1.3.2 Proposed Patient Information Leaflet-clean

SCHEDULING STATUS

S4

EFRIN (film-coated tablet)

Efavirenz

Contains sugar: Lacose monohydrate 255,60 mg

Read this leaflet carefully, before you start taking EFRIN or before you give EFRIN to your child or the patient who you are caring for.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- EFRIN has been prescribed for you personally or for your child or patient who you are caring for and you should not share your medicine or their medicine with other people. It may harm them, even if their symptoms are the same as yours or theirs.

What is in this leaflet

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

1. What EFRIN is and what it is used for

What EFRIN is:

EFRIN contains the active substance efavirenz, which belongs to a class of antiretroviral medicines called non-nucleoside reverse transcriptase inhibitors (NNRTIs). It is an antiretroviral medicine that fights human immunodeficiency virus (HIV) infection by reducing the amount of the virus in blood.

What EFRIN is used for:

EFRIN tablets are used with other medicines in the treatment of the infection caused by the human immunodeficiency virus (HIV). HIV is the virus that causes acquired immune deficiency syndrome (AIDS).

2. What you need to know before you take EFRIN

Do not take EFRIN:

- if you are hypersensitive (allergic) to efavirenz or any of the other ingredients of EFRIN;
- if you are pregnant or breastfeeding;
- You had a liver disorder or liver failure attributed to treatment with EFRIN**.**
- if you have severe liver disease (Child Pugh Grade C);
- if you have a heart condition, such as changes in the rhythm or rate of the heartbeat, a slow heartbeat, or severe heart disease.
- if any member of your family (parents, grandparents, brothers or sisters) has died suddenly due to a heart problem or was born with heart problems.
- if your doctor has told you that you have high or low levels of electrolytes such as potassium or magnesium in your blood.
- if you are currently taking any of the following medicines:
    - terfenadine (used to treat allergy symptoms)

- bepridil (used to treat heart disease)
- cisapride (used to treat heartburn)
- ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine) (used to treat migraine and cluster headaches)
- midazolam or triazolam (used to help you sleep)
- pimozide, imipramine, amitriptyline or clomipramine (used to treat certain mental conditions)
- elbasvir or grazoprevir (used to treat hepatitis C)
- St. John's wort (Hypericum perforatum) (a herbal remedy used for depression and anxiety)
- flecainide, metoprolol (used to treat irregular heart beat)
- certain antibiotics (macrolides, fluoroquinolones, imidazole)
- triazole antifungal agents
- certain antimalarial treatments
- methadone (used to treat opiate addiction)

EFRIN is contra-indicated in adults and children weighing less than 40 kg.

Take special care with EFRIN:

- if you have liver problems;
- if you have a history of psychiatric disorders including inappropriate behaviour (including aggressive reactions),depression, or of substance or alcohol abuse. Tell your doctor immediately if you feel depressed, have suicidal thoughts or have strange thoughts (*see section 4, Possible side effects*);
- 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 EFRIN. Your doctor may give you a different anticonvulsant;

- if you have a history of liver disease, including active chronic hepatitis. Patients with chronic hepatitis B or C and treated with combination antiretroviral agents have a higher risk for 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 EFRIN (*see section 2 Do not take EFRIN*);
- if you have a heart disorder, such as abnormal electrical signal called prolongation of the QT interval;

Once you start taking EFRIN, look out for:

• *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 usually go away after the first 2 to 4 weeks.

• *any signs of skin rash*. If you see any signs of a severe rash with blistering or fever, stop taking EFRIN and tell your doctor at once. If you had a rash while taking another NNRTI, you may be at a higher risk of getting a rash with EFRIN.

• *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 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 tell your doctor immediately. In addition to the opportunistic infections, 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. Autoimmune disorders 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, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.

• *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. If you notice any of these symptoms please inform your doctor.

EFRIN will not cure or prevent HIV infection or AIDS; but it helps to keep HIV from reproducing and appears to slow down the destruction of the immune system. EFRIN will not keep you from spreading HIV to other people.

Children and adolescents:

EFRIN has not been studied in paediatric patients below 3 years of age or who weigh less than 13 kg.

Other medicines and EFRIN

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

Although certain medicines should not be used together at all, in other cases two different medicines may be used together even if an interaction might occur. In these cases your doctor may want to change the dose.

Tell your doctor if you are taking any of the following medicines:

- Indinavir, ritonavir, saquinavir (medicines used in the treatment of HIV infection)
- Clarithromycin, rifamycins (medicines used to treat bacterial infections)
- Oral contraceptives
- Methadone (medicine used to relieve pain)
- St John's Wort (Hypericum perforatum)
- Ginkgo biloba
- Cisapride (medicine used to treat heartburn)
- Midazolam or triazolam (medicines used to help you sleep)
- Medicines used to treat infection with the hepatitis C virus: boceprevir, telaprevir, elbasvir/grazoprevir, simeprevir, sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/voxilaprevir, glecaprevir/pibrentasvir.
- Medicines used to treat bacterial infections, including tuberculosis and AIDS-related mycobacterium avium complex: clarithromycin, rifabutin, rifampicin. Your doctor may consider changing your dose or giving you an alternative antibiotic.
- Medicines used to treat fungal infections (antifungals):
    - voriconazole. EFRIN may reduce the amount of voriconazole in your blood and voriconazole may increase the amount of efavirenz in your blood. Your doctor may adjust the dose of voriconazole.

  - itraconazole. EFRIN may reduce the amount of itraconazole in your blood.
  - posaconazole. EFRIN may reduce the amount of posaconazole in your blood.
- Medicines used to treat malaria:
  - artemether/lumefantrine: EFRIN may reduce the amount of artemether/lumefantrine in your blood.
  - atovaquone/proguanil: EFRIN may reduce the amount of atovaquone/proguanil in your blood.
- Medicines used to treat convulsions/seizures (anticonvulsants): carbamazepine, phenytoin, phenobarbital. EFRIN can reduce or increase the amount of anticonvulsant in your blood. Carbamazepine may make EFRIN less likely to work. Your doctor may need to consider giving you a different anticonvulsant.
- Medicines used to lower blood fats (also called statins): atorvastatin, pravastatin, simvastatin. EFRIN can reduce the amount of statins in your blood. Your doctor will check your cholesterol levels and will consider changing the dose of your statin, if needed.
- Sertraline (a medicine used to treat depression): your doctor may need to change your dose of sertraline.
- Metamizole, a medicine used to treat pain and fever.
- Bupropion (a medicine used to treat depression or to help you stop smoking): your doctor may need to change your dose of bupropion.
- Diltiazem or similar medicines (called calcium channel blockers, which are medicines typically used for high blood pressure or heart problems): when you start taking EFRIN, your doctor may need to adjust your dose of the calcium channel blocker.
- Immunosuppressants such as cyclosporine, sirolimus, or tacrolimus (medicines used to prevent organ transplant rejection): when you start or stop taking EFRIN, your

doctor will closely monitor your plasma levels of the immunosuppressant and may need to adjust its dose.

- Warfarin or acenocoumarol (medicines used to reduce clotting of the blood): your doctor may need to adjust your dose of warfarin or acenocoumarol.
- Medicines that impact heart rhythm:
    - Medicines used to treat heart rhythm problems such as flecainide or metoprolol.
    - Medicines used to treat depression such as imipramine, amitriptyline or clomipramine.
    - Antibiotics, including the following types: macrolides, fluoroquinolones or imidazole.

EFRIN with food and drink and alcohol

EFRIN can be taken with or without food.

Pregnancy and breastfeeding and fertility

If you are pregnant or breastfeeding your baby while taking EFRIN, please consult your doctor, pharmacist or other healthcare professional for advice.

You should not take EFRIN if you are pregnant or breastfeeding your baby or intend to become pregnant *(see section Do not take EFRIN)*.

EFRIN has not been studied in pregnant women. Studies in pregnant animals have found that it causes birth defects in the offspring. A pregnancy test is recommended before starting treatment. It is also recommended that women with the potential to become pregnant use

two methods of contraception. One method should be barrier contraception, such as condoms, and the other method should be an oral or other hormone contraceptive.

It is not known whether EFRIN passes into breast milk. Breastfeeding is therefore not recommended in patients with HIV infection because of the risk of passing the virus onto the nursing infant.

Driving and using machinery

It is not always possible to predict to what extent EFRIN may interfere with the daily activities of a patient. EFRIN may cause drowsiness. Patients should ensure that they do not engage in the above activities until they are aware of the measure to which EFRIN affects them.

EFRIN contains lactose

EFRIN contains lactose, which may have an effect on the control of your blood sugar if you have diabetes mellitus. Patients with the rare hereditary conditions of lactose/fructose or galactose intolerance should not take EFRIN.

3. How to take EFRIN

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

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

- Your doctor will prescribe the appropriate dosage in relation to your age and weight.
- Your doctor will tell you how long your treatment with EFRIN will last.
- Do not suddenly stop taking EFRIN without consulting with your doctor first.
- EFRIN must be taken with or without food.

- The central nervous system side effects (the system that controls most functions of the body and mind) that may occur with EFRIN usually lessen after you have taken the medicine for a while. Also, taking the medicine at bedtime, especially during the first 2 – 4 weeks may lessen these side effects.
- If you have the impression that the effect of EFRIN is too strong or too weak, tell your doctor or pharmacist.

If you take more EFRIN 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.

If you forget to take EFRIN

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

If you miss a dose of EFRIN, take it as soon as possible. However if it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule.

4. Possible side effects

EFRIN can cause side effects.

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

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and lifestyle, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

The most notable unwanted effects reported with EFRIN in combination with other anti-HIV medicines are skin rash and nervous system symptoms such as memory loss, lack of coordination, severe headache and loss of sight or double vision.

You should consult your doctor if you have a rash, since some rashes may be serious; however, most cases of rash disappear without any change to your treatment with EFRIN. Rash was more common in children than in adults treated with EFRIN.

The nervous system symptoms such as memory loss, lack of coordination, severe headache and loss of sight or double vision tend to occur when treatment is first started, but generally decrease in the first few weeks. If you are affected your doctor may suggest that you take EFRIN at bedtime and on an empty stomach. Some patients have more serious symptoms that may affect mood or the ability to think clearly. Some patients have actually committed suicide. These problems tend to occur more often in those who have a history of mental illness. Always notify your doctor immediately if you have these symptoms or any side effects while taking EFRIN.

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

- Swelling of the hands, feet, ankles, face, lips, mouth or throat, which may cause difficulty in swallowing or breathing;
- rash or itching, hives
- fainting;
- tightness in the chest;

- convulsions (seizures);
- fast or abnormal heartbeat;
- fever; chills;
- skin rash; hives
- dizziness;
- liver failure, in some cases leading to death or liver transplant;
- suicidal thoughts or attempting to kill yourself.

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

- Nausea, vomiting;
- diarrhoea;
- worsening of depression;
- headache;

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

Tell your doctor if you notice any of the following:

The following side effects have been reported frequently:

- Trouble in sleeping;
- tiredness; drowsiness; difficulty to concentrate;
- taste disorders;
- itching;

Tests may show:

- increased liver enzymes in the blood;
- increased triglycerides (fatty acids) in the blood.

The following side effects have been reported less frequently:

- Inflammation of the pancreas;
- anorexia;
- abnormal behaviour; forgetfulness; anxiety; confusion; mood changes;
- abnormal vision;
- ringing in the ears; feeling of movement (vertigo);
- flushing;
- asthma;
- heartburn;
- yellow eyes or skin (jaundice);
- hair loss or painful hair follicles;
- eczema; flaking of skin;
- joint or muscle pain;
- breast enlargement in males.

Tests may show:

- increased cholesterol in the blood

The following side effects have been reported but the frequency is unknown:

- increased appetite; changes in body or face shape due to changes in fat distribution; weight gain or loss; you may lose fat from your legs, arms and face, gain fat around the abdomen (tummy) and other internal organs, get larger breasts or fatty lumps on the back of the neck ('buffalo hump');

- abnormal dreams;
- unsteadiness;
- tingling or burning of hands, arms, feet or legs;
- speech impaired;
- tremor (shaking);
- sinusitis; upper respiratory tract infections;
- constipation; indigestion; weakness;
- liver failure;
- acne; dandruff;
- increased sweating;
- discolouration of finger or toe nails;
- increased or decreased sexual drive; impotence;
- intolerance to alcohol;
- flu-like symptoms;
- hyperactivity (autoimmune disorders);
- combination antiretroviral therapy may develop death of bone tissue caused by loss of blood supply to the bone (osteonecrosis). You may experience joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement;
- combination antiretroviral therapy may also cause raised lactic acid and sugar in the blood, increased fat levels in the blood (hyperlipaemia) and resistance to insulin. Your doctor will test for these changes.

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 or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. 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/. By reporting side effects, you can help provide more information on the safety of EFRIN.

5. How to store EFRIN

- Store all medicines out of reach of children.
- Store at or below 30 °C.
- Store in the original package / container.
- Keep the bottle tightly closed.
- 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 EFRIN contains:

- The active substance is:

  Efavirenz 600 mg

- The other ingredients are*:*

  Coscarmellose sodium, microcrystalline cellulose, hydroxy propyl cellulose-L, sodium lauryl sulphate, magnesium stearate. Film-coat: Opadry 03B52874 yellow

Contains sugar: Lactose monohydrate 255,60 mg

What EFRIN looks like and contents of the pack

What EFRIN looks like:

Peach coloured, capsule shaped, film-coated tablets, debossed with “M109” on one side and plain on the other side.

Contents of the pack:

EFRIN is packed in high density polypropylene (HDPE) bottle pack (marketable pack) comprising of wide mouth white HDPE bottle with a white opaque polypropylene (PP) closure with induction sealing in pack sizes of 30’s packed in a carton.

Holder of Certificate of Registration and Manufacturer

Viatris Healthcare (Pty) Ltd

4 Brewery Street, Isando,

Johannesburg, 1600,

Gauteng, South Africa

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Access to the corresponding Professional Information

Can be obtained on the SAHPRA website