Applicant : Eurolab (Pty) Ltd
Proprietary name : Tisumor 12,5 mg & 25 mg & 37,5 mg & 50 mg
Dosage form and strength : Hard capsules 12,5 mg & 25 mg & 37,5 mg & 50 mg
Date of submission : 20 May 2024
Approval date : 22 November 2024

APPROVED PATIENT INFORMATION LEAFLET

SCHEDULING STATUS: S4

TISUMOR 12,5 mg, 25 mg, 37,5 mg & 50 mg hard capsules

Sunitinib

Contains sugar:

12,5 mg hard capsules

Each capsule contains 35,8 mg mannitol.

25 mg hard capsules

Each capsule contains 71,6 mg mannitol.

37,5 mg hard capsules

Each capsule contains 107,4 mg mannitol.

50 mg hard capsules

Each capsule contains 143,2 mg mannitol.

Read all of this leaflet carefully before you start taking TISUMOR

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, nurse, or other health care provider.
- TISUMOR has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

What is in this leaflet

1. What TISUMOR is and what it is used for
2. What you need to know before you take TISUMOR
3. How to take TISUMOR

4. Possible side effects

5. How to store TISUMOR

6. Contents of the pack and other information

1. What TISUMOR is and what it is used for

TISUMOR contains the active substance sunitinib, which is a protein kinase inhibitor. It is used to treat cancer by preventing the activity of a special group of proteins which are known to be involved in the growth and spread of cancer cells.

TISUMOR is used to treat adults with the following types of cancer:

- Gastrointestinal stromal tumour (GIST), a type of cancer of the stomach and bowel, where imatinib (another anticancer medicine) no longer works or you cannot take imatinib. It arises from uncontrolled cell growth of the supporting tissues of these organs. TISUMOR slows down the growth of these cells.
- Metastatic renal cell carcinoma (MRCC), a type of kidney cancer that has spread to other parts of the body. If you have any questions about how TISUMOR works or why this medicine has been prescribed for you, ask your doctor.
- Pancreatic neuroendocrine tumours (pNET).

2. What you need to know before you take TISUMOR

Do not take TISUMOR

- if you are hypersensitive (allergic) to sunitinib or any of the other ingredients of TISUMOR (listed in section 6).
- if you are pregnant or are planning to become pregnant.
- if you are breastfeeding your baby (see Pregnancy and breastfeeding).

Warnings and precautions

Special care should be taken with TISUMOR:

- **If you have high blood pressure.** TISUMOR can raise blood pressure.

  Your doctor may check your blood pressure during treatment with TISUMOR, and you may be treated with medicines to reduce the blood pressure, if needed.
- **If you have or have had blood disease, bleeding problems, or bruising.**

  Treatment with TISUMOR may lead to a higher risk of bleeding or lead to changes in the number of certain cells in the blood which may lead to anaemia or affect the ability of your blood to clot. If you are taking warfarin or acenocoumarole, medicines which thin the blood to prevent blood clots, there may be a greater risk of bleeding. Tell your doctor if you have any bleeding while on treatment with TISUMOR.
- **If you have heart problems**. TISUMOR can cause heart problems. Tell your doctor if you feel very tired, are short of breath, or have swollen feet and ankles.
- **If you have abnormal heart rhythm changes.** TISUMOR can cause abnormality of your heart rhythm. Your doctor may obtain electrocardiograms to evaluate for these problems during your treatment with TISUMOR. Tell your doctor if you feel dizzy, faint, or have abnormal heartbeats while taking TISUMOR.
- **If you have had a recent problem with blood clots in your veins and/or arteries (types of blood vessels) or lungs, including stroke, heart attack, embolism, or thrombosis.** Call your doctor immediately if you get symptoms such as chest pain or pressure, pain in your arms, back, neck or jaw, shortness of breath, cough, numbness, or weakness on 1 side of your body, trouble talking, headache, or dizziness while on treatment with TISUMOR.
- **If you have or have had an aneurysm** (enlargement and weakening of a blood vessel wall) or a tear in a blood vessel wall.

- **If you have or have had damage to the smallest blood vessels known as thrombotic microangiopathy (TMA).** Tell your doctor if you develop fever, fatigue, tiredness, bruising, bleeding, swelling, confusion, vision loss, and seizures.
- **If you have thyroid glands problems.** TISUMOR can cause thyroid gland problems. Tell your doctor if you get tired more easily, generally, feel colder than other people, or your voice deepens whilst taking TISUMOR. Your thyroid function should be checked before you take TISUMOR and regularly while you are taking it. If your thyroid gland is not producing enough thyroid hormone, you may be treated with thyroid hormone replacement.
- **If you have or have had pancreatic or gallbladder disorders.** Tell your doctor if you develop any of the following signs and symptoms: pain in the area of the stomach (upper abdomen), nausea, vomiting, and fever. These may be caused by inflammation of the pancreas or gallbladder.
- **If you have or have had liver problems.** Tell your doctor if you develop any of the following signs and symptoms of liver problems during TISUMOR treatment: itching, yellow eyes or skin, dark urine, and pain or discomfort in the right upper stomach area. Your doctor should do blood tests to check your liver function before and during treatment with TISUMOR, and as clinically indicated.
- **If you have or have had kidney problems**. Your doctor will monitor your kidney function.
- **If you suffer from any gastrointestinal symptoms**, that includes diarrhoea, nausea/vomiting, abdominal pain, indigestion, pain and swelling/sores inside the mouth.
- **If you are going to have surgery or if you had an operation recently**. TISUMOR may affect the way your wounds heal. You will usually be taken off TISUMOR if you are having an operation. Your doctor will decide when to start TISUMOR again.

- **You may be advised to have a dental check-up before you start treatment with TISUMOR.**
- If you have or have had pain in the mouth, teeth and/or jaw, swelling or sores inside the mouth, numbness, or a feeling of heaviness in the jaw, or loosening of a tooth, tell your doctor and dentist immediately.
- If you need to undergo an invasive dental treatment or dental surgery, tell your dentist that you are being treated with TISUMOR in particular when you are also receiving or have received intravenous bisphosphonates. Bisphosphonates are medicines used to prevent bone complications that may have been given for another medical condition.
- **If you have or have had skin and subcutaneous tissue disorders.** While you are on this medicine "pyoderma gangrenosum" (painful skin ulceration) or “necrotising fasciitis” (rapidly spreading infection of the skin/soft tissue that may be life-threatening) may occur. Contact your doctor immediately if symptoms of infection occur around a skin injury, including fever, pain, redness, swelling, or drainage of pus or blood. This event is generally reversible after sunitinib discontinuation. Severe skin rashes (Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme) have been reported with the use of sunitinib, appearing initially as reddish target-like spots or circular patches often with central blisters on the trunk. The rash may progress to widespread blistering or peeling of the skin and may be life-threatening. If you develop a rash or these skin symptoms, seek immediate advice from a doctor.
- **If you have or have had seizures**. Notify your doctor as soon as possible if you have high blood pressure, headache, or loss of sight.
- **If you have diabetes**. Blood sugar levels in diabetic patients should be checked regularly in order to assess if antidiabetic medicine’s dosage needs to be adjusted to minimise the risk of low blood sugar. Notify your doctor as soon as possible if you

experience any signs and symptoms of low blood sugar (fatigue, palpitations, sweating, hunger, and loss of consciousness).

- **If you experience muscle cramps or weakness, numbness, hallucinations, nausea and vomiting, diarrhoea,** as these can be signs of a medical emergency called Tumour Lysis Syndrome (TLS).
- **If you have previously had or have recently tested positive for a hepatitis B infection.**
- **If you develop unexplainable fatigue and experience changes in mental status** as these can be signs of hyperammonaemic encephalopathy.

Children and adolescents

TISUMOR is not recommended for people aged under 18.

Other medicines and TISUMOR

Always tell your health care provider if you are taking any other medicine. (This includes all complementary or traditional medicines.)

Some medicines can affect the levels of TISUMOR in your body. You should inform your doctor if you are taking medicines containing the following active substances:

- ketoconazole, itraconazole – used to treat fungal infections
- erythromycin, clarithromycin, rifampicin –used to treat infections
- ritonavir –used to treat HIV
- dexamethasone – a corticosteroid used for various conditions (such as allergic/breathing disorders or skin diseases)
- phenytoin, carbamazepine, phenobarbitone – used to treat epilepsy and other neurological conditions

- herbal preparations containing St. John's Wort (Hypericum perforatum) – used to treat depression and anxiety

TISUMOR with food and drink

You should avoid drinking grapefruit juice while on treatment with TISUMOR.

Pregnancy and breastfeeding

If you are pregnant or breastfeeding, think you may be pregnant, or are planning to have a baby, ask your doctor or pharmacist or other health care provider for advice before taking this medicine.

You should not take TISUMOR when you are pregnant.

If you are breastfeeding, tell your doctor. You should not breastfeed during treatment with TISUMOR. Male and female fertility may be affected by treatment with TISUMOR.

Male patients treated with TISUMOR should use highly effective contraception, while being treated with TISUMOR and for an additional 4 months after taking the last dose. Female patients and female sexual partners of male patients receiving TISUMOR should use highly effective contraception, while being treated with TISUMOR and for an additional 7 months after taking the last dose.

Driving and using machines

It is not always possible to predict to what extent TISUMOR may interfere with the daily activities of a patient. Patients should ensure that they do not engage in the above activities until they are aware of the measure to which TISUMOR affects them. If you experience dizziness or you feel unusually tired, do not drive, or use machinery until you are feeling normal again.

3. How to take TISUMOR

Do not share medicines prescribed for you with any other person. Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. Your doctor will prescribe a dose that is right for you, depending on the type of cancer to be treated. If you are being treated for:

-GIST or MRCC: the usual dose is 50 mg once daily taken for 28 days (4 weeks), followed by 14 days (2 weeks) of rest (no medicine), in 6-week cycles.

Your doctor will determine the appropriate dose you need to take, as well as if and when you need to stop treatment with TISUMOR. TISUMOR can be taken with or without food. Your doctor will tell you how long your treatment with TISUMOR will last. Do not stop treatment early. If you have the impression that the effect of TISUMOR is too strong or too weak, tell your doctor or pharmacist.

If you take more TISUMOR than you should

In the event of overdosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison centre.

If you forget to take TISUMOR

Do not take a double dose to make up for a forgotten dose.

4. Possible side effects

TISUMOR can have side effects.

Not all side effects reported for TISUMOR are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking TISUMOR, please consult your health care provider for advice.

If any of the following happens, stop taking TISUMOR and tell your doctor immediately or go to the casualty department at your nearest hospital:

- swelling of the hands, feet, ankles, face, lips and mouth or throat, which may cause difficulty in swallowing or breathing,
- rash or itching,
- fainting

These are all very serious side effects. If you have them, you may have had a serious reaction to TISUMOR. You may need urgent medical attention or hospitalisation.

Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:

- Heart complications. Symptoms may include chest pressure or pain, typically on the left side of the body, neck, shoulder, or arm pain, fast heartbeat, heart palpitations or rapid heartbeat, shortness of breath, sweating, feeling tired, loss of appetite, nausea, swollen legs.
- Torsade de pointes – a specific type of abnormal heart rhythm that can lead to sudden cardiac death.
- Abnormal build-up of excess fluid around the heart.
- Coughing up blood, depending on severity.
- Ischaemic stroke (a brief stroke-like attack that, that resolves within minutes to hours, but can be a warning sign of a future stroke).
- A life-threatening complication of an infection. Symptoms include fever, difficulty breathing, low blood pressure, fast heart rate and mental confusion.
- Leg pain or swelling that can be the cause of a blood clot.

- Shortness of breath, chest pain and cough, as it can be signs of a blood clot in the lungs that can be fatal.
- Pleural effusion (water on the lungs) that can be fatal. Symptoms may include coughing, sharp chest pain or shortness of breath.
- Gastrointestinal bleeding, that can be life-threatening.
- Inflammation of the throat (oesophagus), that can be life-threatening.
- Kidney failure that can be fatal. Symptoms include decreased urination, swelling of legs, ankles or feet, shortness of breath, feeling tired, confusion, nausea, weakness, irregular heartbeat.
- Bacterial infection that spreads quickly and results in the death of parts of the body's soft tissue that needs emergency care. Symptoms may include blisters, fever, feeling tired and pain that worsens.
- Thrombotic microangiopathy, a syndrome that forms small blood clots that destroys organs.
- Tumour Lysis Syndrome (TLS). It’s a fatal condition that occurs when a large number of cancer cells die within a short period, releasing their contents into the blood. Symptoms include nausea with or without vomiting, lack of appetite and feeling tired, dark urine, reduced urination, numbness, fits or hallucinations, muscle cramps and spasms, heart palpitations.
- A stroke or brain bleed that may be life-threatening.
- Posterior reversible encephalopathy syndrome (PRES). A neurological, sometimes fatal disorder that presents with headache, fits, loss of consciousness, blurred vision, nausea and vomiting.
- Heart attack. Symptoms include tightness or pain in the chest, neck, back or arms, as well as feeling tired, light-headedness, abnormal heartbeat and anxiety.

- Heart failure. Symptoms include shortness of breath, feeling tired, swollen legs and rapid heartbeat.
- Cardiomyopathy - an acquired or hereditary disease of the heart muscle. Symptoms include breathlessness, swollen legs and feet and a bloated stomach.
- Bleeding tumour that can be fatal.
- Bleeding into the lungs that may be life-threatening.
- Respiratory failure
- Intestinal perforation. Symptoms may include pain or cramps that are often severe and spread across your abdomen, bloating, or a feeling of tightness or swelling, nausea and vomiting, bleeding from the rectum, fever, which is usually delayed and body chills.
- Liver failure. Symptoms include yellowed skin and eyes (jaundice) along with stomach pain and swelling.
- Gallbladder inflammation that may be fatal
- Erythema multiforme, a skin disorder that's considered to be an allergic reaction to medicine or an infection. Symptoms include skin or mouth lesions that have a pink-red centre surrounded by a pale ring border and an outer pink-red ring. The lesions can sometimes be painful or itchy.
- Stevens-Johnson syndrome. Flu-like symptoms appear first, followed by a painful rash that spreads and blisters follows.
- Toxic epidermal necrolysis is a life-threatening skin disorder characterized by a blistering and peeling of the skin.
- Fistula - an abnormal connection that develops between two body parts, such as an organ or blood vessel and another structure that may be life-threatening.
- Rhabdomyolysis, a serious syndrome that develops due to breakdown of muscle tissue that releases a damaging protein into the blood.

These are all serious side effects. You may need urgent medical attention.

Tell your doctor if you notice any of the following:

Frequent side effects:

- Viral infections
- Lung infections
- Abscess
- Fungal infections
- Urinary tract infections
- Skin infections
- An abnormally low count of a type of white blood cell (neutrophils)
- A low number of platelets in the blood.
- Anaemia – a lack of red blood cells.
- A low level of white blood cells in the blood, which can interfere with the ability to fight infection.
- Underactive thyroid. Symptoms include feeling tired, cold sensitivity, constipation, dry skin, and unexplained weight gain.
- Decreased appetite
- Dehydration
- Low blood sugar. Symptoms include confusion, heart palpitations, shakiness, and anxiety.
- Insomnia (sleep disorder)
- Depression
- Dizziness
- Headache
- Taste disturbance

- Weakness, numbness, and pain from nerve damage, usually in the hands and feet
- “Pins-and-needles” sensation
- Numbness
- Excessive physical sensitivity, especially of the skin.
- Swelling around the eyes and eyelid
- Watery eyes/ excessive tearing
- High blood pressure
- Hot flush or flushing
- Nosebleed
- Cough
- Shortness of breath during exercise.
- Throat pain
- Nasal congestion (stuffiness) or dryness
- Inflamed and sore mouth
- Abdominal pain
- Vomiting
- Diarrhoea
- Indigestion
- Nausea
- Constipation
- Acid reflux
- Bloating and swelling of the abdomen
- Abdominal discomfort
- Rectal bleeding
- Bleeding of the gums
- Painful sores in and around mouth

- Intense rectal pain for a short time
- Chapped lips
- Haemorrhoids, also known as piles
- Ongoing or recurrent burning in the mouth with no obvious cause
- Painful, dry or discomfort of the mouth
- Flatulence or feeling gassy
- Burping
- Skin discolouration
- Hand-foot-syndrome. Symptoms include redness similar to sunburn, swelling, feeling of tingling or burning, tightness of the skin, blisters on palms of your hands and soles of your feet.
- Change in hair colour
- Dry or red skin
- Skin reaction
- Eczema – symptoms include dry, itchy skin that can be red, scaly or with bumps and swelling.
- Blisters
- Hair loss
- Acne
- Darkened patches or spots on the skin
- Skin lesions or abnormal growth
- Thickening of skin
- Skin inflammation
- Nail disorder
- Pain in arms and legs
- Joint stiffness

- Back pain
- Pain in muscles, bones, ligaments, tendons or nerves
- Muscle spasms, aches or pains
- Muscle weakness
- Abnormal colouration of urine
- Protein found in urine. Symptoms may include more frequent urination, shortness of breath, tiredness, nausea and vomiting, swelling of the face, belly, feet or ankles, lack of appetite, muscle cramps at night.
- Inflammation of the moist inner lining of some organs and body cavities.
- Feeling tired
- Fluid or water retention
- Fever
- Chest pain
- Pain
- Flu symptoms
- Chills
- Weight loss
- Low white blood cell or platelet count
- Increase in certain enzymes in the body
- Decrease in a protein in red blood cells (haemoglobin)
- Increase in certain waste products made by the body
- Increase in blood pressure

<u>Less frequent side effects:</u>

- Bacterial infections

- Low level of blood cells (pancytopenia). Symptoms may include fatigue, weakness, dizziness, trouble breathing, fast heartbeat, fever, pale skin, purple or red spots on the skin, rash, easy bruising, and abnormal bleeding.
- Allergic reaction
- Painless swelling under the skin
- Overactive thyroid
- Inflammation of the thyroid gland
- Rapid heartbeat that may include fainting and fits.
- A stroke-like attack, that includes symptoms of weakness in the face, arm or leg, especially on one side of the body, vision problems and slurred speech.
- Loss of sense of taste.
- Sudden, severe headache, nausea and vomiting, stiff neck, blurred vision. All symptoms of an aneurysm or a tear of the artery wall.
- Inflammation of the pancreas.
- Anal fistula - a small, infected tunnel that develops between the end of the bowel and the skin near the anus.
- Inflammation of the colon or large intestine
- Abnormal liver function, including the sudden increase or reappearance of HBV (hepatitis B virus).
- Inflammation of the liver
- Pus in the skin
- Severe inflammation of the entire skin surface.
- Osteonecrosis or death of the jawbone, due to lack of blood supply.
- Myopathy, a disease of the muscle in which the muscle fibres do not function properly. This results in muscular weakness.
- Blood in urine

- Nephrotic syndrome is a kidney disorder that causes your body to pass too much protein in your urine.
- Kidney failure.
- Impaired or poor healing abilities
- Increase in a certain enzyme (creatine phosphokinase) in the body that is normally a sign of muscle tissue, brain or heart damage.
- High levels of TSH (Thyroid-stimulating hormone) that may be a sign of hypothyroidism (underactive thyroid).
- Lack of energy, confusion, sleepiness, unconsciousness/coma – these symptoms may be signs of brain toxicity caused by high blood levels of ammonia (hyperammonaemic encephalopathy).

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist, or nurse. You can also report side effects to SAHPRA via the “6.04 Adverse Drug Reaction Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8. By reporting side effects, you can help provide more information on the safety of TISUMOR.

5. How to store TISUMOR

- Store all medicines out of reach of children.
- Do not store your capsules above 30 ºC. Store in the original packaging.
- Do not use this medicine after the expiry date which is stated on carton, bottle, and blister foil after “EXP”. The expiry date refers to the last day of that month.

- This medicine does not require any special storage conditions.
- Do not use this medicine if you notice that the pack is damaged or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What TISUMOR contains

TISUMOR 12.5 mg hard capsules

The active substance is sunitinib. Each capsule contains sunitinib malate equivalent to 12.5 mg sunitinib. The other ingredients are:

- Capsule content: mannitol (E421), croscarmellose sodium, povidone (K-25), and magnesium stearate.
- Capsule shell: gelatin, red iron oxide (E172), black iron oxide (E172) and titanium dioxide (E171).
- Printing ink: shellac, propylene glycol, sodium hydroxide, povidone, and titanium dioxide (E171).

TISUMOR 25 mg hard capsules

The active substance is sunitinib. Each capsule contains sunitinib malate equivalent to 25 mg. The other ingredients are:

- Capsule content: mannitol, croscarmellose sodium, povidone (K-25), and magnesium stearate.
- Capsule shell: gelatin, titanium dioxide (E171), yellow iron oxide (E172), red iron oxide (E172), black iron oxide (E172).

- Printing ink: shellac, propylene glycol, sodium hydroxide, povidone, and titanium dioxide (E171).

TISUMOR 37.5 mg hard capsules

The active substance is sunitinib. Each capsule contains sunitinib malate equivalent to 37.5 mg. The other ingredients are:

- Capsule content: mannitol, croscarmellose sodium, povidone (K-25), and magnesium stearate.
- Capsule shell: gelatin, titanium dioxide (E171), FD&C Yellow #6 (E110) and FD&C Yellow #5 (E102)
- Printing ink: shellac, propylene glycol, sodium hydroxide, povidone, and titanium dioxide (E171)

TISUMOR 50 mg hard capsules

The active substance is sunitinib. Each capsule contains sunitinib malate equivalent to 50 mg. The other ingredients are:

- Capsule content: mannitol, croscarmellose sodium, povidone (K-25), and magnesium stearate.
- Capsule shell: gelatin, titanium dioxide (E171), yellow iron oxide (E172), red iron oxide (E172), and black iron oxide (E172).
- Printing ink: shellac, propylene glycol, sodium hydroxide, povidone, and titanium dioxide (E171)

What TISUMOR looks like and contents of the pack

TISUMOR 12.5 mg is supplied as Dark brown opaque cap and dark brown opaque body, capsule shell size No. 4 imprinted in white ink with "LP" on the cap and "650" on the body and containing yellow to orange granular powder.

TISUMOR 25 mg is supplied as Light brown opaque cap and dark brown opaque body, capsule shell size No. 3 imprinted in white ink with "LP" on the cap and "651" on the body and containing yellow to orange granular powder.

TISUMOR 37.5 mg is supplied as Yellow opaque cap and yellow opaque body, capsule shell size No.2 imprinted in black ink with "LP" on the cap and "652" on the body and containing yellow to orange granular powder.

TISUMOR 50 mg is supplied as Light brown opaque cap and light brown opaque body, capsule shell size No. 2 imprinted in white ink with "LP" on the cap and "653" on the body and containing yellow to orange granular powder.

The capsules are packed in:

- White PVC/ACLAR-Aluminum blisters. The blisters are packed in carton boxes.
- HDPE bottles with PP caps

Holder of Certificate of Registration

Eurolab (Pty) Ltd.

Woodmead Office Park, 3 Stirrup Lane

Van Reenens Avenue

Woodmead

This leaflet was last revised in:

22 November 2024

Registration number(s):

TISUMOR 12,5 mg: 55/26/0238

TISUMOR 25 mg: 55/26/0239

Applicant	: Eurolab (Pty) Ltd
Proprietary name	: Tisumor 12,5 mg & 25 mg & 37,5 mg & 50 mg
Dosage form and strength	: Hard capsules 12,5 mg & 25 mg & 37,5 mg & 50 mg
Date of submission	: 20 May 2024
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TISUMOR 37,5 mg: 55/26/0240

TISUMOR 50 mg: 55/26/0241