Package leaflet: Information for the user

Metoject 10 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 is and what it is used for

Metoject 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

Metoject is indicated for the treatment of: severe, active rheumatoid arthritis in adult patients where treatment with so-called disease modifying antirheumatic drugs (DMARD) is needed

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.

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 severe liver or severe kidney disease or blood disease,
- if you regularly drink large amounts of alcohol,
- if you suffer from a severe infection, e.g. tuberculosis or HIV,
- if you suffer from oral ulcers, stomach ulcers or intestinal ulcers,
- if you are pregnant or breast-feeding,

- if you receive vaccinations with live vaccines at the same time,
- if you suffer from decreased immune defence syndromes.

Warnings and precautions
Talk to your doctor or pharmacist before using Metoject if:
- you are elderly or if you are in a bad condition generally,
- your liver or renal function is impaired,
- you suffer from dehydration (water loss).

Recommended follow-up examinations and safety measures:
Even when Metoject is administered in low doses, severe side effects can occur. In order to detect them in time, check-ups and laboratory tests have to be carried out by your doctor.

Before therapy:
Before starting the treatment, blood samples will be taken in order to carry out certain tests to check that you have enough blood cells, tests to check your liver function, serum albumin (a protein in the blood) and your kidney function. Your doctor will also check if you suffer from tuberculosis (infectious disease in combination with little nodules in the affected tissue) and a chest X-ray will also be taken.

During therapy:
You will have the following tests at least once a month during the first six months and at least every three months thereafter:
- Examination of the mouth and throat for mucosal changes
- Blood tests
- Check of liver function
- Check of kidney function
- Check of respiratory system and if necessary lung function test

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 you must not be vaccinated with live vaccines.

Enlarged lymph nodes (lymphoma) may occur and therapy does then have to be discontinued.

Encephalopathy (a brain disorder)/leukoencephalopathy (a special disorder of the white brain substance) have been reported in cancer patients receiving methotrexate therapy and cannot be excluded if methotrexate is given for other diseases.

Contact your doctor in case you have a persisting cough or breathlessness.

Other medicines and Metoject
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 Metoject is administered at the same time as certain other medicines:
- Medicines harming the liver or the blood count, e.g. leflunomide
- Antibiotics (medicines to prevent/fight certain infections) such as: tetracyclines, chloramphenicol, and non-absorbable broad-spectrum antibiotics, penicillines, glycopeptides, sulphonamides, ciprofloxacin and cefalotin
- Non-steroidal anti-inflammatory drugs or salicylates (medicines against pain and/or inflammation)
- Probenecid (medicine against gout)
- Weak organic acids such as loop diuretics ("water tablets") and pyrazole
- Medicines, which may have adverse effects on the bone marrow, e.g. trimethoprim-sulphamethoxazole (an antibiotic) and pyrimethamine

- Sulphasalazine (antirheumatic medicine)
- Proton-pump inhibitors (medicines against stomach trouble)

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 should be avoided.

Metoject with food, drink and alcohol
Consumption of alcohol as well as excessive consumption of coffee, caffeine-containing soft-drinks and black tea should be avoided during treatment with Metoject.

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 using this medicine.

You must not use Metoject during pregnancy. There is a risk of harm to the foetus and miscarriage.

Men and women must use effective contraception during treatment with Metoject and at least 6 months thereafter.

Breast-feeding should be discontinued prior to and during treatment with Metoject.

Driving and using machines
Adverse reactions affecting the central nervous system, e.g. tiredness and dizziness, may occur during treatment with Metoject. Thus the ability to drive a car or to operate machines may, in certain cases, be impaired. If you feel tired or dizzy you should not drive or use machines. It is your own responsibility to judge whether you are in a condition where you are able to drive a motorised vehicle or conduct work which needs increased alertness. One of the factors that can influence your ability in this aspect is the use of medicines due to their actions and/or side effects. A description of these actions and side effects are available in other sections of this package leaflet. Therefore you should read the whole package leaflet for instruction. In case you are unsure about this you should discuss it with your doctor or pharmacy personnel.

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

Metoject is administered as an injection **once a week <u>only</u>** by your doctor or your nurse. Together with your doctor you decide on a suitable weekday each week for the injection. Metoject may be injected intramuscularly (in a muscle), intravenously (in a vein) or subcutaneously (under the skin).

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 Metoject.

Methotrexate must 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 ample amount of water.

Your doctor decides on the dosage, which is adapted individually to you. Usually it takes 4 – 8 weeks before there is any effect of the treatment. The duration of the treatment is decided by your doctor.

If you experience the effect of Metoject as too strong or too weak, you should talk to your doctor or pharmacist.

If you use more Metoject than you should
Follow your doctor's dosage recommendations. Do not change the dosage by yourself.

If you suspect that you have received too much Metoject, contact your doctor immediately. He will decide on the adequate treatment depending on the severity of the intoxication.

If you forget to use Metoject
Do not use a double dose to make up for a forgotten dose. Ask your doctor for advice. Use the dose prescribed by your doctor as soon as possible and each week thereafter.

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.

The most relevant side effects are effects on the blood forming system and the gastrointestinal tract.

The following side effects may occur:

Very common (may affect more than 1 in 10 people):
- Mouth inflammation, indigestion, nausea, reduced appetite
- Local skin reactions (burning sensation, redness) of injection site following intramuscular or subcutaneous administration. Most of these reactions are of a mild degree.
- Increase in liver enzymes

Common (may affect up to 1 in 10 people):
- Oral ulcers, diarrhoea
- Rash, reddening of the skin, itching
- Headache, tiredness, drowsiness
- Inflammation of the lungs, allergic pulmonary reaction often associated with elevated count of white blood cells. Symptoms are: dry, non-productive cough, shortness of breath and fever.
- Impaired blood cell formation with decrease in the amount of white and/or red blood cells and/or platelets (leucopenia, anaemia, thrombocytopenia)

Uncommon (may affect up to 1 in 100 people):
- Throat inflammation, inflammation of the bowel, vomiting
- Increased sensitivity to light, loss of hair, increased number of rheumatic nodules, shingles, inflammation of blood vessels, herpes-like skin rash, hives
- Precipitation of diabetes
- Dizziness, confusion, depression, cognitive dysfunction
- Cirrhosis, liver atrophy, formation of scar tissue, fatty degeneration of the liver
- Pancytopenia (decrease of all blood cells)
- Inflammation and ulcers of the urinary bladder or vagina, impaired kidney function, disturbed micturition
- Joint pain, muscle pain, osteoporosis

Rare (may affect up to 1 in 1,000 people):
- Gastrointestinal ulcers, malabsorption

- Increased skin pigmentation, acne, blue spots due to vessel bleeding
- Allergic reactions, allergic shock, allergic inflammation of blood vessels, fever, conjunctivitis (red eyes), infection, blood poisoning, wound-healing impairment, decreased number of antibodies in the blood
- Visual disturbances
- Inflammation of the sac around the heart, accumulation of fluid in the sac around the heart, low blood pressure, thromboembolic events
- Lung fibrosis, shortness of breath and bronchial asthma, accumulation of fluid in the sac around the lung
- Kidney failure, impaired urine excretion, absent urine excretion, electrolyte disturbances

Very rare (may affect up to 1 in 10,000 people):
- Haematemesis (vomiting blood), strong bleeding, strong dilatation of the colon
- Changes of skin and mucous membranes (also serious), serious widely spread damage of the skin (loosening of skin), increased pigmentation of the nails, inflammation of the cuticle, 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 intramuscular or subcutaneous administration
- Impaired vision, pain, loss of strength or sensation of numbness or tingling in arms and legs, changes in taste (metallic taste), convulsions, severe headache with fever, paralysis
- Disease of the retina of the eye
- Severely decreased number of white blood cells (e.g. agranulocytose, see below), severe bone marrow depression
- Loss of sexual drive, impotence, reduced sperm count, defective egg formation, defective spermatogenesis, infertility, menstrual disorders, vaginal discharge
- There have been reports of individual cases of lymphoma (enlarged lymph nodes) which subsided in a number of cases once treatment with Metotrexat medac had been discontinued.

Not known (frequency cannot be estimated from the available data):
- Leukoencephalopathy (a disease of the white brain substance)

Metoject can in very rare cases influence the white blood cells so that the immune defence is worsened. In case you have an infection associated with symptoms such as fever with seriously worsened general condition or fever with symptoms of local infections such as throat or mouth pain or difficulty urinating, you should immediately contact your doctor so that a blood sample can rule out a lack of white blood cells (agranulocytose). It is important that you inform him about your medication.

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

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5. How to store Metoject

Keep 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 after "EXP". The expiry date refers to the last day of that month.

6. Contents of the pack and other information

What Metoject contains

- The active substance is methotrexate. 1 ml of solution contains methotrexate disodium corresponding to 10 mg methotrexate.
- The other ingredients are sodium chloride, sodium hydroxide, water for injections.

What Metoject looks like and contents of the pack

Metoject pre-filled syringes contain a clear, yellow solution.
The following pack sizes are available: 0.75 ml, 1 ml, 1.5 ml, 2 ml and 2.5 ml solution for injection in packs of 1, 5, 10 and 30 pre-filled syringes with graduation, with or without injection needle. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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