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

This medicine can be sold with doctor's prescription only

METOJECT 50 mg/ml S.C. Solution for Injection

Pre-filled syringe

Active ingredient and its concentration:
Methotrexate 50 mg/ml

For list of excipients, please see section 6.

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, ask your doctor or pharmacist.
This medicine has been prescribed for your illness only. 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.

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 treatment, 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 a single treatment or combined with corticosteroids in patients that do not respond or in patients that 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 hypersensitive (allergic) to methotrexate or 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 of the oral cavity, stomach or intestine.
- Concomitantly with attenuated live vaccines.

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 liquids).
  - You are elderly or if you are feeling unwell and weak.
- Even when **Metoject 50 mg/ml S.C.** is administered in low dosages, serious side effects may occur. In order to detect side effects on 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 herpes zoster (shingles), tuberculosis, hepatitis B or C] may erupt. During treatment 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 may worsen 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 discontinuation of therapy. 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 using methotrexate for treatment of other diseases.
- Prior to and during treatment, medical examinations should be performed. See section "Tests and follow up".

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines including non-prescription drugs and nutrition supplements. 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 for prevention/treatment of certain infections).
- **Non-steroidal anti-inflammatory drugs** or **salicylates** (medicines for pain and/or inflammation such as acetylsalicylic acid, diclofenac and ibuprofen or pyrazole).
- **Probenecid** (a medicine for gout).
- Weak organic acids, such as **diuretics**
- Medicines which may affect **the bone marrow**, such as trimethoprim-sulfamethoxazole (an antibiotic) and pyrimethamine.
- Other medicines used for the treatment of rheumatoid arthritis such as leflunomide, sulfasalazine (an anti-rheumatic medicine) and azathioprine (immunosuppressive medicine sometimes used in severe forms of rheumatoid arthritis)
- Mercaptopurine (**a cytostatic agent**).
- Retinoids (a medicine for the treatment of **psoriasis** and other dermatological diseases).
- Theophylline (a medicine for **asthma** and other lung diseases).
- Several medicines for the treatment of **stomach disorders** such as omeprazole and pantoprazole.
- Medicines used **to lower the blood sugar level.**
- Vitamins containing **folic acid** may affect the efficacy of the 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 fetus or cause miscarriage. These are 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 women or women planning to become pregnant.
In women of child-bearing age, any possibility of pregnancy must be ruled out by 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 fetus 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 healthcare personnel must not handle and/or administer **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, the risk cannot be completely ruled out. 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 sperm donation 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 such as tiredness and dizziness and thus may compromise the ability to drive or operate machines.
If you feel tired or drowsy, do not drive or operate machinery.
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 manner of treatment 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**, subcutaneously.
You should decide together with your doctor on a suitable weekday on which you will receive your injection each week.

Use in children and adolescents:
The doctor will decide on the appropriate dose in children and adolescents with polyarthritic forms of juvenile idiopathic arthritis.
Do not use Metoject 50 mg/ml 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 events, rinse the affected area immediately with a large amount of water.
If you feel that the effect of the medicine is too strong or too weak, refer to your doctor.

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, 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 in three months:
Examination of the mouth and throat for detection of alterations of the mucosa, blood tests, liver function tests, kidney function tests, examination of the respiratory system and if necessary lung function tests.

If you have accidently taken a higher dose
If you accidently take a higher dose, or if a child accidently swallowed the 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 take the medicine
Do not take a double dose to make up for a forgotten dose.

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

Continue with the treatment as recommended by your doctor.

Even if there is an improvement in your health, **do not discontinue use of this medicine** without consulting your doctor or pharmacist.
Do not take medicines in the dark! Check the label and dose each time you take a 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 are dependent on the dosage and the frequency of injection. Since serious side effects may also occur at low dosages, it is important to be regularly monitored by the doctor. Your doctor will perform tests to check for abnormalities developing in the blood (such as reduced white blood cells, reduced platelets, lymphoma) and changes in the kidneys and liver.

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

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

- 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 of 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, such as fever, chills, pain, sore throat – the medicine can make you more susceptible to infections. Rarely, severe infections like a certain type of pneumonia (pneumocystis jirovecil pneumonia) or 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, nausea, vomiting, disorientation and sensitivity to light may indicate an infection in the membrane of the brain (non-bacterial acute meningitis) (very rare).
- Certain brain disorders (encephalopathy/leukoencephalopathy) have been reported in cancer patients receiving methotrexate. Side effects such as these cannot be excluded when metothrexate is used for the treatment of other illnesses. Signs of this type of brain disorders may be a change in mood, movement disorders (ataxia), visual disturbances or memory disorders (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 oral mucosa, indigestion, nausea, loss of appetite, abdominal pain, abnormal liver functions tests (ASAT, ALAT, Bilirubin, alkaline phosphate).

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

Uncommon side effects:
Throat inflammation, bowel inflammation, vomiting, inflammation of pancreas, black or tarry stools, gastrointestinal ulcers and bleeding, photosensitivity, hair loss, 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, impaired kidney function, urination disturbances, 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 the blood vessels, decreased number of antibodies in the blood, infection (including reactivation of chronic inactive infection), red eyes (conjunctivitis), mood swings (mode 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, scar formation in the lung (lung fibrosis), shortness of breath and bronchial related 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 intestine (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 administration under the skin (formation of sterile abscesses, changes in the fatty tissue), pain, loss of strength or sensation or numbness or tingling in the arms and legs, 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 increase in the number of white blood cells).

Side effects with an unknown frequency:
Increase in the number of certain white blood cells, nosebleed, proteinuria, feeling of weakness.
Bone damage in the jaw (secondary to the excessive increase in the number of white blood cells), tissue destruction at the injection site.

Administration of **Metoject 50 mg/ml S.C.** is locally well tolerated. Only mild local skin reactions were observed, which decreased during treatment.

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 "Report Side Effects of Drug Treatment" that appears on the homepage 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 medicine 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 container.
- The manner of handling and disposing 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 in a clinic intended for treatment with cytotoxic substances and equipped for disposal of the medicine.
  Pregnant health care personnel should not handle and/or administer **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 syringe contains a clear, yellow-brown solution.
The 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 49170.

Manufacturer: medac, Wedel, Germany.

Drug registration number at the national medicine registry of the Ministry of Health: 145-34-33074-01/02/03/04

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