PATIENT INFORMATION LEAFLET

SCHEDULING STATUS

S4

NEFORIM film-coated tablets

300 mg Tenofovir disoproxil fumarate (TDF) equivalent to 245 mg of tenofovir disoproxil or 136 mg of tenofovir, 300 mg lamivudine and 50 mg dolutegravir (as sodium)

Contains sugar: 68 mg lactose and 125 mg of mannitol per tablet

Read all of this leaflet carefully before you start taking NEFORIM

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor, pharmacist, nurse or other health care provider.
- NEFORIM 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 NEFORIM is and what it is used for

NEFORIM is a fixed dose combination of tenofovir disoproxil fumarate, lamivudine and dolutegravir. It is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults aged 18 years and older.

NEFORIM contains three active substances that are used to treat human immunodeficiency virus (HIV) infection:

- Tenofovir disoproxil is a nucleoside reverse transcriptase inhibitor.
- Lamivudine is a nucleoside reverse transcriptase inhibitor.
- Dolutegravir is an integrase inhibitor.

Each of these active substances are also known as antiretroviral medicines. Tenofovir disoproxil and lamivudine work by interfering with an enzyme (reverse transcriptase) that is essential for the virus to multiply. Dolutegravir work by reducing the amount of virus which helps to increase the CD4 cell count in your blood. CD4 cells are a type of white blood cells that are important for fighting the infection.

2. What you need to know before you take NEFORIM

Do not take NEFORIM:

- If you are hypersensitive (allergic) to tenofovir disoproxil, lamivudine or dolutegravir or any of the other ingredients of NEFORIM (listed in section 6).
- If you have moderate or severe liver disease.
- If you have renal disease.
- If you are pregnant or breastfeeding or are a woman of child-bearing age, not using contraception.
- If you are younger than 18 years of age.
- If you are taking dofetilide or pilsicainide for a heart problem.
- If you are taking metformin to control your blood sugar.

Warnings and precautions

Take special care with NEFORIM:

- If you have or have had kidney disease, or if tests have shown problems with your kidneys. NEFORIM may affect your kidneys. Before starting NEFORIM you may need blood tests to check how well your kidneys are working. Blood tests may also be required during treatment to check the health of your kidneys.
- If you have a history of mental illness, including depression, or of substance or alcohol abuse. Tell your health care provider immediately if you feel depressed, have suicidal thoughts or have strange thoughts.
- If you have a history of liver disease, including chronic active hepatitis. Patients with liver disease including chronic hepatitis B or C, who are treated with combination antiretrovirals, have a higher risk of severe and potentially life-threatening liver problems. If you have hepatitis B infection, your health care provider will carefully consider the best treatment regimen for you. Your health care provider may conduct blood tests to check how well your liver is working.
- If you experience any signs of inflammation or infection. In some patients with advanced HIV infection (AIDS) and a history of AIDS-associated (opportunistic) infection, signs, and symptoms of inflammation from such previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to 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 tell your health care provider at once. In addition, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. These may occur many months after the start of

treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, irregular heartbeats, trembling or shaking, or hyperactivity, please inform your health care provider at once.

- If you experience any signs of bone problems. Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The duration of antiretroviral therapy, use of a corticosteroid such as dexamethasone or prednisolone, alcohol consumption, severe suppression of the immune system, and being overweight may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these, tell your health care provider. Bone problems (sometimes resulting in fractures) may also occur due to damage to the kidney cells. Bone fractures may also occur due a decrease in bone density.

Children and adolescents

Safety and effectiveness in paediatric patients and patients younger than 18 years of age have not been established.

Other medicines and NEFORIM

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

It is very important to tell your health care provider if you are taking other medicines that may damage your kidneys. These include:

- aminoglycosides, pentamidine or vancomycin (for bacterial infection)

- amphotericin B (for fungal infection)
- foscarnet, ganciclovir, or cidofovir (for viral infection)
- adefovir dipivoxil (for hepatitis B virus infection)
- tacrolimus (for suppression of the immune system)
- interleukin-2 (to treat cancer)

Medicines containing didanosine (for HIV infection): Taking NEFORIM with medicines that contain didanosine can increase the amount of didanosine in your blood. Rarely, inflammation of the pancreas and lactic acidosis (excess lactic acid in the blood), sometimes causing death, has been reported when medicines containing tenofovir disoproxil and didanosine were taken together. Combining tenofovir disoproxil with didanosine can also reduce the effects of antiretroviral therapy. Your health care provider will carefully consider whether to treat you with a combination of tenofovir disoproxil and didanosine.

If you are currently taking any of the following medicines tell your healthcare provider immediately:

- dofetilide
- antacids, laxatives, or other medicines that contain aluminium, magnesium, sucralfate, or buffered medicines
- metformin
- rifampicin
- didanosine

Taking these medicines with NEFORIM could cause threatening side effects or stop these medicines from working properly.

NEFORIM with food

It is recommended that NEFORIM be swallowed with water, with or without food

Pregnancy and breastfeeding

If you are pregnant or breastfeeding, 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.

NEFORIM is contraindicated in pregnancy and during breastfeeding.

Driving and using machines

It is not always possible to predict to what extent NEFORIM 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 NEFORIM affects them. NEFORIM causes dizziness, impaired concentration and/or drowsiness and may affect the ability to drive and use machines.

NEFORIM contains lactose

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking NEFORIM. Lactose may have an effect on the control of your blood sugar if you have diabetes mellitus.

Each tablet also contains 5,981 mg of sodium which is less than 1 mmol sodium (23 mg) per tablet, essentially sodium-free.

3. How to take NEFORIM

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

Always take NEFORIM exactly as your doctor or pharmacist has told you. Check

with your doctor or pharmacist if you are not sure.

The usual dose is one tablet taken orally, once daily.

NEFORIM should not be used by children younger than 18 years old.

Your doctor will tell you how long your treatment with NEFORIM will last. If you have the impression that the effect of NEFORIM is too strong or too weak, tell your doctor or pharmacist.

If you take more NEFORIM 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 NEFORIM

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

If you stop taking NEFORIM

Don’t stop taking this medicine without talking to your health care provider. Stopping NEFORIM can seriously affect your response to future treatment. If NEFORIM is stopped, speak to your health care provider before you restart taking these tablets. Your health care provider may consider giving you the components of NEFORIM separately if you are having problems or need your dose adjusted.

If you have both HIV infection and hepatitis B, it is especially important not to stop your NEFORIM treatment without talking to your health care provider first. Some patients have had blood tests or symptoms indicating that their hepatitis got worse after stopping treatment. Your health care provider may recommend that you resume hepatitis B treatment if you stop NEFORIM treatment. You may require blood tests to check how your liver is working for 4 months after stopping treatment. In some patients with advanced liver disease or cirrhosis, stopping treatment is not recommended as this may lead to worsening of your hepatitis,

which may be life-threatening.

Tell your health care provider immediately about new or unusual symptoms after you stop treatment, particularly symptoms you associate with hepatitis B infection.

4. Possible side effects

NEFORIM can have side effects.

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

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

Lactic acidosis (excess lactic acid in the blood) is a rare, but serious side effect that can be fatal. The following side effects may be signs of lactic acidosis:

- deep rapid breathing
- drowsiness
- feeling sick (nausea), being sick (vomiting) and stomach pain.

If you think you may have lactic acidosis, contact your healthcare provider immediately.

Other potentially serious side effects:

If you think that you may have any of these serious side effects, talk to your health care provider:

- allergic reaction (hypersensitivity) that may cause severe skin reactions
- swelling of the face, lips, tongue or throat

- angry behaviour, suicidal thoughts, strange thoughts, paranoia, unable to think clearly, mood being
- affected, seeing or hearing things that are not really there (hallucinations), suicide attempts, personality change (psychosis)
- pain in the abdomen (stomach), caused by inflammation of the pancreas

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

Tell your doctor if you notice any of the following:

Frequent

- dizziness, diarrhoea, feeling sick (nausea), being sick (vomiting)
- rashes (including red spots or blotches sometimes with blistering and swelling of the skin), which may be allergic reactions
- feeling weak
- tests may also show decreases in phosphate levels in the blood
- stomach pain
- difficulty sleeping, abnormal dreams, difficulty concentrating, drowsiness
- feeling worried or depressed
- problems with digestion resulting in discomfort after meals, feeling bloated, wind (flatulence)
- loss of appetite
- tiredness
- itching
- hair loss
- disturbances of coordination and balance
- headache

- cough
- irritated or runny nose
- fever (high temperature)
- general feeling of being unwell
- tests may also show:
    - increased fatty acids (triglycerides) or sugar levels in the blood
    - liver and pancreas problems

Less frequent

- back pain caused by kidney problems, including kidney failure
- inflammation of the kidney, passing a lot of urine and feeling thirsty, damage to kidney cells
- fatty liver
- liver failure, in some cases leading to death or liver transplant
- softening of the bones (with bone pain and sometimes resulting in fractures)
- breakdown of muscle, muscle pain or weakness
- decreases in potassium in the blood
- increases in creatinine in the blood
- proteins in urine
- itchy rash to the skin
- joint pain, stiffness, and bone problems, which causes difficult moving
- infection and inflammation

Frequency unknown

- hepatitis
- red blood cell abnormalities

- high blood sugar
- high cholesterol
- difficulty breathing

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 Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website. By reporting side effects, you can help provide more information on the safety of NEFORIM.

5. How to store NEFORIM

Store at or below 25 °C.

Store all medicines out of reach of children.

- Do not store in a bathroom
- Do not use after the expiry date stated on the label / carton / bottle

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 NEFORIM contains

- The active substances are tenofovir disoproxil fumarate, lamivudine and dolutegravir. Each film-coated tablet contains 300 mg tenofovir disoproxil fumarate (TDF) equivalent to 245 mg of tenofovir disoproxil or 136 mg of tenofovir, 300 mg lamivudine and 50 mg dolutegravir (as sodium).
- The other ingredients are*:*

Core tablet: colloidal silicon dioxide, croscarmellose sodium, crospovidone, lactose, magnesium stearate, mannitol (E421), microcrystalline cellulose, povidone, pregelatinised starch, sodium starch glycolate, sodium stearyl fumarate

Film-coat: macrogol/PEG, polyvinyl alcohol (partly hydrolysed), talc, titanium dioxide (E171)

What NEFORIM looks like and contents of the pack

White to off white capsule shaped, biconvex, film-coated tablets debossed with 'TLD' on one side and break-line on the other side.

The break-line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

28 or 30 tablets packed in 100 ml white opaque HDPE container closed with 38 mm white opaque polypropylene ribbed screw cap with liner.

56 or 60 tablets packed in 150 ml white opaque HDPE container closed with 38 mm white opaque polypropylene ribbed screw cap with liner.

84 or 90 tablets packed in 250 ml white opaque HDPE container closed with 53 mm white opaque polypropylene ribbed screw cap with liner.

All pack sizes contain a 3 g molecular sieve canister.

Not all pack sizes may be marketed.

Holder of Certificate of Registration

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Access to the corresponding Professional Information

To follow

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