

PACKAGE LEAFLET: INFORMATION FOR THE USER

Methotrexate 2.5mg Tablets

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed on this leaflet. See section 4.

What is in this leaflet:

1. What Methotrexate Tablets are and what they are used for
2. What you need to know before you take Methotrexate Tablets
3. How to take Methotrexate Tablets
4. Possible side effects
5. How to store Methotrexate Tablets
6. Contents of the pack and other information

1. What Methotrexate Tablets are and what they are used for

The active substance of Methotrexate Tablets, methotrexate, is an antimetabolite and immunosuppressant (medicine which affects the reproduction of the body's cells and reduces the activity of the immune system).

Methotrexate is used to treat:

- active rheumatoid arthritis,
- severe psoriasis, especially plaque-type,
- psoriatic arthritis in adult patients who have tried other treatments but their illness has not improved.

Your doctor will be able to explain how Methotrexate Tablets might help in your particular condition.

2. What you need to know before you take Methotrexate Tablets

Do not take Methotrexate Tablets if you:

- are allergic to methotrexate or any of the other ingredients of this medicine (listed in section 6).
- are pregnant, trying to become pregnant or breast-feeding. Methotrexate may harm your baby (see section on Pregnancy). You and your partner should avoid

conception (becoming pregnant or fathering children) for at least 6 months after your treatment with methotrexate has stopped.

- have severe liver problems, including fibrosis, cirrhosis and recent or active hepatitis.
- have severe kidney problems, including conditions requiring kidney dialysis.
- have any serious blood disorder, including severe anaemia and clotting problems.
- have an alcohol dependency.
- have a medical condition or are receiving medication which lowers your resistance to infection.
- are taking antibiotics which prevent the production of folic acid (vitamin B9) such as co-trimoxazole, which are used to treat bacterial infections.
- have an active infectious disease (e.g. fever, chills, joint pain).
- are being treated with live vaccines.
- have an ulcer of the oral cavity and gut.
- have inflammation of mouth or lips.

Recommended follow-up examinations and precautions

Even if methotrexate is used in low doses, serious side effects can occur. In order to detect them in time, your doctor must perform monitoring examinations and laboratory tests.

Prior to the start of therapy:

Before you start treatment, your blood will be checked to see if you have enough blood cells. Your blood will also be tested to check your liver function and to find out if you have hepatitis. Furthermore, serum albumin (a protein in the blood), hepatitis (liver infection) status and kidney function will be checked. The doctor may also decide to run other liver tests, some of these may be images of your liver and others may need a small sample of tissue taken from the liver in order to examine it more closely. Your doctor may also check to see if you have tuberculosis and they may X-ray your chest or perform a lung function test.

During the treatment:

Your doctor may perform the following examinations:

- examination of the oral cavity and the pharynx for changes in the mucous membrane such as inflammation or ulceration
- blood tests/ blood count with number of blood cells and measurement of serum methotrexate levels
- blood test to monitor liver function
- imaging tests to monitor liver condition
- small sample of tissue taken from the liver in order to examine it more closely
- blood test to monitor kidney function
- respiratory tract monitoring and, if necessary, lung function test

It is very important that you appear for these scheduled examinations.

If the results of any of these tests are conspicuous, your doctor will adjust your treatment accordingly.

Elderly patients

Elderly patients under treatment with methotrexate should be monitored closely by a physician so that possible side effects can be detected as early as possible.

Age-related impairment of liver and kidney function as well as low body reserves of the vitamin folic acid in old age require a relatively low dosage of methotrexate.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking Methotrexate Tablets if you have any of the following conditions. This will help them decide if Methotrexate Tablets are suitable for you:

- have any mild or moderate kidney disease.
- have a stomach ulcer or ulcerative colitis (inflammation and ulceration of the gut).
- have any blood disorders or anaemia.
- have diarrhoea.
- have gastro-intestinal (digestive) problems.
- have severe mouth ulcers.
- have or have ever suffered from mental illness.
- received or you are receiving radiotherapy (x-ray treatment) or UV radiation.
- have received any vaccinations recently or you are due to have any, as methotrexate can reduce their effect.
- have any symptoms or signs of infection.
- have excess fluid, between the lungs and chest wall (pleural effusion) or abdominal swelling (ascites) causing breathlessness.
- develop a persistent cough or develop shortness of breath as it may be associated with serious lung disease.
- special care is also needed in children, the elderly and in those who are in poor physical condition.
- have or have ever had liver damage, dependence on alcohol or abnormal liver function tests.
- have diabetes and are being treated with insulin.
- have an inactive chronic infection, such as herpes zoster, tuberculosis, hepatitis B or C.
- methotrexate temporarily affects sperm and egg production. Methotrexate can cause miscarriage and severe birth defects. You and your partner should avoid having a baby if you are being given methotrexate at the time and for at least 6 months after the end of your treatment with methotrexate. See also section "Pregnancy, breast-feeding and fertility".

Acute bleeding from the lungs in patients with underlying rheumatologic disease has been reported with methotrexate. If you experience symptoms of spitting or coughing up blood you should contact your doctor immediately.

If you, your partner or your caregiver notice new onset or worsening of neurological symptoms including general muscle weakness, disturbance of vision, changes in thinking, memory and orientation leading to confusion and personality changes contact your doctor immediately because these may be symptoms of a very rare, serious brain infection called progressive multifocal leukoencephalopathy (PML).

Other medicines and Methotrexate Tablets

Tell your doctor or pharmacists if you are taking, have recently taken, or might take any other medicines. This includes the following medicines, as the effect of Methotrexate Tablets may be altered when they are taken at the same time:

- vaccinations / live virus vaccines
- ibuprofen, indomethacin (NSAID's, non-steroidal anti-inflammatory drugs) which are used for pain or inflammation
- aspirin or similar medicines (known as salicylates)
- diuretics (water tablets)
- medicines used/taken for diabetes
- antibiotics (used to treat bacterial infections e.g. chloramphenicol, penicillin, sulfonamides, co-trimoxazole, trimethoprim / sulfamethoxazole, ciprofloxacin and tetracyclines)
- thiazides (a group of diuretics used for the treatment of fluid retention e.g. bendroflumethiazide)
- hypoglycaemics (used for lowering blood sugar levels e.g. metformin)
- p-aminobenzoic acid, acitretin (used to treat psoriasis or skin disorders)
- diphenylhydantoin, phenytoin (used to treat epilepsy)
- probenecid, sulfinpyrazone (used to treat gout)
- acitretin (a medicine used to treat psoriasis)
- radiotherapy
- vitamin preparations containing folic acid or similar products
- nitrous oxide (a gas used in general anaesthesia)
- levetiracetam (a medicine used to treat seizures in epilepsy)
- loop diuretics (used to treat hypertension and oedema)
- sulfasalazine, leflunomide (used to treat arthritis)
- cisplatin (used in chemotherapy)
- omeprazole, pantoprazole (used to treat indigestion, stomach acid and ulcers)
- theophylline (used to treat asthma, bronchitis, emphysema)
- mercaptopurine (used to treat acute lymphocytic leukaemia)
- cyclosporine (used in organ transplantation).

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Methotrexate Tablets with food, drink and alcohol

Alcohol should be avoided while receiving methotrexate as it increases the risk of liver damage.

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy

Do not take Methotrexate Tablets during pregnancy except if your doctor has prescribed it for oncology treatment. Methotrexate can cause birth defects, harm the unborn child or cause miscarriage. It is associated with malformations of the skull, face, heart and blood vessels, brain and limbs. It is therefore very important that methotrexate is not given to pregnant women or to women who are planning to become pregnant unless used for oncology treatment.

For non-oncological indications, in women of child-bearing age the possibility of a pregnancy must be ruled out, e.g. by pregnancy tests, before treatment is started.

Do not take Methotrexate Tablets if you are trying to become pregnant. You must avoid becoming pregnant during treatment with methotrexate and for at least 6 months after the end of treatment. Therefore, you must ensure that you are taking effective contraception for the whole of this period (see also section "Warnings and precautions").

If you become pregnant during treatment or suspect you might be pregnant, speak to your doctor as soon as possible. If you do become pregnant during treatment, you should be offered advice regarding the risk of harmful effects on the child through treatment.

If you want to become pregnant, you should speak with your doctor, who may refer you for specialist advice before the planned start of treatment.

Methotrexate can cause birth defects, harm unborn babies or cause miscarriages and so it is very important that it is not given to pregnant patients or patients planning to become pregnant. It may also affect women's periods; they may become less frequent or stop completely. Methotrexate can affect sperm and egg production with the potential to cause birth defects. You and your partner should avoid conception (becoming pregnant or fathering children) for at least six months after your treatment with methotrexate has stopped.

As methotrexate may cause genetic mutations, all women who wish to become pregnant are advised to consult a genetic counselling centre, if possible already prior to therapy, and men should seek advice about the possibility of sperm preservation before starting therapy.

Male fertility

The available evidence does not indicate an increased risk of malformations or miscarriage if the father takes methotrexate less than 30 mg/week. However, a risk

cannot be completely excluded and there is no information regarding higher methotrexate doses. Methotrexate can have a genotoxic effect. This means that the medicine can cause genetic mutations. Methotrexate can affect the production of sperm, which is associated with the possibility of birth defects.

You should avoid fathering a child or to donate semen during treatment with methotrexate and for at least 6 months after the end of treatment. As treatment with methotrexate at higher doses commonly used in cancer treatment can cause infertility and genetic mutations, it may be advisable for male patients treated with methotrexate doses higher than 30 mg/week to consider sperm preservation before the beginning of treatment (see also section "Warnings and precautions").

Breast-feeding

Methotrexate passes into breast milk. You should not take Methotrexate Tablets if you are breast-feeding.

Driving and using machines

Methotrexate Tablets may cause some side effects which could affect your ability to drive or use machinery for example drowsiness, loss of co-ordination or blurred vision. If you experience these symptoms, do not drive or use any tools or machinery. The full list of side effects are listed in section 4.

Methotrexate Tablets contain lactose and sodium

If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicinal product.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Methotrexate Tablets

Important warning about the dose of Methotrexate Tablets:

Take Methotrexate Tablets **only once a week** for the treatment of rheumatoid arthritis and psoriasis. Taking too much of Methotrexate Tablets may be fatal. Please read section 3 of this leaflet very carefully. If you have any questions, please talk to your doctor or pharmacist before you take this medicine.

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. Alcohol should be avoided while receiving methotrexate. The usual dose is:

The recommended dose is:

Dose in rheumatoid arthritis and psoriasis:

Take Methotrexate Tablets only once a week.

Dosage for rheumatoid arthritis:

You will usually take your tablets once a week on the same day each week. The dose will normally be between 7.5 and 20mg. However, this may be changed depending upon your response to treatment.

Elderly

Elderly patients may need smaller doses of methotrexate.

Children

Not recommended for use in children.

Dosage for psoriasis:

Adults: For severe psoriasis, the usual dose is 10 mg to 25 mg by mouth, once weekly. This should be adjusted according to your response to treatment and side effects.

Elderly: No dosage adjustment required.

Children: Not recommended for use in children.

These doses may be adjusted if you are receiving other medication. Your doctor will decide the correct dose for you, if you want more information you should ask your doctor.

If you have the impression that the effect of Methotrexate Tablets is too strong or too weak, talk to your doctor or pharmacist.

If you take more Methotrexate Tablets than you should

This medicine is usually taken once a week. If you take more of the medicine than you should, a physician or nearest hospital casualty department must be contacted immediately. Take your medicine package with you if you go to a doctor or hospital.

Overdose symptoms may include easy bruising or bleeding, unusual weakness, mouth sores, nausea, vomiting, black or bloody stools, coughing up blood or vomit that looks like coffee grounds, and decreased urinating.

Inappropriate intake resulting in overdose can sometimes lead to death. The antidote in case of an overdose is calcium folinate.

If you forget to take Methotrexate Tablets

Take the forgotten dose as soon as you remember if this is within two days. However, if you have missed a dose by more than two days, please contact your doctor for advice. Do not take a double dose to make up for a forgotten dose.

If you stop taking Methotrexate Tablets

Do not stop taking the tablets unless your doctor tells you to. If you have any further questions on how to take this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Methotrexate Tablets can cause side effects, although not everybody gets them. However, Methotrexate is a very toxic medicine and some patients have died, or become very ill whilst being treated with it.

Tell your doctor immediately if you experience any of the following symptoms after taking this medicine. Although they are very rare, these symptoms can be serious.

- **Severe skin rash that causes blistering** (this can affect the mouth and tongue). These may be signs of a condition known as Stevens Johnson Syndrome. Your doctor will stop your treatment in these cases.
- **Persistent cough, pain or difficulty breathing, or becoming breathless**, methotrexate can cause diseases of the lungs e.g. fluid in lungs.
- **Spitting or coughing blood**; this has been reported for methotrexate used in patients with underlying rheumatologic disease.
- **Skin rash and fever with swollen glands**, particularly in the first two months of treatment, as these may be signs of a hypersensitivity reaction.
- **Sore throat, fever, chills, or achiness**, methotrexate can make you more likely to catch infections.
- **Severe allergic reaction (anaphylactic reaction)**, although very rare you may experience a sudden itchy skin rash (hives), swelling of the hands, feet, ankles, face, lips, mouth or throat (which may cause difficulty in swallowing or breathing), wheeze, and you may feel you are going to faint. If this happens you should seek medical attention immediately.

Other side-effects that may occur are:

- Severe mouth ulcers and ulcers of the gut
- Reduction in red blood cells which can make the skin pale and cause weakness or breathlessness
- Reduction in blood platelets which increases risk of bleeding or bruising
- Lung infection (Pneumonia)
- Drowsiness
- Severe skin reaction
- Inflammation of vessels, often with skin rash
- Itchy skin
- Shingles (Herpes Zoster)
- Ringing in the ears
- Abdominal pain
- Indigestion

- Convulsions
- Loss of coordination
- Asthma
- Confusion
- Liver damage (seen as yellowing of the skin and whites of the eye)
- Liver failure
- Kidney damage
- Low levels of white cell count (leukopenia) and red blood cells and cells that clot blood
- Infection, reduced resistance to infection
- Abnormal red blood cell function
- Lung damage/scarred
- Build-up of excess fluid in the lung
- Build-up of fluid or excess fluid in the double layer around the heart
- Abnormal low blood pressure
- Inability to move
- Inability to move in one half of the body
- Dizziness
- Headaches, Blurred vision
- Difficulty sleeping
- Raised blood sugar levels (diabetes mellitus)
- Change in sense of taste
- Loss of ability to speak or understand speech
- Impaired vision
- Brittle bones
- Muscular pain
- Slow thought process
- Mood alteration
- Black or tarry stools
- Skin ulcers and erosions of inflamed areas, in psoriasis patients
- Damaged skin becomes inflamed on re-exposure to radiation and sunlight
- Reduced ability to become pregnant and reduced ability to father children
- Inflammation of the vagina
- Vaginal bleeding
- Menstrual disorders
- Blood in the urine
- Raised liver enzymes
- Weakening or softening of bones
- Unusual sensations in the head
- Anorexia (eating disorders)
- Loss of interest in, or inability to have sex
- Stomach pains and soreness of the mouth, throat and lips
- Inflamed blood vessels

- Feeling sick, being sick and/or diarrhoea, decreased absorption from intestines
- Irritation or swelling of the vaginal tissues
- Vaginal ulcers
- Pain or difficulty in passing urine
- The need to pass urine more often than usual
- Ulcers in urinary bladder
- Joint and muscle pain
- Chills and fever
- Changes in skin and nail colouration
- Bacteria or fungal infection of hand and feet
- Hair loss
- Red spots on the skin, skin lesions, acne, boils
- Redness and shedding of skin (frequency not known)
- Itchiness and rash
- Sensitivity to light
- Eye irritation
- Tiredness and lack of energy
- General feeling of illness
- Other metabolic changes
- Nose bleed (frequency not known)
- Bleeding from the lungs (frequency not known) – this has been reported for methotrexate used in patients with underlying rheumatologic disease
- Lymphoproliferative disorders (excessive growth of white blood cells) (frequency very rare)
- Bone damage in the jaw (secondary to excessive growth of white blood cells) (frequency not known)
- Sensation of numbness or tingling / having less sensitivity to stimulation than normal (frequency very rare)
- Swelling (frequency not known).

Methotrexate may lead to problems with your blood, liver and kidneys. Your doctor will take blood samples to check for these problems and may ask you to have a small sample of your liver taken for testing (liver biopsy).

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via:

Ireland

HPRA Pharmacovigilance

Earlsfort Terrace, IRL - Dublin 2

Tel: +353 1 6764971, Fax: +353 1 6762517

Website: www.hpra.ie, e-mail: medsafety@hpra.ie

Malta

ADR Reporting

Website: www.medicinesauthority.gov.mt/adrportal

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Methotrexate Tablets

Keep this medicine out of the sight and reach of children. Accidental ingestion can be lethal for children.

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

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

Do not use this medicine after the expiry date which is stated on the blister and the carton after EXP. The expiry date refers to the last day of that month.

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.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Methotrexate Tablets contain

Each tablet contains 2.5 mg of the active ingredient methotrexate.

The other ingredients are anhydrous calcium hydrogen phosphate, lactose monohydrate, sodium starch glycolate, microcrystalline cellulose, purified talc and magnesium stearate.

What Methotrexate Tablets look like and contents of the pack

Methotrexate Tablets are yellow coloured, circular, biconvex, uncoated tablets plain on both sides.

Methotrexate 2.5 mg Tablets are available in blister packs of 7, 10, 14, 20, 24, 28, 30, 56, 60, 84, 90, 100 and 112 tablets.

Not all pack sizes may be marketed.

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