Package leaflet: Information for the user

Methotrexate Orion 2.5 and 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 Orion is and what it is used for
2. What you need to know before you take Methotrexate Orion
3. How to take Methotrexate Orion
4. Possible side effects
5. How to store Methotrexate Orion
6. Contents of the pack and other information

1. What Methotrexate Orion is and what it is used for

The active substance of Methotrexate Orion tablets, methotrexate, is a substance with the following properties:
- it suppresses the growth of certain cells in the body that reproduce quickly
- it reduces the activity of the immune system (the body's own defence mechanism).

Methotrexate is used to treat:
- active rheumatoid arthritis in adult patients
- severe recalcitrant disabling psoriasis,which is not adequately responsive to other forms of therapy such as phototherapy, PUVA and retinoids in adult patients
- severe psoriatic arthritis in adult patients
- maintenance treatment of acute lymphoblastic leukaemia (ALL) in adults, adolescents and children aged 3 years and over.

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

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

Do not take Methotrexate Orion:

- if you are allergic (hypersensitive) 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")
- if you have severe liver or kidney disease (your doctor decides the severity of your disease)
- if you have or have had a bone marrow disease or serious blood disorders
- if you have severe acute or chronic infections or immunodeficiency syndrome
- if you have an inflammation of the mucous membrane of the mouth or mouth ulcers
- if you have ulcers in the stomach or in the intestines
- if you suffer from alcoholism

- if you have had a live vaccine recently or are about to have one.

Warnings and precautions

Important warning about the dose of **Methotrexate Orion (**methotrexate):
Take Methotrexate Orion **only once a week** for the treatment of rheumatoid arthritis, psoriasis or psoriatic arthritis.
Taking too much of Methotrexate Orion (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 Orion:
- if you have ever had any liver or kidney disease
- if you are suffering from inactive, chronic infections (e.g. tuberculosis, hepatitis B or C, shingles [herpes zoster]) as they may flare up
- if you are in poor general condition
- if you have problems with your lung function
- if you are particularly overweight
- if you have an abnormal build-up of fluid in the abdomen (ascites) or around the lungs (pleural effusions)
- if you have diabetes mellitus treated with insulin
- if you are dehydrated or suffer from conditions that result in dehydration (vomiting, diarrhoea, constipation, inflammation of the mucous membrane of the mouth).

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.

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

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 section “Pregnancy, breast-feeding and fertility”.

Radiotherapy during use of Methotrexate Orion can increase the risk of soft tissue or bone necrosis. If you had skin problems after radiotherapy (radiation dermatitis) or sunburn, these reactions can recur during methotrexate therapy (recall reactions). Psoriasis skin changes can become worse during treatment with methotrexate if you are under UV light.

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.

Enlarged lymph nodes (lymphoma) may occur in patients receiving low dose methotrexate and if this is the case, therapy must be stopped.

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).

Certain other brain disorders (encephalopathy/leukoencephalopathy) have been reported in cancer patients receiving methotrexate. Such side effects cannot be excluded when methotrexate is used to treat other diseases.

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.

Children, adolescents and elderly

Children, adolescents and the elderly 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.
Use in children below 3 years of age is not recommended due to the insufficient experience in this age group.

Other medicines and Methotrexate Orion

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

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Remember to tell your doctor about your treatment with Methotrexate Orion, if you are prescribed another medicine while the treatment is still ongoing. It is especially important to tell your doctor if you are taking:
- metamizole (synonyms novaminsulfon and dipyrone) (medicine against severe pain and /or fever)
- antibiotics (medicines to prevent/fight certain infections) such as penicillins, sulfonamides, ciprofloxacin, cefalotin, trimethoprim/sulfamethoxazole, tetracycline and chloramphenicol. E.g. penicillins such as amoxicillin may reduce the excretion of methotrexate causing a potential increase in side effects
- other medicines used to treat rheumatoid arthritis such as leflunomide, sulfasalazine and azathioprine
- some medicines against pain and/or inflammation known as non-steroidal anti-inflammatory medicines (e.g. ibuprofen, diclofenac, salicylates like acetylsalicylic acid)
- pyrimethamine (for the prevention and treatment of malaria)
- anticancer agents (e.g. mercaptopurine, 5-fluorouracil, doxorubicin and procarbazine)

- antiepileptic medicines (prevention of seizures)
- omeprazole or pantoprazole (medicines used to stop the production of stomach acid)
- diuretics (water tablets)
- medicines for lowering blood sugar levels such as metformin
- cholestyramine (medicine that binds bile acid and can be used e.g. to lower cholesterol levels)
- cyclosporine (medicine that can suppress or prevent the immune response)
- retinoids (for the treatment of psoriasis and other skin diseases)
- oral contraceptives
- barbiturates (sleeping medicines)
- sedatives
- nitrous oxide (used for general anaesthesia)
- probenecid (medicine used to treat gout)
- theophylline (medicine used to treat respiratory diseases)
- vitamin preparations or other products containing folic acid, folinic acid or their derivatives
- live vaccines.

Methotrexate Orion with food, drink and alcohol

Alcohol as well as large amounts of coffee, caffeine-containing soft drinks and black tea should be avoided during treatment with Methotrexate Orion. Ensure that you drink a lot of fluids during treatment with Methotrexate Orion tablets because dehydration (the reduction of body water) can increase the side effects 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 or pharmacist for advice before taking this medicine.

Pregnancy

Do **not** use Methotrexate Orion during pregnancy except if your doctor has prescribed it for oncology treatment.

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. 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 Orion Pharma 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.

Breast-feeding

Do not breastfeed 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 and there is no information regarding higher methotrexate doses. Methotrexate can have a genotoxic effect. This means that the medicine may cause genetic mutation. 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").

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

Driving and using machines

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

Methotrexate Orion 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 Orion

Always take this medicine 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 must take their tablets orally only **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.

Dosage for rheumatoid arthritis, psoriasis and severe psoriatic arthritis
Take your tablets **once a week** on the same day each week. The usual dose normally is between 7.5 and 15 mg once weekly.

Dosage for maintenance therapy in acute lymphoblastic leukaemia
The doctor will calculate the dosage required from your body surface. Your doctor will decide the correct dose for you. If you want more information you should ask your doctor.

Special populations
Usually reduced dose according to doctor´s prescription is used for elderly patients and for patients with renal or hepatic impairment. See also section 2. "Do not take Methotrexate Orion".

Use in children and adolescents

For children and adolescents with maintenance therapy in acute lymphoblastic leukaemia the doctor will calculate the dose individually, depending on the body surface.

Safe handling of Methotrexate Orion tablets
Proper procedures for safe handling of cytotoxic agents should be administered. Anyone handling methotrexate should wash their hands before and after administering a dose. Disposable gloves should be used when handling methotrexate tablets. Pregnant, planning to be pregnant or breast-feeding women should avoid handling methotrexate tablets, if possible.

Contact with the skin or mucous membrane must be avoided. If methotrexate comes into contact with skin or mucosa, it should be washed immediately and thoroughly with soap and water.

Parents, care givers and patients should be advised to keep methotrexate out of the reach of children, preferably in a locked cupboard.
Accidental ingestion can be lethal for children.

If you take more Methotrexate Orion 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 “Possible side effects”.

Take your medicine package with you if you go to a doctor or hospital. If you used too much methotrexate you will receive calcium folinate to lessen the side effects of methotrexate.

If you forget to take Methotrexate Orion

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.

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

If you stop taking Methotrexate Orion

Do not stop taking Methotrexate Orion unless your doctor tells you to. Should you need to stop taking Methotrexate Orion, your doctor will decide which method is the best 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. 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.

Tell your doctor immediately if you notice any of the following symptoms as these may indicate a serious, potentially life-threatening side effect, which require specific treatment:

- a dry cough and/or pain or difficulty in breathing or shortness of breath, chest pain or fever
- spitting or coughing blood*
- unusual bleeding (including vomiting blood), bruising nose bleeding
- nausea, vomiting, abdominal discomfort or severe diarrhoea
- ulcers in mouth
- black or tarry stools
- serious allergic reaction which causes fever, skin rash, swelling and sometimes a fall in blood pressure
- an extremely intense allergic reaction with skin rashes, commonly in the form of blisters or sores in the oral cavity and eyes, and other mucous membranes such as, for example, genitalia (Stevens-Johnson syndrome, toxic epidermal necrolysis)
- any symptoms of an infection such as fever or a marked worsening in your general state of health or fever with local signs of an infection such as sore throat/inflammation of the throat or mouth or problems passing water, see your doctor immediately. Methotrexate can reduce the number of white blood cells and therefore weaken your immune defences. A blood test will be done to check for reduction in the white blood cells (agranulocytosis).
- yellowing of the skin (jaundice)
- pain or difficulty in passing urine
- thirst and/or frequent urination
- blurred or decreased vision.

Most of the effects listed below will only be seen in patients who are receiving high doses of methotrexate to treat cancer. They are not seen as often and are not as severe at the doses used in the treatment of psoriasis or rheumatoid arthritis.

Very common (may affect more than 1 in 10 people)
- loss of appetite, feeling sick (nausea), vomiting, dyspepsia, stomach pain, stomatitis (soreness of the mouth and lips)
- increase in liver enzyme.

Common (may affect up to 1 in 10 people)
- infections
- reduced blood cell formation with decrease in white and/or red blood cells and/or platelets (leucocytopenia, anaemia, thrombocytopenia)
- headache, dizziness, unusual fatigue, drowsiness,
- infection of the lungs (pneumonia), dry cough
- diarrhoea
- skin rash, skin redness, itchy skin
- alopecia.

Uncommon (may affect up to 1 in 100 people)
- a cancer of the lymph nodes (or tissues)
- diabetes mellitus
- depression, confusion
- convulsions, vertigo
- gastrointestinal ulceration and bleeding
- nosebleeding
- formation of excess fibrous connective tissue in an organ (fibrosis)
- decrease in serum albumin levels
- inflammation of blood vessels, often with skin rash (vasculitis), increased pigmentation of skin, slow wound healing, increase in rheumatic nodules
- sunburn-like reactions due to increased sensitivity of the skin to sunlight
- ulcers and inflamation in the bladder, disturbed urination
- liver damage
- kidney dysfunction
- pain in joint or muscles, decreased bone mineral density a type of bone disease (osteoporosis)
- vaginal inflammation and ulceration
- chills.

Rare (may affect up to 1 in 1 000 people)
- fatal whole-body inflammation (sepsis), herpes zoster
- a blood disorder characterised by the appearance of very large red blood cells (megaloblastic anaemia)
- mood swings
- weakness in movements (also limited to the left or right side of the body only)
- severe visual disturbances
- fluid in the sac around the heart. May cause cardiac tamponade which is a life threatening condition where the heart is unable to pump correctly due to the external pressure. May require medical intervention to drain the fluid and remove the pressure
- hypotension, thromboembolism
- complete or severe weakness of the muscles of respiration, shortness of breath, inflammation of the back of the throat, asthma
- inflamation of the pancreas, inflamed gums
- inflammation of the liver (acute hepatitis)
- skin reactions (acne, skin depigmentation, urticaria, erythema multiforme, burning in skin psoriatic lesions, skin ulcers, red or purple spots due to vessel bleeding), detachment of the nails, darkened areas on the nails
- stress bone fractures
- reduction or lack of urine production, electrolyte disturbances
- menstrual disorders, impotence

Very rare (may affect up to 1 in 10 000 people)
- immune deficiency (hypogammaglobulinaemia), increased susceptibility to infections
- lymphoproliferative disorders (excessive growth of white blood cells)
- insomnia
- brain swelling, difficulty in speaking (dysarthria), irritation, sleepiness, tiredness (lethargy), mild temporary problems in intellectual functions ("brain fog"), having unusual sensations in the head, muscle weakness, sensation of numbness or tingling / having less sensitivity to stimulation than normal, changes in sense of taste (metallic taste)
- redness and irritation of the thin membrane that covers the eye (conjunctivitis), visual impairment, damage to the retina of the eye
- inflammation of blood vessels (vasculitis), vomiting blood
- reactivation of chronic liver inflamation, liver failure
- enlargement of colon associated with inflammation/infection
- infection around a fingernail, deep infection of hair follicles (furunculosis), bruises, acne
- presence of protein or blood in urine, painful urination, bladder inflammation
- low sperm count, enlargement of the breasts in men, vaginal bleeding, loss of libido
- fever.

The following side effects have also been reported but the frequency is not known:

Sepsis resulting in death, abnormally low number of blood cells, bleeding from the lungs*, bone damage in the jaw (secondary to excessive growth of white blood cells), brain desease, pathological change of the white matter of the brain (leukoencephalopathy), alveolitis, physical weakness, increased risk of toxic reactions during radiotherapy, redness and shedding of skin, swelling. Scaly, red skin patches associated with psoriasis may get worse when exposed to sources of ultraviolet light, such as the sun, and taking methotrexate. Problems with skin after radiation therapy (radiation induced dermatitis) or sunburn can reappear when taking methotrexate.

* (has been reported for methotrexate used in patients with underlying rheumatologic disease)

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

United Kingdom

Yellow Card Scheme at:

www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

5. How to store Methotrexate Orion

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 blister or the outer carton. The expiry date refers to the last day of that month.

This medicinal product does not require any special temperature storage conditions. Keep the blisters in the outer carton, in order to protect from light.

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.

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 Orion contains

- The active substance is methotrexate. Each tablet contains 2.5 mg or 10 mg methotrexate (as methotrexate disodium).
- The other ingredients are lactose monohydrate, microcrystalline cellulose and magnesium stearate.

What Methotrexate Orion looks like and contents of the pack

Methotrexate Orion 2.5 mg tablets: Yellow, round, uncoated, flat tablet, scored and engraved with ORN 57 on one side, diameter 6 mm. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Methotrexate Orion 10 mg tablets: Yellow, capsule-shaped, convex, uncoated, tablet, engraved with ORN 59 on one side and score on the other side, length of 14 mm and width of 6 mm. The tablet can be divided into equal doses.

Pack sizes:
Blister pack
2.5 mg: 4, 8, 10, 12, 16, 20, 24, 30, 36, 40, 48, 50, 60, 100 and 120 tablets.

10 mg: 4, 8, 10, 12, 16, 20, 24, 30, 36, 40, 48, 50, 60, 100 and 120 tablets.

Not all pack sizes may be marketed.

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This medicine is authorised in the Member States of the European Economic Area and in the United Kingdom (Northern Ireland) under the following names:

France:	Imenor
Hungary, Ireland, Norway, United Kingdom:	Methotrexate Orion
Iceland, Sweden:	Methotrexate Orion Pharma
Spain:	Metotrexato Semanal Orion Pharma
Denmark, Estonia, Finland, Lithuania:	Trexan
Czech Republic, Poland, Slovakia:	Trexan Neo

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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