evaluated with minimal delay.

Because of the possibility of severe or even fatal toxic reactions, patients should be extensively informed by the treating doctor 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).

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).

Concomitant administration of hepatotoxic or haematotoxic DMARDs (disease-modifying antirheumatic drug, e.g. leflunomide) is not advisable.

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

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).

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.

Deaths have been reported associated with the use of methotrexate in the treatment of psoriasis.

For the treatment of psoriasis, methotrexate should be restricted to severe recalcitrant, disabling psoriasis which is not adequately responsive to other forms of therapy, but only when the diagnosis has been established by biopsy and/or after dermatological consultation.

Full blood counts should be closely monitored before, during and after treatment. If a clinically significant drop in white-cell or platelet count develops, methotrexate should be withdrawn immediately. Patients should be advised to report all symptoms or signs suggestive of infection.

Methotrexate may be hepatotoxic, particularly at high doses or with prolonged therapy. Liver atrophy, necrosis, cirrhosis, fatty changes, and periportal fibrosis have been reported. Since changes may occur without previous signs of gastrointestinal or haematological toxicity, it is imperative that hepatic function be determined prior to initiation of treatment and monitored regularly throughout therapy.

Liver function tests: Particular attention should be given to the appearance of liver toxicity. Treatment should not be instituted or should be discontinued if any abnormality of liver function tests, or liver biopsy, is present or develops during therapy. Such abnormalities should return to normal within two weeks after which treatment may be recommenced at the discretion of the physician.

Check of liver-related enzymes in serum: Temporary increases in transaminases to twice or three times of the upper limit of normal have been reported by patients at a frequency of 13 - 20%. In the case of a constant increase in liver-related enzymes, a reduction of the dose or discontinuation of therapy should be taken into consideration.

Due to its potentially toxic effect on the liver, additional hepatotoxic medicinal products should not be taken during treatment with methotrexate unless clearly necessary and the consumption of alcohol should be avoided or greatly reduced (see section 4.5). Closer monitoring of liver enzymes should be exercised in patients taking other hepatotoxic medicinal products concomitantly (e.g. leflunomide). The same should be taken into account with the simultaneous administration of haematotoxic medicinal products (e.g. leflunomide). Further research is needed to establish whether serial liver function tests or determinations of propeptide of type III collagen are appropriate for detecting hepatotoxicity.

There is no evidence to support use of a liver biopsy to monitor hepatic toxicity in rheumatological indications. For psoriasis patients the need of a liver biopsy prior to and during therapy is controversial. The need of liver biopsy should be evaluated case by case and national recommendations should be followed. This assessment should differentiate between patients with no risk factors and patients with risk factors such as excessive prior alcohol consumption, persistent elevation of liver enzymes,

history of liver disease, family history of inheritable liver disease, diabetes mellitus, obesity, and history of significant exposure to hepatotoxic drugs or chemicals and prolonged methotrexate treatment or cumulative doses of 1.5 g or more.

Renal function should be closely monitored before, during and after treatment by renal function tests and urinalysis. If serum creatinine is increased, the dose should be reduced. As methotrexate is predominantly excreted via the renal route, increased concentrations can be expected in cases of renal impairment, which may result in severe adverse reactions. 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. NSAIDs) or can potentially lead to haematopoietic disorders. In patients with impaired renal function, concomitant administration of NSAIDs is not recommended. Dehydration may also potentiate the toxicity of methotrexate.

Diarrhoea and ulcerative stomatitis are frequent toxic effects and require interruption of therapy, otherwise haemorrhagic enteritis and death from intestinal perforation may occur. Following the occurrence of haematemesis, black coloured stools or blood in the stools, treatment must be discontinued.

In addition other conditions leading to dehydration such as emesis, diarrhoea or stomatitis can increase the toxicity of methotrexate due to 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.

Methotrexate has some immunosuppressive activity and immunological responses to concurrent vaccination may be decreased. Vaccination with live vaccines should be avoided during therapy.

The immunosuppressive effect of methotrexate should be taken into account when immune responses of patients are important or essential. Special attention should be paid in cases of inactive chronic infections (e.g. herpes zoster, tuberculosis, hepatitis B or C) because of their potential activation.

A chest X-ray is recommended prior to initiation of methotrexate therapy.

Pleural effusions and ascites should be drained prior to initiation of methotrexate therapy.

Serious adverse reactions including deaths have been reported with concomitant administration of methotrexate (usually in high doses) along with some non-steroidal anti-inflammatory drugs (NSAIDs).

In the treatment of rheumatoid arthritis, treatment with acetylsalicylic acid and non-steroidal anti-inflammatory drugs (NSAID) as well as small-dose steroids can be continued. One has to take into consideration, however, that coadministration of NSAIDs and methotrexate may involve an increased risk of toxicity. The steroid dose can be reduced gradually in patients who exhibit therapeutic response to methotrexate therapy.

Interaction between methotrexate and other antirheumatic agents, such as gold, penicillamin, hydroxychloroquine, sulfasalazine or other cytotoxic agents, have not been studied comprehensively, and coadministration may involve an increased frequency of adverse reactions.

Concomitant administration of folate antagonists such as trimethoprim/sulfamethoxazole has been reported to cause an acute megaloblastic pancytopenia in rare instances.

If acute methotrexate toxicity occurs, patients may require folinic acid. 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.

Since cases of encephalopathy/leukoencephalopathy have occurred in cancer patients treated with methotrexate, this cannot be ruled out either for patients with non-cancer indications.

Fertility and reproduction

Fertility

Methotrexate has been reported to cause oligospermia, menstrual dysfunction and amenorrhoea in humans, during and for a short period after cessation of therapy, and to cause impaired fertility, affecting spermatogenesis and oogenesis during the period of its administration - effects that appear to be reversible on discontinuing therapy.

Teratogenicity – Reproductive risk
Methotrexate causes embryotoxicity, abortion and foetal defects in humans. Therefore, the possible risks of effects on reproduction, pregnancy loss and congenital malformations should be discussed with female patients of childbearing potential (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 performed during treatment and for at least six months after.

For contraception advice for men see section 4.6.

Precautions
Before beginning methotrexate therapy or reinstituting methotrexate after a rest period, assessment of renal function, liver function and a bone marrow function should be made by history, physical examination and laboratory tests.

Systemic toxicity of methotrexate may also be enhanced in patients with renal dysfunction, ascites, or other effusions due to prolongation of serum half-life.

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.

Patients undergoing therapy should be subject to appropriate supervision so that signs or symptoms of possible toxic effects or adverse reactions may be detected and evaluated with minimal delay. Pre-treatment and periodic haematological studies are essential for the safe use of methotrexate in chemotherapy because of its common effect of haematopoietic suppression. This may occur without warning when a patient is on an apparently safe dose, and any profound drop in blood cell count indicates immediate stopping of the drug and appropriate therapy.

In general, the following laboratory tests are recommended as part of essential clinical evaluation and appropriate monitoring of patients chosen for or receiving methotrexate: complete haemogram; haematocrit; urinalysis; renal function tests; liver function tests and chest X-ray.

The purpose is to determine any existing organ dysfunction or system impairment. The tests should be performed prior to therapy, at appropriate periods during therapy and after termination of therapy.

Methotrexate is bound in part to serum albumin after absorption, and toxicity may be increased because of displacement by certain drugs such as salicylates, sulfonamides, phenytoin, and some antibacterials such as tetracycline, chloramphenicol and para-aminobenzoic acid. These drugs, especially salicylates and sulfonamides, whether antibacterial, hypoglycaemic or diuretic, should not be given concurrently until the significance of these findings is established.

Vitamin preparations containing folic acid or its derivatives may alter response to methotrexate.

Methotrexate should be used with extreme caution in the presence/history of infection, peptic ulcer, ulcerative colitis, debility and old age. Use in patients with active gastrointestinal ulcer disease is contraindicated. If profound leukopenia occurs during therapy, bacterial infection may occur or become a threat. Cessation of the drug and appropriate antibiotic therapy is usually indicated. In severe bone marrow depression, blood or platelet transfusions may be necessary.

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.

The tablets contain lactose. 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

After absorption methotrexate binds partly to serum albumin. Certain medicinal products (e.g. salicylates, sulfonamides phenylbutazone phenytoin, barbiturates, tranquilisers, oral contraceptives, amidopyrine derivatives, p-aminobenzoic acid,

thiazide diuretics, oral hypoglycaemics and doxorubicin) decrease this binding. In such instances the toxicity of methotrexate may increase when coadministered. Since probenecid and weak organic acids, such as "loop-diuretics" as well as pyrazols, reduce tubular secretion, great caution should be exercised when these medicinal products are coadministered with methotrexate.

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

Coadministration of other, potentially nephro- hemato-and hepatotoxic agents (e.g. sulfasalazine, leflunomide and alcohol) with methotrexate should be avoided. Special caution should be exercised when observing patients receiving methotrexate therapy in combination with azathioprine or retinoids.

Methotrexate in combination with leflunomide can increase the risk for pancytopenia.

Antibiotics, like penicillin, 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.

NSAIDs should not be administered before or concurrently with high-dose methotrexate. Concomitant use of some NSAIDs and high-dose methotrexate has been reported to increase and prolong the serum methotrexate concentration in serum and to increase gastrointestinal and haematological toxicity. When using smaller doses of methotrexate, these medicinal products have been found in animals to decrease the tubular secretion of methotrexate and possibly to increase its toxicity. In addition to methotrexate, patients with rheumatoid arthritis have generally been treated, however, with NSAIDs with no problems. It should be noted, however, that the doses of methotrexate used in the treatment of rheumatoid arthritis (7.5 - 15 mg/week) are slightly lower than those used for psoriasis and that higher doses can result in unexpected toxicity.

Vitamin preparations or other products containing folic acid or its derivatives may impair methotrexate efficacy.

Under (pre-)treatment with substances that may have adverse effects on the bone marrow (e.g. sulphonamides, trimethoprim-sulphamethoxazole, chloramphenicol, pyrimethamine), the possibility of marked haematopoietic disorders should be considered.

Co-administration of medicinal products which cause folate deficiency (e.g. sulphonamides, trimethoprim-sulphamethoxazole) can lead to increased methotrexate toxicity. Particular caution should therefore also be exercised in the presence of existing folic acid deficiency.

Bone marrow suppression and reduced folate concentrations have been reported when triamterene and methotrexate were coadministered.

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

There is evidence that coadministration of methotrexate and omeprazole prolongs the elimination of methotrexate via the kidneys. Coadministration of proton pump inhibitors, such as omeprazole or pantoprazole, can cause interactions. In combination with pantoprazole, inhibited renal elimination of the 7-hydroxymethotrexate metabolite, with myalgia and shivering, was reported in one case.

Methotrexate may decrease the clearance of theophylline; theophylline levels should be monitored when used concurrently with methotrexate. Excessive consumption of beverages containing caffeine or theophylline (coffee, soft drinks containing caffeine, 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.

One should be aware of pharmacokinetic interactions between methotrexate, anticonvulsant medicinal products (reduced methotrexate blood levels), and 5-fluorouracil (increased $t_{½}$ 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.

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.

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

Radiotherapy during use of methotrexate can increase the risk of soft tissue or bone necrosis.

Methotrexate increases the plasma levels of mercaptopurine. Combinations of methotrexate and mercaptopurine may therefore require dose adjustment.

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 sections 4.3 and 4.4).

Risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by cytotoxic drug or risk of toxicity enhancement or lose of efficacy of the cytotoxic drug due to increased hepatic metabolism by phenytoin.

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

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.

Pregnancy
Methotrexate is contraindicated during pregnancy in non-oncological indications (see section 4.3). 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). Breast-feeding is therefore to be stopped prior to treatment.

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

4.7 Effects on ability to drive and use machines

Central nervous system symptoms, such as fatigue and dizziness, can occur during treatment with methotrexate which may have minor or moderate influence on the ability to drive and use machines.

4.8 Undesirable effects

Generally the frequency and severity of adverse reactions are dependent of the size of the dose, the dosing frequency, the method of administration and the duration of exposure.

If adverse reactions occur, the dose should be reduced or therapy discontinued and necessary corrective therapeutic measures undertaken, such as administration of calcium folinate (see sections 4.2 and 4.4). Methotrexate therapy should only be resumed with particular caution, after careful consideration of the need for treatment and with increased vigilance for the possible recurrence 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.

Most frequently observed adverse reactions of methotrexate include gastrointestinal disorders (e.g. stomatitis, dyspepsia, abdominal pain, nausea, loss of appetite) and abnormal liver function tests (e.g. increased Alanine aminotransferase (ALAT), Aspartate aminotransferase (ASAT), bilirubin, alkaline phosphatase). Other frequently occurring adverse reactions are leukopenia, anaemia, thrombocytopenia, headache, tiredness, drowsiness, pneumonia, interstitial alveolitis/pneumonitis often associated with eosinophilia, oral ulcers, diarrhoea, exanthema, erythema and pruritus.

The most relevant adverse reaction is suppression of the haematopoietic system and gastrointestinal disorders

The frequencies of the adverse reactions are classified as follows: Very common (≥ 1/10); common (≥1/100 to < 1/10); uncommon (≥1/1000 to < 1/100); rare (≥1/10000 to < 1/1000); very rare (<1/10000), not known (cannot be estimated from the available data).

	Very common	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations		Infections	Opportunistic infections	Herpes zoster Sepsis		Sepsis resulting in death Reactivation of inactive

						chronic infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Lymphoma[1]			
Blood and lymphatic system disorders		Leucopaenia	Bone marrow depression Agranulocytosis Thrombocytopaenia Anaemia Hematopoietic disorders	Megaloblastic anemia	Hypogammaglobulinaemia Lympho-proliferative disorders (see "description" below the table) Lymphadeno-pathy Neutropenia Aplastic anemia	Pancytopenia, Eosinophilia
Immune system disorders			Anaphylactic-type reaction		Immuno-suppression	Anaphylactic shock Allergic reactions
Endocrine disorders				Diabetes mellitus		
Psychiatric disorders				Depression Confusion Mood alterations	Insomnia Psychoses	
Nervous system disorders		Headache Drowsiness Dizziness Fatigue	Vertigo	Hemiparesis Paresis	Irritation Dysarthria Aphasia Lethargy Cerebral oedema Transient subtle cognitive dysfunction Unusual cranial sensations Convulsions Pain, muscular asthenia Changes in sense of taste (metallic taste) Meningism Acute aseptic meningitis Paralysis, Paraesthesia / hypoaesthesia	Encephalopathy/ Leuko-encephalopathy
Eye disorders					Conjunctivitis Blurred vision	Impaired vision Retinopathy
Ear and labyrinth disorders					Tinnitus	
Cardiac disorders				Pericarditis Pericardial effusion Pericardial tamponade		

Vascular disorders				Hypotension Thromboembolism	Vasculitis	
Respiratory, thoracic and mediastinal disorders			Pneumonia Interstitial pneumonitis[4] Interstitial/pulmonary fibrosis	Dyspnoea Pharyngitis[2] Respiratory paralysis	Pneumocystis *jiroveci* –pneumonia and other lung infections Chronic interstitial obstructive lung disease Pleuritis Pleural effusion Dry cough	Interstitial alveolitis[4] Epistaxis Bronchial asthma Pulmonary alveolar haemorrhage
Gastrointestinal disorders[3]	Stomatitis Dyspepsia Anorexia Nausea Vomiting Abdominal pain	Oral ulcers Diarrhoea		Gingivitis Gastrointestinal ulcerations and haemorrhage Enteritis Melaena	Haematemesis	Toxic megacolon Pancreatitis
Hepatobiliary disorders	Abnormal liver function tests (increased ALAT, ASAT, alkaline phosphatase and bilirubin)		Decrease in serum albumin Fatty degeneration of the liver	Hepatotoxicity Periportal fibrosis Liver cirrhosis Acute hepatitis	Reactivation of chronic hepatitis Hepatic failure	
Skin and subcutaneous tissue disorders		Erythematous rash Alopaecia Exanthema	Pruritus Stevens-Johnson´s syndrome Toxic epidermal necrolysis Herpetiform eruptions of the skin Increased skin pigmentation	Photohypersensitivity Acne Depigmentation Urticaria Erythema multiforme Painful damage to psoriatic lesion Skin ulceration Onycholysis Increased nail pigment changes Petechiae Allergic vasculitis Radiation dermatitis and sunburn may be "recalled"	Telangiectasis Furunculosis Ecchymoses Hidradenitis Acute paronchynia	Skin exfoliation / dermatitis exfoliative
Musculoskeletal and connective tissue disorders			Osteoporosis Arthralgia Myalgia Increased rheumatic nodules	Stress fracture		Osteo-necrosis of jaw (secondary to lympho-proliferative disorders)
Renal and urinary disorders			Renal insufficiency Nephropathy Inflammation and ulceration of the urinary bladder	Oliguria Anuria Electrolyte disturbances Azotaemia	Haematuria	Proteinuria

			Disturbed micturition Dysuria			
Pregnancy, puerperium and perinatal conditions						Miscarriage, fetal damages
Reproductive system and breast disorders			Vaginal inflammation and ulceration	Decreased libido Impotence Menstrual disorders	Formation of defective oocytes or sperm cells Transient oligospermia, Infertility Vaginal bleeding Vaginal discharge Gynaecomastia	
General disorders and administration site conditions			Chills	Fever Wound-healing impairment Asthenia		Oedema
Injury, poisoning and procedural complications						Increased risk of toxic reactions (soft tissue necrosis, osteonecrosis) during radiotherapy The psoriatic lesions may get worse from simultaneous exposure to methotrexate and ultraviolet radiation.

[1] Can be reversible (see 4.4).
[2] See section 4.4.
[3] Gastrointestinal severe adverse reactions require often dose reduction. Ulcerative stomatitis and diarrhoea require discontinuation of methotrexate therapy because of the risk of ulcerative enteritis and fatal intestinal perforation.
[4] Can be fatal and is often associated with eosinophilia.

Description of selected adverse reactions
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 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, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie Email: medsafety@hpra.ie.

4.9 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 haematological and gastrointestinal reactions. The toxicity of methotrexate affects mainly the haematopoietic organs. Calcium folinate neutralises effectively the immediate haematopoietic toxic effects of methotrexate. Parenteral calcium folinate therapy should be started within one hour after the administration of methotrexate. The dose of calcium folinate should be at least as high as the dose of methotrexate received by the patient.
Massive overdose requires hydration and alkalinisation of the urine to prevent precipitation of methotrexate and/or its metabolites in the renal tubules. Haemodialysis or peritoneal dialysis has not been found to affect the elimination of methotrexate. Instead, effective clearance of methotrexate has been achieved by intermittent haemodialysis using a so-called "high-flux" dialysator.

Observation of serum methotrexate concentrations is relevant in determining the right dose of calcium folinate and the duration of the therapy.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other immunosuppressants, ATC code: L04AX03.

Methotrexate (4-amino-10-methylfolic acid) is a folic acid antagonist which inhibits the reduction of folic acid and increase of tissue cells. Methotrexate enters the cell through an active transport mechanism of reduced folates. As a result of polyglutamation of methotrexate caused by the folylpolyglutamylate enzyme, the duration of the cytotoxic effect of the drug substance in the cell increases. Methotrexate is a phase-specific substance the main action of which is directed to the S-phase of cell mitosis. It acts generally most effectively on actively increasing tissues, such as malignant cells, bone marrow, fetal cells, skin epithelium, oral and intestinal mucosa as well as urinary bladder cells. As the proliferation of malignant cells is higher than that of most normal cells, methotrexate can slow down the proliferation of malignant cells without causing, however, irreversible damage to normal tissue.

Calcium folinate is a folinic acid which is used to protect normal cells from the toxic effects of methotrexate. Calcium folinate enters the cell through a specific transport mechanism, is converted in the cell into active folates and reverses the inhibition of the precursor synthesis caused by the DNA and RNA.

5.2 Pharmacokinetic properties

The effect of orally administered methotrexate seems to be dependent on the size of the dose. Peak concentrations in serum are reached within 1-2 hours. Generally a dose of methotrexate of 30 mg/m^2 or less is absorbed rapidly and completely. The bioavailability of orally administered methotrexate is high (80-100%) at doses of 30 mg/m^2 or less. Saturation of the absorption starts at doses above 30 mg/m^2 and absorption at doses exceeding 80 mg/m^2 is incomplete.

About half of the absorbed methotrexate binds reversibly to serum protein, but is readily distributed in tissues. The elimination follows a triphasic pattern. Excretion takes place mainly via the kidneys. Approximately 41% of the dose is excreted unchanged in the urine within the first six hours, 90% within 24 hours. A minor part of the dose is excreted in the bile of which there is pronounced enterohepatic circulation. The half-life is approximately 3-10 hours following low dose treatment and 8–15 hours following high dose treatment. If the renal function is impaired, the concentration of methotrexate in serum and in tissues may increase rapidly. Half-life may be prolonged to 4 times the normal length in patients with third spaces (pleural effusion, ascites).

5.3 Preclinical safety data

Chronic toxicity studies in mice, rats and dogs showed toxic effects in the form of gastrointestinal lesions, myelosuppression and hepatotoxicity. Animal studies show that methotrexate impairs fertility, and is embryo- and foetotoxic. Teratogenic effects have been identified in four species (rats, mice, rabbits, cats). In rhesus monkeys no malformations occurred. Methotrexate is mutagenic *in vivo* and *in vitro*. There is evidence that methotrexate causes chromosomal aberrations in animal cells and in human bone marrow cells, but the clinical significance of these findings has not been established. Rodent carcinogenicity studies do not indicate an increased incidence of tumours.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Starch, pregelatinised (potato starch)
Polysorbate 80
Cellulose, microcrystalline
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Container: 3 years
Blister: 3 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

HDPE tablet container with a HDPE screw cap.
Pack sizes: 12, 16, 24, 28, 30 and 100 tablets.

Polyvinylchloride (PVC)/Aluminium foil blisters.
Pack sizes: 24 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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 methotrexate 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.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements for cytotoxic agents.

7 MARKETING AUTHORISATION HOLDER

Orion Corporation
Orionintie 1
FI-02200 Espoo
Finland

8 MARKETING AUTHORISATION NUMBER

PA1327/009/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 27th February 2012

10 DATE OF REVISION OF THE TEXT

September 2020