Package leaflet: Information for the user

Methotrexate Accord 7.5 mg solution for injection in pre-filled injector
Methotrexate Accord 10 mg solution for injection in pre-filled injector
Methotrexate Accord 12.5 mg solution for injection in pre-filled injector
Methotrexate Accord 15 mg solution for injection in pre-filled injector
Methotrexate Accord 17.5 mg solution for injection in pre-filled injector
Methotrexate Accord 20 mg solution for injection in pre-filled injector
Methotrexate Accord 22.5 mg solution for injection in pre-filled injector
Methotrexate Accord 25 mg solution for injection in pre-filled injector
Methotrexate Accord 27.5 mg solution for injection in pre-filled injector
Methotrexate Accord 30 mg solution for injection in pre-filled injector
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 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 or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What [Nationally completed name] is and what it is used for

[Nationally completed name] 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 (the body's own defence mechanism)
- it has anti-inflammatory effects

[Nationally completed name] is indicated for the treatment of

- Rheumatoid arthritis (RA) in adult patients- (RA) is a chronic disease, characterised by inflammation of the 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.

- Polyarthritic forms of severe active juvenile idiopathic arthritis when treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) have not helped. (Juvenile arthritis concerns children and adolescents less than 16 years.)

- Severe Psoriatic arthritis in adult patients (psoriatic arthritis is a kind of arthritis with psoriatric lesions of the skin and nails, especially at the joints of fingers and toes.)

- Severe Psoriasis which has not responded to other forms of treatment (psoriasis is a common chronic skin disease, characterised by red patches covered by thick, dry, silvery, adherent scales.)

- Crohn's Disease in adult patients (Crohn's Disease is a type of inflammatory bowel disease causing symptoms such as abdominal pain, diarrhoea, vomiting or weight loss.)

[Nationally completed name] modifies and slows down the progression of the disease.

2. What you need to know before you use [Nationally completed name]

Do not use [Nationally completed name] 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 mouth ulcers, stomach ulcer or intestinal ulcer.
- receive vaccinations with live vaccines at the same time.
- are pregnant or breast-feeding (see section "Pregnancy, breast-feeding and fertility")

Warnings and precautions
Talk to your doctor or pharmacist or nurse before taking [Nationally completed name] if:
- you are elderly or if you feel generally unwell and weak.
- you have liver problems
- you suffer from dehydration (water loss).
- you have diabetes mellitus and are being treated with insulin.

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.

Special precautionary measures for treatment with [Nationally completed name]
Methotrexate temporarily affects sperm and egg production, which is reversible in most cases. Methotrexate can cause miscarriage and severe birth defects. You must avoid becoming pregnant when using methotrexate and for at least six months after treatment has

stopped 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 treatment is stopped. See also section “Pregnancy, breast-feeding and fertility”.

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).

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.

Inactive, chronic infections (e.g. herpes zoster [shingles], tuberculosis, hepatitis B or C) may flare up during methotrexate treatment.

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 sunburn can reappear under methotrexate therapy (recall reactions). Psoriatic lesions can worsen if you are exposed to UV radiation during treatment with methotrexate.

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

Diarrhoea can be a toxic effect of [Nationally completed name] 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.

Other medicines and [Nationally completed name]
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 [Nationally completed name] is administered at the same time as certain other drugs:

- Antibiotics such as: tetracyclines, chloramphenicol, and non-absorbable broad-spectrum antibiotics, penicillines, glycopeptides, sulfonamides, 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, e.g. trimethoprim-sulfamethoxazole (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 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)
- Metamizole (synonyms novaminsulfon and dipyrone) (medicine against severe pain and /or fever)

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.
[Nationally completed name] 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 [Nationally completed name].

Pregnancy, breast-feeding and fertility

Pregnancy

Do not use [Nationally completed name] 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. 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 has to be stopped prior to and during treatment with [Nationally completed name].

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 [Nationally completed name] 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.

[Nationally completed name] contains sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodiumfree".

3.How to use [Nationally completed name]

Always take 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. Usually it takes 4 – 8 weeks before there is any effect of the treatment.

[Nationally completed name] 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.

Important warning about the dose of [Nationally completed name]:
Use [Nationally completed name] **only once a week** for the treatment of rheumatoid arthritis, Juvenile arthritis, Psoriatic arthritis, Psoriasis, Crohn's disease. Using too much of [Nationally completed name] 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.

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

Use in children and adolescents

The doctor decides on the appropriate dose in children and adolescents with polyarthritic forms of juvenile idiopathic arthritis.

[Nationally completed name] is not recommended in children less than 3 years of age due to insufficient experience in this age group.

Method and duration of administration
[Nationally completed name] 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 [Nationally completed name] is a long-term treatment.
Methotrexate should only be prescribed by physicians, who are familiar with the various characteristics of the medicinal product and its mode of action. If considered appropriate, the treating physician can, in selected cases, delegate subcutaneous administration to the patient.

Patients must be educated to use the proper injection technique. Under no circumstances should you try to inject [Nationally completed name] yourself before you have received such training.

For single use only. Please note that all of the contents have to be used.

The manner of handling and disposal must be consistent with that of other cytostatic preparations in accordance with local requirements. Pregnant health care personnel should not handle and/or administer [Nationally completed name].

Instructions for use:

Please read these instructions in full before using [Nationally completed name] pre-filled injector. This injector requires training by a healthcare professional before use.

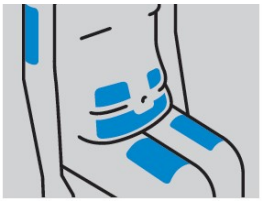
For any problem or question, contact your doctor, pharmacist or nurse.

Before you begin

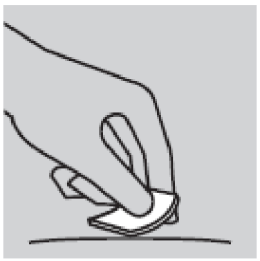
- Choose a clean, well-lit space to administer your medication.
- Check expiration date on package. Do not use if expiration date has passed.
- Gather an alcohol swab and a sharps container

Preparation

- Wash hands with soap under warm running water.



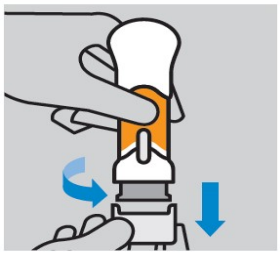
- Choose injection site (Abdomen or thigh if a patient is injecting himself/herself, with the additional option of the back of the arm if a Healthcare Provider or caregiver is assisting them)



- Clean injection site: use an alcohol swab to wipe site clean. Allow to air dry.

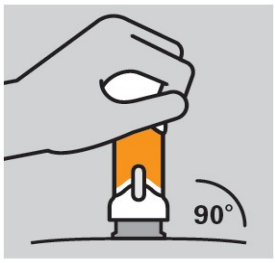
1. **Pre-Injection**

- Inspect liquid in window. Check for any changes in colour, cloudiness or visible particles.

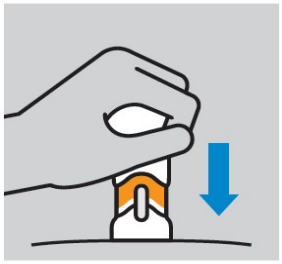


- Remove bottom cap: Twist and pull bottom cap to remove. Keep hands away from needle guard after cap is removed. Do not recap. Dispose of bottom cap immediately. Do not inject if you drop the pre-filled injector after removing cap. Inject within 5 minutes of removing bottom cap.

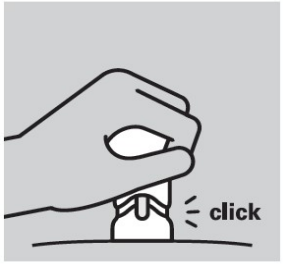
2. Injection



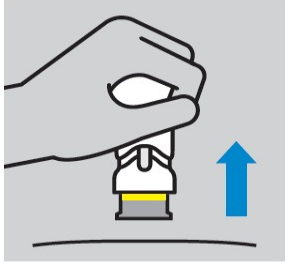
- Place the injector straight onto your skin (about 90 degrees).



- Push the handle straight down: The medicine will be injected as you push. Do this at a speed that is comfortable for you. Do not lift the injector during injection.



- Injection is completed when the handle has been pushed down as far as possible, you hear a click and the orange body is no longer visible.



- Lift straight up: The yellow band indicates that the needle guard is locked.

3. Disposal

- Dispose of the used [Nationally completed name] pre-filled injector: Place injector in an approved sharps container. Regulations vary by region. Check with your doctor or pharmacist for proper disposal instructions. Do not dispose of injector in household trash.

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 or someone around you is injured by the needle, consult your doctor immediately and do not use this [Nationally completed name] pre-filled injector.

If you use more [Nationally completed name] than you should
If you use more [Nationally completed name] than you should, talk to your doctor immediately.

If you forget to use [Nationally completed name]
Do not take a double dose to make up for a forgotten dose.

If you stop using [Nationally completed name]
If you stop using [Nationally completed name], talk to your doctor immediately.

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- may affect up to 1 in 10 people]
- **spitting or coughing blood**; these might be sins 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- 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(oliguria) or absence of urine (anuria);** 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. Severe infections like a certain type of pneumonia (*Pneumocystis jirovecii pneumonia*) or blood poisoning (sepsis) may occur [rare- may affect up to 1 in 1,000 people]
- **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- 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 cause a sharp fall in certain white blood cells (agranulocytosis) and severe bone marrow suppression [very rare- may affect up to 1 in 10,000 people]
- **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]
- **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- may affect up to 1 in 10,000 people]
- 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** -frequency cannot be estimated from the available data**]**
- **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- may affect up to 1 in 10,000 people]

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.
- Sunburn-like reactions due to increased sensitivity of the skin to sunlight, 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.
- Local damage (formation of sterile abscess, changes in the fatty tissue) of injection site.
- Pain, loss of strength, 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.
- Bleeding from the lungs
- Bone damage in the jaw (secondary to excessive growth of white blood cells)
- Redness and shedding of skin
- Swelling
- Tissue destruction at injection site.

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

[***To be completed nationally***]

5. How to store [Nationally completed name]

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

Store below 30 °C.
Keep the pre-filled injector in the outer carton in order to protect from light.

Do not use this medicine after the expiry date which is stated on the label/carton after EXP. The expiry date refers to the last day of that month.

Do not use this medicine if you notice any change in colour or visible particles.

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 [Nationally completed name] contains

- The active substance is methotrexate.

  1 pre-filled injector with 0.15 ml solution contains 7.5 mg methotrexate
  1 pre-filled injector with 0.20 ml solution contains 10 mg methotrexate
  1 pre-filled injector with 0.25 ml solution contains 12.5 mg methotrexate
  1 pre-filled injector with 0.30 ml solution contains 15 mg methotrexate
  1 pre-filled injector with 0.35 ml solution contains 17.5 mg methotrexate
  1 pre-filled injector with 0.40 ml solution contains 20 mg methotrexate
  1 pre-filled injector with 0.45 ml solution contains 22.5 mg methotrexate
  1 pre-filled injector with 0.50 ml solution contains 25 mg methotrexate
  1 pre-filled injector with 0.55 ml solution contains 27.5 mg methotrexate
  1 pre-filled injector with 0.60 ml solution contains 30 mg methotrexate

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

What [Nationally completed name] looks like and contents of the pack

[Nationally completed name] contains a clear, yellow to brown solution.

Nature of container: Pre-filled injector containing a colourless pre-filled glass syringe (type I) with plunger stopper (chlorobutyl elastomeric rubber) and embedded injection needle. The syringe is externally equipped with the device for self-administration (pre-filled injector).

The following pack sizes are available:

- For 0.15 mL, 0.20 mL, 0.25 mL, 0.30 mL, 0.35 mL, 0.40 mL, 0.45 mL,0.50 mL, 0.55 mL and 0.60 mL: pack of 1 or 12 prefilled injectors, multipacks of 4 (4 packs of 1), 6 (6 packs of 1) or 12 (12 packs of 1) pre-filled injectors in a carton.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and 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 2024-12-12.