

Package leaflet: Information for the patient

Methotrexate 2.5 mg Tablets

methotrexate

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 any 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 or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Methotrexate 2.5 mg Tablets are and what they are used for
2. What you need to know before you take Methotrexate 2.5 mg Tablets
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1. What Methotrexate 2.5 mg Tablets are and what they are used for

Methotrexate 2.5 mg Tablets are one of a group of medicines called antimetabolites which affect cell growth, including the growth of cancer cells.

Methotrexate can be used to treat severe cases of psoriasis (a skin disease) and rheumatoid arthritis (a disease of the joints). It is usually used for patients who have tried other treatments but their illness has not improved. It helps patients with psoriasis by killing the cells in the skin which are growing too quickly. It is these fast growing cells which cause the raised patches of skin in psoriasis.

In the treatment of rheumatoid arthritis, methotrexate is thought to stop or reduce inflammation in the joints by altering the body's defence mechanisms in the immune system.

Methotrexate can also be used to treat several kinds of cancer when it and can be given alone or in combination with other medicines. It is usually used in much higher doses when it is used to treat cancer and it will often be given as an injection rather than tablets.

You must talk to a doctor if you do not feel better or if you feel worse.

2. What you need to know before you take Methotrexate 2.5 mg Tablets

Your doctor may perform several tests such as blood tests, x-rays and physical examinations before treatment with Methotrexate 2.5 mg tablets is started, and at regular intervals during treatment.

Do not take Methotrexate 2.5 mg Tablets

- if you are allergic to methotrexate or any of the other ingredients of this medicine (listed in section 6)

- if you are breast-feeding and additionally, for non-oncologic indications (for non-cancer treatment)
- if you are pregnant (see section: Pregnancy, breast-feeding and fertility). You and your partner should avoid conception (becoming pregnant or fathering children) for at least three months after your treatment with methotrexate has stopped
- if you suffer from a problem of excessive drinking (alcoholism)
- if you have severe liver problems, including alcoholic liver disease, fibrosis, cirrhosis, and recent or active hepatitis (inflammation of the liver)
- if you have severe kidney problems, including conditions requiring kidney dialysis
- if you have any serious blood disorders including serious cases of anaemia or abnormal counts of blood cells such as a reduction in white cell count (leucopenia) or platelet number (thrombocytopenia)
- if you have a medical condition or are receiving medication which lowers your resistance to infection
- if you have symptoms which may suggest an active infectious disease (e.g. fever, chills, achiness)
- if you have an ulcer in your mouth or if you have been told by your doctor that you have an ulcer in your gut
- if you have a condition that stops your immune system working as well as it should
- if you have or are due to be given a vaccine recently.
- inflammation of mouth or lips
- are taking antibiotics which prevent the production of folic acid (vitamin B9) such as co-trimoxazole, which are used to treat bacterial infections.

Even though some of the above may be obvious, it is important that your doctor is aware if any of them apply to you.

Warnings and precautions

Important warning about the dose of Methotrexate 2.5 mg Tablets (methotrexate):

Take Methotrexate 2.5 mg Tablets **only once a week** for the treatment of rheumatic or skin diseases (RA, JIA and psoriasis or psoriatic arthritis).

Taking too much of Methotrexate 2.5 mg Tablets (methotrexate) 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.

Talk to your doctor, pharmacist or nurse before taking Methotrexate 2.5 mg Tablets if you:

- have any mild or moderate kidney problems,
- have or have ever had liver damage, dependence on alcohol or abnormal liver function tests
- have any blood disorders or anaemia
- have stomach ulcers or suffer from inflammation and ulceration of the gut
- have severe mouth ulcers

- have gastro-intestinal (digestive) problems
- have problems with your lungs
- have diarrhoea or severe vomiting
- are weak or infirm or have ever suffered from mental illness
- have excess fluid between the lungs and chest wall (pleural effusion) causing breathlessness or in the abdomen causing swelling of the stomach (ascites). These may affect the levels of methotrexate in your blood
- are receiving or intend to receive any vaccine, as methotrexate can reduce their effect
- have diabetes mellitus and taking insulin
- are an elderly patient
- are having radiotherapy (due to the risk of skin and bone damage) or UV radiation
- are or regularly suffer from dehydration
- have any symptoms or signs of infection
- have any long-term infections such as tuberculosis, hepatitis B or C, shingles (herpes zoster)
- 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).

Methotrexate temporarily affects sperm and egg production. Methotrexate can cause miscarriage and severe birth defects. You 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 if you are a woman. If you are a man you should avoid fathering a child if you are being given methotrexate at the time and for at least 3 months after the end of your treatment. See also section “Pregnancy, breast-feeding and fertility”.

Special care is also needed in children, the elderly and in those who are in poor physical condition.

You should avoid solariums and direct sun light during treatment. Methotrexate may make your skin more sensitive to sunlight. Avoid intense sun and do not use sun-beds or a sun-lamp without medical advice. To protect your skin from intense sun, wear adequate clothing or use a sunscreen with a high protection factor.

Even if methotrexate is administered at low dosage, severe side effects can occur. In order to diagnose them early, **regular monitoring by the doctor at short-term intervals is necessary.**

Before treatment is started your doctor may carry out blood tests and also to check how well your kidneys and liver are working. You may also have a chest X-ray. Further tests may also be done during and after treatment. Do not miss appointments for blood tests.

If the results of any of these tests are abnormal, treatment will only be resumed when all readings are back to normal.

Other medicines and Methotrexate 2.5 mg Tablets

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription and herbal or natural medicinal products. Remember to tell your doctor about your treatment with Methotrexate 2.5 mg Tablets, if you are prescribed other medicine while the treatment is still ongoing.

It is especially important to tell your doctor if you are taking or have recently taken:

- metamizole (synonyms novaminsulfon and dipyrone) (medicine against severe pain and /or fever)
- NSAIDs (non-steroidal anti-inflammatory drugs) e.g. ibuprofen or indomethacin,(for relief of pain or inflammation)
- aspirin or similar medicines (known as salicylates)
- diuretics (water pills)
- diphenylhydantoin, phenytoin (for seizures)
- antibiotics including penicillins, ciprofloxacin, sulphonamides, tetracyclines, chloramphenicol, co-trimoxazole, trimethoprim / sulfamethoxazole,
- thiazides (a group of diuretics used for the treatment of fluid retention e.g. bendroflumethiazide)
- p-aminobenzoic acid, retinoids e.g. acitretin (for psoriasis or skin disorders)
- other treatments for rheumatoid arthritis or psoriasis such as leflunomide or azathioprine (used for suppression of inflammatory conditions) or ciclosporin, aspirin, phenylbutazone or amidopyrine
- sulphasalazine (for inflammation of the bowel)
- cisplatin or mercaptopurine (used for cancer)
- cyclosporine (used in organ transplantation).
- probenecid, sulfinpyrazone (for gout)
- omeprazole, pantoprazole (for stomach ulcers, heartburn, reflux)
- theophylline (for asthma)
- anti-folate drugs (e.g. trimethoprim/sulfamethoxazole)
- vitamin preparations containing folic acid or its derivatives
- alcohol (should be avoided)
- live vaccinations
- barbiturates (sleeping injection)
- tranquillisers
- oral contraceptives
- pyrimethamine (used to prevent and treat malaria)
- nitrous oxide (a gas used as an anaesthetic)
- levetiracetam (a medicine used to treat seizures in epilepsy)
- loop diuretics (used to treat hypertension and oedema)
- hypoglycaemic tablets (used to treat diabetes).
- radiotherapy

Methotrexate 2.5 mg Tablets with food, drink and alcohol

You should not drink alcohol whilst you are taking this medicine as it increases the risk of liver damage. You should also avoid drinking too much coffee containing beverages while taking this medicine. Also make sure you drink plenty of liquids during treatment with Methotrexate 2.5 mg Tablets because dehydration (reduction in body water) can increase the risk of side effects.

Pregnancy, breast feeding and fertility

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

Pregnancy

Do not use Methotrexate 2.5 mg 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 use Methotrexate 2.5 mg Tablets if you are trying to become pregnant. 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. 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.

It may also affect women's periods; they may become less frequent or stop completely.

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.

Breast-feeding

Methotrexate 2.5 mg Tablets should not be used during breast-feeding. Methotrexate passes into breast milk. Breast-feeding should be stopped prior to and during treatment with Methotrexate 2.5 mg Tablets.

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 3 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").

Driving and using machines

Methotrexate 2.5 mg Tablets may make you feel tired, dizzy, loss of co-ordination or may give you blurred vision. You should not drive or use machines when you first start to take this medicine until you are certain that you are not getting these side effects. If in any doubt, speak to your doctor before you drive or use machines.

Methotrexate 2.5 mg Tablets contain lactose

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

Information on Sodium content

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

3. How to take Methotrexate 2.5 mg Tablets

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Do not take more tablets than your doctor has told you to. It will not make you better any faster and it may harm you.

ADULTS

Important warning about the dose of Methotrexate 2.5 mg Tablets (methotrexate):

Use Methotrexate 2.5 mg Tablets only once a week for the treatment of rheumatoid arthritis, psoriasis etc. Using too much of Methotrexate 2.5 mg Tablets (methotrexate) 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.

Dose in psoriasis

Take Methotrexate 2.5 mg Tablets only once a week.

The recommended dose is between 10 and 25 mg taken once a week on the same day each week. Take Methotrexate 2.5 mg tablets once a week.

Dose in rheumatoid arthritis

Take Methotrexate 2.5 mg Tablets only once a week.

The recommended dose is between 7.5 and 20 mg taken once a week on the same day each week. These doses may alter as your condition changes. Take Methotrexate 2.5 mg tablets once a week.

- daily administration can lead to serious toxic effects, including death.

Patients with cancer

Your doctor will decide the dose depending on your condition. Methotrexate may be the only drug given or it may be given with other drugs.

Your doctor will want to monitor your progress, usually every 1-2 months, whilst you are receiving Methotrexate 2.5 mg Tablets.

Before, during and after your treatment you may have tests, such as a chest X-ray, physical examination and blood tests to check that your liver and kidneys are working properly.

Do not miss your appointments as these are necessary to ensure that Methotrexate 2.5 mg Tablets are used safely.

Your doctor may give you additional medication to help make sure that methotrexate does not collect in the kidneys.

Use in children

Patients with Cancer

Your doctor will decide the most appropriate dose depending on your condition.

Methotrexate 2.5 mg Tablets should be used in children for any other indication.

Blood monitoring should be done for all patients treated with methotrexate.

Close monitoring of the blood levels should be done including the complete blood counts, urine tests and in some cases blood methotrexate monitoring along with liver and kidney function tests to detect any problems.

If you take more Methotrexate 2.5 mg Tablets than you should

If you have taken more Methotrexate 2.5 mg Tablets than the doctor has told you to, you should get medical help immediately either by calling your doctor or by going to the nearest hospital casualty department. Always take the labelled medicine container with you, whether there are any Methotrexate 2.5 mg Tablets left or not.

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.

The antidote in case of an overdose is calcium folinate.

If you forget to take Methotrexate 2.5 mg Tablets

Take it 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 2.5 mg Tablets

Do not stop taking Methotrexate 2.5 mg Tablets unless your doctor tells you to. Should you need to stop taking Methotrexate Tablets, your doctor will have decided which is the best method for you.

If you have any further questions on the use of this medicine ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine 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.

Serious side effects

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 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.
- serious illness with blistering of the skin, mouth, eyes and genitals. These could be signs of a condition known as Steven Johnsons Syndrome. Your doctor will stop your treatment in these cases.
- severe peeling or blistering of the skin. These could be signs of a condition known as Toxic Epidermal Necrolysis
- lung complaints (symptoms may be general illness; dry, irritating cough; shortness of breath, breathlessness at rest, chest pain or fever); methotrexate can cause diseases of the lungs e.g. fluid in lungs.
- skin rash and fever with swollen glands, particularly in the first two months of treatment, as these may be signs of a hypersensitivity reaction.
- symptoms of altered mental state, inability to concentrate, drowsiness, headaches and tremors. These could be signs of a condition known as encephalopathy
- a serious infection affecting the whole body (sepsis) characterized by fever, chills, rapid breathing and low blood pressure
- symptoms of shortness of breath, weakness, light headedness and cough. These could be signs of a condition known as cardiac tamponade
- symptoms of chest pains after regular activity such as eating, exercise. This could be signs of heart disease
- symptoms of fever, headache and neck stiffness. These could be signs of a condition known as aseptic meningitis
- unusual bleeding (including vomiting blood) or bruising
- severe diarrhoea

- inflammation and ulcers in the mouth, gut and throat
- black or tarry stools
- blood in the urine or stools
- signs of infection, such as fever, chills and feeling ill; methotrexate can make you more likely to catch infections.

- yellowing of the skin (jaundice)
 - pain or difficulty in passing urine
 - thirst and/or frequent urination due to raised blood sugar level (diabetes)
 - fits (convulsions)
 - loss of consciousness
 - if you have a miscarriage or if you believe there may be damage to your unborn child
 - spitting or coughing blood*.
- *(has been reported for methotrexate used in patients with underlying rheumatologic disease).

The following side effects have also been reported:

Very Common: may affect more than 1 in 10 people

- indigestion
- loss of appetite
- nausea (feeling sick), vomiting (being sick)
- stomach pain and soreness of the mouth, throat and lips
- increase in liver enzymes (can be detected by a test carried out by a doctor)
- mouth ulcers
- swelling of your mouth.

Common: may affect up to 1 in 10 people

- a reduction in white blood cells that makes infections more likely
- a reduction in red blood cells which can make the skin pale and cause weakness or breathlessness
- a reduction in cells that clot blood
- headache
- dizziness
- fatigue
- loose stools
- a skin rash with reddening of the skin
- hair loss.

Uncommon: may affect up to 1 in 100 people

- lung damage/scarred
- a lump in your neck, groin or armpits with associated backache, weight loss or night sweats
- decrease in the number of blood cells
- severe reduction in number of white blood cells which makes infections more likely
- confusion
- unusual sensations in the head (vertigo)

- pale skin, weakness, tiredness or difficulties in breathing
- unusual bleeding or bruising
- nose bleed
- itching
- hives on your arms and legs
- sunburn-like reactions due to increased sensitivity of the skin to sunlight
- skin discolouration
- symptoms of back pain, loss of height over time, stooped posture or broken bones that have occurred too easily. This could be a sign of osteoporosis
- muscle pain
- joint pain
- vaginal ulcers or inflammation
- kidney damage
- swelling around your bladder.
- ulcers in urinary bladder
- inflamed blood vessels

Rare: may affect up to 1 in 1,000 people

- liver damage (seen as yellowing of the skin and whites of the eye)
- herpes zoster (shingles) which is a viral disease characterized by a painful skin rash with blisters
- feeling of fullness or pressure in the chest or abdomen, difficulty in breathing or eating, an enlarged lump or swelling under the skin in the neck or collarbone or groin or armpit, weight loss, anemia or a lack of red blood cells, fever, cough, weakness, fatigue, excessive sweating, night sweats, nausea and vomiting (Lymphoproliferative disorders)
- if you are told by your doctor that you have some issues with your red blood cells
- decreased absorption from intestines
- Impaired vision
- depression
- inability to move one half of the body
- fall in blood pressure
- tenderness and swelling of the lower extremities (clot in the veins)
- swelling of the gums
- acne
- appearance of lightened patches on the skin
- skin ulcers and painful erosions of inflamed areas, in psoriasis patients
- small bruises on the skin caused by blood leaking from broken blood vessels
- an increase in rheumatic nodules
- lowered or absence of urine
- if you have too much urea in your urine (your doctor will inform you)
- loss of interest in, or inability to have sex
- lowered sperm count
- menstrual disorders.

Very Rare: may affect up to 1 in 10,000 people

- reduction in red blood cells which can make the skin pale yellow and cause weakness or breathlessness
- severe reduction in blood cells which can cause weakness, bruising or make infections more likely
- liver failure
- swelling of your lymph nodes around the throat and neck
- altered level of blood cells in your body (your doctor will inform you)
- abnormal red blood cell function
- suppressing your immune system, making you more likely to pick up infections
- difficulty sleeping (insomnia)
- irritation
- difficulty with speech
- weakness
- tingling and numbness in your arms or legs
- blurred vision
- eye infection
- chest pain or tightness of chest, with difficulty in breathing
- lung infection (Pneumonia)
- vomiting blood
- dry cough
- abdominal pain, feeling bloated or abdominal tenderness
- boils
- dilatation of small blood vessels causing focal red lesions
- elevation of urea and/or creatinine in the blood
- infertility
- enlargement of breasts
- vaginal bleeding
- fever
- delayed healing of cuts and bruises
- sudden nail infections, fungal infections
- lymphoproliferative disorders (excessive growth of white blood cells).
- change in sense of taste

Not known: frequency cannot be estimated from the available data

- build-up of fluid or excess fluid in the double layer around the heart
- increased likelihood of getting infections
- internal bleeding
- issues with the shape of your blood cells (your doctor will inform you)
- issues with your metabolism
- eye irritation
- fluid buildup in your lungs
- serious liver damage
- absence of menstruation
- tiredness
- chills
- general feeling of illness

- bone damage in the jaw (secondary to excessive growth of white blood cells)
- bleeding from the lungs*
- swelling
- severe skin reaction
- redness and shedding of skin
- bacterial infection of hand and feet
- changes in skin and nail colouration
- raised liver enzymes
- mood alteration
- inability to move
- asthma
- loss of coordination
- ringing in the ears
- drowsiness
- damaged skin becomes inflamed on re-exposure to radiation and sunlight
- slow thought process
- The need to pass urine more often than usual

*(has been reported for methotrexate used in patients with underlying rheumatologic disease).
In a small number of patients methotrexate may cause serious side effects and on rare occasions, death.

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 HPRA Pharmacovigilance
Website: www.hpra.ie

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

5. How to store Methotrexate 2.5 mg Tablets

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after “EXP”.

The expiry date refers to the last day of that month.

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

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 2.5 mg Tablets contain

- The active substance is methotrexate. Each tablet contains Methotrexate sodium equivalent to 2.5 mg methotrexate
- The other ingredients are lactose monohydrate, sodium hydroxide, magnesium stearate, and starch, pregelatinised.

What Methotrexate 2.5 mg Tablets looks like and contents of the pack

Methotrexate 2.5 mg Tablets are round, biconvex, yellow tablets, engraved with “2,5” on one side. They are scored in half on the other side with “M” engraved above the line and “1” below. They are supplied in PVC/aluminium blister packs containing 28 or 30 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder:

Amdipharm Limited,
Unit 17
Northwood House
Northwood Crescent
Northwood
Dublin 9
D09 V504
Ireland

Manufacturer

Haupt Pharma Amareg GmbH, Donaustauer Str. 378, 93055 Regensburg Germany

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