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

The medicine is dispensed with a doctor's prescription only

Methotrexat "Ebewe" 20 mg/ml Solution for Injection

Pre-filled syringe

Methotrexat "Ebewe" 20 mg/ml can be self-injected by the patient but only under the skin (subcutaneously, S.C.).
Never self-inject directly into your vein (intravenously) or into the muscle (intramuscularly).
If necessary, Methotrexat "Ebewe" can be administered directly into the vein or muscle. However, this must be done solely by the medical staff.

Each syringe contains: Methotrexate 20 mg/ml.
For inactive ingredients: please see section 6 of the leaflet – "Further Information" in the leaflet.

Read this leaflet carefully in its entirety before using the medicine: This leaflet contains concise information about the medicine. If you have further questions, refer to the doctor or pharmacist. This medicine has been prescribed for the treatment of your ailment only. Do not pass it on to others. It may harm them, even if it seems to you that their ailment is similar.
For treatment of rheumatoid arthritis, psoriasis and Crohn's disease – the medicine is only intended for use in adults.
For treatment of juvenile idiopathic arthritis (JIA) – the medicine is intended for children above 3 years of age.

1. WHAT IS THE MEDICINE INTENDED FOR?

- For treatment of severe rheumatoid arthritis in adult patients that was properly diagnosed and which does not respond to other forms of treatment.
- For treatment of polyarthritic forms of severe, active juvenile idiopathic arthritis in young patients above 3 years of age, when the response to non-steroidal anti-inflammatory drugs (NSAIDs) has been inadequate.
- For treatment of psoriasis which does not respond adequately to other forms of treatment.
- For treatment of Crohn's disease as monotherapy or in combination with corticosteroids in adult patients who do not respond to treatment with thiopurines.

Therapeutic group: Immunosuppressant, folic acid derivative.

2. BEFORE USING THE MEDICINE

☒ Do not use the preparation:

- **If you are pregnant or breastfeeding (see section 2 "Pregnancy and breastfeeding")**
- **If you have a known hypersensitivity to any of the ingredients of the medicine, including hypersensitivity to methotrexate (see section 6)**
- **If you suffer from liver disease, severe kidney disease or diseases of the blood**
- **If you consume large amounts of alcohol**
- **If you suffer from a severe infection, such as tuberculosis, or other immunodeficiency syndromes (AIDS)**
- **If you suffer from ulcers of the oral cavity or gastrointestinal ulcers**
- **concomitantly with the administration of a live attenuated vaccine**

Special warnings regarding use of the medicine:

- Even when Methotrexat "Ebewe" 20 mg/ml administered S.C. is given in low dosages, severe side effects may occur
- In order to detect side effects in a timely manner, medical examinations and laboratory tests must be performed (see section 3 "Tests and follow-up")
- If you are sensitive to any food or medicine, tell the doctor before taking the medicine
- During treatment with the medicine, you must not be vaccinated with a live attenuated vaccine (see section 2 "Do not use the preparation")
- Radiation-induced dermatitis and sun-burns may reappear during the course of treatment with Methotrexat "Ebewe" 20 mg/ml administered S.C.
- Psoriatic skin changes may be exacerbated during UV-irradiation and concomitant administration of Methotrexat "Ebewe" 20 mg/ml
- Encephalopathy (brain disorder)/leukoencephalopathy (a disorder affecting the white matter in the brain) have been reported in cancer patients receiving Methotrexat "Ebewe" 20 mg/ml, and appearance of these side effects cannot be excluded when using Methotrexat "Ebewe" 20 mg/ml for treatment of other diseases

❗ Before treatment with Methotrexat "Ebewe" 20 mg/ml administered S.C. tell the doctor if:

- you suffer, or have suffered in the past, from impaired liver function
- you feel unwell or suffer from weakness
- you suffer from insulin-dependent diabetes – treatment with methotrexate needs to be monitored
- you suffer from kidney dysfunction
- you are suffering from an infection
- you suffer from lung dysfunction
- you are overweight
- you suffer from accumulation of fluid in the lining of the lungs or in the abdomen (you will need to have the fluid drained before commencing treatment with methotrexate and levels of methotrexate in your blood will need to be monitored)
- If you are dehydrated or suffer from symptoms of dehydration (vomiting, diarrhea)

In rare cases, the medicine may affect your white blood cells and decrease your immunity to infections. If you suffer from an infection accompanied by symptoms of fever and deterioration of your physical condition, or if you suffer from a fever as a result of a localized infection such as sore throat, pain in oral cavity, or difficulty urinating, refer to the attending doctor immediately to check if there is correlation between the infection and a lowered white blood cell count (agranulocytosis).

❗ If you are taking, or have recently taken, other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist.

Especially inform the doctor or pharmacist if you are taking:

- Medicines to relieve pain and reduce inflammation of the non-steroidal anti-inflammatory drugs (NSAIDs) group or salicylates (such as ibuprofen, phenylbutazone, aspirin); these medicines may increase the concentration of methotrexate in the blood and thereby raise the risk of side effects.
- Leflunomide, azathioprine, sulfasalazine, retinoids – concomitant use with methotrexate may cause liver toxicity.
- Antibiotics such as penicillins, tetracyclines, sulfonamides, co-trimoxazole (trimethoprim/sulfamethoxazole), chloramphenicol.
- Phenytoin – medicine for treating epilepsy.
- Nutritional supplements which contain folic acid or derivatives of folic acid.
- Probenecid – a medicine used to treat gout.
- Chemotherapeutic agents such as cisplatin, cytarabine, mercaptopurine.
- Theophylline – a medicine used to treat asthma.
- Furosemide – a diuretic.
- Sulfasalazine – an antirheumatic medicine.
- Azathioprine – an immunosuppressive agent sometimes used for severe cases of rheumatoid arthritis.
- During treatment you must not be vaccinated with live attenuated vaccines (see section: "Do not use the preparation").
- Retinoids (medicines for psoriasis and other dermatological diseases).
- Proton-pump inhibitors (medicines for the treatment of stomach problems, such as omeprazole, pantoprazole, lansoprazole).
- Radiotherapy

❗ Use of the medicine and food:

Do not drink large quantities of coffee, tea or caffeine-containing soft drinks. Make sure to drink large amounts of fluids during treatment with Methotrexat "Ebewe" 20 mg/ml since dehydration (fluid loss) may increase the toxicity of Methotrexat "Ebewe" 20 mg/ml.

❗ Use of the medicine and alcohol consumption:

Do not drink wine or other alcoholic beverages during the course of treatment with the medicine.

❗ Pregnancy and breastfeeding:

Do not use the medicine if you are pregnant, think you may be pregnant, are planning to become pregnant or are breastfeeding.
You should stop breastfeeding prior to treatment with **Methotrexat "Ebewe" 20 mg/ml administered S.C.**
Men and women must use effective methods of contraception during the course of treatment and for 6 months after termination of treatment with **Methotrexat "Ebewe" 20 mg/ml administered S.C.**
In women of child-bearing age, pregnancy must be ruled out with certainty by means of a pregnancy test prior to treatment.
Since methotrexate is genotoxic (damages the genome, the DNA), women who wish to become pregnant should seek genetic consultation, if possible, even before commencing treatment, and men should check the possibility of sperm preservation before starting treatment.
You should stop breastfeeding prior to and during the course of treatment with Methotrexat "Ebewe" 20 mg/ml.

❗ Driving and use of machinery:

Use of this medicine may cause dizziness and impair alertness.
If you experience dizziness or tiredness, do not drive or operate dangerous machinery while using the medicine.
Children should be cautioned against riding a bicycle or playing near the road and the like.

3. HOW SHOULD YOU USE THE MEDICINE?

- Always use according to the doctor's instructions. Check with the doctor or pharmacist if you are uncertain.
- Methotrexat "Ebewe" 20 mg/ml administered S.C. is given **only once a week**, by injection under the skin.
- Usually it takes 4-8 weeks before any effect of the treatment is felt.

If you feel that the effect of the medicine is too strong or too weak, refer to the doctor.
The dosage and treatment regimen will be determined by the doctor only.
You should decide together with the doctor on a suitable weekday on which you will receive your injection each week.
Do not exceed the recommended dose.
Avoid contact of the medicine with the skin and mucous membranes. In such events, immediately rinse the affected area with a large amount of water.
Tests and follow-up –
Before commencing treatment with the medicine, the doctor will refer you to the following tests: blood count, liver function tests, serum albumin (a type of protein in the blood) tests and kidney function test.
In addition, a test to check whether you suffer from tuberculosis as well as a chest X-ray should be performed.
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 alterations of the mucosa, blood tests, liver function tests, kidney function test, examination of the respiratory system and, if necessary, lung function test.
Methotrexate may affect the immune system, vaccination results and the results of immunological tests; inactive chronic infections (such as herpes zoster [shingles], tuberculosis, hepatitis B or C) may flare up.
During treatment with Methotrexat "Ebewe" 20 mg/ml administered S.C. you must not be vaccinated with a live attenuated vaccine.
Methotrexat "Ebewe" 20 mg/ml administered S.C. may cause serious (and sometimes life-threatening) side effects. Therefore, tests to check for abnormalities developing in the blood should be performed (e.g., decrease in white blood cells, decrease in platelets, lymphoma) and changes in the kidney and the liver.
Adhere to the treatment as recommended by the doctor.
Even if there is an improvement in your health, do not discontinue use of the medicine without consulting the doctor or pharmacist. In addition, if you have any further questions regarding the use of the medicine, consult the doctor or pharmacist.

If you accidentally take too high a dosage or if a child has accidentally used the medicine, refer immediately to a doctor or proceed to a hospital emergency room and bring the package of the medicine with you.

If you forget to take this medicine at the required time, take the medicine as soon as you remember, but never take a double dose.
Adhere to the treatment as recommended by the doctor, even if there is an improvement in your health do not discontinue treatment with the medicine without consulting the doctor.

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

4. SIDE EFFECTS

As with any medicine, use of Methotrexat "Ebewe" 20 mg/ml may cause side effects in some users.
Do not be alarmed when 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 administration. Since severe side effects (especially side effects that affect the blood forming system and the gastrointestinal tract) may occur at low dosages, it is important to be regularly monitored by the doctor.
Discontinue treatment with the medicine and refer to the doctor immediately if you suffer from:

- A dry, non-productive cough, shortness of breath and fever – these may be signs of pneumonia (common).
- 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 side effects are uncommon), severe hepatitis (rare), liver failure (very rare).
- Symptoms of allergy such as skin rash, including redness and itching of skin, swelling of the palms of the hands, the soles of the feet, the ankles, face, lips, mouth or throat (may cause difficulty swallowing or breathing) and feeling faint – these may be signs of severe allergic reactions or anaphylactic shock (rare).
- Symptoms of kidney damage such as swelling of the palms of the hands, the ankles or the soles of the feet, or changes in frequency of urination or decrease in amount of urine or absence of urination – these may be signs of kidney failure (rare).
- Symptoms of infection, such as fever, chills, pain, sore throat – the medicine may cause you to be more susceptible to infections. Severe infections such as a certain type of pneumonia or blood poisoning (sepsis) may rarely occur.
- Diarrhea (this may indicate a toxic effect of Methotrexat "Ebewe" 20 mg/ml administered S.C.), severe diarrhea, vomiting blood and black stools or tar colored stools – these symptoms may indicate rare complications of the digestive system such as ulcers of the gastrointestinal tract caused by methotrexate.
- Fever and serious deterioration of your general condition, or sudden fever accompanied by a sore throat or mouth, or urinary problems – very rarely a sharp drop in white blood cells and severe bone marrow suppression may be caused.
- Unexpected bleeding, such as bleeding from the gums, blood in the urine, vomiting blood or bruising – these may be signs of a severely reduced number of blood platelets caused by severe bone marrow suppression (very rare).
- Severe skin rash or blistering of the skin (may also affect your mouth, eyes and genitals) – these may be signs of the very rare condition called Stevens-Johnson syndrome or scalded skin syndrome (toxic epidermal necrolysis).
- Enlargement of the lymph nodes (lymphoma).

Additional side effects:

Very common side effects:
Mouth inflammation, indigestion, nausea, loss of appetite, rise in liver enzymes.

Common side effects:
Mouth ulcers, diarrhea, 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 (leukopenia, anemia, thrombocytopenia).

Uncommon side effects:
Throat inflammation, bowel inflammation, vomiting, photosensitivity, hair loss, increased number of rheumatic nodules, 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 blood cells and platelets, inflammation and ulcer of the urinary bladder or vagina, impaired kidney functions, urination disturbances, joint pain, muscle pain, thinning of the bones (osteoporosis).

Rare side effects:
Increased skin pigmentation, acne, blue spots due to blood vessel bleeding, allergic inflammation of the blood vessels, fever, red eyes, infection, wound healing impairment, decreased number of antibodies in the blood, visual disturbances, pericarditis (inflammation of the sac around the heart), low blood pressure, occlusion of a blood vessel by a dislodged blood clot, lung fibrosis, shortness of breath and bronchial asthma, accumulation of fluid around the heart and the lungs, electrolyte disturbances.

Very rare side effects:
Extensive bleeding, acute dilatation of the intestine, increased pigmentation of the nails, inflammation of the epidermis, deep infection of hair follicles, visible enlargement of small blood vessels, local damage at the injection site following subcutaneous administration (formation of sterile abscesses, changes in the fatty tissue), impaired vision, pain, loss of strength or sensation of numbness or tingling in arms and legs, changes in taste (metallic taste), convulsions, paralysis, severe headache with fever, retinopathy (non-inflammatory eye disorder), loss of sexual drive, impotence, breast enlargement in men, defective sperm formation, menstrual disorder, vaginal discharge, enlargement of lymph nodes (lymphoma).

Side effects of unknown frequency:
Leukoencephalopathy (disorder of the white matter of the brain).
Following subcutaneous administration of Methotrexat "Ebewe" 20 mg/ml you may have a burning sensation or local damage at the injection site.
If one of the side effects worsens, or if you suffer from side effects not mentioned in the leaflet, consult the doctor.

Reporting side effects:
Side effects can be reported to the Ministry of Health via the online side effects report form available at the Ministry of Health homepage www.health.gov.il or via the following link: https://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

5. HOW SHOULD THE MEDICINE BE STORED?

- Avoid poisoning! This medicine and any other medicine must be kept in a safe place out of the reach and sight of children and/or infants to avoid poisoning. This medicine has been prescribed for the treatment of your ailment. In another patient it may cause harm. **Do not give this medicine to your relatives, neighbors or acquaintances.**
- Do not use the medicine after the expiry date (EXP. DATE) that appears on the package. The expiry date refers to the last day of that month. If in doubt, consult the pharmacist who dispensed the medicine to you.
- Store at a temperature below 25°C
- Store in the original package in order to protect from light
- Do not store different medications in the same package
- After the subcutaneous administration, Methotrexat "Ebewe" 20 mg/ml must be disposed of properly in designated waste containers in accordance with the approved requirements of the Ministry of Health of Israel.

6. FURTHER INFORMATION

Inactive ingredients:
Sodium chloride, Sodium hydroxide, Water for injection
The medicine contains 4.13 mg sodium in 1 ml of Methotrexat "Ebewe" 20 mg/ml
Methotrexat "Ebewe" 20 mg/ml can be self-injected by the patient but only under the skin (subcutaneously, S.C.).

Never self-inject directly into your vein (intravenously) or into the muscle (intramuscularly). If necessary, Methotrexat "Ebewe" can be administered directly into a vein or muscle. However, this must be done solely by the medical staff.

Manufacturer and address: Ebewe Pharma, Unterach, Austria.
Importer and license holder: Pharmologic LTD., P.O.Box 3838, Petach Tikva 49130
Telephone: 1800-071-277
Registration number of the medicine in the National Drug Registry of the Ministry of Health: 148-50-33635-00
This Leaflet was checked and approved by the Ministry of Health in November 2015

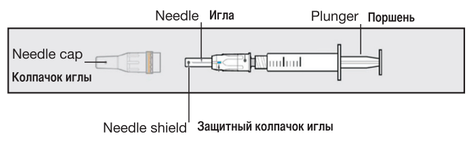
Methotrexat "Ebewe" 20 mg/1 ml Pre-filled syringe for S.C. administration

Метотрексат "Эбеве" 20 мг/ 1 мл в шприце готовом к применению S.C.

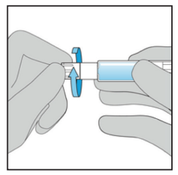
Instructions for subcutaneous administration using a safety needle:

Указания для подкожного введения, с использованием безопасной иглы.

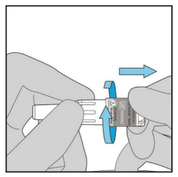
1. **Take the syringe and needle out of the box.**
1. **Выньте шприц и иглу из коробки.**



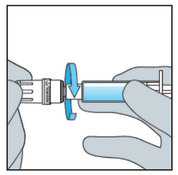
2. **Remove the gray rubber cap from the syringe by turning it, without touching the opening of the syringe. Put down the syringe. The medicine will not leak.**
2. **Удалите серый резиновый колпачок со шприца, повернув его и не касаясь отверстия шприца. Положите шприц. Препарат не вытекает.**



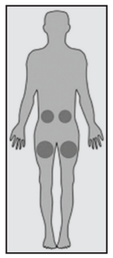
3. **Remove the gray cap of the needle by turning it.**
3. **Поворачивая, удалите серый колпачок с иглы.**



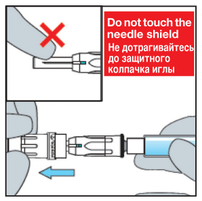
4. **Screw the needle onto the syringe.**
4. **Навиньтите иглу на шприц.**



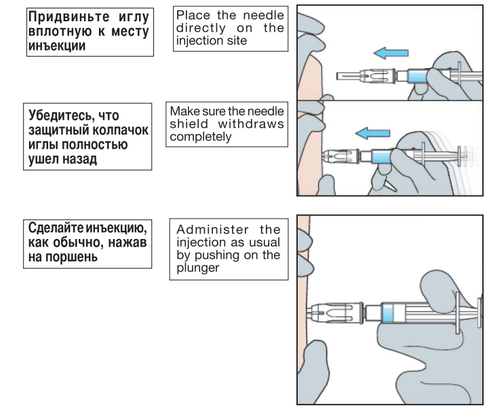
5. **Swab the intended injection site with an alcohol pad using circular movements. Do not touch the site before injecting.**
5. **Протрите выбранное место инъекции спиртовым тампоном при помощи круговых движений. Не касайтесь места инъекции перед инъекцией.**



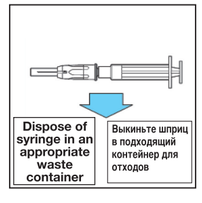
6. **Remove the needle cap by pulling it.**
6. **Потянув, снимите колпачок с иглы.**



7. **Before pushing on the plunger, place the needle directly on the injection site until the needle shield withdraws completely, and only then administer the injection as usual by pushing on the plunger.**
7. **До нажатия на поршень придвиньте иглу вплотную к месту инъекции, так, чтобы защитный колпачок иглы полностью отошел назад. И только затем сделайте инъекцию, как обычно, нажав на поршень.**



8. **After completing the injection, the needle is protected and there is no fear of needle-stick injuries.**
8. **По окончании инъекции игла защищена и не надо опасаться укола ею.**



9. **Use a wipe to pat the injection site but avoid rubbing as this may irritate the skin.**
9. **С помощью тампона похлопайте место инъекции, но не растирайте, так как это может вызвать раздражение кожи.**