Package leaflet: Information for the user

Metoject® 50 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 Metoject 50 mg/ml is and what it is used for

Metoject 50 mg/ml contains methotrexate as active substance.

Methotrexate 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 (body's own defence mechanism).
- it has anti-inflammatory effects.

Metoject 50 mg/ml is indicated for the treatment of
- 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, and severe psoriatic arthritis in adult patients.

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.

Psoriatic arthritis is a kind of arthritis with psoriatic 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.

Metoject 50 mg/ml modifies and slows down the progression of the disease.

2. What you need to know before you use Metoject 50 mg/ml

Do not use Metoject 50 mg/ml
- if you are allergic to methotrexate or any of the other ingredients of this medicine (listed in section 6).
- if you suffer from severe liver or kidney diseases or blood diseases.
- if you regularly drink large amounts of alcohol.
- if you suffer from a severe infection, e.g. tuberculosis, HIV or other immunodeficiency syndromes.
- if you suffer from ulcers in the mouth, stomach ulcers or intestinal ulcers.
- if you are pregnant or breast-feeding (see section "Pregnancy, breast-feeding and fertility").
- if you receive vaccinations with live vaccines at the same time.

Warnings and precautions

Talk to your doctor or pharmacist before using Metoject 50 mg/ml.

Take special care with Metoject 50 mg/ml
- if you are elderly or if you feel generally unwell and weak.
- if your liver function is impaired.
- if you suffer from dehydration (water loss).
- if you have diabetes mellitus and are being treated with insulin

Special precautionary measures for treatment with Metoject 50 mg/ml

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 6 months after treatment has stopped 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.

Elderly patients

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

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

Other precautions

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.
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 Metoject 50 mg/ml you must not be vaccinated with live vaccines.**

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

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

Diarrhoea can be a toxic effect of Metoject 50 mg/ml and requires an interruption of therapy. If you suffer from diarrhoea, please speak to your doctor.

Certain 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.

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

Other medicines and Metoject 50 mg/ml

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Please note that this also applies to medicines that you will take in the future.

The effect of the treatment may be affected if Metoject 50 mg/ml is administered at the same time as certain other medicines:
- **Antibiotics** such as: tetracyclines, chloramphenicol, and non-absorbable broad-spectrum antibiotics, penicillins, glycopeptides, sulphonamides, ciprofloxacin and cefalotin (medicines to prevent/fight certain infections).
- **Non-steroidal anti-inflammatory** drugs or **salicylates** (medicines against pain and/or inflammation).
- **Probenecid** (medicine against gout).
- Weak organic acids like loop **diuretics** ("water tablets").
- Medicines which may have adverse effects on the **bone marrow**, e.g. trimethoprim-sulphamethoxazole (an antibiotic) and pyrimethamine.
- Other **medicines used to treat rheumatoid arthritis** such as leflunomide, sulfasalazine and azathioprine.
- Cyclosporine (for suppressing the immune system).
- Mercaptopurine (a **cytostatic** medicine).
- Retinoids (medicine against **psoriasis** and other dermatological diseases).
- Theophylline (medicine against **bronchial asthma** and other lung diseases).
- Some medicines against stomach trouble such as omeprazole and pantoprazole.
- Hypoglycaemics (medicines that are used to **lower the blood sugar).**

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

Vaccination with live vaccine must be avoided.

Metoject 50 mg/ml 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 Metoject 50 mg/ml.

Pregnancy, breastfeeding and fertility

Pregnancy

Do not use Metoject 50 mg/ml during pregnancy or if you are trying to become pregnant. 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. 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. pregnancy test, before starting treatment.
You must avoid becoming pregnant while 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

Stop breastfeeding prior to and during treatment with Metoject 50 mg/ml.

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 whilst taking methotrexate and for at least 3 months after treatment is stopped.

Driving and using machines

Treatment with Metoject 50 mg/ml 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.

Metoject 50 mg/ml contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially "sodium-free".

3. How to use Metoject 50 mg/ml

Important warning about the dose of Metoject 50 mg/ml (methotrexate):
Use Metoject 50 mg/ml **only once a week** for the treatment of rheumatoid arthritis, psoriasis and psoriatic arthritis. Using too much of Metoject 50 mg/ml (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.

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 dose, which is adapted individually to you. Usually it takes 4–8 weeks before there is any effect of the treatment.

Metoject 50 mg/ml is administered by or under the supervision of a physician or healthcare staff as an injection under the skin (subcutaneous injection) **once a week only**. Together with your doctor you decide on a suitable weekday each week on which you receive your injection.

Method and duration of administration

Metoject 50 mg/ml is injected subcutaneously **once weekly!**
The duration of the treatment is decided by your doctor. Treatment of rheumatoid arthritis, psoriatic arthritis and psoriasis with Metoject 50 mg/ml is a long-term treatment.

The manner of handling and disposal must be consistent with that of other cytostatic preparations in accordance with local requirements. Pregnant healthcare personnel should not handle and/or administer Metoject 50 mg/ml.

At the start of your treatment, Metoject 50 mg/ml may be injected by medical staff. However, your doctor may decide that you can learn how to inject Metoject 50 mg/ml under the skin 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.

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 plenty of water.

If you use more Metoject 50 mg/ml than you should

If you use more Metoject 50 mg/ml than you should, talk to your doctor immediately.

If you forget to use Metoject 50 mg/ml

Do not take a double dose to make up for a forgotten dose.

If you stop using Metoject 50 mg/ml

If you stop using Metoject 50 mg/ml, talk to your doctor immediately.

If you have the impression that the effect of Metoject 50 mg/ml is too strong or too weak, you should talk to 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, and 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 [common]
- **spitting or coughing blood;** these might be signs of bleeding from the lungs [not known]
- **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 in the liver (liver fibrosis), fatty degeneration of the liver [all uncommon], inflammation of the liver (acute hepatitis) [rare] and liver failure [very rare]
- **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]
- **symptoms of kidney damage such as swelling of the hands, ankles or feet or changes in frequency of urination or decrease (oliguria) or absence of urine (anuria)**; these may be signs of kidney failure [rare]
- **symptoms of infections, e.g. fever, chills, achiness, sore throat**; methotrexate can make you more susceptible to infections. Severe infections like a certain type of pneumonia *(Pneumocystis jirovecii pneumonia*) or blood poisoning (sepsis) may occur [rare]
- **symptoms 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); This may happen when a dislodged blood clot causes a blockage of a blood vessel** (thromboembolic event) [rare]
- **fever and serious deterioration of your general condition, or sudden fever accompanied by a sore throat or mouth, or urinary problems**; methotrexate can cause a sharp fall in certain white blood cells (agranulocytosis) and severe bone marrow suppression [very rare]
- **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]
- **symptoms such as severe headache often in combination with fever, neck stiffness, feeling sick, vomiting, disorientation and sensitivity to light** may indicate an inflammation of the membranes of the brain (acute aseptic meningitis) [very rare]
- certain brain disorders (encephalopathy/leukoencephalopathy) have been reported in cancer patients receiving methotrexate. Such side effects cannot be excluded when methotrexate therapy is used to treat other diseases. Signs of this kind of brain disorders may be **altered mental state, movement disorders (ataxia), visual disturbances or disturbances of memory** [not known]
- **severe skin rash or blistering of the skin (this can also affect your mouth, eyes and genitals**); these may be signs of conditions called Stevens Johnson syndrome or burned skin syndrome (toxic epidermal necrolysis/ Lyell's syndrome) [very rare]

The following side effects may occur:

Very common (may affect more than 1 out of 10 people):
- Inflammation of the mouth lining, indigestion, feeling sick, loss of appetite, abdominal pain.
- Abnormal liver function test (ASAT, ALAT, bilirubin, alkaline phosphatase).

Common (may affect up to 1 in 10 people):
- 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.

Uncommon (may affect up to 1 in 100 people):
- Throat inflammation.
- Inflammation of the bowels, vomiting, inflammation of pancreas, black or tarry stools, gastrointestinal ulcers and bleeding.
- Increased sensitivity to light, loss of hair, increased number of rheumatic nodules, skin ulcers, shingles, inflammation of blood vessels, herpes-like skin rash, hives.
- Onset of diabetes mellitus.
- Dizziness, confusion, depression.
- Decrease in serum albumin.
- Decrease in the number of all blood cells and platelets.
- Inflammation and ulcer of the urinary bladder or vagina, reduced kidney function, disturbed urination.
- Joint pain, muscle pain, reduction of bone mass.

Rare (may affect up to 1 in 1,000 people):
- Inflammation of gum tissue.
- Increased skin pigmentation, acne, blue spots on the skin due to vessel bleeding (ecchymosis, petechiae), allergic inflammation of blood vessels.
- Decreased number of anti-bodies in the blood.
- Infection (incl. reactivation of inactive chronic infection), red eyes (conjunctivitis).
- Mood swings (mood alterations).
- Visual disturbances.
- Inflammation of the sac around the heart, accumulation of fluid in the sac around the heart, obstruction of cardiac filling due to fluid in the sac around the heart.
- Low blood pressure.
- Formation of scar tissue in the lung (pulmonary fibrosis), shortness of breath and bronchial asthma, accumulation of fluid in the sac around the lung.
- Stress fracture.
- Electrolyte disturbances.
- Fever, wound-healing impairment.

Very rare (may affect up to 1 in 10,000 people):
- Acute toxic dilatation of the gut (toxic megacolon).
- Increased pigmentation of the nails, inflammation of the cuticles (acute paronychia), deep infection of hair follicles (furunculosis), visible enlargement of small blood vessels.
- Local damage (formation of sterile abscess, changes in the fatty tissue) of injection site.
- Pain, loss of strength or sensation of numbness or tingling/having less sensitivity to stimulation than normal, changes in taste (metallic taste), convulsions, paralysis, meningism.
- Impaired vision, non-inflammatory eye disorder (retinopathy).
- Loss of sexual drive, impotence, male breast enlargement, defective sperm formation (oligospermia), 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:
- Increased number of certain white blood cells.
- Nosebleed.
- Proteins in urine.
- Feeling of weakness.
- Bone damage in the jaw (secondary to excessive growth of white blood cells).
- Tissue destruction at injection site.
- Redness and shedding of skin.
- Swelling.

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, 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 Metoject 50 mg/ml

Keep this medicine out of the sight and reach of children.
Store below 25 °C.
Keep the pre-filled syringes in the outer carton in order to protect from light.
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 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 Metoject 50 mg/ml contains
- The active substance is methotrexate. 1 ml of solution contains methotrexate disodium corresponding to 50 mg methotrexate.
- The other ingredients are sodium chloride, sodium hydroxide and water for injections.

What Metoject 50 mg/ml looks like and contents of the pack
Metoject 50 mg/ml pre-filled syringes contain a clear, yellow-brown solution.
Pre-filled syringes containing 0.30 ml, 0.40 ml, or 0.50 ml solution are available in packs of 1 syringe with embedded s.c. injection needle, graduation and alcohol pads.
Pre-filled syringes containing 0.30 ml, 0.40 ml, or 0.50 ml solution are available in packs of 1 syringe with embedded s.c. injection needle and graduation

Manufacturer
medac Gesellschaft für klinische Spezialpräparate mbH
Theaterstr. 6 22880 Wedel, Germany

Product procured from within the EU, repackaged and distributed by the Parallel Product Authorisation holder:
PCO Manufacturing Ltd., Unit 10, Ashbourne Business Park, Rath, Ashbourne, Co. Meath, Ireland.

Metoject is a registered trademark of medac Gesellschaft für klinische Spezialpräparate mbH

Parallel Product Authorisation Number PPA0465/436/001

This medicinal product is authorised in the Member States of the European Economic Area under the following names:

Ireland Metoject 50 mg/ml Solution for injection, pre-filled syringe

Sweden Metotrexat medac, 50 mg/ml, Injektionsvätska, lösning, förfylld spruta

This leaflet was last revised in October 2023

Instructions for subcutaneous use

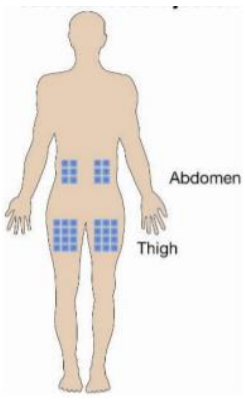
Metoject 50 mg/ml is administered as an injection under the skin once a week only. Carefully read the instructions below before starting your injection, and always use the injection technique advised by your doctor, pharmacist or nurse.

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

Preparation
Select a clean, well-lit and flat working surface.
Wash your hands carefully.
Unpack the methotrexate pre-filled syringe and read the package leaflet carefully. Remove the pre-filled syringe from the packaging at room temperature.
Before use, check the Metoject 50 mg/ml syringe for visual defects (or cracks). In case a small air bubble is visible in the solution, this will not affect your dose nor will it harm you.

Injection site

Areas for subcutaneous injection

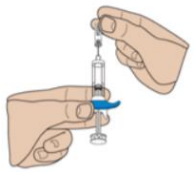


The best sites for injection are:
- upper thighs,
- abdomen except around the navel.

- 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.

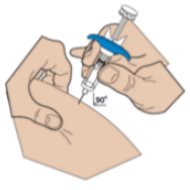
Injecting the solution

1. Choose an injection site and clean the area of and around the chosen injection site with soap and water or disinfectant.
2. Remove the protective plastic cap



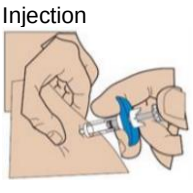
Carefully remove the grey protective plastic cap by pulling it straight off the syringe. If the cap is very stiff, turn it slightly with a pulling movement.
Important: **Do not** touch the needle of the pre-filled syringe!
Note: Once you have removed the cap, perform your injection without delay.

3. 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.

4. 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.

5. Discard the used syringe including the needle into a sharps bin. Do not put it in the household rubbish.

Methotrexate should not come into contact with the surface of the skin or mucosa. If this happens, you must rinse immediately with plenty of water.

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
The manner of handling and throwing away of the medicine and pre-filled syringe must be in accordance with local requirements. Pregnant healthcare personnel should not handle and/or administer Metoject 50 mg/ml.