Package leaflet: Information for the user

Metoject® 10 mg solution for injection in pre-filled pen
Metoject® 15 mg solution for injection in pre-filled pen
Metoject® 20 mg solution for injection in pre-filled pen
Metoject® 25 mg solution for injection in pre-filled pen

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 is and what it is used for

Metoject 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.

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

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

Metoject modifies and slows down the progression of the disease.

2. What you need to know before you use Metoject

Do not use Metoject
- if you are allergic to methotrexate or any of the other ingredients of this medicine (listed in section 6).
- if you suffer from liver or severe kidney diseases or blood diseases.
- if you regularly drink large amounts of alcohol.
- if you suffer from a severe infection, such as tuberculosis, HIV or other immunodeficiency syndromes.
- if you suffer from mouth ulcers, stomach ulcer or intestinal ulcer.
- 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 taking Metoject
- if you are elderly or if you feel generally unwell and weak.
- if you have problems with the way your liver works.
- if you suffer from dehydration (water loss).
- if you have diabetes mellitus and are being treated with insulin.
- Pregnant women should not administer Metoject or handle the pre-filled pen.
- 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.

Special precautionary measures for treatment with Metoject
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 (such as herpes zoster [shingles], tuberculosis, hepatitis B or C) may flare up. **During therapy with Metoject you must not be vaccinated with live vaccines.**

Radiation-induced dermatitis and sunburn 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 if this is the case therapy must be stopped.

Diarrhoea can be a possible side effect of Metoject 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
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 is administered at the same time as certain other medicines:
- **Antibiotics** such as: tetracyclines, chloramphenicol, 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 such as acetylsalicylic acid, diclofenac and ibuprofen or pyrazole).
- **Probenecid** (medicine against gout).
- Weak organic acids like loop diuretics (“water tablets”).
- Medicines which may have adverse effects on the **bone marrow**, such as trimethoprim-sulphamethoxazole (an antibiotic) and pyrimethamine.
- Other **medicines used to treat rheumatoid arthritis** such as leflunomide, sulphasalazine and azathioprine.
- Mercaptopurine (a **cytostatic** agent).
- 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 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

Pregnancy, breast-feeding and fertility

Pregnancy
Do not use Metoject 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 breast-feeding prior to and during treatment with Metoject.

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

Driving and using machines
Treatment with Metoject may cause adverse reactions affecting the central nervous system, such as 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 do not drive or use machines.

Metoject contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose; i.e. essentially “sodium-free”.

3. How to use Metoject

Important warning about the dose of Metoject (methotrexate):
Use Metoject **only once a week** for the treatment of rheumatoid arthritis, and psoriasis and psoriatic arthritis. Using too much of Metoject (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 adjusted individually to you. Usually it takes 4–8 weeks before there is any effect of the treatment.

Metoject is administered subcutaneously (under the skin) 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.

Use in children and adolescents
Metoject is not recommended in children less than 3 years of age due to insufficient experience in this age group.

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

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

Read the Instructions for Use at the end of this leaflet to find guidance on how to correctly use Metoject.
Please note that all of the contents have to be used.
The manner of handling and disposal of the medicine and pre-filled pen must be in accordance with local requirements.

If you use more Metoject than you should
If you use more Metoject than you should, talk to your doctor immediately.

If you forget to use Metoject
Do not take a double dose to make up for a forgotten dose.

If you stop using Metoject
If you stop using Metoject, talk to your doctor immediately.

If you have the impression that the effect of Metoject is too strong or too weak, 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, 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]

In the following, please find the other side effects that may occur:

Very common: may affect more than 1 in 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 ulcer, 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.
- 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 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 (such as burning sensations, erythema, swelling, discolouration, severe itching, pain) 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

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

Store below 25 °C. Do not freeze.
Keep the pre-filled pen in the outer carton in order to protect from light.

Do not use this medicine after the expiry date stated on the carton and pre-filled pen after EXP. The expiry date refers to the last day of that month.

Do not use if this product has deteriorated or is damaged.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to dispose of medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Metoject contains
- The active substance is methotrexate.
  1 pre-filled pen with 0.2 ml solution contains 10 mg methotrexate.
  1 pre-filled pen with 0.3 ml solution contains 15 mg methotrexate.
  1 pre-filled pen with 0.4 ml solution contains 20 mg methotrexate.
  1 pre-filled pen with 0.5 ml solution contains 25 mg methotrexate.
- The other ingredients are sodium chloride, sodium hydroxide and hydrochloric acid for pH adjustment and water for injections.

What Metoject looks like and contents of the pack
This medicinal product is presented as a solution for injection in pre-filled pen.
The solution is clear, yellow-brown.

Metoject pre-filled pen is a three-step auto-injector that has a yellow cap and a yellow injection button.

Metoject is available in packs of 1 pre-filled pen.

The pre-filled syringe within the pen may or may not have graduations on the barrel. These graduations are non-functional.

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.

Parallel Product Authorisation Number: PPA0465/436/002-005

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

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

Ireland, Sweden Metoject

This leaflet was last revised in March 2024

Instructions for Use

Recommendations

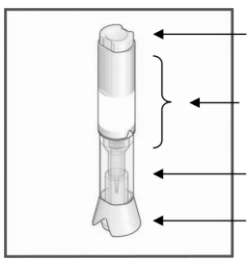
- Carefully read the instructions below before starting your injection.
- Always use the injection technique advised by your doctor, pharmacist or nurse.

Additional information

The manner of handling and disposal of the medicine and pre-filled pen must be in accordance with local requirements. Pregnant women should not administer Metoject or handle the prefilled pen.

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.

Metoject pre-filled pen components:

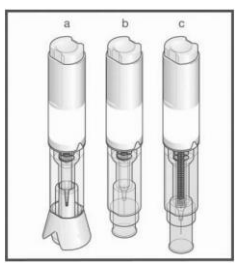


Injection button

Handling area

Transparent control zone

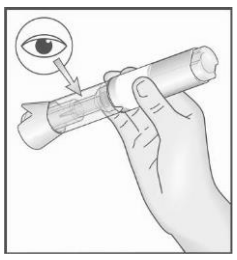
Cap



a) With cap before injection
b) After cap removal before injection
c) After injection

What you need to do before administering your injection

1. Wash your hands very carefully.
2. Remove the system from its packaging.
3. Check the Metoject pre-filled pen before using it:



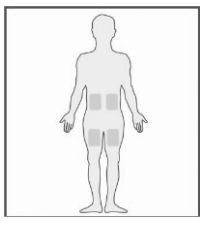
If the Metoject pre-filled pen appears to be damaged **do not use** it. Use another one and contact your doctor, pharmacist or nurse.

In case a small air bubble is visible through the transparent control zone, this will not affect your dose nor will it harm you.

If you are not able to see or to check the system correctly prior to injection, ask someone around you for assistance.

4. Set the Metoject pre-filled pen on a clean flat surface (such as a table).

Where you should administer the injection

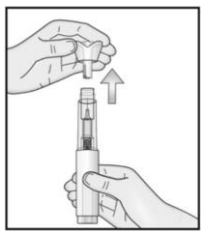


The most appropriate zones for your injection are:

- upper thighs,
- abdomen except around the navel.

- If someone around you administers the injection for you, the person may also use the top of the zone at the back of the arm, just below the shoulder.
- Change the injection area with each injection. This will minimize any reactions at the injection site.
- Never inject into areas where the skin is tender, bruised, red or hard or where you have scars or stretch marks. If you have psoriasis, you should not try to inject directly into any raised, thick, red or scaly skin patches or lesions.

How to prepare the injection



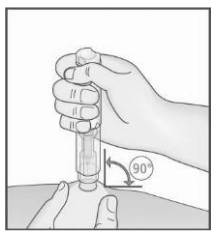
5. Choose an injection site and clean the area of and around the chosen injection site. Clean your skin in the chosen injection zone using soap and water.
6. Hold the Metoject pre-filled pen with one hand in the handling area with the cap pointing upwards.

- Do not remove the cap before you are ready to administer the injection.

7. Use your other hand to gently pull the cap straight off (do not bend or twist the cap). The cap has a small needle shield that should come off with the cap automatically. If the needle shield does not come off, use another pen and contact your doctor, pharmacist or nurse.

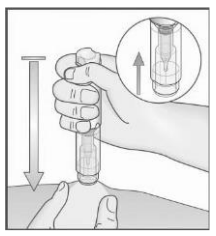
- Do not press the button until you are ready to inject.
  If you are unable to remove the cap, ask someone around you for assistance.

Note: Once you have removed the cap, perform your injection without delay.



8. With your free hand, build a skin fold by gently squeezing the area of the cleaned skin at the injection site.

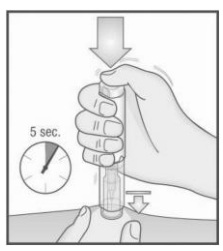
- The fold must be held pinched until the Metoject pre-filled pen is removed from the skin after the injection.



9. Position the uncapped transparent end of Metoject pre-filled pen perpendicular to the fold of skin.
10. **Without pressing the button**, push the Metoject pre-filled pen firmly onto your skin in order to unlock the button.

- If you are unable to push the Metoject pre-filled pen to the stop-point, ask someone around you for assistance.

How to administer the injection:



11. While holding the Metoject pre-filled pen firmly against the skin, **now press the button** with your thumb.

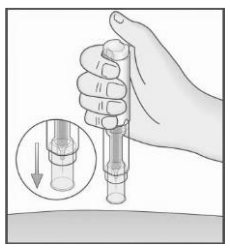
12. You will hear a click which indicates the start of the injection. Keep holding the pen against the raised skin until all of the medicine is injected. This can take up to **5 seconds**.

Note:

Do not remove the Metoject pre-filled pen from the skin before the end of the injection to avoid incomplete injection.

If the injection is not triggered, release the button, make sure that the Metoject pre-filled pen is pressed firmly against the skin and push hard on the button.

If you have difficulty with hearing, count 5 seconds from the moment you have pressed the button and then lift the Metoject pre-filled pen from the injection site.



13. Remove the Metoject pre-filled pen from the injection site, perpendicular to the skin (pull up).

14. The protective shield automatically moves into place over the needle. The protective shield is then locked and the needle is protected.

15. In case of a slight bleeding use a plaster.

Before disposing of the Metoject pre-filled pen, check visually that there is no liquid left in the pen, at the bottom of the **transparent control zone**. If there is liquid left in the pen, not all of the medicine has been injected correctly and you should consult your doctor.

Note

To avoid any injury, **never insert your fingers in the opening of the protective tube** covering the needle. **Do not destroy the pen.**

Whom should you contact in case of need

- For any problem or question, contact your doctor, pharmacist or nurse.
- If you or someone around you is injured by the needle, consult your doctor immediately and dispose of the Metoject pre-filled pen.