

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

<b>Imatinib-Trima 100 mg Film-coated Tablets</b>	<b>Imatinib-Trima 400 mg Film-coated Tablets</b>
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**Composition:**

Each film-coated tablet contains:	Each film-coated tablet contains:
100 mg imatinib (as mesylate)	400 mg imatinib (as mesylate)

**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 your 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 that contains the active ingredient imatinib. This medicine works by inhibiting production of abnormal cells in the diseases listed below; some of these diseases are certain types of cancer.

Imatinib-Trima is indicated for treating adults and children over 3 years old who have Philadelphia chromosome-positive chronic myeloid leukemia in the chronic phase, accelerated phase or in blast crisis phase.

Imatinib-Trima is indicated for treating adults who have been newly diagnosed with Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL), in combination with chemotherapy.

Imatinib-Trima is indicated for treating adults with relapsed or refractory Philadelphia chromosome-positive ALL, as a monotherapy.

Imatinib-Trima is indicated for treating adults with unresectable dermatofibrosarcoma protuberans (DFSP), and adults with recurrent and/or metastatic DFSP who are not eligible for surgery.

Imatinib-Trima is indicated for treating adults with myeloproliferative or myelodysplastic diseases (MDS/MPD) associated with genetic changes in the PDGFR receptor.

Imatinib-Trima is indicated for treating adults with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL).

Imatinib-Trima is indicated for treating adults with aggressive systemic mastocytosis (ASM) without the D816V c-kit mutation.

**Therapeutic group:** antineoplastic.

CML is a cancer of the blood which causes the body to produce too many abnormal white blood cells called myeloid cells.

ALL is a cancer of the blood which causes the body to produce too many abnormal white blood cells called lymphoblast cells.

DFSP is a cancer of the tissue beneath the skin, in which some cells start growing uncontrollably.

MDS/MPD is a group of blood diseases which cause the body to produce too many abnormal blood cells.

HES/CEL is a group of blood diseases which cause the body to

produce too many blood cells called eosinophils.

SM are cancerous tumors which cause the body to produce too many blood cells called mast cells.

### 2. BEFORE USING THE MEDICINE

<b>X Do not use the medicine if:</b>
You are allergic (hypersensitive) to imatinib or any of the other ingredients of the medicine listed in section 6 "Further Information" in this leaflet. If this applies to you, <b>tell your doctor without taking Imatinib-Trima.</b> If you think you may be allergic but are uncertain, ask your doctor for advice.

**Special warnings regarding use of the medicine:**

**⚠ Before starting 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. Imatinib-Trima could cause hepatitis B to become active again, which can be fatal in some cases. Patients will be carefully checked by their doctor to identify signs of this inflammation before starting treatment.

If any of these apply to you, **tell your doctor before taking Imatinib-Trima.**

Imatinib-Trima treatment can only be prescribed by a doctor with experience with medicines for treating blood cancer or cancerous tumors.

Follow the doctor's instructions carefully, even if they differ from the general information contained in this leaflet.

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

During treatment with Imatinib-Trima, your doctor will regularly check that the medicine is working. You will also undergo blood tests and be weighed regularly.

**⚠ If you are taking, or have recently taken, other medicines, including non-prescription medicines and nutritional supplements, tell your doctor or pharmacist.** Especially if you are taking:

**Medicines which may increase blood Imatinib-Trima levels:**

- some medicines used to treat infections, such as: ketoconazole, itraconazole, posaconazole, voriconazole, erythromycin, clarithromycin, or telithromycin;
- 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;
- exercise caution if you are taking a medicine which may increase blood Imatinib-Trima levels.

**Medicines which may lower blood Imatinib-Trima levels:**

- some medicines used to treat epilepsy, such as: carbamazepine, oxcarbazepine, phenobarbital, phenytoin, fosphenytoin, or primidone;
- rifampicin, a medicine used to treat tuberculosis;
- St. John's Wort (also known as Hypericum perforatum) - a herbal product used to treat depression and other conditions;

- dexamethasone, an anti-inflammatory steroidal medicine.

Avoid using the medicines listed above during the course of treatment with Imatinib-Trima. If you are taking any of the medicines listed above, your doctor may replace them with other medicines.

**Using Imatinib-Trima may raise blood levels of the following medicines:**

- cyclosporine, an immunosuppressant;
- warfarin, a medicine used to treat blood coagulation disorders (such as blood clots and thrombosis);
- tacrolimus, sirolimus, medicines used to prevent rejection of a transplanted organ in patients who have undergone organ transplantation;
- fentanyl, alfentanil, fentanyl, bortezomib, docetaxel or quinidine;
- some medicines from the statin family, used to treat high cholesterol level, such as: simvastatin;
- some medicines used to treat mental disorders, such as: benzodiazepines or pimozide;
- some medicines used to treat high blood pressure or heart disorders, such as: calcium channel blockers or metoprolol;
- paracetamol.

**Using Imatinib-Trima may decrease blood levels of the following medicines:**

- Levothyroxine, a medicine given following removal of the thyroid.

In addition, inform your 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

To protect your stomach, take Imatinib-Trima with a meal.

#### ⚠ Pregnancy and breast-feeding

**If you are pregnant or breast-feeding, think you may be pregnant or are planning a pregnancy, consult a doctor or pharmacist before using this 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.

Do not breast-feed during treatment with Imatinib-Trima.

Before starting treatment consult your doctor regarding fertility, if relevant.

#### ⚠ Women of childbearing age

Women of childbearing age must use effective contraception while taking this medicine.

#### ⚠ Elderly people (65 years and older)

Imatinib-Trima can be used in people who are 65 years and older at the same dosage as other adults.

#### ⚠ Children and adolescents (under 18 years old)

Imatinib-Trima can be given to children age 3 years and up who have CML. Growth may be slower than normal in some children and adolescents taking Imatinib-Trima. The doctor will monitor growth on regular visits.

#### ⚠ Driving and using machines

If you experience symptoms like dizziness or drowsiness or if you have blurred vision while using Imatinib-Trima, avoid driving a vehicle or operating 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?

Your doctor has prescribed you with Imatinib-Trima because you have a serious condition. Imatinib-Trima can help you fight this disease. Always use according to the doctor's instructions. Check with your doctor if you are not sure. The dosage and treatment regimen will be determined by the doctor only. The dose determined by your doctor may be changed depending on your response to treatment.

**Do not exceed the recommended dose you were prescribed.**

**Take Imatinib-Trima with a meal; this will help protect your stomach. Swallow the tablets whole with a large glass of water.**

If you are unable to swallow the tablets, you can stir them into a glass of water or apple juice in the following manner:

- Put the tablet(s) in a glass with a sufficient quantity of liquid (approximately 50 ml for a 100-mg tablet and approximately 200 ml for a 400-mg tablet).
- Stir with a spoon until the tablet(s) is/are completely disintegrated.
- Once the tablet(s) has fully disintegrated, drink the entire contents of the glass immediately. Traces of the disintegrated tablet(s) may be left in the glass.

You may split tablets to adjust the dose.

Do not crush the tablets.

Avoid direct contact with the skin or mucous membranes if you split the tablets or they accidentally break or get crushed. If such contact occurs, wash thoroughly. Avoid exposure to crushed tablets.

Use this medicine at specified intervals as prescribed by your doctor.

Take Imatinib-Trima every day until your doctor tells you to stop. Complete the full course of treatment recommended by your doctor.

**Use in children and adolescents**

The doctor will tell you how many Imatinib-Trima tablets to give your child. The Imatinib-Trima dose prescribed to your child depends on the child's condition, body weight, and height.

**Tests and follow-up**

Your doctor will monitor your condition regularly to check if the desired result of the Imatinib-Trima treatment is achieved. You will be asked to regularly undergo blood tests in order to see how well you are tolerating Imatinib-Trima (for example: blood cells, liver and kidney functions, thyroid function). You will be weighed regularly during treatment with Imatinib-Trima.

**If you accidentally took a higher dosage**

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

**If you forget to take the medicine**

If you forget to take this medicine at the specified 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. Continue taking the medicine according to the regular schedule. Do not take a double dose to compensate for a forgotten dose.

Adhere to the treatment as recommended by the doctor.

Even if there is an improvement in your health, do not stop 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 your 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 this list of side effects. You may not experience any of them. 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 patients) or common (occur in 1-10 users in 100 patients) 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 can reduce the number of 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 patients) or rare (occur in 1-10 users in 10,000 patients) side effects:**

- chest pain, irregular heart beat (signs of heart disorders);
- cough, difficulty breathing, chest 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);
- severe rash, red skin with blisters on the lips, eyes, skin or mouth, peeling skin, fever, raised red or purple patches on the skin, itching, burning, pustular eruption (signs of skin disorders);
- 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 problems);
- nausea with diarrhea and vomiting, abdominal pain, or fever (signs of bowel function disorders);
- severe headache, weakness or paralysis of limbs or face, difficulty speaking, sudden loss of consciousness (signs of nervous system problems such as bleeding or swelling in the skull/brain);
- pale skin, tiredness, breathlessness, and dark urine (signs of low levels of red blood cells);
- eye pain, deterioration in vision, bleeding in the eyes;
- hips pain or difficulty walking;
- numb or cold toes and fingers (signs of Raynaud's Syndrome);
- sudden swelling and redness of the skin (signs of a skin inflammation called cellulitis);
- reduced hearing;
- muscle weakness and spasms with an abnormal heart rhythm (signs of changes in blood potassium levels);
- 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 sometimes with nausea and vomiting, with unexpected vaginal bleeding, feeling dizzy or fainting due to low blood pressure (signs of problems in the ovaries or womb);
- nausea, breathlessness, irregular heartbeat, cloudy urine,

tiredness and/or joint discomfort associated with abnormal laboratory test results (such as high potassium, uric acid, and calcium levels, and low phosphorous levels in the blood).

**Side effects of unknown frequency:**

- combination of 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 thirsty (signs of a treatment-related allergic reaction);
- chronic kidney failure;
- recurrence (reactivation) of hepatitis B if you have had viral hepatitis in the past (a liver infection).

If you experience any of the above 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 patients):**

- headache or feeling tired; nausea, diarrhea, vomiting, indigestion; rash; muscle cramps, muscle, bone or joint pain during treatment or after completing treatment with this medicine; swelling around the ankles or puffy eyes; weight gain.

**Common side effects (occur in 1-10 users in 100 patients):**

- 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; nose bleeds; stomach pain or swelling, flatulence, heartburn or constipation; itching; unusual thinning or loss of hair; numbness in the hands or feet; mouth ulcers; painful swollen joints; dry mouth, skin or eyes; decreased or increased skin sensitivity; hot flushes, chills or night sweats.

**Uncommon side effects (occur in 1-10 users in 1,000 patients):**

- upper respiratory tract infection leading to cough, runny or stuffy nose, nasal congestion, sneezing, sore throat, headache, facial pressure; severe headache, sometimes accompanied by nausea, vomiting and sensitivity to light (signs of migraine); flu-like symptoms, urinary tract infection, depression, anxiety, sleepiness, tremor, memory disorder, urge to move a part of the body (usually the leg) to stop the uncomfortable sensation, eye irritation, eye pain or redness, puffy or itchy eyelids, spinning sensation/dizziness, noises (ringing) in the ears, heartbeats with many extra beats, hypertension, peripheral coldness, belching, inflammation of the lips, difficulty swallowing, increased sweating, skin discoloration, brittle nails, broken fingernails and toenails, inflammation of hair follicles, thickened red patches around the elbows and knees, darkening of skin, breast enlargement in men and women, edema of the testicles, erection disorder, heavy or irregular menstruation, sexual disorder, nipple pain, chest pain, feeling generally unwell, viral infection such as cold sores, back pain resulting from kidney disorder, increased urination, increased appetite, ulcer in stomach, joint and muscle stiffness, abnormal laboratory test results.

**Rare side effects (occur in 1-10 users in 10,000 patients):**

- Confusion, nail discoloration.

**Side effects of unknown frequency (the frequency cannot be determined based on the existing data):**

- Reddening and/or swelling of the palms of the hands and soles of the feet which may be accompanied by a tingling sensation and painful burning sensation; slowed growth in children and

adolescents.

If a side effect occurs, if any of the side effects worsen, or if you experience a side effect not mentioned in the leaflet, consult the 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" found on the Ministry of Health homepage ([www.health.gov.il](http://www.health.gov.il)) that directs you to the online form for reporting side effects, or by entering the link:

<https://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdverseEffectMedic@moh.gov.il>

You can also report to mail: [safety@trima.co.il](mailto:safety@trima.co.il)

### 5. HOW TO STORE THE MEDICINE

- Avoid poisoning! This medicine, and any other medicine, must be stored in a safe place out of the reach of children and/or infants, to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by a doctor.
- Even if kept in their original package and stored as recommended, medicines may be kept for a limited period only. Please note the expiry date of the medicine! Do not use this medicine after the expiry date (exp. date) which is indicated 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.
- Keep out of the reach and sight of children.
- Do not store different medicines in the same package.
- Do not use if the package is damaged or shows signs of tampering.

### 6. FURTHER INFORMATION

**In addition to the active ingredient, the medicine also contains inactive ingredients:**

Mannitol, povidone, magnesium stearate, colloidal silicon dioxide, HPMC, titanium dioxide, polyethylene glycol, talc, iron oxide yellow, iron oxide red, iron oxide black

**What the medicine looks like and what are the contents of the package:**

Imatinib-Trima 100 mg – round, biconvex, mocha colour film-coated tablets with a score line on one side.

Imatinib-Trima 400 mg – oblong, biconvex, mocha colour film-coated tablets with a score line on one side.

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

**Manufacturer and registration holder:** Trima Israel Pharmaceutical Products Maabarot Ltd. Maabarot 4023000, Israel.

**Medicine registration numbers 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

This leaflet was checked and approved by the Ministry of Health in: February 2017

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