SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Methotrexate 10 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg methotrexate.

Excipients: 50 mg lactose (as lactose monohydrate).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

Yellow coloured, capsule shaped bi-convex tablets with central break line on one side and plain on other side.

The break line is only to facilitate breaking for ease of swallowing and not to divide into equal doses

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

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

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

Important warning about the dosage of methotrexate:

In the treatment of rheumatoid arthritis and psoriasis, 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 specify the day of intake on the prescription.

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.

Use in patients with renal impairment – dose adjustments

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

Dose adjustments for methotrexate doses <100 mg/m^2 in patients with renal impairment

Creatinine Clearance (ml/min)	% of dose to Administer
>60	100
30-59	50
<30	Methotrexate must not be administered

Patients with 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).

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.

Special note

If changing the oral application to parenteral administration a reduction of the dose may be required due to the variable bioavailability of methotrexate after oral administration.

Method of Administration

Oral.

4.3 Contraindications

- Significantly impaired hepatic function
- Significantly impaired renal function (creatinine clearance less than 30 ml/min)
- Pre-existing blood dyscrasias, such as bone marrow hypoplasia, leukopaenia, thrombocytopaenia 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.

- Methotrexate tablets should not be used concomitantly with drugs with antifolate properties (e.g. co-trimoxazole) (see section 4.5).

4.4 Special warnings and precautions for use

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

Methotrexate should be used with extreme caution in patients with haematological depression, renal impairment, diarrhoea, ulcerative disorders of the GI tract and psychiatric disorders. Hepatic toxicity has been observed, usually associated with chronic hepatic disease. The administration of low doses of methotrexate for prolonged periods may give rise, in particular, to hepatic toxicity. Liver function should be closely monitored. If hepatic function abnormalities develop, methotrexate dosing should be suspended for at least two weeks. It is only appropriate to restart methotrexate provided the abnormalities return to normal and the re-exposure is deemed appropriate.

Particular care and possible cessation of treatment are indicated if stomatitis or GI toxicity occurs as haemorrhagic enteritis and intestinal perforation may result.

Reversible eosinophilic pulmonary reactions and treatment-resistant, interstitial fibrosis may occur, particularly after long-term treatment.

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

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

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 alkalinization, and measurement of serum methotrexate and renal function are recommended.

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

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

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

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

Haematopoietic suppression caused by methotrexate may occur abruptly and with apparently safe dosages. 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 therapy should be withdrawn immediately and appropriate supportive therapy given (see section 4.8, Undesirable Effects). Patients should be advised to report all symptoms or signs suggestive of infection.

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.

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.

<u>Liver function tests</u>

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

Temporary increases in transaminases to two or three times the upper limit of normal have been reported in patients at a frequency of 13-20 %. Persistent elevation of liver enzymes and/or decrease in serum albumin may be indicative for severe

hepatotoxicity. In the event of a persistent increase in liver enzymes, consideration should be given to reducing the dose or discontinuing therapy.

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

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

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

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.

If the patient becomes pregnant while taking this drug, the patient should be appraised of the potential hazard to the foetus.

Methotrexate has some immunosuppressive activity and therefore the immunological response to concurrent vaccination may be decreased. In addition, concomitant use of a live vaccine could cause severe antigenic reaction.

Methotrexate should only be used by clinicians that are familiar with the various characteristics of the drug and its mode of action. Before beginning methotrexate therapy or reinstituting methotrexate after a rest period, a chest x-ray, assessment of renal function, liver function and blood elements 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.

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.

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

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.

Patients with pleural effusions and ascites should be drained prior to initiation of methotrexate therapy. A chest x-ray is recommended prior to initiation of methotrexate therapy or treatment should be withdrawn.

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

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

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

Methotrexate should be withdrawn from patients with pulmonary symptoms and a thorough investigation 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.

Lung manifestations of RA and other connective tissue disorders are recognised to occur. In patients with RA, the physician should be specifically alerted to the potential for methotrexate induced adverse effects on the pulmonary system.

Photosensitivity

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking methotrexate (see section 4.8). Exposure to intense sunlight or UV rays should be avoided unless medically indicated. Patients should use adequate sunprotection to protect themselves from intense sunlight.

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 tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

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, tranquilisers, oral contraceptives, amidopyrine derivatives, p-aminobenzoic acid, thiazide diuretics, doxorubicin, tetracyclines, probenecid, sulfinpyrazone or oral hypoglycaemics will decrease the methotrexate transport function of renal tubules, thereby reducing excretion and almost certainly increasing methotrexate toxicity.

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.

Concurrent use of other, potentially nephro- hemato or hepatotoxic agents (e.g. sulphasalazine, leflunomide and alcohol) 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.

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

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 gastrointestinal toxicity may occur.

Oral antibiotics such as tetracyclines, chloramphenicol and non-absorbable broadspectrum antibiotics may reduce intestinal methotrexate absorption or interfere with the enterohepatic circulation, due to inhibition of the intestinal flora or suppression of bacterial metabolism.

Methotrexate dosage should be monitored if concomitant treatment with aspirin, ibuprofen or indometacin (NSAIDs) is commenced, as concomitant use of NSAID's has been associated with fatal methotrexate toxicity.

Hepatic, hematotoxic and nephrotoxic drugs should be avoided.

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. sulfonamides, trimethoprim-sulfamethoxazole, chloramphenicol, pyrimethamine), the possibility of marked haematopoietic disorders should be considered.

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

Acitretin (a treatment for psoriasis) is metabolised to etretinate. Methotrexate levels may be increased by etretinate and severe hepatitis has been reported following concomitant use.

Bone marrow suppression and decreased folate levels have been described in the concomitant administration of triamterene and methotrexate.

Administration of additional haematotoxic medicinal products increases the likelihood of severe haematotoxic adverse reactions to methotrexate. Concurrent administration of metamizole and methotrexate can increase the haematotoxic effect of methotrexate, especially in elderly patients. Therefore, coadministration should be avoided.

There is evidence that co-administration of methotrexate and omeprazole prolongs the elimination of methotrexate via kidneys. Co-administration 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 t½ of 5--fluorouracil).

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.

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.

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

Vaccination with a live vaccine in patients receiving chemotherapeutic agents may result in severe and fatal infections (see section 4.3). 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).

Cytotoxic agents may impair absorption of phenytoin, which may decrease efficacy of phenytoin and increase the risk for exacerbation of convulsions. Risk of toxicity

enhancement or loss of efficacy of the cytotoxic drug due to increased hepatic metabolism by phenytoin is possible.

Ciclosporin 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.

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

Fertility

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

Women 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 least3 months after cessation of methotrexate. Men should not donate semen during therapy or for3 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

Patients should not breast-feed whilst taking methotrexate.

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

In general, the incidence and severity of side effects are considered to be-related to 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).

The most common adverse reactions of methotrexate are bone marrow suppression and mucosal damage which manifest as ulcerative stomatitis, leukopaenia, 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.

Methotrexate causes adverse reactions most at high and frequently repeated doses, e.g. in the treatment of cancer diseases. Adverse reactions reported on methotrexate are given below according to organ systems.

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).

	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations	Infections	Opportunistic infections	Herpes zoster Sepsis		
Neoplasms benign, malignant and unspecified (including cysts and polyps)		Lymphoma[1]			
Blood and lymphatic system disorders	Leukopaenia	Bone marrow depression Thromboc		Hypogammaglobulinaemia	

	Common	Uncommon	Rare	Very rare	Not known
		ytopaenia Anaemia		Lymphoproliferative disorders (see “description” below)	
Immune system disorders		Anaphylactic-type reaction			
Endocrine disorders			Diabetes mellitus		
Psychiatric disorders			Depression Confusion		
Nervous system disorders	Headache Dizziness Fatigue		Hemiparesis	Irritation Dysarthria Aphasia Lethargy Paraesthesia/ hypoaesthesia	
Eye disorders				Conjunctivitis Blurred vision	
Cardiac disorders				Pericardial effusion Pericarditis	
Vascular disorders		Nosebleed	Hypotension Thromboembolis	Vasculitis	

	Common	Uncommon	Rare	Very rare	Not known
			m		
Respiratory, thoracic and mediastinal disorders		Pneumonitis Interstitial pneumonitis (can be fatal) Interstitial fibrosis	Dyspnoea Pharyngitis[2]	Pneumocystis carinii – pneumonia Chronic interstitial obstructive lung disease Pleuritis Dry cough	Epistaxis Pulmonary alveolar haemorrhage
Gastrointestinal disorders[3]	Stomatitis Anorexia Nausea Vomiting Diarrhoea		Gingivitis Gastrointestinal ulcerations and haemorrhage Enteritis	Haematemesis	
Hepatobiliary disorders	Elevated transaminase concentrations		Hepatotoxicity Periportal fibrosis Liver cirrhosis Acute hepatitis		
Skin and subcutaneous tissue disorders	Erythematous rash Alopecia	Photosensitivity reactions Pruritus Stevens-Johnson´s syndrome	Acne Depigmentation Urticaria Erythema multifor	Telangiectasis Furunculosis Ecchymoses	Skin exfoliation / dermatitis exfoliative

	Common	Uncommon	Rare	Very rare	Not known
		Toxic epidermal necrolysis	me Painful damage to psoriatic lesion Skin ulceration		
Musculoskeletal and connective tissue disorders			Osteoporosis Arthralgia Myalgia Increased rheumatic nodules		Osteonecrosis of jaw (secondary to lymphoproliferative disorders)
Renal and urinary disorders		Renal insufficiency Nephropathy		Dysuria Azotaemia Cystitis Haematuria	
Reproductive system and breast disorders		Vaginal ulceration	Decreased libido Impotence Menstrual disorders	Formation of defective oocytes or sperm cells Transient oligospermia, infertility Vaginal bleeding Gynaecomastia	

	Common	Uncommon	Rare	Very rare	Not known
General disorders and administration site conditions					Oedema

1 Can be reversible (see 4.4).

2 See section 4.4.

3 Gastrointestinal severe adverse reactions require often dose reduction.

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.

Ulcerative stomatitis and diarrhoea require discontinuation of methotrexate therapy because of the risk of ulcerative enteritis and fatal intestinal perforation.

The following adverse reactions have also been reported, but their frequency is not known: pancytopaenia, sepsis resulting in death, miscarriage, fetal damages, increased risk of toxic reactions (soft tissue necrosis, osteonecrosis) during radiotherapy, eosinophilia, alveolitis.

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

Reporting of suspected adverse reactions

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

4.9 Overdose

Leucovorin is a specific antidote for methotrexate and, following accidental overdosage, should be administered within one hour at a dosage equal to, or greater than, the methotrexate dose. It may be administered by i.v. bolus or infusion. Further doses may be required. The patient should be observed carefully and blood transfusions, renal dialysis and reverse barrier nursing may be necessary.

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

Cases of overdose have been reported, sometimes fatal, due to erroneous daily intake instead of weekly intake of oral methotrexate. In these cases, symptoms that have been commonly reported are hematological and gastrointestinal reactions. For example, leukopenia, thrombocytopenia, anemia, pancytopenia, bone marrow suppression, mucositis, stomatitis, oral ulceration, nausea, vomiting, gastrointestinal ulceration, gastrointestinal bleeding. In some cases, no symptoms were reported. There have been reports of death following chronic overdose in the self-administered dosage for rheumatoid arthritis and psoriasis (see Sections 4.2 and 4.4). In these cases, events such as sepsis or septic shock, renal failure, and aplastic anaemia were also reported. In cases of massive overdose, hydration and urinary alkalinisation may be necessary to prevent precipitation of methotrexate and/or its metabolites in the renal tubules. Neither haemodialysis nor peritoneal dialysis has been shown to improve methotrexate elimination. Effective clearance of methotrexate has been reported with acute, intermittent haemodialysis using a high-flux dialyser.

Cases of overdose, sometimes fatal, due to erroneous daily intake instead of weekly intake of oral methotrexate have been reported. In these cases, symptoms that have been commonly reported are haematological and gastrointestinal reactions.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressive agents

ATC code: L04AX03

Methotrexate is a folic acid antagonist and its major site of action is the enzyme dihydrofolate reductase. 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 effect being directed during the S-phase of cell division.

The inhibition of dihydrofolate reductase can be circumvented by the use of leucovorin (folinic acid; citrovorum factor) and protection of normal tissues can be carried out by properly timed administration of leucovorin calcium.

5.2 Pharmacokinetic properties

When given in low doses, methotrexate is rapidly absorbed from the GI tract giving plasma concentrations equivalent to those achieved after i.v. administration. Higher doses are less well absorbed. About 50% has been shown to be protein bound. Biphasic and triphasic plasma clearance has been shown. The majority of the dose is excreted within 24 hours in the urine mainly as unchanged drug.

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.

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

Dibasic Calcium Phosphate (Anhydrous)

Lactose Monohydrate

Sodium starch glycolate

Cellulose, microcrystalline

Purified Talc

Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.

Keep the blister in the outer carton in order to protect from light.

6.5 Nature and contents of container

Amber colour PVC /Aluminium blister- Blister packs of 7, 10, 14,16, 20, 24, 28, 30, 56, 60, 84, 90, 100 and 112 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 product or waste material should be disposed of in accordance with local requirements

7 MARKETING AUTHORISATION HOLDER

Morningside Healthcare Ltd

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LE19 1WP

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20117/0172

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/12/2010

10 DATE OF REVISION OF THE TEXT

05/11/2024