

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Methotrexate 2.5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contain methotrexate 2.5mg

Excipients with known effects

Each 2.5 mg tablet contain 12.50 mg lactose (as lactose monohydrate)

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet

Yellow, circular, biconvex uncoated tablets with dimension of 4.50 mm $\pm$ 0.20 mm plain on both sides

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

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

Rheumatoid arthritis

The usual dose is 7.5 - 15 mg once weekly. The planned weekly dose may be administered in three divided doses over 36 hours. 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. The planned weekly dose administered as three divided doses over 24 hours. 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 patients:

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 occur with increased age.

Patients with renal impairment:

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

Creatinine clearance (ml/min)	Dose
> 50	100 %
20 – 50	50 %
< 20	Methotrexate must not be used

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.

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Warnings

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

Concomitant administration of hepatotoxic or haematotoxic DMARDs (disease-modifying antirheumatic drug, 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.

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. 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.

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 Patients should be informed clearly that in the treatment of psoriasis and rheumatoid arthritis the administration is in most cases once weekly. Patients should be aware of the importance of adhering to the once weekly intakes and that wrong daily administration can result in severe toxic reactions. The prescriber may specify the day of intake on the prescription.

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

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

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

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

Due to its potentially toxic effect on the liver, additional hepatotoxic medicinal products should not be taken during treatment with methotrexate unless clearly necessary and the consumption of alcohol should be avoided or greatly reduced (see section 4.5). Closer monitoring of liver enzymes should be exercised in Patients taking other hepatotoxic medicinal products concomitantly (e.g. leflunomide). The same should be taken into account with the simultaneous administration of haematotoxic medicinal products (e.g. leflunomide).

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.

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 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 (500 mg orally four times a day) is recommended as a preventative 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.

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.

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

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

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

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

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

Interaction between methotrexate and other antirheumatic agents, such as gold, penicillamin, hydroxychloroquine, 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.

Precautions

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

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

Malignant lymphomas may occur in patients receiving low dose methotrexate, in which case therapy must be discontinued. Failure of the lymphoma to show signs of spontaneous regression requires the initiation of cytotoxic therapy.

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.

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.

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

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.

The tablets contains lactose. Patient with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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.

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 nephron and hepatotoxic agents (e.g. sulphasalazine, leflunomide and alcohol) with methotrexate should be avoided. Special caution should be exercised when observing patients receiving methotrexate therapy in combination with azathioprine or retinoids.

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

Enhancement of nephrotoxicity may be seen with 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. Concomitant use of some NSAIDs and high-dose methotrexate has been reported to increase and prolong the serum methotrexate concentration in serum and to increase gastrointestinal and haematological toxicity. When using smaller doses of methotrexate, these medicinal products have been found in animals to decrease the tubular secretion of methotrexate and possibly to increase its toxicity. In addition to methotrexate, patients with rheumatoid arthritis have generally been treated, however, with NSAIDs with no problems. It should be noted, however, that the doses of methotrexate used in the treatment of rheumatoid arthritis (7.5 - 15 mg/week) are slightly lower than those used for psoriasis and that higher doses can result in unexpected toxicity.

Vitamin preparations containing folic acid or its derivatives may change the 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.

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.

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

Methotrexate increases the 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. 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 loss of efficacy of the cytotoxic drug due to increased hepatic metabolism by phenytoin.

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

4.6 Fertility, 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 extremity 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.

Breastfeeding

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

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

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

4.8 Undesirable effects

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

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

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 ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Uncommon: Lymphoma ¹

Blood and lymphatic system disorders

Common: Leukopenia

Uncommon: Bone marrow depression, thrombocytopenia, anaemia.

Very rare: Hypogammaglobulinaemia.

Nervous system disorders

Common: Headache, dizziness, fatigue, paraesthesia in the extremities.

Rare: Hemiparesis.

Very rare: Irritation, dysarthria, aphasia, lethargy

Eye disorders

Very rare: Conjunctivitis, blurred vision.

Cardiac disorders

Very rare: Pericarditis, pericardial effusion.

Vascular disorders

Uncommon: Nosebleed

Rare: Hypotension, thromboembolism.

Very rare: Vasculitis.

Respiratory, thoracic and mediastinal disorders

Uncommon: Pneumonia, interstitial pneumonitis (can be fatal), interstitial fibrosis.

Rare: Dyspnoea, pharyngitis ²

Very rare: Pneumocystis carinii-pneumonia, chronic interstitial obstructive lung disease, pleuritis, dry cough.

Gastrointestinal disorders ³

Common: Stomatitis, anorexia, nausea, vomiting, diarrhoea.

Rare: Gastrointestinal ulcerations and haemorrhage, gingivitis, enteritis.

Very rare: Haematemesis.

Hepatobiliary disorders

Common: Elevated transaminase.

Rare: Acute hepatitis, hepatotoxicity, periportal fibrosis, liver cirrhosis.

Skin and subcutaneous tissue disorders

Common: Erythematous rash, alopecia.

Uncommon: Pruritus, Stevens-Johnson's syndrome, toxic epidermal necrolysis.

Rare: Photohypersensitivity, depigmentation, acne, urticaria, erythema multiforme, painful damage to psoriatic lesion, skin ulceration.

Very rare: Ecchymoses, furunculosis, telangiectasia.

Musculoskeletal and connective tissue disorders

Rare: Arthralgia, myalgia, osteoporosis, increased rheumatic nodules.

Renal and urinary disorders

Uncommon: Renal insufficiency, nephropathy.

Very rare: Dysuria, azotaemia, cystitis, haematuria.

Reproductive system and breast disorders

Uncommon: Vaginal ulceration.

Rare: Decreased libido, impotence, menstrual disorders.

Very rare: Formation of defective oocytes or sperm cells, transient oligospermia, infertility, vaginal bleeding, gynaecomastia.

Infections and infestations

Common: Infections.

Uncommon: Opportunistic infections.

Rare: Herpes zoster, sepsis.

Immune system disorders

Uncommon: Anaphylactic-type reaction

Endocrine disorders

Rare: Diabetes mellitus.

Psychiatric disorders

Rare: Depression, confusion.

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.

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 HPRA Pharmacovigilance Earlsfort Terrace IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

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.

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 folylpolyglutamylase 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

Anhydrous calcium hydrogen phosphate,
Lactose monohydrate,
Sodium starch glycolate,
Microcrystalline cellulose,
Talc,
Magnesium stearate.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

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

Blister: keep the blister in the outer carton in order to protect from light.

HDPE container: store in original container in order to protect from light.

6.5 Nature and contents of container

2.5 mg tablets:

White high density polyethylene container with non CRC high density polyethylene cap with induction wad. Pack size: 25 or 100 tablets

Amber colour Polyvinylchloride (PVC)/Plain Aluminium blister foil. Pack size: 10, 24, 25, 28 30, 50 or 100 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Cipla (EU) Limited
Hillbrow House,
Hillbrow Road,
Esher,
Surrey KT10 9NW,
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA1809/014/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20th February 2015.

10 DATE OF REVISION OF THE TEXT