Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) - 1986

This medicine is dispensed with a doctor's prescription only

Methotrexat "Ebewe" 2.5 mg Tablets

Composition:
Each tablet contains methotrexate 2.5 mg.

Inactive ingredients and allergens: See section 2 "Important information about some of this medicine's ingredients" and section 6 "Additional information".

Important warning about the dosage of Methotrexat "Ebewe" 2.5 mg Tablets:
For treatment of psoriasis and rheumatoid arthritis and some of the hematological indications (according to the treatment protocol determined by your doctor), take Methotrexat "Ebewe" 2.5 mg Tablets once a week.
Do not take the medicine daily. If you take the medicine daily, you may experience severe side effects and complications which may be fatal.
Choose a day of the week which is most suitable for you. To remember on which day of the week you should take Methotrexat "Ebewe", it is recommended to keep a tracking diary.

Read the entire leaflet carefully before you start using this medicine.
This leaflet contains concise information about this medicine. If you have any further questions, consult your doctor or pharmacist.
This medicine has been prescribed to treat your illness. Do not pass it on to others. It may harm them, even if it seems to you that their medical condition is similar to yours.

In addition to the patient information leaflet, Methotrexat "Ebewe" 2.5 mg Tablets also has a patient safety information card.
This card contains important safety information that you need to know and that you should follow before you start and during treatment with Methotrexat "Ebewe" 2.5 mg Tablets. Carefully read the patient safety information card and patient information leaflet before using this medicine.
Keep the card in case you need to read it again.

1. What is this medicine intended for?

- For treatment of acute lymphoblastic leukemia
- For treatment of Burkitt's lymphoma
- For treatment of severe psoriasis unresponsive to other therapies
- For treatment of adult patients with severe, active rheumatoid arthritis who are unresponsive/intolerant to other therapies

Therapeutic group:
The active ingredient methotrexate is a folic acid analogue acting as an anti-neoplastic (preventing cell growth) and immunomodulatory (regulating immune system activity) substance.

2. Before using this medicine

Do not use this medicine if:

- You are sensitive (allergic) to methotrexate (the active ingredient) or to any of the other ingredients in this medicine (see section 6 – "Additional information").
- You are pregnant, trying to become pregnant or breastfeeding (see "Pregnancy, breastfeeding and fertility" under section 2). Methotrexate may harm your baby (see section "Pregnancy, breastfeeding and fertility" below). You and your partner should avoid conception for at least 6 months after discontinuing treatment with methotrexate.
- You have severe liver problems including fibrosis (scarring), cirrhosis and recent or active hepatitis (liver inflammation) (or doctor's decision regarding the severity of the disease).
- You have severe kidney problems including conditions requiring dialysis (or doctor's decision regarding the severity of the disease).
- You have serious blood problems including severe anaemia (low levels of white and red blood cells) and clotting problems.
- You have a medical condition or are receiving a medication which lowers your resistance to infections.
- You are taking an antibiotic which prevents the production of folic acid (vitamin B9), such as trimoxazole, which is used to treat bacterial infections.
- You have an active infectious disease (e.g. fever, chills, joint pain, etc.).
- You have a severe or existing infection, e.g. tuberculosis and acquired immunodeficiency syndrome (HIV).
- You receive a live vaccine at the same time.
- Your alcohol consumption is high.

Special warnings about using this medicine
Before using Methotrexat "Ebewe" 2.5 mg Tablets, tell your doctor if:

- You have blood disorders or anaemia
- You have diabetes mellitus treated with insulin
- You have mild to moderate kidney disease
- You have gastrointestinal disorders such as gastric ulcer, inflammation of the guts, inflammation of the mucous membranes of the mouth
- You are dehydrated or suffer from conditions which may cause dehydration (vomiting, diarrhoea, stomatitis)
- You suffer or have ever suffered from mental illness
- You have problems with your lung function
- You are severely overweight
- You have prolonged inactive infections [e.g. tuberculosis, hepatitis B or C, shingles (herpes zoster)]
- You have a medical condition which causes build-up of fluids in the lining of the lungs or abdomen (the fluid will need to be drained before methotrexate treatment is started)
- You have received or are receiving radiotherapy (X-ray treatment)
- You have received any vaccinations recently or you are due to have a vaccination soon, as methotrexate can reduce their effect.

Use in elderly patients
Methotrexate should be used in elderly patients with extreme caution.
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.
Reduced liver or kidney function, as well as low body reserves of the vitamin folic acid in old age, require a lower dosage of methotrexate.

Children and adolescents
Methotrexate should be used in children with extreme caution.
There is no information regarding the safety and efficacy of using this medicine in children, except for the indication of blood cancer treatment.

Tests and follow-up
Even if methotrexate is used in low dosages, serious side effects may occur. In order to detect them on time, your doctor must perform monitoring examinations and laboratory tests.
Prior to starting of treatment:
Before you start treatment, your blood should be checked to see if you have enough blood cells. Your blood should also be tested to check your liver function and to verify that you don't have liver inflammation (hepatitis). Furthermore, albumin (a protein in the blood), liver infection (hepatitis) status and kidney function should be checked. Your doctor may also want to perform other liver tests, including liver imaging and even examination of a sample taken from the liver.
Your doctor may also want to check if you have tuberculosis, and may refer you for chest X-ray or 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 including number of blood cells and measurement of serum methotrexate levels
- blood tests to monitor liver function
- imaging tests to monitor liver function
- taking a small sample from the liver in order to examine it more closely
- blood tests to monitor kidney function
- respiratory tract monitoring and, if necessary, a 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.

If you have experienced skin problems after radiation therapy (radiation induced dermatitis) and sunburns, these conditions can reappear during methotrexate therapy (recall reaction).
Methotrexate temporarily affects sperm or egg production. Methotrexate may cause miscarriages and severe birth defects. You and your partner should avoid conception during methotrexate treatment and for at least 6 months after discontinuing treatment with methotrexate. See also "Pregnancy, breastfeeding and fertility" under this section.
Methotrexate may cause inflammation of the lungs with breathlessness. If you develop a persistent cough, pain or difficulty breathing or breathlessness, you should seek medical attention.
Acute bleeding from the lungs has been reported in patients with rheumatic disease using methotrexate. If you experience symptoms of spitting or coughing up blood, you should contact your doctor immediately.
Your doctor will want to monitor your progress on a weekly basis until therapy is stable. Thereafter you will be monitored every 2-3 months, whilst taking the medicine. These check-ups may include blood and urine tests for blood cell count and to make sure that your liver and kidneys are working properly. It is important that you do not miss any blood tests. You may also have to perform a chest X-ray and a physical examination to check for swelling of the lymph nodes (glands located in the neck, armpits and groin). Any unusual swelling should be reported to your doctor.
Methotrexate will only be given under the supervision of a doctor experienced in its administration.

Drug interactions
If you are taking or have recently taken other medicines, including nonprescription medications and dietary supplements, tell your doctor or pharmacist. Particularly if you are taking:
It is especially important to inform your doctor if you are taking metamizole (dipyrone) used for severe pain and/or fever.
You should also inform your doctor if you are taking:

- non-steroidal anti-inflammatory drugs (NSAIDs), e.g. ibuprofen, indomethacin or aspirin (for pain relief or inflammation)
- antibiotics (used to treat bacterial infections, e.g. chloramphenicol, penicillin, sulphonamides, trimethoprim/sulfamethoxazole, ciprofloxacin and tetracyclines)
- p-aminobenzoic acid, acitretin (for treatment of psoriasis or skin diseases)
- other medicines for rheumatoid arthritis or psoriasis such as leflunomide, sulphasalazine (also used for ulcerative colitis), phenylbutazone, or amidopyrine
- diphenylhydantoins, phenytoin (used to treat epilepsy)
- probenecid, sulfinpyrazone (used to treat gout)
- cancer treatments
- barbiturates (sleeping injections)
- live vaccines
- vitamin preparations or oral iron preparations containing folic acid
- tranquilisers, nitrous oxide (used in general anaesthesia)
- azathioprine (used to prevent rejection of organ transplants)
- anticonvulsant drugs
- oral contraceptives
- pyrimethamine (used to prevent and treat malaria)
- proton pump inhibitors, e.g. omeprazole or pantoprazole (used to treat severe heartburn or ulcers)
- theophylline (used to treat asthma)

Using this medicine and food
Avoid excessive consumption of drinks containing caffeine, including coffee, soft drinks containing caffeine and black tea.

Using this medicine and alcohol consumption
Avoid alcohol consumption during methotrexate treatment.

Pregnancy, breastfeeding and fertility
Ask your doctor or pharmacist for advice before taking any medicine.

Pregnancy
Do not use methotrexate during pregnancy, except if your doctor has prescribed the treatment for an oncological indication.
Methotrexate may cause birth defects, harm the unborn child or cause a miscarriage. Methotrexate treatment is associated with malformations of the skull, face, heart and blood vessels, brain and limbs. It is therefore very important that the medicine is not given to pregnant women or to women who are planning to become pregnant, unless used for an oncological indication.
When used for non-oncological indications in women of child-bearing age, the possibility of pregnancy must be ruled out by pregnancy tests before treatment is started. Do not use methotrexate if you are trying to become pregnant. You must avoid becoming pregnant for at least 6 months after the end of methotrexate treatment. Therefore, you must use effective contraception for the entire period (see also section "Special warnings about using this medicine").
If you become pregnant during treatment or suspect you might be pregnant, contact your doctor as soon as possible. If you do become pregnant during treatment, you should receive full information regarding the risk of possible harmful effects on the fetus due to the treatment.
If you want to become pregnant, speak with your doctor, who will refer you to an appropriate specialist.

Breastfeeding
Do not use methotrexate during breastfeeding.

Male fertility
The available evidence does not indicate an increased risk of malformations or miscarriages if the father is treated with methotrexate at a dosage below 30 mg/week. However, the risk cannot be completely excluded and there is no information regarding higher methotrexate dosages. Methotrexate may have a genotoxic effect. This means that this medicine may cause genetic mutations. Methotrexate may affect the production of sperm, with the potential of causing birth defects.
You should avoid fathering a child or donating sperm during treatment with methotrexate and for at least 6 months after the end of methotrexate treatment. As treatment with methotrexate at high dosages commonly used in oncological indications may cause infertility and genetic mutations, it is advisable for a male patient treated with methotrexate dosage higher than 30 mg/week to consider the option of sperm preservation before starting treatment (see also section "Special warnings about using this medicine").

Driving and using machines
Use of methotrexate may cause side effects affecting the central nervous system, such as tiredness and dizziness. In some cases, this may impair the ability to drive and/or use machines. If you feel tired or dizzy, avoid driving or using machines.

Important information about some of this medicine's ingredients
This medicine contains lactose. If you have been told by your doctor that you have an intolerance to certain sugars, consult your doctor before taking this medicine. Each tablet contains 78.60 mg lactose monohydrate.

3. How to use this medicine?

Important warning about the dosage of Methotrexat "Ebewe" 2.5 mg Tablets:
For treatment of psoriasis and rheumatoid arthritis and some of the hematological indications (according to the treatment protocol determined by your doctor), take Methotrexat "Ebewe" 2.5 mg Tablets once a week.
Do not take the medicine daily. If you take the medicine daily, you may experience severe side effects and complications which may be fatal.
Choose a day of the week which is most suitable for you. To remember on which day of the week you should take Methotrexat "Ebewe", it is recommended to keep a tracking diary.

Always use this medicine according to your doctor's instructions. Check with your doctor or pharmacist if you are not sure about your dosage or about how to take this medicine.
Only your doctor will determine your dosage and how you should take this medicine.
During treatment, your doctor will refer you for blood tests to check your blood cells and to make sure that your liver and kidneys are working properly. It is important that you do not miss any blood tests. If you feel that the effect of methotrexate is too strong or too weak, talk to your doctor or pharmacist

Do not exceed the recommended dose.

Mode of administration
Do not chew! Swallow the medicine with some water.

If you have accidentally taken more Methotrexat "Ebewe" 2.5 mg Tablets than you should
If you have taken more tablets than the doctor has told you to, you should get medical help immediately - call your doctor or go to the emergency room. Always bring the medicine package with you, whether there are any tablets left or not. Inappropriate intake resulting in overdose may lead to severe toxic side effects and even death. Overdose symptoms include easy bruising or bleeding, unusual weakness, mouth ulcers, nausea, vomiting, black or bloody stool, coughing up blood or vomit that looks like coffee grounds and decreased urination.
See also section 4 "Side effects". The antidote in case of an overdose is calcium folinate.
If you have taken an overdose, or if a child has accidentally swallowed some medicine, immediately see a doctor or go to a hospital emergency room and bring the medicine package with you.

If you forget to take Methotrexat "Ebewe" 2.5 mg Tablets
Take the medicine as soon as you remember, if this is within the last two days. However, if you have forgotten a dose by more than two days, contact your doctor. **Do not take a double dose to make up for the forgotten tablet.**
Adhere to the treatment as recommended by your doctor.

If you stop taking Methotrexat "Ebewe" 2.5 mg Tablets
Do not stop using Methotrexat "Ebewe" 2.5 mg Tablets unless your doctor tells you to. If you need to stop using the medicine, your doctor will decide how this should be done.

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

4. Side effects

Like with all medicines, using Methotrexat "Ebewe" 2.5 mg Tablets may cause side effects in some users. Do not be alarmed by this list of side effects; you may not experience any of them.

Contact your doctor straight away if you experience sudden wheeziness, difficulty breathing, swelling of the eyelids, face or lips, rash or itching (especially if affecting the entire body).

Serious side effects
If you develop any of the following side effects, contact your doctor as soon as you can:

- inflammation of the lungs (symptoms may be general sensation of illness, dry, irritating cough, shortness of breath, breathlessness at rest, chest pain or fever)
- spitting or coughing up blood (has been reported in patients with rheumatic disease taking methotrexate)
- severe peeling or blistering of the skin (this may also affect the mouth and tongue). These may be signs of a condition known as Stevens-Johnson syndrome. Your doctor will stop your treatment in these cases
- acute allergic reaction (anaphylactic reaction). This condition is very rare. You may experience a sudden itchy skin rash (hives), swelling of the hands, feet, ankles, face, lips, mouth or throat (which may cause difficulties swallowing or breathing), wheezing and sensation of fainting
- skin rash and fever with swollen glands, particularly in the first two months of treatment. These may be signs of an allergic reaction
- unusual bleeding (including vomiting blood) or bruising
- acute diarrhoea
- ulcers in the mouth
- black or tarry stool
- blood in the urine or stool
- tiny red spots on the skin
- fever
- yellowing of the skin (jaundice) and whites of the eyes. This is a sign of liver damage
- pain or difficulty in passing urine
- thirst and/or frequent urination
- seizures
- loss of coordination
- loss of ability to speak or understand speech
- weakness and inability to move one side of the body or the whole body
- loss of consciousness
- blurred or decreased vision
- swelling of the hands, ankles and feet (which may be a sign of kidney damage)
- brain disorders

Methotrexate may cause a reduction in the number of white blood cells and your resistance to infections may be decreased. If you experience an infection with symptoms such as fever and acute deterioration of your general condition, or fever with local infection symptoms such as sore throat/sore pharynx/sore mouth or urinary problems, you should see your doctor immediately. A blood test will be performed to check for possible reduction in white blood cells (agranulocytosis). It is important to inform your doctor about using this medicine.
Methotrexate may cause serious (that may be even life-threatening) side effects. Therefore, your doctor will perform tests to check for abnormalities developing in the blood (e.g. low white blood cell count, low platelet count, lymphoma) and changes in kidney and liver function.

The following side effects have been reported:

Very common side effects (affect 1-10 in 10 users)

- loss of appetite
- nausea
- vomiting
- abdominal pain
- inflammation and ulcers in the throat
- increase in liver enzymes

Common side effects (affect 1-10 in 100 users)

- reduced formation of white and/or red blood cells and/or platelets (leukopenia, anaemia, thrombocytopenia)
- headache
- tiredness
- drowsiness
- pneumonia with dry, non-productive cough
- shortness of breath
- diarrhoea
- rash
- reddening of the skin
- itching

Uncommon side effects (affect 1-10 in 1000 users)

- decrease in the number of blood cells and platelets
- dizziness
- confusion
- depression
- fits
- inflammation of blood vessels
- lung damage
- ulcers and bleeding in the digestive tract
- liver function disorders
- diabetes
- decreased blood protein levels
- nettle rash
- sunburn-like reaction due to increased sensitivity of the skin to sunlight
- brown skin
- hair loss
- increase in subcutaneous tissue nodules (in rheumatic diseases)
- shingles (herpes zoster)
- painful psoriasis
- joint or muscle pain
- osteoporosis (reduction of bone mass)
- inflammation and ulcers of the bladder (possibly with blood in the urine)
- painful urination
- acute allergic reaction
- inflammation and ulcers in the vagina
- slow wound healing

Rare side effects (affect 1-10 in 10,000 users)

- inflammation of the sac around the heart (pericarditis)
- fluids in the sac around the heart
- severe visual disturbance
- mood fluctuations
- low blood pressure
- blood clots
- sore throat
- breathing disorders
- asthma
- inflammation of the digestive tract
- bloody stool
- inflamed gums
- abnormal digestion
- acute inflammation of the liver (hepatitis)
- change in the colour of nails
- acne
- red or purple spots due to bleeding from blood vessels
- bone fractures
- kidney failure
- decrease or absence of urination
- electrolyte imbalance
- defective sperm formation
- menstruation disorders

Very rare side effects (affect less than 1 in 10,000 users)

- infections
- acute bone marrow suppression
- liver failure
- swollen glands
- sleeplessness
- pain
- muscle weakness
- sensation of pins and needles
- changes in sense of taste (metallic taste)
- inflammation of the lining of the brain causing paralysis or vomiting
- red eyes
- damage to the retina of the eye
- fluid in the lungs
- vomiting blood
- herpes (cold sores)
- protein in the urine
- fever
- loss of sex drive
- problems having an erection
- infection around a fingernail
- severe complication of the digestive tract (toxic megacolon)
- boils
- small blood vessels in the skin (spider veins)
- fungal infections
- damage to the blood vessels of the skin
- vaginal discharge
- infertility
- male breast enlargement (gynaecomastia)
- lymphoproliferative disorders (uncontrolled growth of white blood cells)
- hypersensitivity of the skin to sunlight. You may have a rash, redness, swelling or severe sunburn

Side effects of unknown frequency (the frequency of these effects has not been established yet)

- bleeding from the lungs (has been reported in patients with rheumatic disease taking methotrexate)
- bone damage in the jaw (secondary to uncontrolled growth of white blood cells)
- redness and shedding of skin

If you experience any side effect, if any side effect gets worse, or if you experience a side effect not mentioned in this leaflet, consult your doctor.

Reporting side effects
You can report side effects to the Ministry of Health by following the link 'Reporting Side Effects of Drug Treatment' on the Ministry of Health home page (www.health.gov.il) which links to an online form for reporting side effects. You can also use this link: https://sideeffects.health.gov.il

5. How to store the medicine?

Prevent poisoning! To prevent poisoning, keep this, and all other medicines, in a closed place, out of the reach and sight of children and/or infants. Do not induce vomiting unless explicitly instructed to do so by a doctor.
Do not use the medicine after the expiry date (exp. date) which is stated on the package. The expiry date refers to the last day of that month.

Storage conditions:
Store below 25°C.

Do not throw away any medicine, in particular Methotrexat "Ebewe" 2.5 mg Tablets, via wastewater or household waste (since this is a cytotoxic agent). Ask the pharmacist how to throw away medicines you no longer use. This will help protect the environment.

6. Additional information

In addition to the active ingredient, this medicine also contains:
lactose monohydrate, maize starch, microcrystalline cellulose, magnesium stearate, colloidal silicone dioxide

What the medicine looks like and contents of the pack
Light yellow round shaped tablets; may contain yellow and red particles.
Methotrexat "Ebewe" 2.5 mg tablets come in a blister pack of 10, 30 tables or in a plastic bottle pack that contains 50 tablets.
Not all pack sizes may be marketed.

License Holder and importer's name and address: Sandoz Pharmaceuticals Israel Ltd., P.O.Box 9015, Tel Aviv, Israel.

Revised in February 2025.

Registration number of the medicine in the National Drug Registry of the Ministry of Health: 129-29-30819-00