Package leaflet: Information for the user

Methotrexate 10 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, 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 is and what it is used for
2. What you need to know before you take Methotrexate
3. How to take Methotrexate
4. Possible side effects
5. How to store Methotrexate
6. Contents of the pack and other information

1. What Methotrexate is and what it is 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 in adult patients
- severe resistant disabling psoriasis, which is not adequately responsive to other forms of therapy such as phototherapy, PUVA, and retinoids
- severe psoriatic arthritis in adult patients.

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

Do not take Methotrexate if:
- you have significant liver disease (your doctor decides the severity of your disease)
- you have significant kidney disease (your doctor decides the severity of your disease)
- you have or have had a bone marrow disease or serious blood disorders
- you are allergic to methotrexate or any of the other ingredients of this medicine (listed in section 6)
- you are pregnant or breast-feeding (see also section “Pregnancy, breast-feeding and fertility”)
- you have an impaired immune system
- you have severe acute or existing infections e.g tuberculosis or HIV
- your alcohol consumption is high
- you have inflammation or ulcers in your mouth
- you have active phase gastrointestinal ulcers (e.g. peptic ulcer or ulcerative colitis)
- During methotrexate therapy concurrent vaccination with live vaccines must not be carried out.

Warnings and precautions

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

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.

Please tell your doctor or pharmacist if any of the following conditions concern or have concerned you:
- Diabetes mellitus treated with insulin
- You have received any vaccinations recently or are you due to have any
- You are using any other medicines or vitamin products (Please see section "Other medicines and Methotrexate")
- You have inactive, prolonged infections (e.g. tuberculosis, hepatitis B or C, shingles [herpes zoster])
- You have had ulcerations in your stomach or bowel (peptic ulcer or ulcerative colitis)
- You are in poor general condition
- You have or have had any liver or kidney disease
- You have problems with lung function
- You are severely overweight
- You have abnormal accumulation of liquid in the abdomen or in the cavity between the lungs and chest wall (ascites, pleural effusions)
- You are dehydrated or suffer from conditions leading to dehydration (e.g. dehydration as a result of vomiting, diarrhoea or inflammation of the mouth and lips).

If you have experienced problems with your skin after radiation therapy (radiation induced dermatitis) or sun-burn, these conditions can reappear when taking methotrexate.

Diarrhoea can be a possible side effect of Methotrexate and requires an interruption of therapy. If you suffer from diarrhoea please speak to your doctor.

Special precautionary measures for treatment with Methotrexate
Methotrexate temporarily affects sperm and egg production, which is reversible in most cases. Methotrexate can cause miscarriage and severe birth defects. You must avoid becoming pregnant when using methotrexate and for at least six months after treatment has stopped. See also section "Pregnancy, breast-feeding and fertility".

Skin changes caused by psoriasis can worsen during treatment with methotrexate if exposed to ultraviolet irradiation.

Before the start of treatment and recommended follow-up examinations and precautions
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.

Even when methotrexate is used at low doses, serious side effects can occur. Your doctor will carry out blood and urine tests to make sure that any side effects are identified quickly.

Brain disease (encephalopathy/leukoencephalopathy) has been reported as a side effect in patients receiving methotrexate for treating cancer; it cannot be excluded that this may also happen when you take Methotrexate tablets for the treatment of rheumatoid arthritis or psoriasis.

Other medicines and Methotrexate

Other concomitant medication may affect the efficacy and safety of this medicine. Methotrexate may also affect the efficacy and safety of other medications.

Please 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, if you are prescribed another medicine while the treatment is still ongoing. It is especially important to tell your doctor if you are using:

- certain antibiotics (such as penicillins, glycopeptides, ciprofloxacin, cefalotin, sulfonamides, trimethoprim/sulfamethoxazole, tetracycline and chloramphenicol)
- agents that may be harmful to kidneys and liver (e.g. sulfasalazine and leflunomide [medicines for rheumatic diseases], alcohol)
- anticancer agents (e.g. doxorubicin, cisplatin, mercaptopurine)
- anticonvulsant medicines such as phenytoin or levetiracetam (medicine often used to treat epilepsy)
- a medicine that binds bile acid and can be used e.g. to lower cholesterol levels (cholestyramine)
- medicines against pain and/or inflammation known as non-steroidal anti-inflammatory medicines (e.g. diclofenac and ibuprofen, salicylates like acetylsalicylic acid (aspirin) and pyrazoles like metamizole)
- omeprazole or pantoprazole (medicine used to stop the production of stomach acid)
- diuretics, triamterene (water tablets)
- medicines for lowering blood sugar levels such as metformin
- probenecid (medicine used to treat gout)
- theophylline (medicine used to treat respiratory diseases)
- cyclosporine (an agent that can suppress or prevent the immune response)
- barbiturates (sleeping injection)
- tranquillisers
- oral contraceptives
- other treatments for rheumatoid arthritis or psoriasis such as azathioprine, leflunomide, sulphasalazine (a medicine that besides arthritis and psoriasis is also used to treat and ulcerative colitis), phenylbutazone, or amidopyrine
- retinoids (used to treat psoriasis and other skin disorders)
- pyrimethamine (which is used to prevent and treat malaria)
- vitamin preparations containing folic acid
- any vaccination with a live vaccine (must be avoided), such as measles, mumps, influenza or yellow fever vaccines.

Tell your physician about use of Methotrexate during your next visits.

Methotrexate with food, drink and alcohol

Alcohol should be avoided during methotrexate therapy and you should avoid excessive consumption of coffee, soft drinks containing caffeine and black tea as this may enhance side effects or interfere with the efficacy of methotrexate. Also, make sure you drink plenty of liquids during treatment with methotrexate because dehydration (reduction in body water) can increase the toxicity of methotrexate.

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 for advice before taking this medicine.

<u>Pregnancy</u>

Do **not** use Methotrexate during pregnancy or if you are trying to become pregnant. Methotrexate can cause birth defects, harm the unborn child or cause miscarriages. It is associated with malformations of the skull, face, heart and blood vessels, brain and limbs. Therefore, it is very important that Methotrexate is not given to pregnant patients or patients planning to become pregnant. In women of child-bearing age any possibility of pregnancy must be excluded with appropriate measures, e.g. a pregnancy test before starting treatment. You must avoid becoming pregnant whilst taking methotrexate and for at least 6 months after treatment is stopped by using reliable contraception throughout this time (see also section "Warnings and precautions").

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

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

Breast-feeding

Do not breast-feed during treatment, because methotrexate passes into breast milk. If your attending doctor considers treatment with methotrexate absolutely necessary during the lactation period, you must stop breast-feeding.

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. Methotrexate may be genotoxic. This means that the medicine may cause genetic mutation. Methotrexate can affect sperm with the potential to cause birth defects. Therefore, you should avoid fathering a child or to donate semen whilst taking methotrexate and for at least **6** months after treatment is stopped.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

You can feel fatigue and dizziness during Methotrexate treatment. Do not drive or use machines if you have such symptoms.

Methotrexate contains lactose

These tablets contain 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.

3. How to take Methotrexate

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

- Patients with rheumatoid arthritis, psoriasis or psoriatic arthritis take their tablets orally **once a week** on the same day each week.
- Do not take tablets more often than your doctor has told you to.
- **Daily administration can lead to serious toxic effects, including death.**
- Take the tablets with a glass of water whilst sitting upright or standing.

Recommended dose:

Dose in rheumatoid arthritis, psoriasis and severe psoriatic arthritis:
Take Methotrexate only once a week.
The recommended dose is 7.5-15 mg **orally**, **once weekly**.
This should be adjusted according to your response to treatment and side effects.
Proper procedures for safe handling of cytotoxic agents should be administered. Anyone handling methotrexate should wash their hands after administering a dose. Disposable gloves should be used when handling methotrexate tablets. Women who are pregnant, planning to be or breast-feeding should not handle methotrexate.

If you take more Methotrexate than you should

If you take (or someone else has taken) more of the medicine than you should, a physician or nearest hospital casualty department must be contacted immediately.

An overdose of methotrexate can lead to severe toxic reactions, including death. 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. See also section 4.

Take your medicine package with you if you go to a doctor or hospital.

If you forget to take Methotrexate

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 a forgotten dose.

Make sure before your holiday or trip that you have enough of your medicine.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. In general, the incidence and severity of adverse reactions of methotrexate are related to dose and frequency of administration. Most adverse reactions are reversible if detected early.

Serious side effects
Contact your doctor or hospital emergency department immediately if you have any of the following symptoms:

- A cough producing a thick mucus, difficulty breathing, fever or shortness of breath. You may be suffering from pneumonitis, pulmonary fibrosis or pneumonia. (**Uncommon**: may affect up to 1 in 100 people)
- Spitting or coughing blood
- Tightness in your chest, difficulty breathing, swelling of the face, throat or hands, feeling dizzy or faint. These could be signs of a severe allergic reaction. (**Uncommon**: may affect up to 1 in 100 people)
- Severe skin reactions, including peeling and blistering of the skin, mouth, eyes and genitals and numerous pus filled spots with a fever. You could be suffering from Stevens-Johnson syndrome or toxic epidermal necrolysis. (**Uncommon**: may affect up to 1 in 100 people)
- Fever and deterioration of your general condition, or fever with local infections such as in the throat or mouth. You may have a reduced number of white blood cells (possibly due to bone marrow depression) and your resistance to infection may be decreased. (**Uncommon**: may affect up to 1 in 100 people)

- Loss of appetite, nausea, itchy skin, yellowing of the skin or eyes, fever, swollen or tender stomach. You may be suffering from inflammation or damage of the liver. (**Rare** : may affect up to 1 in 1,000 people)
- Vomiting blood, passing black tar-like stools and pain in the stomach. You may have a stomach ulcer or bleeding. (**Rare**: may affect up to 1 in 1,000 people)
- Cramping pain, heavy ache or swelling in the leg, redness, breathlessness, chest pain or sudden collapse. You may have a blood clot. (**Rare**: may affect up to 1 in 1,000 people)
- Blood in the urine (**Very rare**: may affect up to 1 in 10,000 people), pain or difficulties in passing urine (**Uncommon**: may affect up to 1 in 100 people), reduction or lack of urine production (**Rare**: may affect up to 1 in 1,000 people). You may be suffering from kidney damage (**Uncommon**: may affect up to 1 in 100 people).
- A high temperature, chills and shivering, a fast heartbeat, rapid breathing, confusion or dizziness. You may have sepsis as the result of an infection. (**Rare**: may affect up to 1 in 1,000 people)
- Difficulty of speaking or communicating. (**Very rare**: may affect up to 1 in 10,000 people)
- Convulsions (**Very rare**: may affect up to 1 in 10,000 people) or certain brain disorders (encephalopathy/leucoencephalopathy) (**Not known**: frequency cannot be estimated from the available data).

Other side effects

Very common side effects (may affect more than 1 in 10 people):
Inflammation of throat or sore mouth and lips, dyspepsia, loss of appetite, nausea, vomiting, stomach pain, an increase in liver enzymes.

Common side effects (may affect up to 1 in 10 people):
Infections, diarrhoea, exhaustion, tiredness, headache, dizziness, drowsiness, exanthema, rash or large red spots on the skin, hair loss, mouth ulcers.

Uncommon side effects (may affect up to 1 in 100 people):
Vertigo, reduced blood clotting, changes to your blood count, anaemia, decrease in serum albumin levels, fatty liver, itching, herpes-like eruptions of the skin, increased pigmentation of skin, osteoporosis, pain in joints or muscles, appearance of local tissue lumps, ulcers of the bladder, vaginal inflammation and ulcers, swelling of the lymph nodes (may be a sign of a cancer of the lymphatic system [lymphoma]), chills.

Rare side effects (may affect up to 1 in 1,000 people)**:**
A blood disorder characterised by the appearance of very large red blood cells (megaloblastic anaemia), depression, confusion, mood fluctuations, weakness in movements, also only limited to the left or right side of the body, diabetes, low blood pressure, inflammation of the heart sac, accumulation of fluid in the heart sac, shortness of breath, stopping breathing, inflamed gums, inflammation of the small intestine, bloody stools, sore throat, acne, whitening of the skin, raised itchy rash, sensitivity to light, burning in psoriatic lesions on the skin, skin ulcers, shingles or painful skin rash, detachment of the nail, darkened areas on the nails, red or purple spots due to bleeding from blood vessels, allergic inflammation of blood vessels, skin lesions resembling sunburn or dermatitis after radiotherapy, stress bone fracture, abnormal levels of electrolytes in blood, menstrual disorders, difficulty having an erection, reduced sex drive, physical weakness, fever, slow wound healing.

Very rare side effects (may affect up to 1 in 10,000 people):
Serious disorders of bone marrow, increased susceptibility to infections, lymphoproliferative disorders (excessive growth of white blood cells), insomnia, psychoses, reduced levels of antibodies, feeling irritable, lack of energy, mild temporary problems in intellectual functions (“brain fog”), having unusual sensations in the head, brain swelling, ringing in ears, pain, muscle weakness, pins and needles, changes in sense of taste (metallic taste), inflammation of the lining of the brain, paralysis, blurred vision, eye infection, inflammation of the linings around the lungs, accumulation of fluid around the lungs, liver failure, inflammation of blood vessels, chronic obstructive lung disease, dry

cough, vomiting of blood, boils, blood like bruises or small blood vessels on the surface of the skin, inflammation of sweat glands, fingernail infections, fertility problems, low sperm count, infertility, vaginal bleeding or discharge, enlargement of male breast tissue, sensation of numbness or tingling / having less sensitivity to stimulation than normal.

The following have also been reported but the frequency is not known:
Abnormally low number of blood cells, sepsis resulting in death, reactivation of inactive chronic infection, impaired vision, damage to the retina of the eye, enlargement of colon associated with inflammation/infection, pancreatitis, bone damage in the jaw (secondary to excessive growth of white blood cells), pathological change of the white matter of the brain (leukoencephalopathy), nosebleed, redness and shedding of skin, asthma, presence of protein in urine, miscarriage, foetal damages, swelling, increased risk of toxic reactions during radiotherapy, increase in the number of white blood cells, inflammation of the lung tissue, bleeding from the lungs. Scaly, red skin patches associated with psoriasis may get worse when exposed to sources of ultraviolet light, such as the sun, and taking Methotrexate.

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 the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Methotrexate

Keep this medicine out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

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

Keep the tablet container in the outer carton, in order to protect from light.

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

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 contains

- The active substance is methotrexate, each tablet contains 10 mg.
- The other ingredients are: Lactose monohydrate, maize starch, starch, pregelatinised (potato starch), polysorbate 80, cellulose, microcrystalline and magnesium stearate.

What Methotrexate looks like and contents of the pack

Tablet: Yellow, convex, capsule-shaped, scored and engraved with M 10 on one side, length 8 mm, breadth 4.5 mm. The tablet can be divided into equal halves.

Pack sizes 10, 16, 24, 25, 30 and 100 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

To be completed nationally

Manufacturer

Orion Corporation Orion Pharma
Orionintie 1
FI-02200 Espoo
Finland

This medicinal product is authorised in the Member States of the EEA under the following names:

Czech Republic Hungary Latvia Poland Slovakia	Trexan
Lithuania	Methotrexate Orion
Ireland UK	Methotrexate
France	Imeth

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