PATIENT INFORMATION LEAFLET

SCHEDULING STATUS: S4

TACROLIMUS 0,5 TEVA

TACROLIMUS 1 TEVA

TACROLIMUS 5 TEVA

Tacrolimus

Contains Sugar

Each TACROLIMUS 0,5 TEVA capsule contains 109,1 mg lactose anhydrous.

Each TACROLIMUS 1 TEVA capsule contains 108,6 mg lactose anhydrous.

Each TACROLIMUS 5 TEVA capsule contains 104,6 mg lactose anhydrous.

Read all of this leaflet carefully before you start taking TACROLIMUS TEVA.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor, pharmacist, nurse or other healthcare provider.
- TACROLIMUS TEVA 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 TACROLIMUS TEVA is and what it is used for**
2. **What you need to know before you take TACROLIMUS TEVA**
3. **How to take TACROLIMUS TEVA**
4. **Possible side effects**
5. **How to store TACROLIMUS TEVA**
6. **Contents of the pack and other information**

1. What TACROLIMUS TEVA is and what it is used for:

TACROLIMUS TEVA belongs to a group of medicines called immune suppressants. TACROLIMUS TEVA is used to control your body's immune response enabling your body to accept the transplanted organ. TACROLIMUS TEVA is often used in combination with other medicines that also suppress the immune system.

2. What you need to know before you take TACROLIMUS TEVA:

Do not take TACROLIMUS TEVA:

- if you are allergic (hypersensitive) to tacrolimus or to any antibiotic belonging to the subgroup of macrolide antibiotics (e.g. erythromycin, clarithromycin, josamycin)
- if you are allergic (hypersensitive) to any of the other ingredients of TACROLIMUS TEVA
- if you are pregnant and breast feeding
- as TACROLIMUS TEVA may alter the metabolism of oral contraceptives, other forms of contraception should be used
- with live attenuated vaccines
- with ciclosporin
- with grapefruit juice.

Warnings and precautions:

Talk to your doctor, pharmacist before taking TACROLIMUS TEVA.

- You will need to take TACROLIMUS TEVA every day as long as you need immunosuppression to prevent rejection of your transplanted organ. You should keep in regular contact with your doctor.
- Whilst you are taking TACROLIMUS TEVA your doctor may want to carry out a number of tests (including blood, urine, heart function, visual and neurological tests) from time to time. This is quite normal and will help your doctor to decide on the most appropriate dose of TACROLIMUS TEVA for you.
- Avoid taking any herbal remedies, e.g. St. John's wort (*Hypericum perforatum*) or any other herbal products as this may affect the effectiveness and the dose of TACROLIMUS TEVA that you need to receive. If in doubt please consult your doctor prior to taking any herbal products or remedies.
- If you have liver problems or have had a disease which may have affected your liver, please tell your doctor as this may affect the dose of TACROLIMUS TEVA that you receive.

- If you feel strong abdominal pain accompanied or not with other symptoms, such as chills, fever, nausea or vomiting.
- If you have diarrhoea for more than one day, please tell your doctor, because it might be necessary to adapt the dose of TACROLIMUS TEVA that you receive.
- If you have an alteration of the electrical activity of your heart called QT-prolongation.
- Limit your exposure to sunlight and UV light whilst taking TACROLIMUS TEVA by wearing appropriate protective clothing and using a sunscreen with a high sun protection factor. This is because of the potential risk of malignant skin changes with immunosuppressive therapy.
- If you need to have any vaccinations, please inform your doctor beforehand. Your doctor will advise you on the best course of action.
- Patients treated with TACROLIMUS TEVA have been reported to have an increased risk of developing lymphoproliferative disorders (see **section 4**). Ask your doctor for specific advice on these disorders.
- Do not switch between different types of tacrolimus formulations.
- If you are taking any medicines mentioned below under **Taking other medicines with TACROLIMUS TEVA**.
- If you have tuberculosis.
- Patients treated with TACROLIMUS TEVA have been reported to have an abnormality of some cells in the blood that is associated with a virus that is commonly known as Epstein-Barr Virus (EBV).
- TACROLIMUS TEVA should not be administered together with ciclosporin.
- Patients switched to TACROLIMUS TEVA rescue therapy should not receive concomitantly anti-lymphocyte treatment.
- Patients treated with TACROLIMUS TEVA have been reported to develop posterior reversible encephalopathy syndrome (PRES). If patients taking TACROLIMUS TEVA present with symptoms indicating PRES such as headache, altered mental status, seizures, and visual disturbances, a radiological procedure (e.g. MRI) should be performed. If PRES is diagnosed, adequate blood pressure control and immediate discontinuation of TACROLIMUS TEVA is advised. Most patients completely recover after appropriate measures are taken.
- The use of TACROLIMUS TEVA is not recommended in children and adolescents under 18 years.

Precaution for handling:

Direct contact with any part of your body like your skin or eyes, or breathing in of injection solutions, powder or granules contained in tacrolimus products should be avoided during preparation. If such contact occurs, wash the skin and eyes.

Tell your doctor immediately if during treatment you suffer from:

Problems with your vision such as blurred vision, changes in colour vision, difficulty in seeing detail or if your field of vision becomes restricted.

Other medicines and TACROLIMUS TEVA:

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines (this includes all complementary or traditional medicines). Your doctor may need to change the dose of these other medicines or take other precautions. In some cases you may have to stop taking one of the medicines. This applies especially to the medicines listed below taken at the same time with TACROLIMUS TEVA:

TACROLIMUS TEVA must not be taken with ciclosporin.

TACROLIMUS TEVA blood levels can be affected by other medicines you take, and blood levels of other medicines can be affected by taking TACROLIMUS TEVA which may require interruption, an increase or a decrease in TACROLIMUS TEVA dose. Some patients have experienced increases in tacrolimus blood levels while taking other medicines. This could lead to serious side effects, such as kidney problems, nervous system problems, and heart rhythm disturbances (see **section 4**). An effect on the TACROLIMUS TEVA blood levels may occur very soon after starting the use of another medicine, therefore frequent continued monitoring of your TACROLIMUS TEVA blood level may be needed within the first few days of starting another medicine and frequently while treatment with the other medicine continues. Some other medicines may cause tacrolimus blood levels to decrease, which could increase the risk of rejecting the transplanted organ. In particular, you should tell your doctor if you are taking or have recently taken medicines with active substances like:

- antifungal medicines and antibiotics (particularly so-called macrolide antibiotics) used to treat infections e.g. ketoconazole, fluconazole, itraconazole, posaconazole, voriconazole, clotrimazole, isavuconazole,

miconazole, telithromycin, erythromycin, clarithromycin, josamycin, azithromycin, rifampicin, rifabutin, isoniazid and flucloxacillin

- letermovir, used to prevent illness caused by CMV (human cytomegalovirus)
- HIV protease inhibitors (e.g. ritonavir, nelfinavir, saquinavir), the booster medicine cobicistat, and combination tablets or HIV non-nucleoside reverse transcriptase inhibitors (efavirenz, etravirine, nevirapine) used to treat HIV infection
- HCV protease inhibitors (e.g. telaprevir, boceprevir, the combination ombitasvir/paritaprevir/ritonavir with or without dasabuvir, elbasvir/grazoprevir, and glecaprevir/pibrentasvir), used to treat hepatitis C infection
- nilotinib and imatinib idelalisib, ceritinib, crizotinib, apalutamide, enzalutamide, or mitotane (used to treat certain cancers)
- mycophenolic acid, used to suppress the immune system to prevent transplant rejection
- medicines for stomach ulcer and acid reflux (e.g. omeprazole, lansoprazole or cimetidine)
- antiemetics, used to treat nausea and vomiting (e.g. metoclopramide)
- magnesium-aluminium-hydroxide (antacid), used to treat heartburn
- hormone treatments with ethinylestradiol (e.g. the oral contraceptive pill) or danazol
- medicines for high blood pressure or heart problems such as nifedipine, nicardipine, diltiazem and verapamil
- anti-dysrhythmic medicines (amiodarone) used to control dysrhythmia (uneven beating of the heart)
- medicines known as statins used to treat elevated cholesterol and triglycerides
- the anti-epileptic medicines carbamazepine, phenytoin or phenobarbital
- metamizole, used to treat pain and fever
- the corticosteroids prednisolone and methylprednisolone
- the anti-depressant nefazodone
- herbal preparations containing St. John's wort (*Hypericum perforatum*) or extracts of *Schisandra sphenanthera*
- cannabidiol (uses amongst others include treatment of seizures).

Tell your doctor if you are receiving treatment for hepatitis C. The medicine treatment for hepatitis C may change your liver function and may affect blood levels of tacrolimus. Tacrolimus blood levels may fall or may increase

depending on the medicines prescribed for hepatitis C. Your doctor may need to closely monitor tacrolimus blood levels and make necessary adjustments of TACROLIMUS TEVA dose after you start treatment for hepatitis C.

Tell your doctor if you are taking or need to take ibuprofen, amphotericin B, antibiotics (cotrimoxazole, vancomycin, or so-called aminoglycoside antibiotics such as gentamicin), or antivirals (e.g. acyclovir, ganciclovir, cidofovir, or foscarnet). These may worsen kidney or nervous system problems when taken together with TACROLIMUS TEVA.

Your doctor also needs to know if you are taking potassium supplements or potassium sparing diuretics (e.g., amiloride, triamterene, or spironolactone), or the antibiotics trimethoprim or cotrimoxazole that may increase levels of potassium in your blood, certain pain killers (so called NSAIDs, e.g. ibuprofen), anticoagulants, or oral medication for diabetic treatment, while you take TACROLIMUS TEVA.

If you need to have any vaccinations, please inform your doctor beforehand.

TACROLIMUS TEVA with food and drink:

You should generally take TACROLIMUS TEVA on an empty stomach or at least one hour before or 2 to 3 hours after a meal. Grapefruit and grapefruit juice should be avoided while taking TACROLIMUS TEVA.

Pregnancy and breast feeding:

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

Pregnancy:

You should not be taking TACROLIMUS TEVA if you are pregnant.

Breast feeding:

TACROLIMUS TEVA is excreted into breast milk. Therefore, you should not breast feed whilst taking TACROLIMUS TEVA.

Driving and using machines:

Do not drive or use any tools or machines if you feel dizzy or sleepy, or have problems seeing clearly after taking TACROLIMUS TEVA. These effects are more frequently observed if TACROLIMUS TEVA is taken in conjunction with alcohol use.

It is not always possible to predict to what extent TACROLIMUS TEVA 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 TACROLIMUS TEVA affects them.

TACROLIMUS TEVA contains lactose, sodium and lecithin (soya):

TACROLIMUS TEVA contains lactose. If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per capsule that is to say essentially sodium free.

The printing ink used on TACROLIMUS TEVA capsules 0,5 mg and 1 mg contains soya lecithin. If you are allergic to peanut or soya, talk to your doctor to determine whether you should use this medicine.

3. How to take TACROLIMUS TEVA:

Do not share medicines prescribed for you with any other person.

Always take TACROLIMUS TEVA exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Make sure that you receive the same TACROLIMUS TEVA every time you collect your prescription, unless your transplant specialist has agreed to change to a different TACROLIMUS TEVA medicine.

TACROLIMUS TEVA should be taken twice a day. If the appearance of TACROLIMUS TEVA is not the same as usual, or if dosage instructions have changed, speak to your doctor or pharmacist as soon as possible to make sure that you have the right medicine.

The starting dose to prevent the rejection of your transplanted organ will be determined by your doctor calculated according to your body weight. Initial doses just after transplantation will generally be in the range of 0,075 to 0,30 mg per kg body weight per day depending on the transplanted organ.

Your dose depends on your general condition and on which other immunosuppressive medication you are taking. Regular blood tests by your doctor will be required to define the correct dose and to adjust the dose from time to time. Your doctor will usually reduce your TACROLIMUS TEVA dose once your condition has stabilised. Your doctor will tell you exactly how many capsules to take and how often.

TACROLIMUS TEVA is taken orally twice daily, usually in the morning and evening.

You should generally take TACROLIMUS TEVA on an empty stomach or at least 1 hour before or 2 to 3 hours after the meal.

The capsules should be swallowed whole with a glass of water.

Take the capsules immediately following removal from the blister.

Avoid grapefruit and grapefruit juice while taking TACROLIMUS TEVA.

Do not swallow the desiccant contained in the foil wrapper.

If you take more TACROLIMUS TEVA than you should:

Possible side effects include kidney, nervous system, and heart disturbances, sugar intolerance, high blood pressure, and electrolyte disorders. Over-immunosuppression may increase the risk for severe infections.

If you have accidentally taken too much TACROLIMUS TEVA see your doctor or contact your nearest hospital emergency department immediately.

The treatment of overdose is supportive and will be based on your symptoms.

If you forget to take TACROLIMUS TEVA:

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

If you have forgotten to take your TACROLIMUS TEVA capsules, wait until it is time for the next dose, and then continue as before.

If you stop taking TACROLIMUS TEVA:

Stopping your treatment with TACROLIMUS TEVA may increase the risk of rejection of your transplanted organ.

Do not stop your treatment unless your doctor tells you to do so.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects:

TACROLIMUS TEVA can have side effects.

Not all side effects reported for this medicine are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking TACROLIMUS TEVA, please consult your doctor, pharmacist or other healthcare provider for advice.

TACROLIMUS TEVA reduces your body's own defence mechanism to stop you rejecting your transplanted organ. Consequently, your body will not be as good as usual at fighting infections. So if you are taking TACROLIMUS TEVA you may therefore catch more infections than usual such as infections of the skin, mouth, stomach and intestines, lungs and urinary tract. Some infection could be serious or fatal and may include infections caused by bacteria, viruses, fungi, parasites, or other infections.

Tell your doctor immediately if you get signs of an infection including:

- fever, cough, sore throat, feeling weak or generally unwell
- memory loss, trouble thinking, difficulty walking or loss of vision - these may be due to a less frequent, serious brain infection, which can be fatal (Progressive Multifocal Leukoencephalopathy or PML).

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

- allergic and anaphylactic reactions with the following symptoms: a sudden itchy rash (hives), swelling of hands, feet, ankle, face, lips, mouth or throat (which may cause difficulty in swallowing or breathing) and you may feel you are going to faint.

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

Severe side effects may occur, including the ones listed below. Tell your doctor immediately if you have or suspect you may have any of the following serious side effects:

Serious frequent side effects:

- gastrointestinal perforation: strong abdominal pain accompanied or not with other symptoms, such as chills, fever, nausea or vomiting

- insufficient function of your transplanted organ
- blurred vision

Serious less frequent side effects:

- Thrombotic Thrombocytopenic Purpura (or TTP) a condition characterised by fever and bruising under the skin that may appear as red pinpoint dots, with or without unexplained extreme tiredness, confusion, yellowing of the skin or eyes (jaundice), with symptoms of acute renal failure (low or no urine output)
- blindness
- *Torsades de Pointes*: change in the heart frequency that can be accompanied or not of symptoms, such as chest pain (angina), faint, vertigo or nausea, palpitations (feeling the heartbeat) and difficulty breathing
- Stevens-Johnson syndrome: unexplained widespread skin pain, facial swelling, serious illness with blistering of skin, mouth, eyes and genitals, hives, tongue swelling, red or purple skin rash that spreads, skin shedding
- toxic epidermal necrolysis: erosion and blistering of skin or mucous membranes, red swollen skin that can detach in large parts of the body
- haemolytic uraemic syndrome, a condition with the following symptoms: low or no urine output (acute renal failure), extreme tiredness, yellowing of the skin or eyes (jaudince) and abnormal bruising or bleeding and signs of infection.

Serious side effects – frequency not known:

- optimistic infections (bacterial, fungal, viral and protozoal): prolonged diarrhoea, fever and sore throat
- benign and malignant tumours have been reported following treatment as a result of immunosuppression
- cases of pure red cell aplasia (a very severe reduction in red blood cell counts), haemolytic anaemia (decreased number of red blood cells due to abnormal breakdown accompanied with tiredness) and febrile neutropenia (a decrease in the type of white blood cells which fight infection, accompanied by fever) have been reported. It is not known exactly how often these side effects occur. You may have no symptoms or depending on the severity of the condition, you may feel: fatigue, apathy, abnormal paleness of the skin (pallor), shortness of breath, dizziness, headache, chest pain and coldness in hands and feet

- cases of agranulocytosis (a severely lowered number of white blood cells accompanied with ulcers in the mouth, fever and infection(s)). You may have no symptoms or you may feel sudden fever, rigors and sore throat
- allergic and anaphylactic reactions with the following symptoms: a sudden itchy rash (hives), swelling of hands, feet, ankle, face, lips, mouth or throat (which may cause difficulty in swallowing or breathing) and you may feel you are going to faint
- posterior reversible encephalopathy syndrome (PRES): headache, confusion, mood changes, fits, and disturbances of your vision. These could be signs of a disorder known as posterior reversible encephalopathy syndrome, which has been reported in some patients treated with TACROLIMUS TEVA
- optic neuropathy (abnormality of the optic nerve): problems with your vision such as blurred vision, changes in colour vision, difficulty in seeing detail or restriction of your field of vision.

The side effects listed below may also occur after receiving TACROLIMUS TEVA and could be serious:

Frequent side effects include:

- increased blood sugar, diabetes mellitus, increased potassium in the blood
- difficulty in sleeping
- trembling, headache
- increased blood pressure
- liver function tests abnormal
- diarrhoea, nausea
- kidney problems
- reduction in blood cell counts (platelets, red or white blood cells), increase in white blood cell counts, changes in red blood cell counts (seen in blood tests)
- reduced magnesium, phosphate, potassium, calcium or sodium in the blood, fluid overload, increased uric acid or lipids in the blood, decreased appetite, increased acidity of the blood, other changes in the blood salts
- anxiety symptoms, confusion and disorientation, depression, mood changes, nightmare, hallucination, mental disorders
- fits, disturbances in consciousness, tingling and numbness (sometimes painful) in the hands and feet, dizziness, impaired writing ability, nervous system disorders

- increased sensitivity to light, eye disorders
- ringing sound in your ears
- reduced blood flow in the heart vessels, faster heartbeat
- bleeding, partial or complete blocking of blood vessels, reduced blood pressure
- shortness in breath, changes in the lung tissue, collection of liquid around the lung, inflammation of the pharynx, cough, flu like symptoms
- inflammations or ulcers causing abdominal pain or diarrhoea, bleeds in the stomach, inflammations or ulcers in the mouth, collection of fluid in the belly, vomiting, abdominal pains, indigestion, constipation, flatulence, bloating, loose stools, stomach problems
- changes in liver enzymes and function, yellowing of the skin due to liver problems, liver tissue damage and inflammation of the liver
- itching, rash, hair loss, acne, increased sweating
- pain in joints, limbs, back and feet, muscle spasms
- insufficient function of the kidneys, reduced production of urine, impaired or painful urination
- general weakness, fever, collection of fluid in your body, pain and discomfort, increase of the enzyme alkaline phosphatase in your blood, weight gain, and feeling of temperature disturbed.

Less frequent side effects:

- changes in blood clotting, reduction in all blood cell counts
- dehydration, reduced protein or sugar in the blood, increased phosphate in the blood
- coma, bleeding in the brain, stroke, paralysis, brain disorder, speech and language abnormalities, memory problems
- blurring of the vision due to abnormality in the lens of the eye
- impaired hearing
- irregular heartbeat, stop of heartbeat, reduced performance of your heart, disorder of the heart muscle, enlargement of the heart muscle, stronger heartbeat, abnormal ECG, heart rate and pulse abnormal
- blood clot in a vein of a limb, shock
- difficulties in breathing, respiratory tract disorders, asthma
- obstruction of the gut, increased blood level of the enzyme amylase, reflux of stomach content in your throat, delayed emptying of the stomach

- dermatitis, burning sensation in the sunlight
- joint disorders
- inability to urinate, painful menstruation and abnormal menstrual bleeding
- failure of some organs, influenza like illness, increased sensitivity to heat and cold, feeling of pressure on your chest, jittery or abnormal feeling, increase of the enzyme lactate dehydrogenase in your blood, weight loss
- small bleeds in your skin due to blood clots
- increased muscle stiffness
- deafness
- collection of fluid around the heart
- acute breathlessness
- cyst formation in your pancreas
- problems with blood flow in the liver
- increased hairiness
- thirst, fall, feeling of tightness in your chest, decreased mobility, ulcer
- muscular weakness
- echocardiogram abnormal
- liver failure, narrowing of the bile vessel
- painful urination with blood in the urine
- increase of fat tissue
- abnormality of the optic nerve (optic neuropathy).

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

Reporting of side effects:

If you get side effects, talk to your doctor, pharmacist or nurse. You can also report side effects to SAHPRA via the **6.04 Adverse Reaction Reporting 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 TACROLIMUS TEVA.

5. How to store TACROLIMUS TEVA:

Store all medicine out of reach of children.

Store at or below 30 °C.

Keep in the original package (within foil pouch) to protect from moisture and light.

Do not use the tablets after the expiry date shown on the container.

Return the expired medicine to your pharmacist for safe disposal. Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

6. Contents of the pack and other information:

What TACROLIMUS TEVA contains:

The active substance is tacrolimus.

TACROLIMUS 0,5 TEVA: Each capsule contains 0,5 mg tacrolimus.

TACROLIMUS 1 TEVA: Each capsule contains 1,0 mg tacrolimus.

TACROLIMUS 5 TEVA: Each capsule contains 5,0 mg tacrolimus.

The other ingredients are:

Capsule content:

Povidone K-30

Croscarmellose sodium (E468)

Lactose

Magnesium stearate

Capsule shell TACROLIMUS 0,5 TEVA:

Titanium dioxide (E171)

Yellow Iron Oxide (E172)

Gelatine

Capsule shell TACROLIMUS 1 TEVA:

Titanium dioxide (E171)

Gelatine

Capsule shell TACROLIMUS 5 TEVA:

Titanium dioxide (E171)

Red Iron Oxide (E172)

Gelatine

What TACROLIMUS TEVA looks like and contents of the pack:

TACROLIMUS 0,5 TEVA: Ivory cap and ivory body hard shell capsules with white powder.

TACROLIMUS 1 TEVA: White cap and white body hard shell capsules with white powder.

TACROLIMUS 5 TEVA: Red cap and red body hard shell capsules with white powder.

TACROLIMUS TEVA capsules are packed into transparent PVC/PVdC-Aluminium blister packs. Each blister strip contains 10 capsules.

The blister strips are then packed with a desiccant in an aluminium foil sachet.

The foil sachet(s) are placed within an outer carton.

Pack sizes: 20, 30, 50, 60, 90 and 100 capsules.

Not all pack sizes may be marketed.

Holder of Certificate of Registration:

Teva Pharmaceuticals (Pty) Ltd.

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This leaflet was last revised in:

9 November 2022

Marketing authorization number(s):

TACROLIMUS 0,5 TEVA: 48/34/0315

TACROLIMUS 1 TEVA: 48/34/0316

TACROLIMUS 5 TEVA: 48/34/0317