PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) - 1986
The medicine is dispensed with a doctor's prescription only

Imatinib-Trima 100 mg
Film-coated Tablets

Imatinib-Trima 400 mg
Film-coated Tablets

Composition:

Each film-coated tablet contains:

Imatinib (as mesylate) 100 mg

Each film-coated tablet contains:

Imatinib (as mesylate) 400 mg

Inactive ingredients: see section 6 "Further Information".

Read this leaflet carefully in its entirety before using the medicine. Keep this leaflet. You may need to read it again. 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 you. 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.

1. WHAT IS THE MEDICINE INTENDED FOR?

Imatinib-Trima is a medicine containing an active substance called imatinib. The medicine works by inhibiting the production of the abnormal cells in the diseases listed below, some of which are certain types of cancer.

- Imatinib-Trima is indicated for the treatment of adults and children 3 years of age and above, with Philadelphia chromosome-positive chronic myeloid leukemia in the chronic phase, accelerated phase or blast crisis phase.
- Imatinib-Trima is indicated for the treatment of adults with Kit-positive (CD117) metastatic malignant and/or unresectable gastrointestinal stromal tumors (GIST).
- Imatinib-Trima is indicated as an adjunct therapy in adults after complete tumor resection of the Kit-positive (CD117) GIST.
- Imatinib-Trima is indicated for the treatment of adults with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL), in combination with chemotherapy.
- Imatinib-Trima is indicated for the treatment of adults with relapsed or refractory Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL) as monotherapy.
- Imatinib-Trima is indicated for the treatment of adults with unresectable dermatofibrosarcoma protuberans (DFSP) and of adults with recurrent and/or metastatic DFSP who are not eligible for surgery.
- Imatinib-Trima is indicated for the treatment of adults with myeloproliferative or myelodysplastic diseases (MDS/MPD) associated with genetic changes in the PDGF receptor.
- Imatinib-Trima is indicated for the treatment of adults with hyper-eosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL), with or without a mutation in FIP1L1-PDGFRα fusion kinase.
- Imatinib-Trima is indicated for the treatment of adults with aggressive systemic mastocytosis (ASM) without the D816V c-kit mutation.

Therapeutic group: Antineoplastic

Chronic myeloid leukemia (CML) is a cancer of white blood cells. White blood cells usually help the body fight infection. In CML-type leukemia, certain abnormal white blood cells (called myeloid cells) start to grow uncontrollably.
GIST are cancerous tumors of the stomach and the bowels. They arise from uncontrolled growth of the cells in tissues that support these organs.
Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL) is a cancer of the white blood cells. The white blood cells usually help the body fight infection. In ALL-type leukemia, certain abnormal white blood cells (called lymphoblasts), start to grow uncontrollably. Imatinib-Trima inhibits growth of these cells.
Dermatofibrosarcoma protuberans (DFSP) is a malignant tumor of the tissue beneath the skin, in which some cells start growing uncontrollably. Imatinib-Trima inhibits growth of these cells.
Myeloproliferative or myelodysplastic diseases (MDS/MPD) is a group of blood diseases in which certain blood cells start to grow uncontrollably. Imatinib-Trima inhibits growth of these cells in a certain subtype of these diseases.
Hypereosinophilic syndrome or chronic eosinophilic leukemia (HES/CEL) is a group of blood diseases in which certain blood cells (called eosinophils) start to grow uncontrollably. Imatinib-Trima inhibits growth of these cells in a certain subtype of these diseases.
Aggressive systemic mastocytosis (ASM) are malignant tumors which cause the body to produce too many blood cells called mast cells.

2. BEFORE USING THE MEDICINE

Do not use the medicine if:

you are allergic (hypersensitive) to imatinib or any of the additional ingredients contained in the medicine detailed in section 6 "Further Information" in this leaflet. If this applies to you, **tell your doctor without taking Imatinib-Trima**. If you think you may be allergic, but are uncertain, consult with your doctor.

Special warnings regarding use of the medicine:

Before treatment with Imatinib-Trima, tell the doctor if:
- you are suffering, or have suffered in the past, from a liver, kidney, or heart problem.
- you are taking the medicine levothyroxine due to removal of the thyroid.
- you have ever had, or might now have, hepatitis B. This is because Imatinib-Trima could cause hepatitis B to become active again, which can lead to death in certain cases. Patients will be carefully checked by their doctor to detect signs of this inflammation before starting treatment.
- If you experience signs of bruising, bleeding, fever, tiredness and confusion during the course of treatment with Imatinib-Trima, contact your doctor. This may be a sign of damage to blood vessels called thrombotic microangiopathy (TMA).

If any of these apply to you, **tell the doctor before taking Imatinib-Trima.**
You may be more sensitive to the sun during treatment with Imatinib-Trima. It is important to cover sun-exposed areas of skin and use sunscreen with a high sun protection factor (high SPF). These precautions are also relevant for children.
Imatinib-Trima treatment will only be prescribed by a doctor with experience with medicines for treating blood cancer or solid tumors.
Follow the doctor's instructions carefully, even if they differ from the general information appearing in this leaflet.

During treatment with Imatinib-Trima, inform the doctor immediately if you gain weight very quickly. Imatinib-Trima may cause your body to retain water (severe fluid retention).

Children and adolescents (below 18 years of age)
Imatinib-Trima is given to children from the age of 3 years and above for CML.
For the other indications, Imatinib-Trima is not indicated for children and adolescents below 18 years of age. In some children and adolescents taking Imatinib-Trima, growth may be slower than normal. The doctor will monitor the growth at regular visits.

Tests and follow up
The doctor will monitor your condition regularly, to check whether the desired effect of Imatinib-Trima treatment is being obtained. You will be asked to regularly perform blood tests to see if you are tolerating Imatinib-Trima (e.g., blood cells, liver and kidney function, thyroid function). You will be weighed regularly during the course of treatment with Imatinib-Trima.

Drug interactions
If you are taking, or have recently taken, other medicines, including non-prescription medicines (such as paracetamol) or nutritional supplements (such as St. John's wort), tell the doctor or pharmacist. Some medicines can interfere with the effect of Imatinib-Trima when taken together. They may increase or decrease the effect of Imatinib-Trima, lead to increased side effects or make Imatinib-Trima less effective. Imatinib-Trima may do the same to some other medicines.
In particular, tell the doctor if you are taking:

Medicines which may increase blood Imatinib-Trima levels:
some medicines used to treat AIDS (HIV), such as indinavir, lopinavir/ritonavir, ritonavir, saquinavir or nelfinavir;
some medicines used to treat hepatitis C, such as telaprevir or boceprevir;
some medicines used to treat fungal infections, such as ketoconazole, itraconazole, posaconazole, voriconazole;
some medicines used to treat bacterial infections, such as erythromycin, clarithromycin or telithromycin.
Exercise caution if you are taking a medicine which may increase blood Imatinib-Trima levels.

Medicines which may lower blood Imatinib-Trima levels:
dexamethasone, an anti-inflammatory steroidal medicine;
some medicines used to treat epilepsy, such as phenytoin, carbamazepine, oxcarbazepine, phenobarbital, fosphenytoin or primidone;
rifampicin, a medicine to treat tuberculosis;
Hypericum perforatum (also known as St. John's wort) - a herbal product to treat depression and other conditions.

Use of the above medicines should be avoided during the course of treatment with Imatinib-Trima. If you are taking any of the aforementioned medicines, the doctor may prescribe other medicines for you.

Medicines whose blood levels may increase due to use of Imatinib-Trima:
cyclosporine, an immunosuppressant medicine;
warfarin, a medicine to treat blood coagulation disorders (such as blood clots and thrombosis); or other medicines for treatment of blood coagulation disorders;
sirolimus, tacrolimus - medicines to prevent rejection of a transplanted organ in patients who have undergone organ transplantation;
fentanyl, alfentanil - medicines to treat pain;
terfenadine, to treat allergy;
bortezomib, docetaxel, medicines to treat cancer;
quinidine;
some medicines from the statin family, that treat high cholesterol level, such as simvastatin;
some medicines to treat mental disorders, such as benzodiazepines or pimozide;
some medicines to treat hypertension or heart disorders, such as calcium channel blockers or metoprolol;
ergotamine, diergotamine to treat migraine;
paracetamol.

Medicines whose blood levels may decrease following use of Imatinib-Trima:
levothyroxine – a medicine given following removal of the thyroid.
In addition, inform the doctor **if you are already taking Imatinib-Trima** and have been prescribed a new medicine, including non-prescription medicines that you have not taken previously during Imatinib-Trima treatment.

Use of the medicine and food
Take Imatinib-Trima with a meal to protect your stomach.

Pregnancy, breastfeeding, and fertility
If you are pregnant or breastfeeding, think you may be pregnant or are planning a pregnancy, consult a doctor before using the medicine.
Imatinib-Trima is not recommended for use during pregnancy unless clearly necessary, as it may harm your baby. Your doctor will discuss with you the risks associated with taking Imatinib-Trima during pregnancy.
Women of child-bearing age must use effective contraception during the course of treatment with Imatinib-Trima and for 15 days after completing the treatment.
Do not breast-feed during treatment with Imatinib-Trima and for 15 days after completing the treatment, as it may harm your baby.
Patients concerned about their fertility during the course of treatment with Imatinib-Trima should consult a doctor.

Driving and using machinery
If you experience dizziness or drowsiness, or if you have blurred vision while using Imatinib-Trima, do not drive a vehicle or operate any tools or machines until you feel well.
Children should be cautioned against riding a bicycle or playing near roads and the like.

3. HOW SHOULD YOU USE THE MEDICINE?

The doctor has prescribed Imatinib-Trima for you because you suffer from a serious illness. Imatinib-Trima can help you fight this disease.
Always use the preparation according to the doctor's instructions. It is important that you do so for as long as instructed by a doctor. Check with the doctor or pharmacist if you are uncertain about the dosage and treatment regimen of the preparation. The dosage and treatment regimen will be determined by the doctor only.
The usual dosage is generally:
Use in adults
Your doctor will tell you exactly how many tablets of Imatinib-Trima to take.
If you are being treated for chronic myeloid leukemia (CML): Depending on your condition, the recommended dosage is either 400 mg or 600 mg to be taken **once** a day.
If you are being treated for gastrointestinal stromal tumors (GIST):
The recommended dosage is 400 mg, to be taken **once** a day. For treatment of CML and GIST diseases, your doctor may prescribe a higher or lower dosage depending on how you respond to the treatment.
If the doctor decides on a daily dosage of 800 mg, take 400 mg in the morning and 400 mg in the evening.
If you are being treated for Ph-positive acute lymphoblastic leukemia (ALL):
The recommended dosage is 600 mg to be taken **once** a day.
If you are being treated for myelodysplastic/ myeloproliferative diseases (MDS/MPD):
The recommended dosage is 400 mg to be taken **once** a day.
If you are being treated for hypereosinophilic syndrome/ chronic eosinophilic leukemia HES/CEL:
The recommended dosage is 400 mg, to be taken **once** a day.
In certain cases, the doctor may recommend a starting dosage of 100 mg **once** a day, and, if necessary, the doctor will consider increasing the dosage to 400 mg **once** a day, depending on your reaction to treatment.
If you are being treated for dermatofibrosarcoma protuberans (DFSP):
The recommended dosage is 800 mg per day, to be taken as 400 mg in the morning and 400 mg in the evening.
If you are being treated for aggressive systemic mastocytosis (ASM):
The recommended dosage is 400 mg **once** per day.
In certain cases, the doctor may recommend a starting dosage of 100 mg **once** a day, and, if necessary, the doctor will consider increasing the dosage to 400 mg **once** a day, depending on your reaction to treatment.

A 400 mg dosage can be taken either as one tablet of 400 mg or four tablets of 100 mg.
A 600 mg dosage is to be taken as one tablet of 400 mg plus two tablets of 100 mg.
The dosage determined by the doctor may change, depending on your reaction to treatment.

Use in children and adolescents
The doctor will instruct you how many tablets of Imatinib-Trima to give to your child. The dosage of Imatinib-Trima given will depend on your child's condition, body weight and height.
For patients with CML, the maximal dosage for children should not exceed 600 mg.
The treatment can be given to your child either as a once-daily dose or alternatively, the daily dose can be split into two administrations (half in the morning and half in the evening).
Do not exceed the recommended dose.

Duration of treatment
Take Imatinib-Trima every day, until your doctor instructs you to stop.

Method of administration
Take Imatinib-Trima with a meal. This will help protect you from stomach problems while taking Imatinib-Trima.
Swallow the tablets whole with a large glass of water.
If you are unable to swallow the tablets, you can dissolve them into a glass of water or apple juice in the following manner:
- Use approximately 50 ml for a 100 mg tablet or 200 ml for a 400 mg tablet.
- Stir with a spoon until the tablet(s) is/are completely dissolved.
- After the tablet(s) dissolve(s), drink the entire contents of the whole glass immediately. Traces of the dissolved tablet(s) may be left in the glass.

You may split the tablets.
Do not crush the tablets.
Avoid direct contact of the skin or mucous membranes with split tablets or accidentally broken/crushed tablets. If such contact occurs, rinse thoroughly. Avoid exposure to crushed tablets.

If you accidentally took a higher dosage
If you took an overdose, or if a child has accidently swallowed the medicine, refer to the doctor immediately or proceed to a hospital emergency room and bring the medicine package with you. You may need medical supervision.

If you forget to take the medicine
If you forgot to take this medicine at the designated time, take it as soon as you remember.
However, if it is almost time to take the next dose, do not take the forgotten dose.
Thereafter, continue taking the medicine as per the regular schedule.
Do not take a double dose to compensate for a forgotten dose.
Adhere to the treatment regimen recommended by the doctor. Even if there is an improvement in your health, do not stop treatment with the medicine without consulting a doctor.
If you are unable to take the medicine as prescribed by the doctor or if you feel you no longer need it, consult the doctor immediately.

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 Imatinib-Trima may cause side effects in some users. Do not be alarmed by the list of side effects. You may not experience any of them. These side effects are usually mild to moderate.

Some side effects may be serious. Refer to a doctor immediately if you experience any of the side effects listed below:

Very common (occur in more than 1 user in 10) or common (occur in 1-10 users in 100) side effects:
- Rapid weight gain. Imatinib-Trima may cause your body to retain water (severe fluid retention);
- Signs of infection such as: fever, severe chills, sore throat or mouth ulcers. Imatinib-Trima may cause reduction in white blood cells, so you might get infections easily;
- Unexpected bleeding or signs of bruising (when you have not been injured).

Uncommon (occur in 1-10 users in 1,000) or rare (occur in 1-10 users in 10,000) side effects:
- Chest pain, irregular heart rhythm (signs of heart disorders);
- Cough, difficulty breathing, or pain when breathing (signs of lung disorders);
- Light-headedness, dizziness or fainting (signs of low blood pressure);
- Nausea with loss of appetite, dark-colored urine, yellowing of the eyes or skin (signs of liver disorders);
- Rash, red skin with blisters on the lips, eyes, skin or mouth, peeling skin, fever, raised red or purple skin patches, itching, burning sensation, pustular rash (signs of a skin disorder);
- Severe abdominal pain, vomiting blood, black or bloody stools (signs of gastrointestinal disorders);
- Blood in the urine;
- Severely decreased urine output, feeling thirsty (signs of kidney disorders);
- Nausea with diarrhea and vomiting, abdominal pain or fever (signs of bowel disorders);
- Severe headache, weakness or paralysis of the limbs or face, difficulty speaking, sudden loss of consciousness (signs of problems in nervous system function such as bleeding or swelling in skull/brain);
- Pale skin, tiredness, breathlessness and dark urine (signs of low levels of red blood cells);
- Eye pain or deterioration in vision, bleeding in the eyes;
- Pain in the bones or joints (signs of osteonecrosis);
- Blisters on skin or mucous membranes (signs of pemphigus);
- Numbness or coldness in fingers and toes (signs of Raynaud's syndrome);
- Sudden swelling and redness of the skin (signs of a skin inflammation called cellulitis);
- Difficulty hearing;
- Muscle weakness and muscle spasms with an abnormal heart rhythm (signs of changes in the level of blood potassium);
- Signs of bruising;
- Stomach pain with nausea;
- Muscle spasms with a fever, red-brown urine, muscle pain or weakness (signs of muscle disorders);
- Pelvic pain occasionally accompanied by nausea and vomiting, with unexpected vaginal bleeding, feeling dizzy or fainting due to low blood pressure (signs of disturbances in the ovaries or womb);
- Nausea, shortness of breath, irregular heartbeat, cloudy urine, tiredness and/or joint discomfort accompanied by abnormal laboratory test results (e.g., high potassium, uric acid and calcium levels and low phosphorous levels in the blood);
- Blood clots in small blood vessels (thrombotic microangiopathy).

Side effects of unknown frequency (effects whose frequency has not yet been established):
- Combination of a widespread severe rash, nausea, fever, high levels of certain white blood cells or yellow skin or eyes (signs of jaundice) with breathlessness, chest pain/discomfort, severely decreased urine output and feeling of thirst (signs of a treatment-related allergic reaction);
- Chronic renal failure;
- Recurrence (reactivation) of hepatitis B, if you have had hepatitis in the past (a liver infection).

If you experience any of these effects, **refer to the doctor immediately.**

Additional side effects:
Refer to a doctor if any of the side effects listed below affects you severely:
Very common side effects (occur in more than 1 user in 10):
- Headache or feeling tired;
- Nausea, vomiting, diarrhea or indigestion, abdominal pain;
- Rash;
- Muscle cramps, muscle, bone or joint pain during treatment with Imatinib-Trima or after discontinuing treatment with Imatinib-Trima;
- Swelling, e.g., around the ankles or puffy eyes;
- Weight gain;
- Anemia (reduced red blood cells).

Common side effects (occur in 1-10 users in 100):
- Anorexia, weight loss or a disturbed sense of taste;
- Feeling dizzy or weak;
- Sleeping difficulties (insomnia);
- Discharge from the eye with itching, redness and swelling (conjunctivitis), watery eyes or blurred vision, swollen eyelids;
- Nosebleeds;
- Pain or swelling in the abdomen, flatulence, heartburn or constipation;
- Itching;
- Unusual hair loss or thinning;
- Numbness of the hands or feet, paresthesia;
- Mouth ulcers;
- Pain with swelling of the joints;
- Dry mouth, skin or eyes;
- Decreased or increased skin sensitivity;
- Hot flushes, chills or night sweats;
- Erythema;
- Shortness of breath, cough;
- Increased liver enzymes.

Uncommon side effects (occur in 1-10 users in 1,000):
Painful red lumps on the skin, skin pain, skin reddening (inflammation of fatty tissue under the skin); cough, runny or stuffy nose, feeling of pressure or pain when pressing the area above the eyes or on the sides of the nose, nasal congestion, sneezing, sore throat, blocked nose, sore throat, with or without headache (signs of upper respiratory tract infection); severe headache felt as a throbbing pain or pulsing sensation, usually on one side of the head and sometimes accompanied by nausea, vomiting and photosensitivity (signs of migraine); flu-like symptoms; pain or burning sensation while passing urine, increased body temperature, pain in groin or pelvic area, red- or brown-colored or cloudy urine (signs of urinary tract infection); pain and swelling of the joints (signs of arthralgia); a constant feeling of sadness and loss of interest, which stops you carrying out your normal activities (signs of depression); a feeling of apprehension and worry along with physical symptoms such as pounding heart, sweating, trembling, dry mouth (signs of anxiety); sleepiness, drowsiness, excessive sleep; trembling/shaky movements (tremor); memory disorder; overwhelming urge to move the legs (restless leg syndrome); hearing noises (ringing, humming) in the ears that have no external source (tinnitus); hypertension; hematomas; burping; inflammation of the lips; difficulty swallowing; increased sweating; skin discoloration; brittle nails; red bumps or white-headed pimples around the roots of the hair, possibly with pain, itching or burning sensation (signs of inflammation of the hair follicles, also called folliculitis); skin rash with flaking or peeling (dermatitis); breast enlargement in men and women; dull pain or feeling of heaviness in the testicles or lower abdomen, pain during urination, sexual intercourse or ejaculation, blood in urine (signs of edema of the testicles); inability to get or keep an erection (erectile dysfunction); heavy or irregular menstrual period, difficulty achieving/maintaining sexual arousal; decreased sexual desire; nipple pain; generally feeling unwell (malaise), viral infection such as cold sore; lower back pain resulting from kidney disturbance; increased frequency of passing urine; increased appetite; pain or burning sensation in upper abdomen or chest (heartburn); nausea, vomiting, acid reflux, feeling of fullness and bloating, black-colored stools (signs of stomach ulcer); joint and muscle stiffness; abnormal laboratory test results; eye irritation, eye pain or redness, swelling/itching of the eyelids; excessive heartbeats; peripheral coldness; thickened red patches around the elbows and knees (psoriasis); darkening of the skin; chest pain (angina pectoris); swollen lymph nodes.

Rare side effects (occur in 1-10 users in 10,000):
Confusion, nail discoloration, fungal infection, cardiac arrest, seizures, glaucoma, cataract, arthritis.

Side effects whose frequency is unknown (effects whose frequency has not yet been established):
- Reddening and/or swelling on the palms of the hands and soles of the feet, which may be accompanied by a tingling sensation and burning pain;
- Skin lesions that are painful and/or covered with blisters;
- Slowed growth in children and adolescents.

Side effects in patients with aggressive systemic mastocytosis (ASM)
All patients with aggressive systemic mastocytosis (ASM) experienced at least one side effect at some point.

Side effects that were reported at the highest frequency were: diarrhea, nausea, ascites, muscle cramps, shortness of breath, tiredness, peripheral edema, anemia, itch, rash and lower respiratory tract inflammation.

If a side effect occurs, if one of the side effects worsens, or if you suffer from a side effect not mentioned in the leaflet, consult your doctor.

Side effects can be reported to the Ministry of Health by clicking on the link "Reporting Side Effects of Drug Treatment" found on the Ministry of Health homepage (www.health.gov.il) that directs you to the online form for reporting side effects, or by entering the link: https://sideeffects.health.gov.il
You can also report by email to safety@trima.co.il

5. HOW TO STORE THE MEDICINE

Avoid poisoning! This medicine, and any other medicine, should be kept in a closed place out of the reach and sight of children and/or infants in order to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by a doctor.
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.
Store in a dry place, below 25°C.
Store in the original package.
Protect from moisture.
Do not use if the package is damaged or shows signs of tampering.
Do not discard medicines in the wastewater or household waste bin. Ask the pharmacist how to dispose of medicines that are no longer in use. These measures will help protect the environment.

6. FURTHER INFORMATION

In addition to the active ingredient, the medicine also contains:
Inactive ingredients:
mannitol, povidone, magnesium stearate, colloidal silicon dioxide.
The film-coating contains:
HPMC, titanium dioxide, talc, polyethylene glycol, iron oxide yellow, iron oxide red, iron oxide black.
What the medicine looks like and the contents of the package:
Imatinib-Trima 100 mg – round, mocha-colored, biconvex, film-coated tablet with a score line on one side.
Imatinib-Trima 400 mg – oblong, mocha-colored, biconvex, film-coated tablet with a score line on one side.

Packs contain 10/20/30/60 tablets packaged in blisters (not all package sizes may be marketed).

Name and address of manufacturer and registration holder: Trima Israel Pharmaceutical Products Maabarot LTD., Maabarot 4023000, Israel.

Revised in July 2023 according to the MOH guidelines.

Registration numbers of the medicine in the National Drug Registry of the Ministry of Health:
Imatinib-Trima 100 mg film-coated tablets: 157-59-34527-00
Imatinib-Trima 400 mg film-coated tablets: 157-60-34379-00

Maabarot 4023000
Israel Pharmaceutical Products
Maabarot Ltd.

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