Package leaflet: Information for the user

Methotrexate Orion 25 mg/ml solution for injection, pre-filled syringe

methotrexate

Read all of this leaflet carefully before you start using 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 or pharmacist.
- 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. 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

Methotrexate Orion is a substance with the following properties:
- it interferes with 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)
- it has anti-inflammatory effects.

Methotrexate Orion is used for the treatment of:
- active rheumatoid arthritis (RA) in adult patients
- polyarthritic forms (when five or more joints are involved) of severe, active juvenile idiopathic arthritis (JIA) when the response to non-steroidal anti-inflammatory drugs (NSAIDs) has been inadequate
- severe recalcitrant disabling psoriasis, which is not adequately responsive to other forms of therapy such as phototherapy, PUVA, and retinoids, and severe psoriasis arthritis (affecting the joints) in adult patients
- moderate steroid-dependent Crohn's disease in adults, in combination with corticosteroids to induce remission
- maintenance of remission of moderate steroid-dependent Crohn's disease, as monotherapy, in adults who have responded to methotrexate.

Rheumatoid arthritis (RA) is a chronic collagen disease, characterised by inflammation of the synovial membranes (joint membranes). These membranes produce a fluid which acts as a lubricant for many joints. The inflammation causes thickening of the membrane and swelling of the joint.

Juvenile arthritis concerns children and adolescents less than 16 years. Polyarthritic forms are indicated if 5 or more joints are affected within the first 6 months of the disease.

Psoriatic arthritis is a kind of arthritis with psoriatric lesions of the skin and nails, especially at the joints of fingers and toes.

Psoriasis is a common chronic skin disease, characterised by red patches covered by thick, dry, silvery, adherent scales.

Methotrexate Orion modifies and slows down the progression of the disease.

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

Do not use Methotrexate Orion if you:
- are allergic to methotrexate or any of the other ingredients of this medicine (listed in section 6)
- suffer from severe liver or kidney diseases or blood diseases
- regularly drink large amounts of alcohol
- suffer from a severe infection, e.g. tuberculosis, HIV or other immunodeficiency syndromes
- suffer from inflammation of the mucous membrane of the mouth, ulcers in the mouth, stomach ulcer or intestinal ulcer
- are pregnant or breast-feeding (see section "Pregnancy, breast-feeding and fertility")
- receive vaccinations with live vaccines at the same time.

Warnings and precautions

Talk to your doctor or pharmacist before taking Methotrexate Orion if:
- you are elderly or if you feel generally unwell and weak
- your liver or kidney function is impaired
- you have diabetes mellitus you have inactive, prolonged infections (e.g. tuberculosis, hepatitis B or C, shingles [herpes zoster])
- you have problems with lung function
- you are severely overweight
- you have an abnormal build-up of fluid in the abdomen (ascites) or around the lungs (pleural effusions)
- you are dried out (dehydrated) or suffer from conditions leading to dehydration (e.g. dehydration as a result of vomiting, diarrhoea or inflammation of the mucous membrane of the mouth).

Methotrexate may affect your immune system and vaccination results. It may also affect the result of immunological tests. Inactive, chronic infections (e.g. herpes zoster [shingles], tuberculosis, hepatitis B or C) may flare up. During therapy with Methotrexate Orion you must not be vaccinated with live vaccines.

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.

Radiation induced dermatitis and sun-burn can reappear during methotrexate therapy (recall reactions). Psoriatic lesions can exacerbate during UV-irradiation and simultaneous administration of methotrexate.

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.

Enlarged lymph nodes (lymphoma) may occur and therapy must then be stopped.

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

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.

Special precautionary measures for treatment with Methotrexate Orion
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”.

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
Dosage instructions depend on patient´s body weight.
Use in children below 3 years of age is not recommended due to the insufficient experience in this age group.

Children and 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.

Other medicines and Methotrexate Orion
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

The effect of the treatment may be affected if Methotrexate Orion is administered at the same time as certain other medicines:

- metamizole (synonyms novaminsulfon and dipyrone) (medicine against severe pain and /or fever)
- Penicillins (e.g. amoxicillin) and certain antibiotics (glycopeptides, sulfonamides, ciprofloxacin, cefalotin) may reduce the excretion of methotrexate causing a potential increase in side effects
- Other antibiotics (such as trimethoprim/sulfamethoxazole, tetracyclines and chloramphenicol)
- Some medicines against pain and/or inflammation known as non-steroidal anti-inflammatory drugs (e.g. diclofenac and ibuprofen, salicylates like acetylsalicylic acid)
- Probenecid (medicine against gout)
- Diuretics ("water tablets")
- Medicinal products, which may have adverse effects on the bone marrow, e.g. trimethoprim-sulphamethoxazole (an antibiotic) and pyrimethamine
- Other medicines for rheumatoid arthritis or psoriasis, such as leflunomide, azathioprine (also used to prevent rejection after an organ transplant), sulfasalazine (also used for ulcerative colitis), phenylbutazone or amidopyrine
- Antiepileptic medicines (prevention of seizures) such as carbamazepine, phenytoin, phenobarbital, primidone
- Cancer treatments (e.g. 5-fluorouracil, mercaptopurine and doxorubicin and procarbazine during high-dose methotrexate therapy)
- Retinoids (medicine against psoriasis and other dermatological diseases)
- Theophylline (medicine against bronchial asthma and other lung diseases)
- Proton-pump inhibitors (medicines against stomach trouble)
- Hypoglycaemics (medicines that are used to lower the blood sugar)
- Cholestyramine (medicine that binds bile acid and can be used e.g. to lower cholesterol levels)
- Ciclosporine (an agent that can suppress or prevent the immune response)
- Barbiturates (sleeping injection)
- Tranquillisers
- Oral contraceptives
- Nitrous oxide (general anaesthetic).

Vitamins containing folic acid may impair the effect of your treatment and should only be taken when advised by your doctor.

Radiotherapy during use of methotrexate can increase the risk of soft tissue and bone damage.

Vaccination with live vaccine should be avoided.

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 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 or pharmacist for advice before taking this medicine.

<u>Pregnancy</u>
Do not use Methotrexate Orion 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
Breast feeding should be stopped prior to and during treatment with Methotrexate Orion.

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 production with the potential to cause birth defects. Therefore, 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.

Driving and using machines
Treatment with Methotrexate Orion may cause adverse reactions affecting the central nervous system, e.g. tiredness and dizziness. Thus the ability to drive a vehicle and/or to operate machines may, in certain cases, be compromised. If you feel tired or drowsy you should not drive or use machines.

Methotrexate Orion contains sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per pre-filled syringe, i.e. essentially 'sodium-free'.

3. How to use Methotrexate Orion

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.
Your doctor decides on the dosage, which is adjusted individually. It usually takes 4–8 weeks to see effects of methotrexate on rheumatoid arthritis, 2–6 weeks on psoriasis vulgaris and psoriatic arthritis and 8–12 weeks on Crohn's disease.

Important warning about the dose of Methotrexate Orion (methotrexate):
Use Methotrexate Orion **only once a week** for the treatment of rheumatic diseases, psoriasis, psoriatic arthritis and Crohn's disease. Using 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.

Methotrexate Orion is administered by or under the supervision of a physician or healthcare staff as an injection **once a week only**. Together with your doctor you decide on a suitable weekday each week on which you receive your injection. **Incorrect dosing can lead to serious side effects, including death**. Methotrexate Orion may be injected intramuscularly (in a muscle) or subcutaneously (under the skin).

Use in children and adolescents
As there is very little data about giving the medicine intravenously in children and adolescents, it must only be injected under the skin or into a muscle.

The doctor decides on the appropriate dose in children and adolescents with polyarthritic forms of juvenile idiopathic arthritis.
Methotrexate Orion is not recommended in children less than 3 years of age due to insufficient experience in this age group.

Method and duration of administration
Methotrexate Orion is injected **once weekly!**
The duration of the treatment is determined by the treating physician. Treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis vulgaris, psoriatic arthritis and Crohn's disease with Methotrexate Orion is a long-term treatment.

At the start of your treatment, Methotrexate Orion may be injected by medical staff. However, your doctor may decide that you can learn how to inject Methotrexate Orion yourself. You will receive appropriate training for you to do this. Under no circumstances should you attempt to inject yourself, unless you have been trained to do so.

Please refer to the instructions for use at the end of the leaflet.

The manner of handling and disposal must be consistent with that of other cytostatic preparations in accordance with local requirements. Women who are pregnant, planning to be or breast-feeding should not handle and/or administer Methotrexate Orion.

Methotrexate should not come into contact with the surface of the skin or mucosa. In the event of contamination, the affected area must be rinsed immediately with soap and water.

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

If you use more Methotrexate Orion than you should
Do not change the dosage by yourself!
Use Methotrexate Orion according to the doctor's orders or according to the dosage directions stated in this package leaflet. If you use more of this 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. 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 "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 use Methotrexate Orion
Do not take a double dose to make up for forgotten individual doses, but continue taking the ordered dose. Ask your doctor for advice.

If you stop taking Methotrexate Orion
You should not interrupt or discontinue your treatment with Methotrexate Orion, unless you have discussed this with your doctor. If you suspect severe side effects, contact your doctor immediately for advice.

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.

The frequency as well as the degree of severity of the side effects depends on the dosage level and the frequency of administration. As severe side effects may occur even at low dosage, it is important that you are monitored regularly by your doctor. Your doctor will do **tests to check for abnormalities**

developing in the blood (such as low white blood cells, low platelets, lymphoma) and changes in the kidneys and the liver.

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

- **persistent dry, non-productive cough, shortness of breath and fever**; these may be signs of an inflammation of the lungs (pneumonia) [common - may affect up to 1 in 10 people]
- **spitting or coughing blood**, these may be signs of bleeding from the lungs [not known - frequency cannot be estimated from the available data]
- **symptoms of liver damage such as yellowing of the skin and whites of the eyes**; methotrexate can cause chronic liver damage (liver cirrhosis), formation of scar tissue of the liver (liver fibrosis), fatty degeneration of the liver [all uncommon - may affect up to 1 in 100 people], inflammation of the liver (acute hepatitis) [rare - may affect up to 1 in 1 000 people] and liver failure [very rare - may affect up to 1 in 10 000 people]
- **allergy symptoms such as skin rash including red itchy skin, swelling of the hands, feet, ankles, face, lips, mouth or throat (which may cause difficulty in swallowing or breathing) and feeling you are going to faint**; these may be signs of severe allergic reactions or an anaphylactic shock [rare - may affect up to 1 in 1 000 people]
- **symptoms of kidney damage such as swelling of the hands, ankles or feet or changes in frequency of urination or decrease or absence of urine**; these may be signs of kidney failure [rare - may affect up to 1 in 1 000 people]
- **symptoms of infections, e.g. fever, chills, achiness, sore throat**; methotrexate can make you more susceptible to infections. Rarely [may affect up to 1 in 1 000 people] severe infections like a certain type of pneumonia (*Pneumocystis jiroveci pneumonia*) or blood poisoning (sepsis) may occur.
- **severe diarrhoea, vomiting blood and black or tarry stools**; these symptoms may indicate an uncommon [may affect up to 1 in 100 people] severe complication of the gastrointestinal system caused by methotrexate e.g. gastrointestinal ulcers
- **symptoms associated with the blockage (occlusion) of a blood vessel by a dislodged blood clot (thromboembolic event) such as weakness of one side of the body (stroke) or pain, swelling, redness and unusual warmth in one of your legs (deep vein thrombosis)**; methotrexate can cause thromboembolic events [rare - may affect up to 1 in 1 000 people]
- **fever and serious deterioration of your general condition, or sudden fever accompanied by a sore throat or mouth, or urinary problems**; methotrexate can very rarely [may affect up to 1 in 10 000 people] cause a sharp fall in white blood cells (agranulocytosis) and severe bone marrow suppression
- **unexpected bleeding, e.g. bleeding gums, blood in the urine, vomiting blood or bruising**, these can be signs of a severely reduced number of blood platelets caused by severe courses of bone marrow depression [very rare - may affect up to 1 in 10 000 people]
- **severe skin rash or blistering of the skin (this can also affect your mouth, eyes and genitals)**; these may be signs of the very rare [may affect up to 1 in 10 000 people] conditions called Stevens Johnson syndrome or burned skin syndrome (toxic epidermal necrolysis).

The following side effects have also been reported:

Very common (may affect more than 1 user in 10):
- Mouth inflammation, indigestion, nausea (feeling sick), loss of appetite, abdominal pain
- Increase in liver enzymes (can be detected by a test carried out by a doctor).

Common (may affect 1 to 10 users in 100):
- Mouth ulcers, diarrhoea
- Rash, reddening of the skin, itching
- Headache, tiredness, drowsiness
- Reduced blood cell formation with decrease in white and/or red blood cells and/or platelets (leukopenia, anaemia, thrombocytopenia).

Uncommon (may affect 1 to 10 users in 1 000):
- Inflammation of the bowels, vomiting, inflammation of the pancreas
- Throat inflammation
- Loss of hair, increased number of rheumatic nodules, shingles, inflammation of blood vessels, herpes-like skin rash, hives
- Sunburn-like reactions due to increased sensitivity of the skin to sunlight.
- Onset of diabetes mellitus
- Dizziness, confusion, depression
- Decrease in serum albumin
- Decrease in the number of blood cells and platelets
- Inflammation and ulcer of the urinary bladder or vagina, reduced kidney function, disturbed urination
- Joint pain, muscle pain, osteoporosis (reduction of bone mass).

Rare (may affect 1 to 10 users in 10 000):
- Increased skin pigmentation, acne, blue spots due to vessel bleeding
- Allergic inflammation of blood vessels, fever, red eyes, infection, wound-healing impairment, decreased number of antibodies in the blood
- Mood swings
- Visual disturbances
- Inflammation of the sac around the heart, accumulation of fluid in the sac around the heart
- Low blood pressure
- Lung fibrosis, shortness of breath and bronchial asthma, accumulation of fluid in the sac around the lung
- Electrolyte disturbances
- Bone fractures
- Infection (including reactivation of inactive chronic infection)
- Gingivitis.

Very rare (may affect less than 1 user in 10 000):
- Profuse bleeding, toxic megacolon (acute toxic dilatation of the gut)
- Increased pigmentation of the nails, inflammation of the cuticles, furunculosis (deep infection of hair follicles), visible enlargement of small blood vessels
- Local damage (formation of sterile abscess, changes in the fatty tissue) of injection site following administration into a muscle or under the skin
- Impaired vision, pain, loss of strength, sensation of numbness or tingling / having less sensitivity to stimulation than normal, changes in taste (metallic taste), convulsions, paralysis, severe headache with fever and stiff neck (can be symptoms of meningitis)
- Retinopathy (noninflammatory eye disorder)
- Loss of sexual drive, impotence, male breast enlargement (gynaecomastia), defective sperm formation, menstrual disorder, vaginal discharge
- Enlargement of lymphatic nodes (lymphoma)
- Lymphoproliferative disorders (excessive growth of white blood cells).

Not known: (frequency cannot be estimated from the available data):
- Susceptibility to infections
- Leukoencephalopathy (a disease of the white brain substance)
- Nosebleed
- Redness and shedding of skin
- Inflammation of sweat glands, detachment of the nail, skin rash which may form blisters and looks like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge)
- Bone damage in the jaw (secondary to excessive growth of white blood cells)
- Presence of protein in urine
- Chills, feeling of weakness
- Tissue destruction at injection site
- Swelling.

When methotrexate is given by the intramuscular route, local undesirable effects (burning sensation) or damage (formation of sterile abscess, destruction of fatty tissue) at the site of injection can occur commonly. Subcutaneous application of methotrexate is locally well tolerated. Only mild local skin reactions were observed, decreasing during therapy.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. 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 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 label of the pre-filled syringe and the carton after "EXP.". The expiry date refers to the last day of that month.

Keep the pre-filled syringes in the outer carton in order to protect from light. Do not store above 25°C. Do not refrigerate or freeze.

Do not use this medicine if you notice the solution is not clear and free of particles or if the container is damaged.

This medicinal product must not be mixed with other medicinal products.
The product has to be used immediately after opening.

For single use only. Any unused solution should be discarded!

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

6. Contents of the pack and other information

What Methotrexate Orion contains
The active substance is methotrexate.
1 ml of solution for injection contains 25 mg methotrexate.

1 pre-filled syringe with 0.3 ml contains 7.5 mg methotrexate.
1 pre-filled syringe with 0.4 ml contains 10 mg methotrexate.
1 pre-filled syringe with 0.6 ml contains 15 mg methotrexate.
1 pre-filled syringe with 0.8 ml contains 20 mg methotrexate.
1 pre-filled syringe with 1.0 ml contains 25 mg methotrexate.

The other ingredients are: sodium chloride, sodium hydroxide (for pH adjustment) and water for injections.

What Methotrexate Orion looks like and contents of the pack
Methotrexate Orion is a clear, yellowish solution for injection available in pre-filled syringes with attached needle.

Each box contains 1, 4, 5, 6, 10 or 12 pre-filled syringes with 0.3 ml, 0.4 ml, 0.6 ml, 0.8 ml or 1.0 ml solution for injection.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
[to be completed nationally]

Manufacturer
[to be completed nationally]

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

[to be completed nationally]

This leaflet was last revised in 2024-12-13

Instructions for use

Carefully read the instructions below before starting your injection, and always use the injection technique advised by your doctor, pharmacist or nurse.

For any problem or question, contact your doctor, pharmacist or nurse.

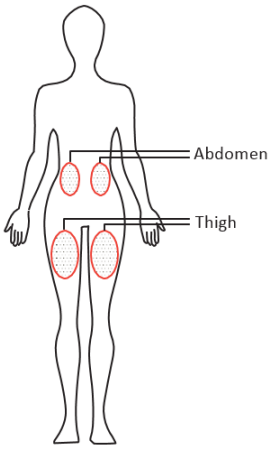
Preparation
Select a clean, well-lit and flat working surface.
You need:
- 1 Methotrexate Orion pre-filled syringe
- 1 alcohol pad.

Wash your hands carefully. Disposable gloves should be used when handling methotrexate. Before use, check the Methotrexate Orion syringe for visual defects (or cracks).

Injection site

The best sites for injection are:
- upper thighs
- abdomen except around the navel.

Areas for subcutaneous injection

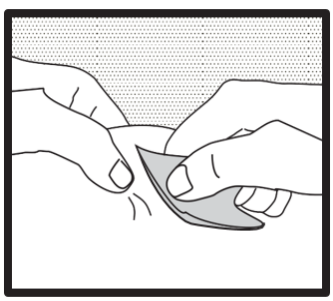


- If someone is helping you with the injection, he/she may also give the injection into the back of your arms, just below the shoulder.
- Change the injection site with each injection. This may reduce the risk of developing irritations at the injection site.
- Never inject into skin that is tender, bruised, red, hard, scarred or where you have stretch marks. If you have psoriasis, you should try not to inject directly into any raised, thick, red or scaly skin patches or lesions.

Injecting the solution

1. Unpack the methotrexate pre-filled syringe and read the package leaflet carefully. Remove the pre-filled syringe from the packaging at room temperature.

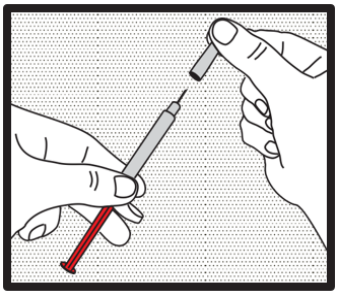
2. Disinfection



Choose an injection site and disinfect it with a swab soaked in disinfectant.

Allow at least 60 seconds for the disinfectant to dry.

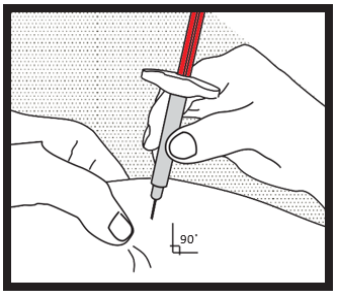
3. Remove the protective plastic cap



Carefully remove the grey protective plastic cap by pulling it straight off the syringe. If the cap is very stiff, turn it slightly with a pulling movement. When you remove the needle cover, there may be a drop of liquid at the end of the needle; this is normal. Take care not to let the drop fall on the skin.

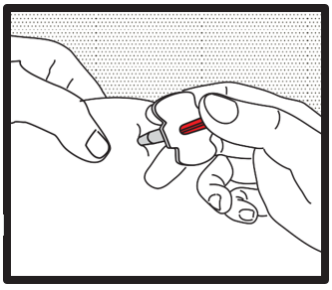
Important: **Do not** touch the needle of the pre-filled syringe or allow it to touch any surface! Do not touch or bump the plunger. Doing so could cause the liquid to leak out.

4. Inserting the needle



Using two fingers, pinch up a fold of skin and quickly insert the needle into the skin at a 90-degree angle.

5. Injection



Insert the needle fully into the fold of skin. Push the plunger down slowly and inject the liquid underneath your skin. Hold the skin securely until the injection is completed.
Carefully pull the needle straight out.

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. Spillages must be wiped immediately.

Anyone handling methotrexate should wash their hands after administering a dose.

If you or someone around you is injured by the needle, consult your doctor immediately and do not use this pre-filled syringe.

Disposal and other handling

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

Women who are pregnant, planning to be or breast-feeding should not handle and/or administer this medicine.