

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Methotrexate 2.5mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Methotrexate sodium equivalent to 2.5mg of methotrexate per tablet.

For excipients see 6.1.

3 PHARMACEUTICAL FORM

Tablet

Round, convex, yellow slightly mottled tablets; engraved with '2.5' on one side scored in half on the other side and engraved with 'M' above the score line and 'T' below it.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The treatment of neoplastic disease. The treatment of severe cases of uncontrolled 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

Adults and Children

Methotrexate may be given by oral, intramuscular, intravenous (bolus injection or infusion), intrathecal and intra-arterial routes of administration. Dosages are based on the patient's body weight or surface area except in the case of intrathecal administration when a maximum dose of 15mg is recommended. Doses should be reduced in cases of haematological deficiency and hepatic or renal impairment. Larger doses (greater than 100mg) are usually given by intravenous infusion over periods not exceeding 24 hours. Part of the dose may be given in an initial rapid intravenous injection.

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.

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

Choriocarcinoma and other trophoblastic tumours: Non- metastatic gestational trophoblastic neoplasms have been treated successfully with 0.25-1mg /kg up to a maximum of 60mg intramuscularly every 48 hours for four doses, followed by Calcium Leucovorin rescue. This course of treatment is repeated at seven day intervals until levels of urinary chorionic gonadotrophin hormone return to normal. Not less than four courses of treatment are usually necessary. Patients with complications, such as extensive metastases, may be treated with methotrexate in combination with other cytotoxic drugs.

Methotrexate has also been used in similar doses for the treatment of hydatidiform mole and chorio-adenoma destruens.

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

Methotrexate 15mg/m², given parenterally or orally once weekly, in combination with other drugs appears to be the treatment of choice for maintenance of drug-induced remissions.

Meningeal leukaemia in children: Doses up to 15mg, intrathecally, at weekly intervals, until the CSF appears normal (usually two to three weeks), have been found useful for the treatment of meningeal leukaemia.

Although intravenous doses of the order of 50mg/m² of methotrexate do not appreciably penetrate the CSF, larger doses of the order of 500mg/m² or greater do produce cytotoxic levels of methotrexate in the CSF. This type of therapy has been used in short courses, followed by administration of Calcium Leucovorin, as initial maintenance therapy to prevent leukaemic invasion of the central nervous system in children with poor prognosis lymphocytic leukaemia.

Lymphoma: Non-Hodgkin's lymphoma, e.g. childhood lymphosarcoma has recently been treated with 3-30mg/kg (approximately 90-900mg/m²) of methotrexate given by intravenous injection and infusion followed by administration of Calcium Leucovorin with the higher doses. Some cases of Burkitt's lymphoma, when treated in the early stages with courses of 15mg/m² daily orally for five days, have shown prolonged remissions. Combination chemotherapy is also commonly used in all stages of the disease.

Breast cancer: Methotrexate, in intravenous doses of 10-60mg/m², is commonly included in cyclical combination regimes with other cytotoxic drugs in the treatment of advanced breast cancer. Similar regimes have also been used as adjuvant therapy in early cases following mastectomy and/or radiotherapy.

Osteogenic sarcoma: The use of methotrexate alone and in cyclical combination regimes has recently been introduced as an adjuvant therapy to the primary treatment of osteogenic sarcoma by amputation with or without prosthetic bone replacement. This has involved the use of intravenous infusions of 20-300mg/kg (approximately 600-9,000mg/m²) of methotrexate followed by Calcium Leucovorin rescue. Methotrexate has also been used as the sole treatment in metastatic cases of osteogenic sarcoma.

Bronchogenic carcinoma: Intravenous infusions of 20-100mg/m² of methotrexate have been included in cyclical combination regimes for the treatment of advanced tumours. High doses with Calcium Leucovorin Rescue have also been employed as the sole treatment.

Head and neck cancer: Intravenous infusions of 240-1,080mg/m² with Calcium Leucovorin rescue have been used both as pre-operative adjuvant therapy and in the treatment of advanced tumours. Intra-arterial infusions of methotrexate have been used in the treatment of head and neck cancers.

Bladder carcinoma: Intravenous injections or infusions of methotrexate in doses up to 100mg every one or two weeks have been used in the treatment of bladder carcinoma with promising results, varying from only symptomatic relief to complete though unsustained regressions. The use of high doses of methotrexate with Calcium Leucovorin Rescue is currently being evaluated.

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

In most cases of severe uncontrolled psoriasis, unresponsive to conventional therapy, 10-25 mg orally once a week and 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: It is recommended that a test dose of 5-10mg should be administered, one week prior to therapy to detect idiosyncratic adverse reactions.

In adults with severe, acute, classical or definite rheumatoid arthritis who are unresponsive or intolerant to conventional therapy, 7.5mg orally once weekly or divided oral doses of 2.5mg at 12 hour intervals for 3 doses (7.5mg) as a course once weekly. The schedule may be adjusted gradually to achieve an optimal response but should not exceed a total weekly dose of 20mg. Once response has been achieved, the schedule should be reduced to the lowest possible effective dose.

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 have not been established, other than in cancer chemotherapy.

4.3 Contraindications

- Significantly impaired hepatic function
- Significantly impaired renal function
- Pre-existing blood dyscrasias, such as bone marrow hypoplasia, significant anaemia, leucopenia, or thrombocytopenia
- Alcoholism
- Severe acute or chronic infections and immunodeficiency syndrome
- Pregnancy and breast-feeding (see also section 4.6).
- Hypersensitivity to methotrexate or any of the excipients
- During methotrexate therapy concurrent vaccination with live vaccines must not be carried out

4.4 Special warnings and precautions for use

Methotrexate must be used only by physicians experienced in antimetabolite chemotherapy. Because of the possibility of fatal or severe toxicity, the physician should fully inform the patient of the risks involved and provide close medical supervision.

Monitoring (prior to starting treatment) – see also below

Before beginning or reinstating methotrexate after a rest period, the patient's renal, liver and bone marrow function should be assessed by history, physical examination and laboratory tests. A chest X-ray should also be taken (see Respiratory effects below).

Monitoring (during and after treatment) – see also below

- During treatment patients should be appropriately supervised so that toxic signs or symptoms, or adverse reactions may be detected and evaluated with minimal delay.
- Full blood count (including haematocrit), hepatic and renal function tests (including urinalysis) should be carried out every week until treatment is stabilized, thereafter every 2 to 3 months throughout treatment.
- More frequent check-ups be necessary when
 - the dose is increased
 - there is an increased risk of raised methotrexate blood levels (e.g. dehydration, impaired renal function, additional or increased dose of medicines, such as NSAIDs, administered concomitantly (see below & section 4.5).
- Haematopoietic suppression is common and may occur without warning when a patient is on an apparently "safe" dose, so full blood counts should be closely monitored during and after treatment. If any clinically significant drop in blood cell count occurs, methotrexate should be stopped immediately and appropriate therapy instituted. Patients should be advised to report all signs and symptoms suggestive of infection or of a blood dyscrasia.

Use in psoriasis

- Deaths have been reported associated with the use of methotrexate in psoriasis, so its use should be restricted to severe recalcitrant, disabling disease which is not adequately responsive to other forms of therapy, and only when the diagnosis has been established by biopsy and/or after

dermatological consultation (see also sections 4.1 and 4.2).

- The patient should be clearly informed that, in most cases of psoriasis, methotrexate is taken once weekly and that daily/more frequent administration can result in severe toxicity.
- In longer-term treatment liver biopsies should be performed (see Hepatotoxicity below).

Use in rheumatoid arthritis (RA)

- The patient should be clearly informed that, in most cases of RA, methotrexate is taken once weekly and that daily/more frequent administration can result in severe toxicity.
- When to perform a liver biopsy in rheumatological indications (cumulative dose/duration of therapy) has not been clearly established (see also below).

Other warnings/precautions

- Pleural effusions and ascites should be drained before methotrexate is started. Methotrexate can accumulate in these fluids and may be re-excreted into the circulation, prolonging the serum half-life and resulting in unexpected toxicity (eg myelosuppression – see below).
- Methotrexate should be used with extreme caution in
 - debility
 - extreme youth (see section 4.2)
 - old age (see section 4.2).
- Adequate hydration prior to and during treatment is required to limit the risk of renal toxicity (see below).
- Folate deficiency may increase methotrexate toxicity.
- Systemic toxicity may follow intrathecal use (appropriate monitoring required).
- Tumour lysis syndrome may occur in patients with rapidly growing tumours.
- If acute methotrexate toxicity occurs patients may require folinic acid (to neutralise bone marrow effects). Plasma methotrexate levels should be

monitored in order to calculate the appropriate dose.

Hepatotoxicity

- Methotrexate is hepatotoxic, particularly at high doses or with prolonged therapy. Liver atrophy, necrosis, cirrhosis, fatty changes, and periportal fibrosis have been reported. Changes may occur without prior signs of toxicity, so it is imperative that hepatic function be determined before treatment is started and monitored regularly throughout therapy (see above).

- 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 %, however methotrexate should not be started or should be discontinued if there are any clinically relevant abnormalities of liver function tests or liver biopsy. If such abnormalities return to normal within two weeks, the physician may consider it appropriate to re-start methotrexate.

- Additional hepatotoxic drugs should not be taken during treatment with methotrexate unless clearly necessary and the consumption of alcohol should be avoided or greatly reduced (see below and section 4.5).

- Risk factors for the development of hepatotoxicity primarily include
 - Daily (rather than weekly) dosing
 - History of alcohol abuse
 - History of liver disease including hepatitis B or C
 - Family history of hereditary hepatopathy.

- Other factors that may indicate an increased risk include
 - Diabetes mellitus
 - Adiposity
 - History of exposure to hepatotoxic medicines or chemicals.

Liver biopsies

- Liver biopsies should be considered after cumulative doses > 1.0 to 1.5g, if hepatic impairment is suspected.

- In patients with risk factors (see above), liver biopsy is recommended during or shortly after starting methotrexate. Since a small percentage of patients discontinue therapy for various reasons after 2-4 months, the first biopsy can be delayed to a time after this initial phase (ie when longer-term therapy is proposed).

- In low risk patients with RA, there is no robust evidence to support use of a liver biopsy to monitor hepatic toxicity (see above).
- In case of longer-term treatment of psoriasis with methotrexate, liver biopsies should be performed.

Haematological effects (myelosuppression)

- Methotrexate can suppress haematopoiesis. This can occur abruptly and with apparently “safe” doses. Monitoring is therefore required (see above).
- In patients with malignant disease (with existing bone marrow aplasia, leucopenia, thrombocytopenia, and/or anaemia) methotrexate should be used with considerable caution, if at all.
- If there are clinically significant falls in white cell or platelet counts, methotrexate should be stopped immediately.

Respiratory effects

- A chest X-ray is recommended prior to initiation of methotrexate therapy as acute or chronic interstitial pneumonitis, often associated with blood eosinophilia may occur. Deaths have been reported. Typically symptoms include dyspnoea, cough (especially a dry, non-productive cough), and fever. Patients with RA are particularly at risk.
- Patients should be informed of the risk, monitored for relevant symptoms at every visit and advised to contact their doctor immediately should they develop persistent cough or dyspnoea.
- Methotrexate should be withdrawn from patients with pulmonary symptoms and a thorough investigation undertaken to exclude infection as potentially fatal opportunistic infections (including *Pneumocystis carinii*) may occur
- If methotrexate induced lung disease is suspected treatment with corticosteroids should be initiated and treatment with methotrexate should not be restarted.
- If interstitial fibrosis develops it may be treatment-resistant

Renal effects

- Methotrexate is excreted primarily by the kidneys. Its use in patients with renal impairment should only be undertaken with extreme caution. Renal function should be closely monitored before, during and after treatment. Caution should be exercised if there is significant renal impairment as its use may result in accumulation/toxicity with additional renal damage.
- In renal impairment the dose of methotrexate should be reduced. High doses may cause precipitation of it or its metabolites in the renal tubules. A high fluid throughput and alkalinisation 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 500mg orally four times a day) is recommended as a preventive measure.
- Monitoring of serum methotrexate levels are recommended.

Gastro-intestinal effects

- Diarrhoea and ulcerative stomatitis are frequent toxic effects and require interruption of therapy, otherwise haemorrhagic enteritis and death from intestinal perforation may occur.
- Extreme caution should be exercised if there is peptic ulcer or ulcerative colitis.

Effects on fertility and reproduction (pregnancy & breast-feeding) - see also sections 4.3 and 4.6

- Methotrexate affects gametogenesis and may result in decreased fertility which is thought to be reversible on discontinuation of therapy.
- It may impair menstrual function with consequent amenorrhoea, during and for a short period after therapy has stopped.
- It causes embryotoxicity, abortion and foetal death and/or congenital anomalies in humans. It is therefore contraindicated in pregnancy. An existing pregnancy should be excluded with certainty before starting methotrexate.
- Following administration to man or woman conception should be avoided by using an effective contraceptive method for at least 6 months after stopping

methotrexate.

- Methotrexate passes into breast milk with consequent toxicity to the baby. Breast feeding is contraindicated during lactation.

Immunosuppressive activity

- The immunosuppressive effect of methotrexate should be taken into account when immune responses of patients are important or essential. Special attention should be paid in cases of inactive chronic infections (e.g. herpes zoster, tuberculosis, hepatitis B or C) because of their potential activation.
- Extreme caution is required in the presence of acute infection. If infection occurs or becomes a threat during methotrexate use, it should be stopped. Appropriate antibiotic therapy is usually indicated.
- Responses to concurrent vaccination may be decreased. Vaccination with live vaccines are contraindicated during methotrexate therapy as severe antigenic reactions may occur (see section 4.3).

Development of malignant lymphomas

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.

Serious skin reactions

Severe (occasionally fatal) skin reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme have been reported within a few days of a single or multiple doses of methotrexate.

Concurrent medication (see also section 4.5)

DMARDs (disease-modifying antirheumatic drugs)

Concomitant administration of hepatotoxic or haematotoxic DMARDs (e.g. leflunomide) is not advisable. Due to the possibility of fatal or severe toxic reactions, the patient should be fully informed by the physician of the risks involved and be under constant supervision.

NSAIDs

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

- In the treatment of rheumatoid arthritis, treatment with acetylsalicylic acid and NSAIDs as well as small-dose steroids can be continued, but the possible increased risk of toxicity needs to be borne in mind. The steroid dose can be reduced gradually in patients who exhibit therapeutic response to methotrexate.
- Interaction between methotrexate and other antirheumatic agents, such as gold, penicillamine, hydroxychloroquine, sulphasalazine or other cytotoxic agents, have not been studied comprehensively but coadministration may involve an increased frequency of adverse reactions.

Folate antagonists

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

Vitamin preparations

If these contain folic acid (or its derivatives) they may alter the response to Methotrexate.

Other hepatotoxic/haematotoxic drugs

Closer monitoring of liver enzymes and/or blood counts should be exercised in patients taking other hepatotoxic and/or haematotoxic medicines concomitantly.

Binding to albumin

Methotrexate is part-bound to serum albumin 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.

Concomitant other therapies (radiotherapy: ultraviolet radiation/PUVA)

- Methotrexate used concurrently with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis
- Psoriatic lesions may get worse if methotrexate is combined with ultraviolet radiation/PUVA

Lactose intolerance

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

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent use contra-indicated

Live vaccines - severe antigenic reactions may occur (see sections 4.3 and 4.4).

Avoid concomitant use

General anaesthesia – nitrous oxide increases the antifolate effect of methotrexate (increased frequency of stomatitis).

Antipsychotics – increased risk of agranulocytosis with olanzapine.

Retinoids – plasma concentrations of methotrexate increased by acitretin – also increased risk of hepatotoxicity.

Azopropazone – excretion of methotrexate reduced.

NSAIDs (see also below) should not be administered before or concurrently with high-dose methotrexate - increased and prolonged serum methotrexate concentrations with consequent increased gastrointestinal and haematological toxicity.

Other hepato-, myelo- or nephrotoxic drugs

Sulfamethoxazole and trimethoprim (as co-trimoxazole) – increased risk of haematological toxicity.

Considerable caution required

Probenecid & weak organic acids (eg loop diuretics: pyrazoles) - excretion of methotrexate reduced (increased risk of toxicity).

Caution required

Analgesics

- NSAIDs (see also above) – In animals low doses of methotrexate with NSAIDs have been found to decrease the tubular secretion of methotrexate and possibly to increase its toxicity. However patients with rheumatoid arthritis (or psoriasis) have been treated concurrently with methotrexate 7.5 - 15 mg/week without significant problems.
- Aspirin and other salicylates - possible alteration of the pharmacokinetics of methotrexate/increased risk of toxicity

Antibacterials

- Neomycin (and possibly tetracycline, chloramphenicol: non-absorbable broad spectrum antibiotics) – reduced absorption of methotrexate.
- Ciprofloxacin – excretion of methotrexate possibly reduced (increased risk of toxicity).
- Doxycycline, sulphonamides, tetracyclines - increased risk of methotrexate toxicity.
- Penicillin – reduced excretion of methotrexate - increased risk of toxicity (hematological and gastrointestinal).

Antiepiletics

- Antifolate effect of methotrexate increased by phenytoin.
- Phenytoin – absorption possible decreased by cytotoxics (risk of exacerbation of convulsions).
- Enzyme-inducing antiepiletics – increased/altered metabolism and/or clearance of methotrexate.
- Carbamazepine, phenytoin and valproate serum levels can be reduced by antineoplastic drugs with seizures if the antiepileptic doses are not raised appropriately.

Antimalarials

Pyrimethamine – increased anti-folate effect of methotrexate.

Cardiac glycosides

Digoxin absorption decreased by cytotoxics.

Ciclosporin

Increased risk of toxicity.

Corticosteroids

Increased risk of haematological toxicity.

Cytotoxics

Increased risk of pulmonary toxicity (see sections 4.4 & 4.8).

Immunosuppressants

Leflunomide – risk of toxicity (see also section 4.4).

Theophylline

Methotrexate possibly increases plasma concentrations of theophylline.

Ulcer-healing drugs – proton pump inhibitors

Omeprazole and pantoprazole – excretion of methotrexate possibly reduced (increased risk of toxicity).

Vitamin preparations

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

Potassium – sparing diuretics

Triamterene - bone marrow suppression and reduced folate concentrations have been reported when triamterene and methotrexate were coadministered.

Other possible interactions

Oral hypoglycaemics – possible reduced methotrexate excretion.

Thiazide diuretics – possible reduced methotrexate excretion.

4.6 Pregnancy and lactation

Pregnancy

Use of methotrexate is contraindicated throughout pregnancy (see section 4.3), since there is evidence of a teratogenic risk in humans (craniofacial, cardiovascular and extremital malformations) and in several animal species (see section 5.3).

In women of child-bearing age, any existing pregnancy must be excluded with certainty by taking appropriate measures, e.g. pregnancy test, prior to initiating therapy.

Women must not become pregnant during and at least 6 months after treatment with methotrexate and must therefore practise an effective form of contraception.

If, nevertheless, pregnancy occurs during this period, medical advice should be given regarding the risk of harmful effects on the child associated with treatment.

As methotrexate may be genotoxic, women who wish to become pregnant are advised to consult a genetic counselling centre, if possible, already prior to therapy.

Lactation

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.

Male fertility

Methotrexate may be genotoxic. Men treated with methotrexate are therefore recommended not to father a child during treatment and up to 6 months afterwards. Since treatment with methotrexate can lead to severe and possibly irreversible disorders in spermatogenesis, men should seek advice about the possibility of sperm preservation before starting therapy.

Both men and women receiving methotrexate should be informed of the potential risk of adverse effects on reproduction. Women of childbearing potential should be fully informed of the potential hazard to the foetus should they become pregnant during methotrexate therapy.

Defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, and infertility have been reported in patients receiving methotrexate.

4.7 Effects on ability to drive and use machines

Methotrexate can cause dizziness, fatigue, blurred vision and eye-irritation, which may affect the ability to drive or operate machinery.

4.8 Undesirable effects

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

If adverse reactions occur, the dose should be reduced or therapy discontinued and necessary corrective therapeutic measures undertaken, such as administration of calcium folinate (see sections 4.2 and 4.4).

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.

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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1000$ to $< 1/100$); rare ($\geq 1/10000$ to $< 1/1000$); very rare ($< 1/10000$), not known (cannot be estimated from the available data).

	Common	Uncommon	Rare	Very rare
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	Leucopaenia	Bone marrow depression Thrombocytopaenia Anaemia		Hypogammaglobulinaemia
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
Eye disorders				Conjunctivitis Blurred vision
Cardiac disorders				Pericardial effusion Pericarditis
Vascular disorders		Nosebleed	Hypotension Thromboembolism	Vasculitis
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
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	Erythematous rash	Pruritus Stevens-Johnson's	Photohypersensitivity	Telangiectasis

tissue disorders	Alopecia	syndrome Toxic epidermal necrolysis	Acne Depigmentation Urticaria Erythema multiforme Painful damage to psoriatic lesion Skin ulceration	Furunculosis Ecchymoses
Musculoskeletal and connective tissue disorders			Osteoporosis Arthralgia Myalgia Increased rheumatic nodules	
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

¹ Can be reversible (see 4.4).

² See section 4.4.

³ Gastrointestinal severe adverse reactions require often dose reduction. Ulcerative stomatitis and diarrhoea require discontinuation of methotrexate therapy because of the risk of ulcerative enteritis and fatal intestinal perforation.

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

relationship between methotrexate and myocardial ischemia. Rarely, neutropenic sepsis leading to fatality has also been reported

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

In rare cases, following intrathecal administration, a tumour lysis syndrome has been observed. Features include hyperkalaemia, hyperuricaemia and hyperphosphataemia with hypocalcaemia; renal damage and arrhythmias can follow.

4.9 Overdose

The toxicity of methotrexate affects mainly the haematopoietic organs. Calcium folinate neutralises effectively the immediate haematopoietic toxic effects of methotrexate. Parenteral calcium folinate therapy should be started within one hour after the administration of methotrexate. The dose of calcium folinate should be at least as high as the dose of methotrexate received by the patient.

Massive overdose requires hydration and alkalinisation of the urine to prevent precipitation of methotrexate and/or its metabolites in the renal tubules. Haemodialysis or peritoneal dialysis has not been found to affect the elimination of methotrexate. Instead, effective clearance of methotrexate has been achieved by intermittent haemodialysis using a so-called "high-flux" dialysator.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

Calcium folinate is a folinic acid which is used to protect normal cells from the toxic effects of methotrexate. Calcium folinate enters the cell through a specific transport

mechanism, is converted in the cell into active folates and reverses the inhibition of the precursor synthesis caused by the DNA and RNA.

5.2 Pharmacokinetic properties

The effect of orally administered methotrexate seems to be dependent on the size of the dose. Peak concentrations in serum are reached within 1–2 hours. Generally a dose of methotrexate of 30 mg/m² or less is absorbed rapidly and completely. The bioavailability of orally administered methotrexate is high (80–100%) at doses of 30 mg/m² or less. Saturation of the absorption starts at doses above 30 mg/m² and absorption at doses exceeding 80 mg/m² 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

Lactose monohydrate, Magnesium Stearate and Pregelatinised Starch.

6.2 Incompatibilities

It is inadvisable to mix flurouracil and methotrexate. Other drugs should not be mixed

with methotrexate in the same infusion container.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Polypropylene bottles -28 or 100 tablets

HDPE bottles- 28 or 100 tablets

PVC/Aluminium blisters – 24, 28 or 30 tablets

Not all pack sizes may be marketed

6.6 Special precautions for disposal

Cytotoxic drugs should only be handled by trained personnel in a designated area.
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 vesicant and should not cause harm if it comes in contact with the skin. It should, of course, be washed off with water immediately. 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 Leuovorin cover should be given.

Cytotoxic preparations should not be handled by pregnant staff.

Any spillage or waste material 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

Goldshield Pharmaceuticals Limited

NLA Tower

12-16 Addiscombe Road

Croydon

Surrey

CR0 0XT

UK.

8 MARKETING AUTHORISATION NUMBER(S)

PL 12762/0231

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

27th September, 1989

10 DATE OF REVISION OF THE TEXT

18/01/2012