Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Methotrexate 2.5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains methotrexate sodium equivalent to 2.5 mg methotrexate.

Excipient with known effect
Each tablet also contains 66.16 mg of lactose monohydrate.
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet.
Round, biconvex, yellow tablets, engraved with script '2.5' on one side, scored in half on the other side and engraved with a block letter 'M' above the score and '1' below; approximately ¼ inch in diameter.

The scoreline is only to facilitate breaking of tablet for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Methotrexate is indicated in the treatment of neoplastic disease, also severe cases of psoriasis unresponsive to conventional therapy.

The treatment of adults with severe, active, classical or definite rheumatoid arthritis who are unresponsive or intolerant to conventional therapy.

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.

Adults and Children: Methotrexate has been used with beneficial effects in a wide variety of neoplastic diseases, alone and in combination with other cytotoxic agents, hormones, radiotherapy or surgery. Dosage schedules therefore vary considerably, depending on the clinical use, particularly when intermittent high-dose regimes are followed by the administration of calcium leucovorin (calcium folinate) to rescue normal cells from toxic effects. Doses of methotrexate should be reduced in cases of haematological deficiency and hepatic or renal impairment.

Examples of doses of methotrexate that have been used for particular indications are given below.

Leukaemia in Children: In acute lymphocytic leukaemia, remissions are usually best induced with a combination of corticosteroids and other cytotoxic agents.

Methotrexate 15 mg/m^2, given orally once weekly, in combination with other drugs appears to be the treatment of choice for maintenance of drug-induced remissions.

Lymphoma: Some cases of Burkitts's lymphoma, when treated in the early stages with courses of 15 mg/m^2 daily orally for five days, have shown prolonged remissions. Combination chemotherapy is also commonly used in all stages of the disease.

Dosage and administration with reference to psoriasis and rheumatoid arthritis

Important warning about the dosage of Methotrexate 2.5 mg Tablets (methotrexate)
In the treatment of psoriasis and rheumatoid arthritis, Methotrexate 2.5 mg Tablets (methotrexate) **must only be taken once a week.**

Dosage errors in the use of Methotrexate 2.5 mg Tablets (methotrexate) **can result in serious adverse reactions, including death.**
Please read this section of the summary of product characteristics very carefully.

Adults:
It is recommended that a test dose of 5-10 mg should be administered parenterally, one week prior to therapy to detect idiosyncratic adverse reactions.

Psoriasis: In most cases of severe uncontrolled psoriasis, unresponsive to conventional therapy, 10 - 25 mg orally once a week adjusted by the patient's response is recommended.

The use of methotrexate in psoriasis may permit the return to conventional topical therapy which should be encouraged.

Rheumatoid arthritis: In adults with severe, acute classical or definite rheumatoid arthritis who are unresponsive or intolerant to conventional therapy, the recommended initial dose is 7.5 mg methotrexate 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 response has been achieved, the schedule should be reduced to the lowest possible effective dose.

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

Special populations

Patients with impaired renal function: Methotrexate should be used with caution in patients with impaired renal function. The dose should be adjusted as follows:

Creatinine clearance (ml/min)	**% of dose that should be administered**
>50	100% of dose
20-50	50% of dose
<20	Methotrexate must not be used

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

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: Due to diminished hepatic and renal function and decreased folate stores, methotrexate should be used with extreme caution in elderly patients, a reduction in dosage should be considered and these patients should be closely monitored for early signs of toxicity.

Children: Safety and effectiveness in children has not been established, other than in cancer chemotherapy.

Method of Administration
Methotrexate 2.5 mg is for oral administration.

4.3 Contraindications

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- significantly impaired hepatic function (see section 4.2)
- liver disease including fibrosis, cirrhosis, recent or active hepatitis

- significantly impaired of renal function (creatinine clearance less than 30 ml/min) for methotrexate doses <100 mg/m^2,and moderate renal impairment (creatinine clearance less than 60 ml/min) for methotrexate doses >100 mg/m^2 (see section 4.2)
- pre-existing blood dyscrasias, such as bone marrow hypoplasia, significant anaemia, leucopenia, or thrombocytopenia
- serious, acute or chronic infections such as tuberculosis and HIV
- alcohol abuse
- stomatitis, ulcers of the oral cavity and known active gastrointestinal ulcer disease
- severe acute or chronic infections and laboratory evidence of immunodeficiency syndrome
- breast-feeding (see section 4.6)
- during methotrexate therapy concurrent vaccination with live vaccines must not be carried out.
- methotrexate should not be used concomitantly with drugs with antifolate properties (e.g. co-trimoxazole) (see section 4.5).

Additionally, <u>for non-oncological indications</u>

- pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

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

The prescriber should make sure patients understand that Methotrexate 2.5 mg Tablets (methotrexate) should only be taken once a week.

Patients should be instructed on the importance of adhering to the once weekly intakes.

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 must be used only by physicians experienced in antimetabolite chemotherapy. Due to the possibility of fatal or severe toxic reactions, the patient should be fully informed by the physician of the risks involved and the recommended safety measures.

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

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

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 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).

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.

Patients receiving low-dose methotrexate should:

- Have a full blood count and renal and liver function tests before starting treatment. These should be repeated weekly until therapy is stabilised, thereafter patients should be monitored every 2-3 months throughout treatment.

- Patients should report all symptoms and signs suggestive of infection, especially sore throat. Any infections should be attended to, before initiation of methotrexate therapy

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. 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. 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.

Diabetic patients who are treated with insulin have increased risk for liver toxicity.

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.

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).

- **renal function** should be monitored by renal function tests and urinalysis. 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/m^2 not be given (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.

Treatment with methotrexate doses of >100 mg/m^2 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.

Renal lesions may develop if the urinary flow is impeded and urinary pH is low, especially if large doses have been administered.

Methotrexate may cause renal damage that may lead to acute renal failure. Close attention to renal function including adequate hydration, urine alkalinisation by oral or intravenous administration of sodium bicarbonate (5 x 625mg tablets every three hours) or acetazolamide (500 mg orally four times a day), and measurement of serum methotrexate and renal function are recommended.

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

Methotrexate may cause adverse urinary tract reactions, such as cystitis and haematuria.

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.

There is no evidence to support use of a liver biopsy to monitor hepatic toxicity in rheumatological indications. In case of longer-term treatment of severe forms of psoriasis with methotrexate, liver biopsies should be performed on account of the hepatotoxic potential.

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. nonsteroidal 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. A high fluid throughput and alkalinisation of the urine by oral or intravenous administration of sodium bicarbonate or acetazolamide is recommended as a preventive measure.

Progressive multifocal leukoencephalopathy (PML)
Cases of progressive multifocal leukoencephalopathy (PML) have been reported in patients receiving methotrexate, mostly in combination with other immunosuppressive medication. PML can be fatal and should be considered in the differential diagnosis in immunosuppressed patients with new onset or worsening neurological symptoms.

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) 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 undertaken 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 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
- Methotrexate may trigger tumour lysis syndrome in patients with rapidly growing tumour.
- **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
- Vitamin preparationsor 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.** Lesions of psoriasis may be aggravated by concomitant exposure to ultraviolet radiation.

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.

The disappearance of methotrexate from plasma should be monitored, if possible. This is recommended in particular when high, or very high doses are administered in order to permit calculation of an adequate dose of leucovorin (folinic acid) rescue.

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

Use in Psoriasis:
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. The patient should be clearly informed that, in cases of psoriasis, methotrexate is taken once weekly. The prescriber should specify the day of intake on the prescription. Patients should be aware of the importance of adhering to the once-weekly intake as daily or more frequent administration can result in severe toxicity.

Use in Rheumatoid arthritis (RA)
The patient should be clearly informed that in, cases of RA, methotrexate is taken once weekly. The prescriber should specify the day of intake on the prescription. Patients should be aware of the importance of adhering to the once-weekly intake as daily or more frequent administration can result in severe toxicity.

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.

It has proven useful to differentiate between patients with normal and elevated risk of hepatotoxicity.

a) Patients without risk factors
According to current medical standard of knowledge, liver biopsy is not necessary before a cumulative dose of 1.0-1.5 g is reached.
b) Patients with risk factors
These primarily include:
- anamnestic alcohol abuse
- persistent increase in liver enzymes
- anamnestic hepatopathy including chronic hepatitis B or C
- familial anamnesis with hereditary hepatopathy and secondarily (with possibly lower relevance):
- diabetes mellitus
- adiposity
- anamnestic exposure to hepatotoxic medicines or chemicals.

Liver biopsy is recommended for these patients during or shortly after initiation of therapy with methotrexate. Since a small percentage of patients discontinues therapy for various reasons after 2-4 months, the first biopsy can be delayed to a time after this initial phase. It should be performed when longer-term therapy can be assumed.

Repeated liver biopsies are recommended after a cumulative dose of 1.0-1.5 g is achieved.
No liver biopsy is necessary in the following cases:
- elderly patients
- patients with an acute disease
- patients with contraindication for liver biopsy (e.g. cardiac instability, altered blood coagulation parameters)
- patients with poor expectance of life.
More frequent check-ups may become necessary
- during the initial phase of treatment
- when the dose is increased

- during episodes of a higher risk of elevated methotrexate blood levels (e.g. dehydration, impaired renal function, additional or elevated dose of medicines administered concomitantly, such as non-steroidal anti-inflammatory drugs).

Methotrexate has been shown to be teratogenic; it has caused foetal death and/or congenital anomalies. Therefore it is not recommended in women of childbearing potential unless there is appropriate medical evidence that the benefits can be expected to outweigh the considered risks. Pregnant psoriatic patients must not receive methotrexate (see section 4.6).

Renal function should be closely monitored before, during and after treatment. Caution should be exercised if significant renal impairment is disclosed. The dose of methotrexate in patients with renal impairment should be reduced. 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 (5 x 625 mg tablets every three hours) or acetazolamide (500 mg orally four times a day) is recommended as a preventive measure. Methotrexate is excreted primarily by the kidneys. Its use in the presence of impaired renal function may result in accumulation of toxic amounts or even additional renal damage.

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, 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.

Most adverse reactions are reversible if detected early. When adverse reactions do occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken. If necessary, this includes the use of calcium folinate and/or acute, intermittent haemodialysis with high-flux dialyzer.

Methotrexate should be used with extreme caution in patients with psychiatric disorders. Patients with pleural effusions and ascites should be drained prior to initiation of methotrexate therapy or treatment should be withdrawn.

Methotrexate affects gametogenesis during the period of its administration and may result in decreased fertility which is thought to be reversible on discontinuation of therapy.

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

A chest X-ray is recommended 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, sulphasalazine 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/sulphamethoxazole has been reported to cause an acute megaloblastic pancytopenia in rare instances.

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

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. This will include a routine examination of lymph nodes and patients should report any unusual swelling to the doctor.

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.

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).

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.

If this drug is used during pregnancy for antineoplastic indications, or if the patient becomes pregnant while taking this drug, the patient should be appraised of the potential hazard to the foetus.

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.

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

Methotrexate should be used with extreme caution in the presence of infection, peptic ulcer, ulcerative colitis, debility, and in extreme youth and old age. 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.

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

Teratogenicity – Reproductive risk
Methotrexate causes embryotoxicity, abortion and foetal malformations in humans. Therefore, the possible effects on reproduction, pregnancy loss and congenital malformations should be discussed with female patients of childbearing age (see section 4.6). In non-oncologic indications, the absence of pregnancy must be confirmed before methotrexate is used. If women of a sexually mature age are treated, effective contraception must be used during treatment and for at least six months after.

For contraception advice for men see section 4.6.

Excipient

The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, 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).

After absorption methotrexate binds partly to serum albumin. Certain medicinal products (e.g. salicylates, sulfonamides and phenytoin) 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.

Penicillins can decrease the renal clearance of methotrexate and haematological and gastrointestinal toxicity has been observed in combination with high- and low-dose methotrexate. These events occur with greater frequency in the elderly.

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- and hepatotoxic agents (e.g. sulphasalazine, leflunomide and alcohol) with methotrexate should be closely monitored for possible increased hepatotoxicity.

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.

Enhancement of nephrotoxicity may be seen when high-dose methotrexate is administered in combination with a potentially nephrotoxic chemotherapeutic agent (e.g. cisplatin).

NSAIDs should not be administered before or concurrently with high-dose methotrexate as fatal methotrexate toxicity has been reported. Methotrexate dosage should be monitored if concomitant treatment with aspirin, ibuprofen or indomethacin (NSAID's) is commenced. 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.

Hepatic, hematotoxic and nephrotoxic drugs should be avoided.

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 Eretinate and severe hepatitis has been reported following concurrent use.

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

Methotrexate is extensively protein bound and may displace, or be displaced by, other acidic drugs. The concurrent administration of agents such as diphenylhydantoins, acidic anti-inflammatory agents, salicylates, phenylbutazone, phenytoin, barbiturates, tranquillisers, oral contraceptives, diuretics, hypoglycaemics, doxorubicin, tetracyclines, amidopyrine derivatives, sulfonamides, probenecid or sulfinpyrazone, 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 such as "loop-diuretics" as well as pyrazols may also reduce tubular methotrexate secretion and thus cause indirect dose elevations, too. Great caution should be exercised when these medicinal products are coadministered with methotrexate.

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.

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, 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. This effect can be reduced by the use of folinic acid rescue. (see section 4.2)

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

Trimethoprim/sulfamethoxazole has been reported in rare cases to increase bone marrow suppression in patients treated with methotrexate, presumably because of the increased antifolate effect.

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 (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.

Methotrexate may decrease the clearance of theophylline; theophylline levels should be monitored when used concurrently with methotrexate.

Methotrexate increases the plasma levels of mercaptopurine. Combination of methotrexate and mercaptopurine may therefore require dose 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 vaccinal and test results (immunological procedures to record the immune reaction). Vaccination with a live vaccine in patients receiving chemotherapeutic agents may result in severe and fatal infections. Concomitant use with a live vaccine is not recommended.

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.

Ciclosporine may potentiate methotrexate efficacy and toxicity. There is a risk of excessive immunosuppression with risk of lymphoproliferation when the combination is used.

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

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

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

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

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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females
Women must not get pregnant during methotrexate therapy, and effective contraception must be used during treatment with methotrexate and at least 6 months thereafter (see section 4.4). Prior to initiating therapy, women of childbearing potential must be informed of the risk of malformations associated with methotrexate and any existing pregnancy must be excluded with certainty by taking appropriate measures, e.g. a pregnancy test. During treatment pregnancy tests should be repeated as clinically required (e.g. after any gap of contraception). Female patients of reproductive potential must be counselled regarding pregnancy prevention and planning.

Contraception in males
It is not known if methotrexate is present in semen. Methotrexate has been shown to be genotoxic in animal studies, such that the risk of genotoxic effects on sperm cells cannot completely be excluded. Limited clinical evidence does not indicate an increased risk of malformations or miscarriage following paternal exposure to low-dose methotrexate (less than 30 mg/week). For higher doses, there is insufficient data to estimate the risks of malformations or miscarriage following paternal exposure.
As precautionary measures, sexually active male patients or their female partners are recommended to use reliable contraception during treatment of the male patient and for at least 3 months after cessation of methotrexate. Men should not donate semen during therapy or for 3 months following discontinuation of methotrexate.

Pregnancy
Methotrexate is contraindicated during pregnancy in non-oncological indications (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 disease-matched patients treated with drugs other than methotrexate.

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

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

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

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

4.7 Effects on ability to drive and use machines

Methotrexate can cause dizziness and fatigue during treatment, methotrexate has 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. However, as severe adverse reactions may occur even at lower doses, it is indispensable that the doctor monitors patients regularly at short intervals.

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 caution, under close assessment of the necessity for treatment and with increased alertness for possible reoccurrence of toxicity.

The most common adverse reactions of methotrexate are bone marrow suppression and mucosal damage which manifest as ulcerative stomatitis, leucopaenia, nausea and other gastrointestinal disorders. These adverse reactions are generally reversible and corrected in about two weeks after the single dose of methotrexate has been reduced or dose interval increased and/or calcium folinate is used. Other frequently occurring adverse reactions include e.g. malaise, abnormal fatigue, chills and fever, dizziness and reduced immunity to infections.

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

In the antineoplastic treatment, myelosuppression and mucositis are the predominant dose-limiting toxic effects of methotrexate. The severity of these reactions depends on the dose, mode and duration of application of methotrexate. Mucositis generally appears about 3 to 7 days after methotrexate application, leucopenia and thrombocytopenia follow a few days later. In patients with unimpaired elimination mechanisms, myelosuppression and mucositis are generally reversible within 14 to 28 days.

The 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).

System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not known
Infections and infestations		Infections caused by the cytomegalovirus	Opportunistic infections[1]	Herpes zoster infections, Sepsis		Infection susceptibility increased, Sepsis resulting in death, Neutropenic sepsis Respiratory or cutaneous bacterial infections Reactivation of inactive chronic infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Lymphoma[2]	Lympho-proliferative disorders (partly reversible)		
Blood and lymphatic system disorders		Leukopaenia, Thrombocytopenia (which are usually reversible), Anaemia	Bone marrow depression[8] (especially at high-dose of methotrexate), Pancytopenia, Agranulocytosis, Haematopoietic disorders	Megaloblastic anaemia	Hypo-gamma-globulinemia, Aplastic anaemia, Lymphadenopathy, Eosinophilia, Neutropenia Lymphoproliferative disorders	Haemorrhage from various sites, Abnormal red cell morphology Infection
Immune system disorders			Anaphylactic type reaction		Immuno-suppression,	Allergic reaction, anaphylactic

					Aseptic meningitis	shock.
Endocrine disorders				Diabetes mellitus		Metabolic disorders
Psychiatric disorders			Confusion	Depression	Insomnia	Mood alterations, psychoses.
Nervous system disorders		Headache Dizziness Fatigue	Vertigo, Seizure, Leukoencephalopathy, Encephalopathy	Hemiparesis	Irritation, Dysarthria, Aphasia, Lethargy, Asthenia Paresthesia of the extremities, Hypoaesthesia Dysgeusia	Drowsiness, Paresis, Convulsions, Cerebral oedema, Transient subtle cognitive dysfunction, Unusual cranial sensations Pain Changes in sense of taste (metallic taste), Meningism Paralysis.
Eye disorders				Visual disturbances	Conjunctivitis Blurred vision	Eye irritation Retinopathy.
Ear and labyrinth disorders						Tinnitus
Cardiac disorders				Pericardial tamponade	Pericardial effusion Pericarditis	Myocardial ischemia
Vascular disorders			Nosebleed, Vasculitis	Hypotension Thrombo-embolism Thrombo-embolic events[3]		
Respiratory, thoracic and mediastinal disorders		Pulmonary complications due to acute or chronic interstitial alveolitis/pneumonitis[4] which can be fatal and is often associated with	Pneumonitis Interstitial/ pulmonary fibrosis	Dyspnoea Pharyngitis[5]	*Pneumocystis carinii/jiroveci* pneumonia and other lung infection, Chronic interstitial	Acute pulmonary oedema, Syndrome consisting of pleuritic pain and pleural

		eosinophilia			obstructive lung disease Pleuritis Dry cough	thickening Pulmonary alveolar haemorrhage[6] Pleurisy, Non-productive cough Thoracic pain Pleural effusion Bronchial asthma Respiratory paralysis
Gastrointestinal disorders[7]	Anorexia, Nausea, Vomiting, Abdominal pain, Stomatitis, Dyspepsia, Inflammation and ulcerations of the mucous membrane of mouth and throat	Diarrhoea	Gastrointestinal ulcerations and haemorrhage	Gingivitis Enteritis, Melaena, Gingivitis, Malabsorption	Haematemesis, Toxic megacolon	Pancreatitis
Hepatobiliary disorders	Elevated transaminase concentrations (ASAT, ALAT),			Hepatotoxicity Periportal fibrosis Liver cirrhosis Acute hepatitis	Reactivation of chronic hepatitis or death., Acute liver degeneration, Liver insufficiency	Acute liver trophy, Necrosis Elevated alkaline phosphatase and bilirubin, decrease in serum albumin,
Skin and		Erythematous rash	Pruritus,		Telangiectasis,	Recall

subcutaneous tissue disorders		Alopaecia	Stevens-Johnson's syndrome, Toxic epidermal necrolysis, Urticaria, Photosensitivity, Skin pigmentation	Acne, Depigmentation Erythema multiforme, Cutaneous erythematous eruptions, Painful damage to psoriatic lesion, Skin ulceration, Ecchymosis	Furunculosis, Acute paronychia, Nocardiosis, Mycosis (Histoplasma and crptococcus)	phenomenon[9] Exanthema, Pigmentary changes Onycholysis, Increased pigmentation, Petechia, Allergic vasculitis, hidradenitis, Herpetiform eruptions of the skin, Hyperpigmentation of the nails Skin exfoliation Dermatitis exfoliative
Musculoskeletal and connective tissue disorders			Osteoporosis, Arthralgia, Myalgia,	Stress fracture, Increased rheumatic nodules		Osteonecrosis of jaw (secondary to lymphoproliferative disorders)
Renal and urinary disorders			Renal insufficiency Nephropathy, Bladder inflammation Bladder ulcer,	Oliguria, Anuria, Renal failure, Uraemia	Proteinuria, Dysuria Azotaemia Cystitis Haematuria	Electrolyte disturbance Disturbed micturition
Reproductive system and breast disorders			Vaginal ulceration, Vaginal inflammation	Decreased libido, Impotence, Menstrual disorders, Transient oligospermia,	Formation of defective oocytes or sperm cells infertility Vaginal bleeding Gynaecomastia	Amenorrhoea, Miscarriage, Fetal damages, Vaginal discharge.

Injury, poisoning and procedural complications						Increased risk of toxic reactions (soft tissue necrosis, osteonecrosis) during radiotherapy
General disorders and administration site conditions					Pyrexia, Impaired healing	Malaise, Chills, Sudden death Oedema

[1] May be fatal in some cases
[2] Can be reversible (see 4.4). 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. Methotrexate may trigger tumour lysis syndrome in patients with rapidly growing tumour.
[3] Including arterial and cerebral thrombosis, thrombophlebitis, deep vein thrombosis, retinal vein thrombosis, pulmonary embolism).
[4] 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
[5] See section 4.4.
[6] (has been reported for methotrexate used in rheumatologic and related indications)
[7] 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.
[8] Bone marrow depression may lead to decreased resistance to infection and sepsis
[9] The recall phenomenon has been reported in both radiation and solar damaged skin. Lesions of psoriasis may worsen with concomitant UV therapy. Radiation dermatitis and sunburn may be "recalled".

The psoriatic lesions may get worse from simultaneous exposure to methotrexate and ultraviolet radiation.

In the treatment of rheumatoid arthritis, Methotrexate induced lung disease is a potentially serious adverse drug reaction which may occur acutely at any time during therapy. It is not always fully reversible.

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

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.

Symptoms
The toxicity of methotrexate affects mainly the haematopoietic organs 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.

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.

Symptoms of an overdose are mainly the same as the undesirable effects, but stronger.

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

Management
Calcium folinate neutralises effectively the immediate haematopoietic toxic effects and toxic undesirable effects of methotrexate. In cases of accidental overdose, parenteral calcium folinate therapy should be administered intravenously or intramuscularly within one hour and dosing continued until the serum levels of methotrexate are below 10^{-7} mol/l. The dose of calcium folinate should be at least as high as the dose of methotrexate received by the patient. Other supporting therapy such as a blood transfusion, renal dialysis and reverse barrier nursing may be required.

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.

Treatment measures for methotrexate overdosage can be discontinued when the serum methotrexate level has fallen below the level of $5x10^{-8}$ M (10) (see section 4.4).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other immunosuppressive agents, ATC code: L04AX03.

Mechanism of action
Methotrexate (4-amino-10-methylfolic acid) is a folic acid antagonist which inhibits the reduction of folic acid and increase of tissue cells. Its major site of action is the enzyme dihydrofolate reductase. 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. Its main effect is inhibition of DNA synthesis but it also acts directly both on RNA and protein synthesis. 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

Absorption
Orally administered, the absorption of methotrexate seems to be dose-dependent. Peak serum levels are reached within 1 to 2 hours. Generally, at doses of 30 mg/m^2 or less, methotrexate 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 of doses exceeding 80 mg/m^2 is incomplete. After parenteral injection, peak serum levels are seen in about one half this period. After intramuscular injection, peak serum concentrations occur in 30 to 60 minutes.

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 µg/ml have been measured in the liquor.

Biotransformation
Average terminal half-life is 6-7 hours and demonstrates considerable variation (3-17 hours). The half-life is approximately 3–10 hours following low dose treatment and 8–15 hours following high dose treatment. 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 41 % of the dose is excreted unchanged in the urine within the first six hours, 90 % within 24 hours. 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 and the concentration of methotrexate in serum and in tissues may increase rapidly. Impaired elimination in presence of hepatic insufficiency is not known.

Methotrexate does not enter the cerebrospinal fluid at oral or parenteral therapeutic doses. However, cytotoxic concentrations (>10-7 M) can be achieved in the CSF with high doses (>500 mg/m^2). When high drug concentrations are indicated, direct intrathecal administration should be used.

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 studies show that methotrexate impairs fertility and is embryo- and foetotoxic. Methotrexate is mutagenic in vivo and in vitro. There is evidence that methotrexate causes cromosomal 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.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate
Starch-Pregelatinised
Magnesium Stearate
Sodium Hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25ºC. Store in the original container in order to protect from light.

6.5 Nature and contents of container

PVC/Aluminium blister packs containing 28 or 30 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For instructions on administration see section 4.2.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. Cytotoxic drugs should only be handled by trained personnel in a designated area. Refer to local cytotoxic guidelines before use. The work surface should be covered with disposable plastic -backed absorbent paper. Protective gloves and goggles should be worn to avoid the drug accidentally coming into contact with the skin or eyes. Methotrexate is not a vesicant and should not cause harm if comes into contact with the skin. It should of course be washed off with water immediately. Medical advice should be sought if the eyes are affected.

Any transient stinging may be treated with bland cream. If there is any danger of systemic absorption of significant quantities of methotrexate by any route, Calcium Leucovorin cover should be given. Cytotoxic preparations should not be handled by pregnant staff. Any spillage or waste material should be dealt with by trained personnel, wearing appropriate personal protective equipment as outlined above, may be disposed of by incineration. We do not make any specific recommendations with regards to the temperature of the incinerator.

7 MARKETING AUTHORISATION HOLDER

Amdipharm Limited
Temple Chambers
3 Burlington Road
Dublin 4
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1142/030/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 May 1983

Date of last renewal: 23 May 2008

10 DATE OF REVISION OF THE TEXT

March 2023