

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

The medicine is dispensed with a doctor’s prescription only

EVETOR 2.5, 5, 10 Tablets

Composition:

Each tablet contains:

Evetor 2.5: Everolimus 2.5 mg

Evetor 5: Everolimus 5 mg

Evetor 10: Everolimus 10 mg

Inactive and allergenic ingredients in the preparation: See section 2 “Important information regarding some of the ingredients of the medicine” and section 6 “Further Information”.

Read the 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. Do not pass it on to others. It may harm them even if it seems to you that their ailment is similar.

1. WHAT IS THE MEDICINE INTENDED FOR?

Evetor 2.5, 5, 10 is intended for:

- Treatment of patients with a brain tumor of the subependymal giant cell astrocytoma (SEGA) type associated with tuberous sclerosis complex (TSC) for whom surgery is not appropriate.
- Treatment of adult patients with a kidney tumor known as angiomyolipoma (AML) when the kidney tumor does not require immediate surgery. This type of tumor is connected with a genetic condition known as tuberous sclerosis complex.
- Treatment of patients with advanced neuroendocrine tumors of pancreatic origin that cannot be surgically removed, that are locally advanced or have metastasized.
- Treatment of advanced hormone receptor-positive and HER2-negative breast cancer, in conjunction with exemestane, in postmenopausal women without symptomatic metastatic disease spread to internal organs, after recurrence or progression of the disease following treatment with non-steroidal aromatase inhibitors.
- Treatment of advanced kidney cancer (advanced renal cell carcinoma [RCC]), after other treatments that target vascular endothelial growth factor (VEGF-targeted therapy) have not helped stop the disease.
- Treatment of locally advanced, metastatic or unresectable, well-differentiated (1 or 2) non-functional neuroendocrine tumors of lung or gastrointestinal origin in adults with progressive disease.

Therapeutic group: Anticancer medicine

Evetor is a medicine whose active ingredient is called everolimus. It is an anti-tumor medicine which reduces the blood supply to cancer cells and can thus reduce the growth and spread of cancer cells.

Evetor can also reduce the size of kidney tumors called renal angiomyolipomas and SEGA brain tumor cells. The latter two tumors are caused by a genetic disorder called tuberous sclerosis complex (TSC).

2. BEFORE USING THE MEDICINE

Evetor will only be prescribed to you by a doctor with experience in treating cancer or by a specialist in the treatment of patients with tuberous sclerosis complex.

Follow all the doctor’s instructions carefully. They may differ from the general information contained in this leaflet.

If you have any questions about **Evetor** or why it has been prescribed for you, refer to the doctor.

Do not use the medicine if:

- You are allergic** (hypersensitive) to everolimus, to similar substances such as sirolimus, temsirolimus, or to any of the other ingredients contained in the medicine and that are listed in section 6 “Further Information” of this leaflet. If you have had an allergic reaction in the past or if you think you are allergic, consult the doctor.

Special warnings regarding use of the medicine
Before treatment with Evetor, tell the doctor if:

- You have any problems with your liver or you have previously had any diseases which may have affected your liver. If this is the case, your doctor may need to prescribe a different dose of **Evetor** or stop treatment temporarily or permanently.
- You have diabetes (high blood sugar levels). **Evetor** may cause an increase in blood sugar levels and worsen diabetes. This may lead to a need for medication such as insulin and/or an oral anti-diabetic medicine. Tell the doctor if you experience increased thirst or an increased frequency of urination.
- You need to receive a vaccine during treatment with **Evetor**, as the vaccination may be less effective. It is important to consult with the doctor about children suffering from brain tumors of the SEGA type, regarding completion of a childhood series of vaccinations before treatment with **Evetor**.
- You have a high level of cholesterol. **Evetor** may elevate the level of cholesterol and/or other blood lipids.
- You have recently undergone major surgery, or if you still have an unhealed wound as a result of the surgery. **Evetor** may increase the risk of problems with wound healing.
- You have any sort of infection. It may be necessary to treat

your infection before starting treatment with **Evetor**.

- You have previously had a viral liver inflammation of type B (hepatitis B), as it may be reactivated during your treatment with **Evetor** (see section 4: “Side effects”).
- You suffer, or have suffered in the past, from kidney problems.
- You have received or are about to receive radiation treatment (radiotherapy).

In addition, Evetor may:

- Weaken your immune system. Therefore, you may be at risk of getting an infection while you are taking **Evetor**. If you develop a fever or show other signs of an infection, consult the doctor. Some infections may be severe and may have fatal consequences in adults and children.
- Impact your kidney function. Therefore, the doctor will monitor your kidney function while you are taking **Evetor**.
- Cause shortness of breath, cough and fever (see also section 4 “Side effects”).
- Cause development of mouth sores (mouth ulcers). The doctor might change or stop your **Evetor** treatment. You may need treatment with a mouthwash, gel or other product. Some mouthwashes and gels can make ulcers worse, so do not try anything without first checking with the doctor. The doctor might restart treatment with **Evetor** at the same dose or at a lower dose.

- Cause complications with radiation therapy. Severe complications of radiation therapy (such as shortness of breath, nausea, diarrhea, skin rashes and soreness in the mouth, gums and throat), including fatalities, have been observed in some patients who were taking everolimus concomitantly with radiation treatment, or who took everolimus shortly after undertaking radiation therapy. In addition, so called “radiation recall syndrome”, comprising skin redness or lung inflammation at the site of previous radiation therapy, has been reported in patients who had radiation treatment in the past.

Tell the doctor if you are planning to have radiation therapy in the near future, or if you have previously undertaken radiation therapy.

Inform your doctor immediately if you experience these symptoms.

Children and adolescents (under 18 years of age)

Evetor is intended for treating children and adolescents with a SEGA brain tumor associated with tuberous sclerosis complex (TSC), but whose liver function is normal. The safety and efficacy of **Evetor** in children under one year of age who have a SEGA brain tumor associated with tuberous sclerosis complex (TSC), have not been established. No data are available.

Evetor is not intended for use in children and adolescents for other approved indications.

Tests and follow-up

Before and during treatment with **Evetor** you will have routine blood tests to monitor the number of blood cells (white blood cells, red blood cells and platelets) in your body, to see if **Evetor** is having an adverse effect on these cells. Blood tests will also be carried out to check kidney function (levels of creatinine, blood urea nitrogen or urinary protein), liver function (blood level of transaminases) and blood sugar, fat, and cholesterol levels, since all these can also be affected by **Evetor**.

If you are taking **Evetor** to treat a SEGA brain tumor associated with tuberous sclerosis complex (TSC), regular blood tests are necessary in order to measure your blood **Evetor** level as this will help the doctor decide the amount of **Evetor** needed to be taken.

Drug interactions

Evetor may affect the way some other medicines work. If you are taking other medicines at the same time as **Evetor**, the doctor might need to modify the dosage of **Evetor** or the dosage of the other medicines.

If you are taking, or have recently taken other medicines, including non-prescription medications and nutritional supplements, tell the doctor or pharmacist. In particular, if you are taking:

The following medicines may increase the risk of side effects with **Evetor**:

- Anti-fungal medicines used to treat fungal infections, such as: ketoconazole, itraconazole, voriconazole, fluconazole.
- Medicines used to treat types of bacterial infections, antibiotics such as: clarithromycin, telithromycin or erythromycin.
- Medicines used for treatment of AIDS (HIV) such as: ritonavir.
- Verapamil or diltiazem, medicines used for treatment of heart conditions or high blood pressure.
- A medicine used to regulate heartbeat: dronedarone.
- A medicine used to prevent the body from rejecting organ transplants: cyclosporine.
- A medicine which inhibits the growth of abnormal cells: imatinib.
- Angiotensin-converting enzyme (ACE) inhibitors, medicines used for treatment of high blood pressure or other cardiovascular problems, such as: ramipril.
- Nefazodone, a medicine used for treatment of depression.
- Cannabidiol (used among other things to treat seizures).

The following medicines can reduce the efficacy of **Evetor**:

- A medicine used for treatment of tuberculosis: rifampicin.
- Efavirenz or nevirapine, used for treatment of AIDS (HIV).
- St. John’s wort – a herbal medicine used for treatment of depression and other conditions (also known as *Hypericum perforatum*).
- Dexamethasone, a corticosteroid used to treat a wide variety of conditions including inflammations or problems with the immune system.

- Medicines used to treat seizures or epileptic fits, anti-epileptics such as: phenytoin, carbamazepine or phenobarbital.

These medications should be avoided during treatment with **Evetor**. If you are taking any of these medicines, the doctor may prescribe a different medicine or change the dosage of **Evetor**. For patients with TSC who are taking anti-seizure medications, a change in anti-seizure medication dosage (increase or decrease) may necessitate a change in the **Evetor** dosage; the doctor will decide upon this. If the dosage of your anti-seizure medicine changes, please inform the doctor.

Use of the medicine and food

This medicine can be taken with or without food, but be consistent and take it in the same way every day.

Do not drink grapefruit juice or eat grapefruit during treatment with **Evetor**. This may increase the amount of medicine in your blood, possibly to a harmful level.

Pregnancy, breast-feeding, and fertility

Pregnancy

Evetor could harm the fetus and is not recommended during pregnancy. Tell the doctor if you are pregnant or think that you may be pregnant. The doctor will discuss with you whether you should take **Evetor** during your pregnancy.

Fertility

Women of child-bearing age should use a highly effective contraceptive method (such as condoms or oral contraceptives) during treatment with **Evetor**, and for 8 weeks after treatment has stopped. If you think that you may be pregnant, ask your doctor for advice **before** taking any more **Evetor**.

Evetor may affect male and female fertility. If you are interested in becoming pregnant – consult the doctor.

Absence of menstrual periods (amenorrhea) in women who previously had periods has been observed in some women who took **Evetor**.

Breast-feeding

Evetor could harm your breast-fed baby. Do not breast-feed during treatment with **Evetor** and for two weeks after the last dose of **Evetor**. Tell your doctor if you are breast-feeding.

Driving and operating machinery

Exercise extreme caution while driving or operating machinery while using the medicine, particularly if you feel unusually tired, since tiredness is a very common to common side effect of **Evetor**.

Children should be cautioned against riding bicycles or playing near the road, etc.

Important information regarding some of the ingredients of the medicine

Evetor contains lactose (milk sugar). If you have been told by a doctor that you are sensitive to some sugars, consult the doctor before taking **Evetor**.

3. HOW SHOULD YOU USE THE MEDICINE?

Always use the preparation according to the doctor’s instructions.

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.

If you suffer from certain side effects (see section 4 “Side effects”) during treatment with **Evetor**, it is possible that the doctor may need to reduce the dosage of **Evetor** that you take, or to instruct you to stop the treatment with **Evetor** temporarily or permanently.

Do not exceed the recommended dose.

Method of administration

Take **Evetor** by mouth, once a day, at about the same time every day, consistently either with or without food.

Swallow the tablet(s) whole with a glass of water.

There is no information about chewing, halving, or crushing the tablet.

If you are taking **Evetor** tablets to treat tuberous sclerosis complex with SEGA and you are unable to swallow the tablets, you can stir them into a glass of water:

- Put the required tablet(s) into a glass containing approximately 30 ml (2 tablespoons) of water.
- Gently stir the contents until the tablet(s) break apart (approximately 7 minutes) and drink immediately.
- Refill the glass with the same amount of water (approximately 30 ml), gently mix in any remaining medicine and drink the entire contents to make sure that you get the full dose of **Evetor**.
- If necessary, drink additional water to wash out any residue in your mouth.

Instructions for caregivers regarding use and handling of Evetor tablets

Caregivers are advised to avoid contact with suspensions of **Evetor**. Wash hands thoroughly before and after preparing the suspension.

If you have accidentally taken a higher dose

If you have taken an overdose, or if a child or any other person has accidentally swallowed the medicine, refer immediately to a doctor or go to a hospital emergency room and bring with you the medicine package and the leaflet, so that the doctor will know what you have taken. Urgent medical treatment may be necessary.

If you forget to take the medicine

If you forget to take the medicine at the scheduled time, take your next dose at the next scheduled time and consult the doctor. Do not take a double dose to make up for the dose that was missed.

Adhere to the treatment as recommended by the doctor.

If you stop taking the medicine

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 the doctor or pharmacist.

4. SIDE EFFECTS

As with any medicine, use of **Evetor** 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.

Stop taking **Evetor** and seek medical help immediately if you or your child experience any of the following signs of an allergic reaction:

- Difficulty in breathing or swallowing
- Swelling of the face, lips, tongue or throat (signs of angioedema)
- Severe itching of the skin, with a red rash or raised bumps

Serious side effects of Evetor include:

Serious side effects during the treatment of hormone receptor-positive advanced breast cancer, advanced kidney cancer, and advanced neuroendocrine tumors of pancreatic, gastrointestinal or lung origin include:

Very common side effects, effects occurring in more than one in ten users

- Rise in body temperature, chills (signs of infection)
- Fever, coughing, difficulty breathing, wheezing (signs of inflammation of the lung, inflammatory process of lung tissue [pneumonitis])

Common side effects, effects occurring in 1-10 in 100 users

- Excessive thirst, high urine output, increased appetite with weight loss, tiredness (signs of diabetes)
- Bleeding (hemorrhage), for example, in the gut wall
- Severely decreased urine output (signs of kidney failure)

Uncommon side effects, effects occurring in 1-10 in 1,000 users

- Fever, skin rash, joint pain and inflammation, tiredness, loss of appetite, nausea, jaundice (yellowing of the skin), pain in the upper right abdomen, pale stool, dark urine (may be signs of hepatitis B reactivation)
- Breathlessness, difficulty breathing when lying down, swelling of the feet or legs (signs of heart failure)
- Swelling and/or pain in one of the legs, usually in the calf, redness or warm skin in the affected area (signs of blockage of a blood vessel [vein] in the legs caused by a blood clot)
- Sudden onset of shortness of breath, chest pain or coughing up blood (potential signs of pulmonary embolism, a condition that occurs when one or more arteries in the lungs become blocked)
- Severely decreased urine output, swelling in the legs, feeling confused, pain in the back (signs of sudden kidney failure)
- Rash, itching, hives, difficulty in breathing or swallowing, dizziness (signs of serious allergic reaction also known as hypersensitivity)

Rare side effects, effects occurring in 1-10 in 10,000 users

- Shortness of breath or rapid breathing (signs of acute respiratory distress syndrome)

If you experience any of these side effects, tell your doctor immediately, as they might have life-threatening consequences.

Serious side effects during the treatment of patients with a kidney tumor known as angiomyolipoma associated with tuberous sclerosis complex and of patients with a brain tumor of the subependymal giant cell astrocytoma type associated with tuberous sclerosis complex include:

Very common side effects, effects occurring in more than one in ten users

- Fever, coughing, difficulty in breathing, wheezing (signs of inflammation of the lung due to infection [pneumonia])

Common side effects, effects occurring in 1-10 in 100 users

- Swelling, feeling of heaviness or tightness, pain, limited mobility of body parts (potential sign of an abnormal build-up of fluid in soft tissue due to a blockage in the lymphatic system [lymphoedema])
- Rash, itching, hives, difficulty in breathing or swallowing, dizziness (signs of serious allergic reaction also known as hypersensitivity)
- Fever, coughing, difficulty in breathing, wheezing (signs of inflammation of the lung, inflammatory process of lung tissue [pneumonitis])

Uncommon side effects, effects occurring in 1-10 in 1,000 users

- Rash of small fluid-filled blisters appearing on reddened skin (signs of a viral infection that could be potentially severe, also known as herpes zoster)
- Fever, chills, rapid breathing and heart rate, rash, and possibly confusion and disorientation (signs of serious infection also known as sepsis)

If you experience any of these side effects, refer to the doctor immediately, as they might have life-threatening consequences.

Additional side effects:

Other side effects during treatment of hormone receptor-positive advanced breast cancer, advanced kidney cancer or advanced neuroendocrine tumors of pancreatic, gastrointestinal or lung origin include:

Very common side effects, effects occurring in more than one in ten users

High levels of sugar in the blood (hyperglycemia); loss of appetite; disturbed taste; headache; nosebleeds; cough; mouth ulcers; upset stomach including nausea or diarrhea; skin rash; itching; feeling weak or tired; tiredness, breathlessness, dizziness, pale skin, signs of low level of red blood cells (anemia); swelling of arms, hands, feet, ankles or other part of the body (signs of edema); weight loss; high level of lipids in the blood (hypercholesterolemia).

Common side effects, effects occurring in 1-10 in 100 users

Spontaneous bleeding or bruising (signs of low level of platelets [thrombocytopenia]); breathlessness (dyspnea); thirst, low urine output, dark urine, dry flushed skin, irritability (signs of dehydration); trouble sleeping (insomnia); headache, dizziness (signs of high blood pressure [hypertension]); swelling of a part of the arm or the whole arm (including the fingers) or legs (including the toes), a feeling of heaviness, limited mobility, discomfort (possible symptoms of lymphoedema); fever, sore throat, mouth ulcers due to infections (signs of low level of white blood cells [leukopenia, lymphopenia and/or neutropenia]); fever; inflammation of the inner lining of the mouth, stomach, gut; dry mouth; heartburn (dyspepsia); vomiting; difficulty in swallowing (dysphagia); abdominal pain; acne; rash and pain on the palms of the hands or soles of the feet (hand-foot syndrome); skin reddening (erythema); joint pain; pain in the mouth; menstruation disorders such as irregular periods; high level of lipids in the blood (hyperlipidemia, raised triglycerides); low level of potassium in the blood (hypokalemia); low level of phosphate in the blood (hypophosphatemia); low level of calcium in the blood (hypocalcemia); dry skin, skin exfoliation, skin lesions; nail disorders, breaking of nails; mild hair loss; abnormal results of liver blood tests (increased alanine and aspartate aminotransferase); abnormal results of renal blood tests (increased creatinine); eyelid swelling; protein in the urine.

Uncommon side effects, effects occurring in 1-10 in 1,000 users

Weakness, spontaneous bleeding or bruising and frequent infections with signs such as fever, chills, sore throat or mouth ulcers (signs of low level of blood cells [pancytopenia]); loss of sense of taste (ageusia); coughing up blood (hemoptysis); menstruation disorders such as absence of periods (amenorrhea); passing urine more often during the day; chest pain; abnormal wound healing; hot flushes; discharge from the eye with itching and redness, pink or red eyes (conjunctivitis).

Rare side effects, effects occurring in 1-10 in 10,000 users

Tiredness, breathlessness, dizziness, pale skin (signs of low levels of red blood cells possibly due to a type of anemia called pure red cell aplasia); swelling of the face, around the eyes, mouth, and inside the mouth and/or throat, as well as the tongue and difficulty breathing or swallowing (also known as angioedema) may be signs of an allergic reaction.

Side effects whose frequency is not known (frequency has not yet been established)

Reaction at the site of previous radiation treatment, such as skin redness or lung inflammation (so called radiation recall syndrome); worsening of radiation treatment side effects.

If these side effects become severe, please consult your doctor and/or pharmacist. Most of the side effects are mild to moderate and will generally disappear within a few days after stopping treatment.

Other side effects during the treatment of patients with a kidney tumor known as angiomyolipoma associated with tuberous sclerosis complex and of patients with a brain tumor of the subependymal giant cell astrocytoma type associated with tuberous sclerosis complex include:

Very common side effects, effects occurring in more than one in ten users

Upper respiratory tract infection; sore throat and runny nose (nasopharyngitis); headache, pressure in the eyes, nose or cheek area (signs of inflammation of the sinuses and nasal passages [sinusitis]); urinary tract infection; high level of lipids in the blood (hypercholesterolemia); decreased appetite; headache; cough; mouth ulcers; diarrhea; vomiting; acne; skin rash; feeling tired; fever; menstruation disorders such as absence of periods (amenorrhea) or irregular periods; sore throat (pharyngitis); headache, dizziness, signs of high blood pressure (hypertension).

Common side effects, effects occurring in 1-10 in 100 users

Middle ear infection; swollen and bleeding gums (signs of gum inflammation [gingivitis]); skin inflammation (cellulitis); high level of lipids in the blood (hyperlipidemia, raised triglycerides); low level of phosphate in the blood (hypophosphatemia); high level of sugar in the blood (hyperglycemia); tiredness, breathlessness, dizziness, pale skin (signs of low level of red blood cells [anemia]); fever, sore throat or mouth ulcers due to infections (signs of low levels of white blood cells [leukopenia, lymphopenia, neutropenia]); spontaneous bleeding or bruising (signs of low level of platelets [thrombocytopenia]); mouth pain; nosebleeds; stomach upset such as nausea; abdominal pain; severe pain in the lower abdomen and pelvic area that may be sharp, with menstrual irregularities (ovarian cyst); excess amount of gas in the bowels (flatulence); constipation; abdominal pain, nausea, vomiting, diarrhea, swelling of the abdomen (signs of inflammation of the mucous membrane lining the stomach, also

known as gastritis or viral gastroenteritis); dry skin, itching; an inflammatory condition of the skin characterized by redness, itching, and oozing liquid-filled cysts which become crusted, scaly, or hardened (dermatitis acneiform); hair loss; protein in the urine; menstruation disorders such as heavy periods (menorrhagia) or vaginal bleeding; trouble sleeping (insomnia); irritability; aggression; high level of an enzyme in the blood called lactate dehydrogenase that gives information about the health of certain organs; higher blood level of ovulation triggering hormone (increased luteinizing hormone [LH]); weight loss.

Uncommon side effects, effects occurring in 1-10 in 1,000 users

Muscle spasm, fever, red-brown urine, these are possibly signs of a muscle disorder (rhabdomyolysis); cough with phlegm, chest pain, fever (signs of inflammation of airways, also known as viral bronchitis); disturbed taste; menstruation disorders such as delayed periods; higher blood level of the female reproductive hormone (increase in follicle stimulating hormone [FSH]).

Side effects whose frequency is not known (frequency has not yet been established)

Reaction at the site of previous radiation treatment, such as skin redness or lung inflammation (so called radiation recall syndrome); worsening of radiation treatment side effects.

If these side effects become severe, please refer to the doctor and/or pharmacist. Most of the side effects are mild to moderate and will generally disappear within a few days after stopping treatment.

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

Hepatitis B reactivation has been observed in some patients taking **Evetor**. Tell the doctor if you experience symptoms of hepatitis B during treatment with **Evetor**. The first symptoms may include fever, skin rash, joint pain and inflammation. Other symptoms may include fatigue, loss of appetite, nausea, jaundice (yellowing of the skin), and pain in the upper right abdomen. Pale stools or dark urine may also be signs of hepatitis.

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) that directs you to the online form for reporting side effects, or by entering the link:

<https://sideeffects.health.gov.il>

Additionally, you can report to “Unipharm Ltd.": <https://unipharm.co.il>

5. HOW SHOULD THE MEDICINE BE STORED?

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 the doctor.

Do not use the medicine after the expiry date (exp. date) which appears on the package. The expiry date refers to the last day of that month.

Store below 25°C.

Store in the original package to protect from light and moisture. Do not discard medicines in the household waste bin. Ask the pharmacist how to dispose of medicines no longer in use. These measures will help protect the environment.

6. FURTHER INFORMATION

In addition to the active ingredient the medicine also contains: Lactose, anhydrous, Crospovidone (type A), Hydroxypropylmethylcellulose (HPMC), Magnesium stearate and Butylhydroxytoluene (BHT).

Each **Evetor 2.5** tablet contains 74.5 mg lactose.

Each **Evetor 5** tablet contains 149 mg lactose.

Each **Evetor 10** tablet contains 298 mg lactose.

What does the medicine look like and what are the contents of the package:

The tablets are white to slightly yellowish