PATIENT INFORMATION LEAFLET

SCHEDULING STATUS: S4

ATENEF

(efavirenz 600 mg/ emtricitabine 200 mg/ tenofovir disoproxil fumarate 300 mg film-coated tablets)

Sugar free

Read all of this leaflet carefully before you start taking ATENEF

- 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.
- ATENEF 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 ATENEF is and what it is used for

ATENEF is a fixed dose combination containing three antiretroviral medicines; efavirenz, emtricitabine and tenofovir that work by interfering with an enzyme (reverse transcriptase) that is essential for the virus to multiply.

ATENEF is used to treat Human Immunodeficiency Virus (HIV) infection in adults aged 18 years and over. It is used alone as a complete regimen or in combination with other antiretroviral agents for the treatment

of HIV-1 infection in adults.

2. What you need to know before you take ATENEF

Do not take ATENEF:

- If you are hypersensitive (allergic) to efavirenz, emtricitabine, tenofovir disoproxil fumarate or any of the other ingredients of ATENEF (listed in section 6).
- If you are pregnant or breastfeeding.
- If you have moderate to severe problems with your kidney(s).
- If you had a liver disorder or liver failure attributed to treatment with ATENEF.
- If you are currently taking any of the following medicines:
  - astemizole (used to treat hay fever or other allergies)
  - bepridil (used to treat heart disease)
  - cisapride (used to treat heartburn)
  - ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine) [used to treat migraines and cluster headaches]
  - midazolam or triazolam (used to help you sleep)
  - pimozide (used to treat certain mental conditions)
  - voriconazole (used to treat fungal infections)

If you are taking any of these medicines, tell your doctor immediately. Taking these medicines with ATENEF could cause serious or life-threatening side effects or stop these medicines from working properly.

Warnings and precautions

Tell your doctor or health care provider before being given ATENEF.

Take special care with ATENEF:

- if you are taking other medicines that contain efavirenz, emtricitabine, tenofovir disoproxil, or lamivudine or adefovir dipivoxil. ATENEF should not be taken with any of these medicines.
- If you have or have had kidney disease, or if tests have shown problems with your kidneys. ATENEF is not recommended if you have moderate to severe kidney disease.

ATENEF may affect your kidneys. Before starting treatment, your doctor may order blood tests to assess kidney function. Your doctor may also order blood tests during treatment to monitor your kidneys.

ATENEF tablets are not usually taken with other medicines that can damage your kidneys (see "Other medicines and Atenef").

- if you have a history of mental illness, including depression, or of substance or alcohol abuse. Tell your doctor immediately if you feel depressed, have suicidal thoughts or have strange thoughts.
- if you have a history of convulsions (fits or seizures) or if you are being treated with anticonvulsant therapy such as carbamazepine, phenobarbital and phenytoin. If you are taking any of these medicines, your doctor may need to check the level of anticonvulsant medicine in your blood to ensure that it is not affected while taking ATENEF tablets. Your doctor may give you a different anticonvulsant.
- 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. Your doctor may conduct blood tests in order to check how well your liver is working or may switch you to another medicine. If you have severe liver disease, do not take ATENEF tablets.
- if you have hepatitis B infection, your doctor will carefully consider the best treatment regimen for you. Symptoms of your hepatitis may become worse after discontinuation of ATENEF. Your doctor may then conduct blood tests at regular intervals in order to check how well your liver is working independent of a history of liver disease, your doctor will consider regular blood tests to check how your liver is working.
- if you are diabetic, overweight or have high cholesterol. Combination antiretroviral therapies (including ATENEF) may raise blood sugar levels, increase blood fats (hyperlipaemia), cause changes to body fat, and resistance to insulin.
- if you are over 65 years. Insufficient numbers of patients over 65 years of age have been studied. If you are over 65 years of age and are prescribed ATENEF tablets, your doctor will monitor you carefully.
- if you are under 18 years of age. The use of ATENEF tablets in children and adolescents has not yet been studied and should therefore not be given to children and adolescents under 18 years of age.

Tell your doctor if any of the following happens while on treatment with ATENEF:

- Possible signs of lactic acidosis. Some HIV medicines, including ATENEF, can cause lactic acidosis (excess of lactic acid in your blood), together with an enlarged liver and/or fatty infiltration of the liver. Deep, rapid breathing, drowsiness, and symptoms such as feeling sick (nausea), vomiting and stomach pain, might indicate the development of lactic acidosis. This rare but serious side effect has occasionally been fatal. Lactic acidosis occurs more often in women, particularly if they are very overweight, and people with liver disease. While you are being treated with ATENEF, your doctor will monitor you closely for any signs that you may be developing lactic acidosis.
- "Flare-ups" of Hepatitis B Virus (HBV) infection, in which the disease suddenly returns in a worse way than before if you have HBV and you stop taking ATENEF. Your healthcare provider will monitor your condition for several months after stopping ATENEF if you have both HIV and HBV infection and may recommend treatment for your HBV.
- Signs of dizziness, difficulty sleeping, drowsiness, difficulty concentrating or abnormal dreaming. These side effects may start in the first 1 or 2 days of treatment and may go away after the first 2 to 4 weeks.
- Any signs of skin rash. Rashes may be caused by ATENEF. If you see any signs of a severe rash with blistering or fever, stop taking ATENEF and tell your doctor at once. If you had a rash while taking another another medicine for HIV, you may be at higher risk of getting a rash with ATENEF.
- Any signs of inflammation or infection. In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from 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.
- 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 length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, 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.

- Mitochondrial dysfunction: Some patients taking combination antiretroviral therapy may develop mitochondrial dysfunction, which may be presented as blood disorders [anaemia (symptoms include fatigue, decreased energy, weakness, shortness of breath, light headedness, palpitations, looking pale), neutropenia (symptoms include fevers and frequent infections)], metabolic disorders (such as lipid disorder). Some late-onset neurological disorders may develop (such as fits, abnormal behaviour).

- Changes in bone mineral density (thinning bones): It is not known whether long-term use of ATENEF will cause damage to your bones. If you have had bone problems in the past, your doctor may need to do tests to check your bone mineral density or may prescribe medicines to help your bone mineral density.

Children and adolescents

ATENEF is not recommended in children and adolescents less than 18 years of age.

Also remember the following precautions:

- ATENEF is not a cure for HIV infection. You can still pass on HIV when taking this medicine, so it is important to take precautions to avoid infecting other people through sexual contact or blood transfer.
- While taking ATENEF you may still develop infections or other illnesses associated with HIV infection.

You must remain under the care of your doctor or health care provider while taking ATENEF.

ATENEF may interfere with the results of some of the laboratory tests (such as urine cannabinoid test). Tell your doctor about your medicines if you have to undergo any such test.

If the above applies to you or if you are not sure if any of the above applies to you, talk to your doctor before taking ATENEF tablets.

Your doctor will tell you whether it is safe for you to start taking ATENEF.

Please consult your doctor, even if these statements were applicable to you at any time in the past.

Other medicines and ATENEF:

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

You must not take ATENEF tablets with certain medicines. These are listed under Do not take ATENEF tablets. They include some common medicines and some herbal remedies (including St. John's wort) which can cause serious interactions.

ATENEF should not be taken with any other medicines that contain efavirenz, emtricitabine, tenofovir disoproxil, or lamivudine or adefovir dipivoxil.

Tell your doctor if you are taking other medicines which may damage your kidneys. Some examples include:

- aminoglycosides, vancomycin (medicines for bacterial infections)
- foscarnet, acyclovir, ganciclovir, cidofovir, valacyclovir and valganciclovir (medicines for viral infections).

ATENEF tablets may interact with other medicines. As a result, the amounts of ATENEF tablets or other medicines in your blood may be affected. This may stop your medicines from working properly, or may make any side effects worse. In some cases, your doctor may need to adjust your dose or check your blood levels. It is important to tell your doctor if you are taking any of the following:

- Medicines containing didanosine (for HIV infection).
- Other medicines used for HIV infection containing indinavir, amprenavir, fosamprenavir calcium, lopinavir/ritonavir, ritonavir, or ritonavir boosted atazanavir or saquinavir.
- Medicines used to lower blood fats (also called statins): atorvastatin, pravastatin, simvastatin.
- Medicines used to treat convulsions/seizures (anticonvulsants): carbamazepine, phenytoin, phenobarbital.
- Medicines used to treat bacterial infections, including tuberculosis and AIDS-related *Mycobacterium avium* complex: clarithromycin, rifabutin, rifampicin.
- Medicines used to treat fungal infections (antifungals): itraconazole, ketoconazole.

- Hormonal contraceptive, such as birth control pills (ethinyl estradiol), or a contraceptive implant [for example, depomedroxyprogesterone acetate (DMPA), etonogestrel]. See **Pregnancy, breastfeeding and fertility**.
- Methadone, a medicine used to treat opiate addiction.
- Sertraline, a medicine used to treat depression.
- Diltiazem or similar medicines (called calcium channel blockers), such as felodipine, nicardipine, nifedipine, verapamil.
- Medicines used to prevent organ transplant rejection (also called immuno-suppressants), such as ciclosporin or sirolimus.
- Warfarin (a medicine used to reduce clotting of the blood).

Taking ATENEF with food and drink

ATENEF should be taken on an empty stomach.

Pregnancy, breastfeeding and fertility

You should not use ATENEF if you are pregnant or breastfeeding your baby.

If you are pregnant or breastfeeding your baby, 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 ATENEF.

Pregnancy:

Women should not get pregnant during treatment with ATENEF and for 12 weeks thereafter. Your doctor may require you to take a pregnancy test to ensure you are not pregnant before starting treatment with ATENEF.

You need to use a reliable form of barrier contraception (for example, a condom) with other methods of contraception including oral (pill) or other hormonal contraceptives (for example, implants, injection). Efavirenz, one of the active components of ATENEF, may remain in your blood for a time after therapy is stopped. Therefore, you should continue to use contraceptive measures, as above, for 12 weeks after you stop taking ATENEF.

Tell your doctor immediately if you are pregnant or intend to become pregnant.

Serious birth defects have been seen in unborn animals and in the babies of women treated with efavirenz

during pregnancy. If you have taken ATENEF during your pregnancy, your doctor may request regular blood tests and other diagnostic tests to monitor the development of your child.

Breastfeeding:

Do not breast-feed during treatment with ATENEF. Both HIV and the ingredients of ATENEF may pass through breast milk and cause serious harm to your baby.

Driving and using machines

ATENEF may make you feel dizzy or drowsy and may affect your concentration. Do not drive or operate machinery until you know how ATENEF affects you.

3. HOW TO TAKE ATENEF:

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

Always take ATENEF exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Adults

The usual dose for adults is one tablet taken each day by mouth. ATENEF tablets should be taken on an empty stomach. Swallow ATENEF tablets whole with water.

ATENEF tablets must be taken every day.

It can help to take ATENEF tablets at bedtime. This may make some side effects (for example, dizziness, drowsiness) less troublesome.

Children and adolescents

ATENEF tablets are not recommended for patients less than 18 years of age.

Patients with Kidney Problems

ATENEF tablets are not recommended for patients with moderate to severe problems with their kidney(s).

Your doctor will tell you how long your treatment with ATENEF will last. Do not stop treatment early. If you have the impression that the effect of ATENEF is too strong or too weak, tell your doctor or pharmacist.

If you take more ATENEF than you should:

In the event of overdosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison control centre. Keep the medicine with you so that you can easily describe what you have taken.

If you forget to take ATENEF:

It is important not to miss a dose of ATENEF.

If you do miss a dose of ATENEF, take it as soon as you can, and then take your next dose at its regular time.

If it is almost time for your next dose anyway, do not take the missed dose. Wait and take the next dose at the regular time. Do not take a double dose to make up for a forgotten tablet.

If you vomit the tablet (within 1 hour after taking ATENEF), you should take another tablet. Do not wait until your next dose is due. You do not need to take another tablet if you were sick more than 1 hour after taking ATENEF.

If you stop taking ATENEF:

Don't stop taking ATENEF without talking to your doctor. Stopping ATENEF can seriously affect your response to future treatment. If ATENEF are stopped, speak to your doctor before you restart taking ATENEF. Your doctor may consider giving you the components of ATENEF separately if you are having problems or need your dose adjusted

When your supply of ATENEF starts to run low, get more from your doctor or pharmacist. This is very important because the amount of virus may start to increase if the medicine is stopped for even a short time. The virus may then become harder to treat.

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

4. Possible side effects

ATENEF can have side effects.

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

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

- Skin troubles such as lumpy skin rash or “hives”
- Swelling of the hands, feet, ankles, face, lips, and mouth or throat, which may cause difficulty in swallowing or breathing,
- Wheezing, chest pain or tightness
- Fainting

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

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:

- ***Severe skin conditions***

- Stevens Johnson Syndrome (rare skin condition with severe blisters and bleeding in the lips, eyes, mouth, nose and genitals).
- Erythema multiforme (severe condition of the skin that may affect the mouth and other parts of the body. Symptoms include: red, often itchy spots, similar to the rash of measles, which starts on the limbs and sometimes on the face and the rest of the body. The spots may blister or may progress to form raised, red, pale-centred marks. Those affected may have fever, sore throat, headache and/or diarrhoea).

- ***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

These side effects may be due to a condition called lactic acidosis (build-up of an acid in the blood).

- ***Serious liver problems (hepatotoxicity)***

- Your skin or the white part of your eyes turns yellow (jaundice)

- Your urine turns dark
- Your bowel movements (stools) turn light in colour
- You don't feel like eating food for several days or longer,
- You feel sick to your stomach (nausea)
- You have lower stomach area pain (abdominal pain).

These side effects may be due to a condition called hepatotoxicity with liver enlargement (hepatomegaly) and fat deposits in the liver (steatosis) which sometimes occurs in patients taking anti-HIV medicines.

- ***Serious psychiatric problems***

These include depression, strange thoughts, or angry behaviour, thoughts of suicide. These problems may occur more often in patients who have had mental illness.

- ***Kidney disease***
- If you have any of the following symptoms, it may be due to a kidney disease:

  - where you pass little or no urine

  -drowsiness, nausea, vomiting, breathlessness

- ***Pancreatitis:***
- Severe stomach pain or cramps
- Nausea
- Vomiting.

These side effects may be due to a condition called pancreatitis which sometimes occurs in patients taking anti-HIV medicines.

- Temporary paralysis or weakness of muscles (Rhabdomyolysis)
- Seizures (fits)
- Numbness, tingling or burning sensation or pain in the feet and/ or hands; these may be symptoms of peripheral neuropathy, a nerve disorder, but may be serious.
- Pneumonia (a serious lung infection with the following symptoms: fever, chills, shortness of breath, cough, phlegm and occasionally blood).

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

Tell your doctor or pharmacist if you notice any of the following:

Frequent side effects:

- Changes in body fat. Changes in body fat develop in some people receiving antiretroviral therapy. 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.

-Skin discolouration (small spots or freckles),

-Headache, dizziness, difficulty in sleeping or excessive sleeping, impaired concentration, abnormal dreams, abnormal walk, abnormal coordination, balance disturbances, decreased sensations, abnormal sensations, tremor, nervousness.

-Indigestion, constipation, dry mouth, stomach discomfort or fullness, relieved by belching or passing wind, increased appetite

-Anxiety

Less Frequent side effects:

-Joint pains, muscle pain, back pain

-Flushing

-Palpitations (feeling your heartbeat)

-Enlarged breasts in male patients

-Abnormal vision, ringing in ears, incoherent speech

-Increased urination

-Increased sensitivity to sunlight caused by some medicines (photoallergic dermatitis)

-Diabetes insipidus (a condition in which the kidneys are unable to conserve water). The symptoms include excessive thirst and/or increased urination.

There may be changes in the results of certain laboratory tests:

- deranged liver function tests,
- increased blood amylase,
- increased blood sugar levels,
- increased creatine kinase levels,
- decrease in haemoglobin values,
- increased cholesterol, triglyceride levels,
- decreased neutrophil count (a type of white blood cells that protect against infection),
- deranged kidney function tests,
- decreased potassium or phosphorus levels in blood,

- protein in urine.

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 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 **ATENEF**.

5. How to store ATENEF

Store at or below 25 °C..

Protect from moisture.

Do not store in a bathroom.

Store in the original container.

Keep the container tightly closed.

Store all medicines out of the reach of children.

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

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

Return all unused medicine to your pharmacist.

6. Contents of the pack and other information

What ATENEF contains

The three active substances are:

Efavirenz (600 mg),

emtricitabine (200 mg) and

tenofovir disoproxil fumarate (300 mg)

The other ingredients are: Microcrystalline cellulose , croscarmellose sodium, ferric oxide red, magnesium stearate, hydroxypropyl cellulose and sodium lauryl sulfate. The film-coat contains polyvinyl alcohol – part. hydrolysed, titanium dioxide, macrogol/PEG 3350 and talc.

What ATENEF looks like and contents of the pack

The tablets are white to off-white, capsule shaped, film-coated tablets debossed with 'RF21' on one side and plain on the other side.

28, 30, 84 or 90 Tablets packed in a white opaque HDPE bottle. The HDPE bottle is packed with or without an outer cardboard carton.

HDPE bottle pack for 28 and 30:

The HDPE bottle is a white, opaque 100 ml HDPE bottle with a white polypropylene, round cylindrical 38 mm cap with a heat seal liner.

HDPE bottle pack for 84 and 90:

The HDPE bottle is a white, opaque 250 ml HDPE bottle with a white polypropylene, round cylindrical 38 mm cap with a heat seal liner.

The cap is a white polypropylene, round cylindrical cap with a heat seal liner and printed with "SEALED for YOUR PROTECTION" in black. The bottle also contains a desiccant.

Holder of Certificate of Registration

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