

**PATIENT INFORMATION LEAFLET****SCHEDULING STATUS: S4****TLADEEZ (film-coated tablet)****Lamivudine****Tenofovir disoproxil fumarate****Dolutegravir sodium****Contains sugar (lactose monohydrate 136 mg) and sweetener (mannitol 131,4 mg)****Read all of this leaflet carefully before you start taking TLADEEZ.**

- 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.
- TLADEEZ 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.

TLADEEZ may lead to serious problems with your liver or cause too much acid in your blood. If left untreated, this may even cause death. The safety and efficacy of TLADEEZ in patients who are infected with both human immunodeficiency virus (HIV) and hepatitis B virus (HBV) have not been established. TLADEEZ should not be used for the treatment of chronic HBV infection. You should be closely monitored by your

doctor for several months if you are infected with HBV and discontinue the use of TLADEEZ, as your hepatitis can get worse.

**What is in this leaflet**

1. What TLADEEZ is and what it is used for
2. What you need to know before you take TLADEEZ
3. How to take TLADEEZ
4. Possible side effects
5. How to store TLADEEZ
6. Contents of the pack and other information

**1. What TLADEEZ is and what it is used for**

TLADEEZ belongs to a group of medicines, known as antiretrovirals.

Combination antiretroviral medicines, such as TLADEEZ, are used in the treatment of HIV-1 (human immunodeficiency virus) infection in adults aged 18 years and older.

**2. What you need to know before you take TLADEEZ****Do not take TLADEEZ**

- If you are hypersensitive (allergic) to tenofovir disoproxil fumarate, lamivudine, dolutegravir or any of the other ingredients in TLADEEZ tablets.
- If you have or had kidney problems (see *Take special care with TLADEEZ*).
- If you are pregnant or breastfeeding your baby (see *Pregnancy, breastfeeding and fertility*).

- If you are a woman of child-bearing age and you are not using highly effective contraception.
- If you are taking any other tenofovir-containing or other lamivudine-containing, or emtricitabine-containing medicines.
- If you are taking a medicine called adefovir dipivoxil (used for the treatment of chronic hepatitis B).
- If you are taking a medicine called dofetilide and pilsicainide (used for the treatment of abnormal heartbeat – cardiac dysrhythmias).
- If you are taking a medicine called didanosine (used for the treatment of HIV infection).
- If you are taking a medicine called metformin (used for the treatment of diabetes).
- If you are younger than 18 years of age.
- If you have moderate to severe liver failure.

### **Take special care with TLADEEZ**

TLADEEZ does not cure or prevent HIV infection; however, it helps to keep HIV from reproducing and appears to slow down the destruction of the immune system.

TLADEEZ will not keep you from spreading HIV to other people. Appropriate precautions must continue to be used.

If the following applies to you, you have to take special care when taking TLADEEZ:

- You are a female, overweight or have been taking nucleoside-containing medicines for a long time, as you are more likely to get lactic acidosis (build-up of lactic acid

in the body) (see information about lactic acidosis under *Possible side effects*). You should contact your doctor or report to the nearest hospital if you experience drowsiness, nausea, vomiting, stomach pain and develop rapid, or hard breathing.

- **Kidney problems.** Before starting treatment, your doctor may order blood tests to assess your kidney function. Your doctor may also order blood tests during treatment to monitor how your kidneys work.
- **Bone problems.** Some people taking combination medicines for HIV develop a condition called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). You must contact your doctor if you experience joint aches and pain, joint stiffness or difficulty in movement. TLADEEZ may also reduce your bone mineral density and this may increase your risk of developing a bone fracture. Please report any bone or joint pain to your doctor or other healthcare professional (see *Possible side effects*).
- **Liver problems.** If you have liver problems including Hepatitis B virus infection. Your doctor may ask you to go for regular blood tests to monitor your liver function (see *Possible side effects*).
- **Opportunistic infections.** Signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment such as TLADEEZ is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please inform your doctor immediately.
- **Pancreas disorders.** If you develop abdominal pain, nausea, vomiting, contact your doctor as it could indicate problems with your pancreas.

- **Changes in body fat.** Changes in body fat develop in some patients taking TLADEEZ. These changes may include an increased amount of fat in the upper back and neck (“buffalo hump”), in the breasts and around the trunk. Loss of fat from the legs, arms and face may also happen. The cause and long-term health effects of these fat changes are not known.
- **Skin rash, fever, or other symptoms of an allergy.** Such symptoms may include generally feeling unwell, severe tiredness, muscle or joint pain, blisters, ulcers in the mouth, itchy or teary eyes, and swelling of the face. You need to report to your doctor or nearest hospital immediately should you develop any of these symptoms (see *Possible side effects*).
- TLADEEZ helps to control (treat) HIV infection but is not a cure. You will need to take it every day. You must not stop taking TLADEEZ without first talking to your doctor. If you are concerned that you may be developing symptoms of a hypersensitivity reaction, call your doctor immediately who will advise whether you must stop taking TLADEEZ. You may continue to develop other infections and other illnesses associated with HIV disease. You should therefore keep in regular contact with your doctor while you are taking TLADEEZ.
- Treatment with TLADEEZ has not been shown to reduce the risk of passing HIV infection to others through sexual contact or contaminated blood. If you are sexually active you should continue to use appropriate precautions to prevent this.
- To protect other people from becoming infected with HIV:
  - **a condom must be used** when you have oral or penetrative sex.

- **blood transfer should be avoided** – for example, needles must not be shared.

TLADEEZ may increase blood fat (triglyceride) and cholesterol levels, blood sugar levels and give raise to abnormal liver enzyme levels. Your doctor may ask you to go for regular blood tests to monitor your blood cholesterol, sugar, fat and liver enzyme levels.

### **Taking TLADEEZ with food and drink**

TLADEEZ can be taken without regard to food.

### **Pregnancy, breastfeeding and fertility**

Do not take TLADEEZ tablets if you are pregnant or breastfeeding (see *Do not take TLADEEZ tablets*). TLADEEZ could seriously harm your unborn child if you fall pregnant while on treatment or if you start taking TLADEEZ in the first few weeks of your pregnancy.

If you are pregnant or breastfeeding your baby, please consult your healthcare professional for advice before taking TLADEEZ. You should ensure that you always used effective contraception while you are taking TLADEEZ. Your healthcare professional can advise you on which contraceptives to take. Never stop taking TLADEEZ without first consulting your healthcare professional as your HIV condition may become worse.

If you are thinking about having a baby, do not stop using TLADEEZ and contraception before you have talked to your healthcare professional. If you think you are pregnant go to your healthcare professional to get a pregnancy test and to be advised on your future HIV treatment and on a pregnancy management plan.

## **DOLUTEGRAVIR**

### **Women of childbearing potential**

Women of childbearing potential should be counselled about the potential risk of neural tube defects with dolutegravir (see below), including consideration of using effective contraceptive measures.

Perform pregnancy testing before initiation of TLADEEZ in women of childbearing potential to exclude inadvertent (unintentional) use of TLADEEZ during the first trimester of pregnancy.

If a woman plans pregnancy, the benefits and the risks of starting or continuing treatment with dolutegravir versus using another antiretroviral regimen should be discussed with her.

### **Pregnancy**

Use of dolutegravir during pregnancy was associated with a small increase in the prevalence of neural tube defects (0.19%) compared to non-dolutegravir regimens (0.11%). Most neural tube defects occur within the first 4 weeks of embryonic development after conception (approximately 6 weeks after the last menstrual period).

If a pregnancy is confirmed in the first trimester while on dolutegravir, the benefits and risks of continuing dolutegravir versus switching to another antiretroviral regimen should be discussed with the patient, taking the gestational age and the critical time period of neural tube defect development into account.

Dolutegravir may be used during the second and third trimester of pregnancy when the expected benefit outweighs the potential risk to the foetus. Dolutegravir was shown to cross the placenta in humans, leading to significant exposure to the foetus, but the implications of such exposure are not yet known.

### **Breast-feeding**

HIV infected women should not breast-feed their infants in order to avoid transmission of HIV or follow appropriate guidelines.

Dolutegravir is excreted in human breast milk, and there is significant exposure to the neonate/infants due to slow elimination; the half-life of dolutegravir in the new born was 33 hr compared to 14 hr in the adults. There is insufficient information on the effects of dolutegravir in neonates/infants.

### **Fertility**

There are no data on the effects of dolutegravir on human male or female fertility. Animal studies indicate no effects of dolutegravir on male or female fertility (see section 5.3).

**Driving and using machinery**

TLADEEZ may affect the ability to drive and use machines. TLADEEZ may make you feel tired, weak, lightheaded or dizzy.

Make sure you know how you react to TLADEEZ before you drive, use machines, or do anything else that could be dangerous.

**Important information about some of the ingredients of TLADEEZ**

TLADEEZ tablets contains lactose. Patients with the rare hereditary conditions of lactose or galactose intolerance should not take TLADEEZ.

TLADEEZ tablets contains mannitol and may have a laxative effect.

TLADEEZ contains lactose and mannitol which may have an effect on the control of your blood sugar if you have diabetes mellitus.

If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking TLADEEZ.

**Taking other medicines with TLADEEZ:**

Always tell your healthcare professional if you are taking any other medicine. (This includes complementary or traditional medicines).

**Do not take** TLADEEZ if you are already taking any of the following medicines:

- Other medicines that contain tenofovir disoproxil fumarate, lamivudine or emtricitabine, either alone, or in other formulations.

**TLADEEZ should not be used with these medicines because they contain the same or similar active ingredients as TLADEEZ.**

- Medicines that contain didanosine. Tenofovir disoproxil fumarate (an ingredient in TLADEEZ) may cause the amount of didanosine in your blood to increase. You may need to be followed more carefully if you are taking TLADEEZ and didanosine together. The dose of didanosine may need to be reduced.
- Adefovir dipivoxil (used for the treatment of chronic hepatitis B).
- Zalcitabine (antiretroviral treatment).
- Trimethoprim, as in co-trimoxazole (an antibiotic), may cause an increase in TLADEEZ plasma levels. If you have no kidney disease, a dosage adjustment is not necessary.
- Rifampicin (antibiotic used to treat several types of bacteria) may decrease the blood levels of dolutegravir.
- Isoniazid (antibiotic used to treat tuberculosis) increased the concentration
- Polyvalent cation-containing antacids. Recommended to be administered 2 hours before or 6 hours after TLADEEZ.

Some patients who are taking TLADEEZ may continue to experience infections and the use of antibiotics may have to be considered.

### **3. How to take TLADEEZ**

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

Treatment should be prescribed and initiated by a doctor experienced in the management of HIV infection.

Always take TLADEEZ exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

The usual dose of TLADEEZ is one tablet once a day.

TLADEEZ must be taken without regard of food.

You can only take TLADEEZ if you are older than 18 years.

### **If you have taken more TLADEEZ than you should**

In the event of overdose, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison control center.

### **If you forget to take TLADEEZ**

If you forget to take a dose of TLADEEZ, take it as soon as you remember and then continue as before.

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

### **Effects when treatment with TLADEEZ is stopped**

You should not stop treatment unless your doctor instructs you to. When your TLADEEZ supply starts to run low, get more from your healthcare provider or pharmacy. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short time. The virus may develop resistance to the ingredients in TLADEEZ and become harder to treat.

If you have the impression that the effect of TLADEEZ is too strong or too weak, talk to your doctor or pharmacist.

#### **4. Possible side effects**

TLADEEZ can have side effects.

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

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

- Sudden swelling of the skin or mucous membranes (e.g. throat or tongue) with difficulty breathing and/or itching and rash (see *Take special care with TLADEEZ*).

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to TLADEEZ.

- Serious liver problems (hepatitis) with liver enlargement (hepatomegaly) and fat in the liver (steatosis) (see *Take special care with TLADEEZ*). The following are signs of the liver problems:
  - Yellow discolouration of the skin and the white part of your eyeballs.
  - Darkening of your urine.
  - Your bowel movements turn lighter in colour.
  - You feel sick to your stomach (nausea).
  - You have stomach pain.

You may need urgent medical attention or hospitalisation.

### **LACTIC ACIDOSIS:**

**Some people who have taken medicines like TLADEEZ (nucleoside analogues) have developed a serious condition called lactic acidosis (build-up of acid in the blood). Lactic acidosis can be a medical emergency and may need to be treated in the hospital. Call your doctor immediately if you get the following signs or symptoms of lactic acidosis:**

- You feel very weak or tired.
- You have unusual (not normal) muscle pain.
- You have trouble breathing.
- You have stomach pain with nausea and vomiting.
- You feel cold, especially in your arms and legs.

- You feel dizzy or lightheaded.
- You have a fast or irregular heartbeat.

This side effect can cause inflammation of the pancreas, liver and kidney failure, and has occasionally been fatal. Lactic acidosis also occurs more often in women, particularly if they are overweight. If you have liver disease, you may also be more at risk of getting this condition. While you are being treated with TLADEEZ, your doctor will monitor you closely for any signs that you may be developing lactic acidosis.

Inform your doctor, pharmacist or other healthcare provider immediately if you notice any of the following serious side-effects:

*Those that occur frequently:*

- Nausea, vomiting (see *Take special care with TLADEEZ*)
- Upper stomach pain
- Joint pain (arthralgia)
- Muscle pain
- Fever

*Those that occur less frequently:*

- Fever, skin rash or any other signs of infection, such as boils or blisters
- Pallor, severe fatigue and heart palpitations, which may be due to low red blood cell counts
- Increased bruising or bleeding

- Rash or any other symptoms that may be due to an allergic reaction (see *Take special care with TLADEEZ*)
- Abnormal sensation of tingling, numbness or burning (paraesthesia)
- Difficulty urinating, dark urine, or foul-smelling urine, or more or less frequent urination, as this may indicate kidney problems (see *Take special care with TLADEEZ*)
- Severe bone pain or bone fractures (see *Take special care with TLADEEZ*)
- Shortness of breath (dyspnea)

If you notice any of the following less serious side-effects, inform your doctor, pharmacist or other healthcare provider during your next visit or if you find them to be intolerable:

*Those that occur frequently:*

- Headache
- Difficulty in sleeping (insomnia) or feeling low or depressed or anxious
- Cough, runny or blocked nose
- Dizziness with ringing in the ears
- Runny stomach, flatulence
- Itching
- Hair loss
- Feeling tired, weak (fatigue)
- Feeling of bodily discomfort (malaise)

*Those that occur less frequently:*

- Mild stomach pain or discomfort
- Weight gain or change in body shape (see *Take special care with TLADEEZ*)

*Those for which the frequency is not known:*

- Loss of appetite, poor digestion

If you notice any side effects not mentioned in this leaflet, please inform the medical practitioner or pharmacist.

### **Reporting of side effects**

If you get side effects, talk to your doctor or pharmacist or nurse. You can also report side effects to SAHPRA via the “**6.04 Adverse Drug 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 TLADEEZ.

### **5. How to store TLADEEZ**

STORE ALL MEDICINES OUT OF REACH OF CHILDREN.

Store at or below 30 °C. Store in the original container. Do not remove from the carton until required for use. Keep the bottle tightly closed.

Do not use after the expiry date stated on the label.

Return all unused medicine to your pharmacist.

Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

## 6. Contents of the pack and other information

### What TLADEEZ contains

Each film-coated tablet contains the active substances:

Lamivudine	300 mg
Tenofovir disoproxil fumarate	300 mg
Dolutegravir sodium equivalent to	
Dolutegravir	50 mg

The other ingredients are: croscarmellose sodium, lactose monohydrate, magnesium stearate, mannitol, microcrystalline cellulose; povidone; sodium starch glycolate {film-coating colourant: Opadry II white: macrogol / PEG 4000; polyvinyl alcohol – part. Hydrolysed; talc; titanium dioxide}

Contains sugar (lactose monohydrate 136 mg) and sweetener (mannitol 131,4 mg)

### What TLADEEZ looks like and contents of the pack

White to off white, film-coated, capsule-shaped, biconvex bevelled edge tablet debossed with “M” on one side and “LTD” on the other side of the tablet.

TLADEEZ will be packed in a round, white or blue, opaque High-Density Polyethylene (HDPE) bottle, round wide mouth, with white or blue opaque polypropylene (PP) screw closure and with wad containing aluminium induction sealing liner. Packed in an outer carton.

Pack sizes of 28's, 30's, 84's, 90's and 180's.\*

\* Not all pack sizes may be marketed

**Holder of Certificate of Registration**

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