PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS REGULATIONS (PREPARATIONS) - 1986

This medicine is dispensed with a doctor's prescription only

METOJECT 50 mg/ml S.C.

Solution for injection
Pre-filled syringe

Active ingredient and concentration:
methotrexate 50 mg/ml

For information about inactive ingredients and allergens in this medicine see section 2 under 'Important information about some of this medicine's ingredients', and section 6 'Additional information'.

Read this entire leaflet carefully before you start taking this medicine. This leaflet contains concise information about the medicine. If you have any further questions, contact your doctor or pharmacist.
This medicine has been prescribed for your illness. Do not pass it on to others. It may harm them, even if you think that their illness is the same as yours.

For the treatment of rheumatoid arthritis, psoriasis and Crohn's disease – the medicine is intended for use in adults only.
For the treatment of juvenile idiopathic arthritis (JIA) - the medicine is intended for children over 3 years of age.

Metoject S.C. is given once a week, by injection under the skin.
Do not use this medicine daily. Daily use can cause side effects and serious complications which could lead to death.
Choose a weekday with your doctor. To help you remember on which day you are given Metoject, you are advised to keep a diary.

1. What is the medicine used for?

- In cases of severe rheumatoid arthritis in adult patients that was properly diagnosed according to rheumatological standards and when the patients did not respond to other forms of antirheumatic therapy, including non-steroidal anti-inflammatory drugs (NSAIDs) and usually a trial of at least one or more disease-modifying antirheumatic drugs (DMARDs).
- Active and severe juvenile idiopathic arthritis in patients over 3 years of age that involves several joints, and when treatment with non-steroidal anti-inflammatory drugs (NSAIDs) is not sufficient.
- For the symptomatic control of severe recalcitrant psoriasis in adults, which is not adequately responsive to other forms of therapy, and only when the diagnosis has been established, as by biopsy and/or after dermatological consultation.
- For treatment of mild to moderate Crohn's Disease in adults as monotherapy or combined with corticosteroids in patients that do not respond or in patients who have low tolerance to treatment with thiopurines.

Therapeutic group: Folic acid analogue

2. Before using the medicine

Do not use the medicine if:

- You are sensitive (allergic) to methotrexate or to any of the other ingredients of the medicine (see section 6).
- You are pregnant or breastfeeding **(see section 'Pregnancy, breastfeeding and fertility' below)**.
- You suffer from severe liver diseases, severe kidney diseases or severe blood diseases.
- You consume large amounts of alcohol.
- You suffer from a severe infection, such as tuberculosis, AIDS or other immunodeficiency syndromes.
- You suffer from ulcers in the oral cavity, stomach or intestines.
- Concomitantly with attenuated live vaccine.

Special warnings about the use of this medicine

- **Before taking Metoject 50 mg/ml S.C., tell your doctor if:**
  - You suffer from impaired liver function.
  - You suffer from dehydration (loss of fluids).
  - You are elderly or if you are feeling unwell and weak.
  - You have diabetes and are taking insulin.
- Even when **Metoject 50 mg/ml S.C.** is administered in low dosages, serious side effects may occur. In order to detect side effects in time, medical examinations and laboratory tests need to be performed (see section 'Tests and follow up').
- Methotrexate may affect your immune system and vaccination results. It may also affect the result of immunological tests. Inactive, chronic infections [such as shingles (herpes zoster), tuberculosis, hepatitis B or C] may flare up. During therapy with this medicine, you must not be vaccinated with live attenuated vaccines (see 'Do not use the medicine if').
- 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. See also section 'Pregnancy, breastfeeding and fertility'.
- 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.
- Radiation induced dermatitis and sun-burn can reappear during treatment with methotrexate.
- Psoriatic lesions can exacerbate during UV-irradiation and concomitant administration of methotrexate.
- Enlarged lymph nodes may occur. In such case, therapy must be stopped.
- Diarrhoea is a side effect that can occur following use of the medicine and requires interruption of therapy (see section 4 'Side effects'). If you suffer from diarrhoea, speak to your doctor.
- Certain brain disorders (encephalopathy/leukoencephalopathy) have been reported in cancer patients that have received methotrexate. Side effects such as these cannot be excluded when methotrexate is used to treat other diseases.
- If you, your relative or your caregiver notice new onset or worsening of neurological symptoms including muscle weakness, disturbances of vision, changes in thinking, changes in memory or orientation leading to confusion or personality changes - contact your doctor immediately. These effects may be symptoms of a serious brain infection called progressive multifocal leukoencephalopathy (PML) (very rare).

- Prior to and during treatment, medical examinations should be performed. See section 'Tests and follow up'.

Children and adolescents:
Do not use **Metoject 50 mg/ml S.C.** in children under 3 years of age due to lack of experience in this age group.

Elderly patients:
Elderly patients under treatment with methotrexate should be monitored closely by a doctor so that side effects can be detected as early as possible. Age-related impairment of liver and kidney function as well as low reserves of folic acid in old age require a relatively low dosage of methotrexate.

Tests and follow up

Before starting treatment with the medicine:
Before starting to use this medicine, the doctor will refer you to the following tests: blood count, liver function or other diagnostic tests to monitor liver condition, serum albumin (a type of protein in the blood) and kidney function tests.
Additionally, your doctor will check whether you suffer from tuberculosis (an infectious disease in combination with little nodules in the affected tissue) and perform a chest X-ray.
During treatment:
During the first 6 months of treatment you will have to undergo the following tests at least once a month, and afterwards at least once every three months:
Examination of the mouth and throat for detection of changes in the mucosa, blood tests, liver function tests or other diagnostic tests to monitor liver condition, kidney function tests, examination of the respiratory system and if necessary, lung function test.

Drug interactions

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines including non-prescription drugs and nutritional supplements. Please note that this also applies to medicines you will take in the future. Especially if you are taking:

- **Antibiotics** such as tetracyclines, chloramphenicol, and non-absorbable broad-spectrum antibiotics, penicillins, glycopeptides, sulphonamides, ciprofloxacin and cefalotin (medicines to prevent/treat 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** (a medicine against gout).
- Weak organic acids, like **diuretics**.
- Medicines which may adversely affect **the bone marrow**, e.g., trimethoprim-sulfamethoxazole (an antibiotic) and pyrimethamine.
- Other **medicines** used **to treat rheumatoid arthritis** such as leflunomide, sulfasalazine (an anti-rheumatic medicine) and azathioprine (an immunosuppressive medicine sometimes used in severe forms of rheumatoid arthritis)
- Mercaptopurine (a medicine that **inhibits cell division**).
- Retinoids (a medicine for the treatment of **psoriasis** and other dermatological diseases).
- Theophylline (a medicine against **asthma** and other lung diseases).

- Some medicines for the treatment of **stomach trouble** such as omeprazole and pantoprazole.
- Medicines used **to lower the blood sugar level.**
- Vitamins containing **folic acid** may impair the effect of your treatment and should only be taken when advised by your doctor.
- During treatment, you must not be vaccinated with live attenuated vaccines (see 'Do not use the medicine if').

Use of this medicine and food
Do not drink large amounts of coffee, tea or caffeine-containing soft drinks during treatment with the medicine.

Use of this medicine and alcohol consumption
Do not drink wine or other alcoholic beverages during treatment with this medicine.

Pregnancy, breastfeeding and fertility
Pregnancy
Do not use **Metoject 50 mg/ml S.C.** 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 not be given to pregnant women or women 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 whilst taking methotrexate and for at least 6 months after treatment is stopped by using reliable contraception throughout this time (see also section 'Special warnings about the use of this medicine').
If you do become pregnant during treatment or suspect you might be pregnant, speak to your doctor as soon as possible. You should be given information regarding the risk of harmful effects on the unborn child during the course of 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

Pregnant members of the medical staff must not handle and/or inject **Metoject 50 mg/ml S.C.**

Breastfeeding
Stop breastfeeding prior to and during treatment with **Metoject 50 mg/ml S.C.**

Male fertility
The available evidence does not indicate an increased risk of malformations or miscarriage if the father takes methotrexate at a lower dosage than 30 mg/week. However, a risk cannot be completely excluded. Methotrexate may be genotoxic. This means that the medicine might cause genetic mutation. Methotrexate can affect sperm production with the potential to cause birth defects. Therefore, you should avoid fathering a child or donating semen whilst taking methotrexate and for at least 6 months after treatment is stopped.

Driving and use of machinery
Use of this medicine may cause side effects that affect the central nervous system, e.g. tiredness and dizziness and thus the ability to drive or operate machines may be compromised. If you feel tired or drowsy, do not drive or operate machines.
As for children, they should be warned against bicycle riding or playing near roads, etc.

Important information about some of the ingredients of this medicine:
This medicine contains less than 23 mg sodium per dose, i.e. is essentially “sodium-free”.

3. How to use this medicine?
Always use the medicine according to your doctor's instructions. Check with your doctor or pharmacist if you are not sure about the dosage and treatment regimen of the medicine.
The dosage and treatment regimen will be determined by the doctor only and adjusted individually to your medical condition. Usually it takes 4–8 weeks before there is any effect of the treatment. Treatment with **Metoject 50 mg/ml S.C.** is long term.

Metoject 50 mg/ml S.C. is administered by medical staff (not by self-injection) **once a week only**, as a subcutaneous injection.
Together with your doctor you decide on a suitable weekday on which you receive your injection each week.

Use in children and adolescents
The doctor decides on the appropriate dose in children and adolescents with polyarthritic forms of juvenile idiopathic arthritis.
Do not use **Metoject 50 mg/ml S.C.** in children under 3 years of age due to insufficient experience in this age group.

Do not exceed the recommended dose.

Avoid contact of this medicine with the skin and mucosa. In such cases, the affected area must be rinsed immediately with plenty of water.
If you feel that the effect of the medicine is too strong or too weak, refer to your doctor.

If you have accidently taken a higher dose
If you accidently take a higher dose, or if a child accidently swallowed some medicine, refer to the doctor or proceed to a hospital emergency room immediately and bring the package of the medicine with you.

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

Adhere to the treatment as recommended by your doctor.

Even if your health improves, **do not stop treatment with this medicine** without consulting your doctor or pharmacist.

If you stop using the medicine
If you stop taking the medicine, refer to the doctor immediately.

Do not take medicines in the dark! Check the label and dose each time you take medicine. Wear glasses if you need them.
If you have any further questions about the use of this medicine, consult your doctor.

4. Side effects:

Like all medicines, **Metoject 50 mg/ml S.C.** can cause side effects in some users. Do not be alarmed while reading the list of side effects; you may not suffer from any of them.
The frequency and severity of the side effects depend on the dosage and the frequency of injection. As severe side effects may occur even at low dosages, 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 reduced white blood cells, reduced platelets, lymphoma) and changes in the kidneys and the liver.

The frequency of side effects is rated in the following manner:
Very common side effects – effects that appear in more than one out of 10 users
Common side effects – effects that appear in 1-10 out of 100 users
Uncommon side effects - effects that appear in 1-10 out of 1,000 users
Rare side effects – effects that appear in 1-10 out of 10,000 users
Very rare side effects – effects that appear in up to 1 out of 10,000 users

Inform your doctor immediately upon the appearance of the following symptoms that may indicate serious, potentially life-threatening side effects and that require immediate medical intervention:

- 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 (unknown frequency)
- Symptoms of liver damage such as yellowing of the skin and whites of the eyes - liver cirrhosis, formation of scar tissue in the liver, fatty degeneration of the liver (these effects are uncommon), acute inflammation of the liver (rare), 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 of urine (oliguria) or absence of urine (anuria) - these may be signs of kidney failure (rare).
- Symptoms of infection, e.g. fever, chills, achiness, sore throat – the medicine can make you more susceptible to infections. Rarely, severe infections like a certain type of pneumonia (pneumocystis jirovecii pneumonia) or blood poisoning (sepsis) may occur (rare).
- Symptoms associated with the blockage of a blood vessel by a dislodged blood clot (thromboembolic event) such as weakness of one side of the body (stroke) or pain, swelling, redness and unusual warmth in one of your legs (deep vein thrombosis); methotrexate may cause thromboembolic events (rare).
- Fever and serious deterioration of your general condition, or sudden fever accompanied by a sore throat or mouth, or urinary tract problems. Methotrexate can cause a sharp fall in certain type of white blood cells (agranulocytosis) and severe bone marrow suppression (very rare).
- Unexpected bleeding, such as 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 suppression of the bone marrow (very rare).
- Symptoms such as severe headache, sometimes combined with fever, neck stiffness, feeling sick, vomiting, disorientation and sensitivity to light may indicate an inflammation of the membranes of the brain (acute non-bacterial meningitis) (very rare).

- 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. Signs of this kind of brain disorders may be altered mental state, movement disorders (ataxia), visual disturbances or disturbances of memory (unknown frequency).
- Severe skin rash or blistering of the skin (this can also affect your mouth, eyes and genitals) - these may be signs of the very rare conditions called Stevens Johnson syndrome or burned skin syndrome (toxic epidermal necrolysis/Lyell's syndrome) (very rare).

Additional side effects

Very common side effects:
Inflammation of the mouth lining, indigestion, feeling sick, loss of appetite, abdominal pain, abnormal liver function tests (ASAT, ALAT, bilirubin, alkaline phosphatase).

Common side effects:
Mouth ulcers, diarrhoea, rash, redness of the skin, itching, headache, tiredness, drowsiness, reduced blood cell formation with decrease in white and/or red blood cells and/or platelets.

Uncommon side effects:
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 side effects:
Inflammation of the gum tissue, increased skin pigmentation, acne, blue spots on the skin due to blood vessel bleeding, allergic inflammation of blood vessels, decreased number of anti-bodies in the blood, infection (including 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 (lung fibrosis), shortness of breath and bronchial asthma, accumulation of fluid in the sac around the lungs, stress fracture, electrolyte disturbances, fever, wound-healing impairment.

Very rare side effects:
Acute toxic dilatation of the gut (toxic megacolon), increased pigmentation of the nails, inflammation of the cuticles, deep infection of hair follicles (furunculosis), visible enlargement of small blood vessels, local damage of injection site following subcutaneous injection (formation of sterile abscesses, changes in the fatty tissue), pain, lack of strength or sensation or numbness or tingling, changes in taste (metallic taste), convulsions, paralysis, neck stiffness, 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 increase in the number of white blood cells).

Side effects with an unknown frequency:
Increase in the number of certain white blood cells, nosebleed, proteins in urine, feeling of weakness.

Bone damage in the jaw (secondary to the excessive increase in the number of white blood cells), tissue destruction at injection site, oedema, redness and shedding of skin.

Injection of **Metoject 50 mg/ml S.C.** is locally well tolerated. Only mild local skin reactions were observed, decreasing during therapy.

If a side effect appears, if any of the side effects worsens, or if you experience side effects not listed in this leaflet, consult your doctor.

Reporting side effects
Side effects can be reported to the Ministry of Health by clicking on the link 'Reporting Side Effects of Drug Treatment' that appears on the home page of the Ministry of Health's website (www.health.gov.il) which refers to an online form for reporting side effects, or via the following link: https://sideeffects.health.gov.il

5. How to store the medicine?

- Avoid poisoning! This medicine and all other medicines should be kept in a closed place out of the reach and sight of children and/or infants to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by your doctor.
- Do not use the medicine after the expiry date (exp. date) stated on the package. The expiry date refers to the last day of that month. If in doubt, consult the dispensing pharmacist.
- Store at a temperature below 25°C.
- Store in the original package in order to protect from light.
- Do not store different medicines in the same package.
- The manner of handling and destruction of **Metoject 50 mg/ml S.C.** must be consistent with that of other cytostatic preparations in accordance with local requirements. Treatment should only take place at a clinic intended for treatment with cytotoxic substances and equipped for destruction of the medicine. Pregnant health care personnel should not handle and/or inject **Metoject 50 mg/ml S.C.**

6. Additional information

In addition to the active ingredient, this medicine also contains:

sodium chloride, sodium hydroxide, water for injections.

What the medicine looks like and contents of the package

Metoject pre-filled syringes contain a clear, yellow-brown solution.
The medicine package contains a needle attached to a syringe, with or without a safety system (the safety system is intended to prevent needle stick injury and reuse of the needle).

Package sizes: 7.5 mg/0.15 ml; 10 mg/0.2 ml; 12.5 mg/0.25 ml; 15 mg/0.3 ml; 17.5 mg/0.35 ml; 20 mg/0.4 ml; 22.5 mg/0.45 ml; 25 mg/0.5 ml; 27.5 mg/0.55 ml; or 30 mg/0.6 ml.
Each package contains 1, 4, 6, 12 or 24 pre-filled syringes.

Not all package sizes may be marketed.

License holder: Tzamal Bio-Pharma Ltd., 20 Hamagshimim St., Petach-Tikva.

Manufacturer's name and address: medac Gesellschaft für klinische Spezialpräparate mbH, Wedel, Germany.

Registration number of the medicine in the National Drug Registry of the Ministry of Health: 145-34-33074

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