PATIENT INFORMATION LEAFLET

SCHEDULING STATUS

S4

CITENVIR 600/200/300 film-coated tablets

Efavirenz, emtricitabine and tenofovir disoproxil fumarate

Sugar free

Read all of this leaflet carefully before you start taking CITENVIR.

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

CITENVIR contain 3 medicines, efavirenz, emtricitabine and tenofovir disoproxil fumarate (also called tenofovir DF). Each of these medicines is also known as antiretroviral medicines.

CITENVIR can be used alone as a complete regimen, or in combination with other anti-HIV-1 medicines to treat HIV-1 infection in adults.

2. What you need to know before you take CITENVIR

Do not take CITENVIR

- If you are allergic to efavirenz, emtricitabine and tenofovir disoproxil fumarate, or any of the ingredients of **CITENVIR**.
- If you had a liver disorder or liver failure attributed to treatment with **CITENVIR**.
- If you have severe liver impairment
- If you have a heart condition, such as an abnormal electrical signal called prolongation of the QT interval that puts you at high risk for severe heart rhythm problems (Torsade de Pointes).
- 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 suffering from moderate to severe kidney problems (renal impairment).
- If you take astemizole or terfenadine (used to treat hay fever or other allergies).
- If you take bepridil (used to treat heart disease).
- If you take cisapride (used to treat heartburn).
- If you take elbasvir/grazoprevir (used to treat hepatitis C).
- If you take ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine) (used to treat migraines and cluster headaches).
- If you take midazolam or triazolam (used to help you sleep).
- If you take pimozide, imipramine, amitriptyline or clomipramine (used to treat certain mental conditions).
- If you take voriconazole (used to treat fungal infections).
- If you take St. John's wort (*Hypericum perforatum*) (a herbal remedy used for depression and anxiety).
- If you take flecainide, metoprolol (used to treat irregular heart beat).
- If you take certain antibiotics (macrolides, fluoroquinolones, imidazole).
- If you take triazole antifungal agents.
- If you take certain antimalarial agents.

- If you take methadone (used to treat opiate addiction).
- If you are pregnant or breastfeeding your baby.

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

Warnings and precautions

Take special care with **CITENVIR**:

- If you have serious liver problems (hepatotoxicity) or liver enlargement (hepatomegaly).
- If you have a history of mental illness including depression.
- 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 **CITENVIR**. Your doctor may give you a different anticonvulsant.
- If you are pregnant.
- If you are suffering from kidney problems (renal impairment). **CITENVIR** is not recommended if you have moderate to severe kidney disease.

  CITENVIR 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.

  CITENVIR is not usually taken with other medicines that can damage your kidneys (see "Other medicines and **CITENVIR**"). If this is unavoidable, your doctor will monitor your kidney function once a week.
- If you have a heart disorder, such as abnormal electrical signal called prolongation of the QT interval.
- If you have any signs of skin rash.
- **CITENVIR** may cause lactic acidosis, together with an enlarged liver, which can be fatal. Deep, rapid breathing, drowsiness, and non-specific symptoms such as nausea, vomiting and stomach pain, might indicate the development of lactic acidosis.
- If you became pregnant while taking **CITENVIR** your baby may develop blood and nervous system disorders. Your doctor will monitor your baby's condition.

- Pancreatitis is a dangerous inflammation of the pancreas that may cause death. Tell your doctor right away if you develop stomach pain, nausea or vomiting. These can be signs of pancreatitis.
- Tell your doctor if you have liver disease (including hepatitis B). **CITENVIR** should not be used to treat chronic hepatitis B virus infection (HBV; an ongoing liver infection). Tell your doctor if you have or think you may have HBV.
- **CITENVIR** may change your body shape, by changing the way body fat is distributed. You may lose fat from your legs, arms and face and/or gain fat around the abdomen (tummy) and internal organs; get larger breasts or fatty lumps on the back of the neck (buffalo hump).
- If you are taking **CITENVIR** for the first time you may develop a condition known as Immune Reconstitution Inflammatory Syndrome (IRIS), within the first few months of treatment. This condition can cause opportunistic infections that are being treated to become worse, or opportunistic diseases that were asymptomatic to be unmasked. Tell your doctor or healthcare professional if your general health worsens or if you think you may have an infection. You should not stop taking **CITENVIR**. Your doctor will treat the infections appropriately.
- You may develop a condition known as osteonecrosis while taking **CITENVIR**. Seek medical advice if you experience joint aches and pain, joint stiffness or difficulty in movement.

Children and adolescents

Do not give **CITENVIR** to children and adolescents under 18 years of age. The use of **CITENVIR** in children and adolescents has not been studied.

Other medicines and CITENVIR

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

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

- You should not take **CITENVIR** with some medicines, e.g. calcium channel blockers (bepridil), ergot derivatives (dihydroergotamine, ergometrine, ergotamine and methylergometrine), gastrointestinal medicines (cisapride), antipsychotics (pimozide), and sedatives and hypnotics (midazolam and triazolam).

- Antibacterials - Rifampicin, increased dose of efavirenz may be necessary.
- Antifungals - Voriconazole, due to increased plasma concentrations of efavirenz, a decreased dose of efavirenz and increased dose of voriconazole is advised.
- Grapefruit - the metabolism of efavirenz may be inhibited by concomitant ingestion of grapefruit or grapefruit juice.
- Antidiabetics - Metformin - Fatal lactic acidosis has been reported when given concomitantly with didanosine, stavudine and tenofovir.
- St. John's wort (*Hypericum perforatum*) (may decrease the plasma concentration of efavirenz).

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

- aminoglycosides, vancomycin (medicines for bacterial infections);
- foscarnet, ganciclovir, cidofovir (medicines for viral infections);
- amphotericin B, pentamidine (medicines for fungal infections);
- interleukin-2 (to treat cancer);
- non-steroidal anti-inflammatory drugs (NSAIDs, to relieve bone or muscle pains).

CITENVIR may interact with other medicines, including herbal preparations such as Ginkgo biloba extracts. As a result, the amounts of CITENVIR 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 or pharmacist if you are taking any of the following:

- Medicines containing didanosine (for HIV infection): Taking **CITENVIR** with other antiviral medicines that contain didanosine can raise the levels of didanosine in your blood and may reduce CD4 cell counts. Inflammation of the pancreas and lactic acidosis (excess lactic acid in the blood), which sometimes caused death, have been reported rarely when medicines containing tenofovir disoproxil and didanosine were taken together. Your doctor will carefully consider whether to treat you with medicines containing tenofovir and didanosine.
- Other medicines used for HIV infection: The following protease inhibitors: darunavir, indinavir, lopinavir/ritonavir, ritonavir, or ritonavir boosted atazanavir or saquinavir. Your doctor may consider giving

you an alternative medicine or changing the dose of the protease inhibitors. Also, tell your doctor if you are taking maraviroc.

- Medicines used to treat infection with the hepatitis C virus: elbasvir/ grazoprevir, glecaprevir/pibrentasvir, sofosbuvir/velpatasvir, sofosbuvir/ velpatasvir/voxilaprevir.
- Medicines used to lower blood fats (also called statins): Atorvastatin, pravastatin, simvastatin. **CITENVIR** 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.
- Medicines used to treat convulsions/seizures (anticonvulsants): Carbamazepine, phenytoin, phenobarbital. **CITENVIR** can reduce the amount of the anticonvulsant in your blood. Carbamazepine can reduce the amount of efavirenz, one of the components of **CITENVIR**, in your blood. Your doctor may need to consider giving you a different anticonvulsant.
- Medicines used to treat bacterial infections, including tuberculosis and AIDS-related mycobacterium avium complex: Clarithromycin, rifabutin, rifampicin. Your doctor may need to consider changing your dose or giving you an alternative antibiotic. In addition, your doctor may consider giving you an additional dose of efavirenz to treat your HIV infection.
- Medicines used to treat fungal infections (antifungals): Itraconazole or posaconazole. **CITENVIR** can reduce the amount of itraconazole or posaconazole in your blood. Your doctor may need to consider giving you a different antifungal.
- Medicines used to treat malaria: Atovaquone/proguanil or artemether/ lumefantrine. **CITENVIR** may reduce the amount of atovaquone/proguanil or artemether/lumefantrine in your blood.
- Hormonal contraceptive, such as birth control pills, an injected contraceptive (for example, Depo-Provera), or a contraceptive implant (for example, Implanon): You must also use a reliable barrier method of contraception (see “Pregnancy and breast-feeding”). **CITENVIR** may make hormonal contraceptives less likely to work. Pregnancies have occurred in women taking efavirenz, a component of **CITENVIR**, while using a contraceptive implant, although it has not been established that the efavirenz therapy caused the contraceptive to fail.
- Sertraline, a medicine used to treat depression, as your doctor may need to change your dose of sertraline.
- Bupropion, a medicine used to treat depression or to help you stop smoking, as your doctor may need to change your dose of bupropion.

- Diltiazem or similar medicines (called calcium channel blockers): When you start taking **CITENVIR**, your doctor may need to adjust your dose of the calcium channel blocker.
- Medicines used to prevent organ transplant rejection (also called immunosuppressants), such as cyclosporine, sirolimus or tacrolimus. When you start or stop taking **CITENVIR** 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.
- Ginkgo biloba extracts (herbal preparation).

CITENVIR with food and drink

- **CITENVIR** can be taken as one tablet, once a day orally on an empty stomach.
- Do not take with grapefruit or grapefruit juice.

Pregnancy and Breastfeeding

Do not take **CITENVIR** if:

- You are pregnant.
- You are breastfeeding your baby.

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 healthcare provider for advice before taking **CITENVIR**.

Women should not get pregnant during treatment with **CITENVIR** 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 **CITENVIR**.
If you could get pregnant while receiving **CITENVIR**, 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 **CITENVIR**, 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 **CITENVIR**.

Do not breastfeed during treatment with **CITENVIR**. Both HIV and the ingredients of **CITENVIR** may pass through breast milk and cause serious harm to your baby.

Driving and using machines

CITENVIR may affect the performance of skilled tasks including driving.

You may get side effects after taking **CITENVIR:** dizziness, impaired concentration, and/or drowsiness. If this happens, do not drive or use machines that require you to be alert.

It is not always possible to predict to what extent **CITENVIR** 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 **CITENVIR** affects them.

3. HOW TO TAKE CITENVIR

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

- **CITENVIR** should be swallowed whole with a half a glass of water.
- **For adults:** The dose of **CITENVIR** is one tablet, once daily, taken orally on an empty stomach. Dosing at bedtime may improve the tolerability of nervous system symptoms.
- Because **CITENVIR** is a fixed-dose combination, it should not be prescribed for patients requiring dosage adjustment such as those with moderate or severe renal impairment (creatinine clearance less than 50 mL/min).
- Not recommended for use in patients less than 18 years of age.

Always take **CITENVIR** exactly as your doctor or pharmacist has instructed you. You should check with your doctor or pharmacist if you are unsure. If you have the impression that the effect of **CITENVIR** is too strong or too weak, talk to your doctor or pharmacist.

If you take more CITENVIR than you should

If you have accidentally taken too many **CITENVIR** tablets, contact your doctor or nearest emergency department for advice. Keep the tablet bottle with you so that you can easily describe what you have taken.

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 CITENVIR

If you forgot to take a dose, take it as soon as you remember unless it is nearly time for your next dose. Do not take a double dose to make up for forgotten individual doses.

If you stop taking CITENVIR

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

When your supply of **CITENVIR** 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 both HIV infection and hepatitis B, it is especially important not to stop your **CITENVIR** treatment without talking to your doctor first. Some patients have had blood tests or symptoms indicating that their hepatitis has got worse after stopping emtricitabine or tenofovir disoproxil (two of the three components of **CITENVIR**). If **CITENVIR** is stopped your doctor may recommend that you resume hepatitis B 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.

4. Possible side effects

CITENVIR can have side effects.

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

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

- Difficulty in breathing, with or without swelling of the face, lips, tongue and/or throat.
- Swelling of the face, lips, tongue and/or throat, which may cause difficulty in swallowing.
- Severe itching of the skin (with raised lumps).
- Allergic reaction (hypersensitivity) that may cause severe skin reactions (Stevens-Johnson syndrome, erythema multiforme, see section 2)

Also, stop taking **CITENVIR** and talk to your doctor immediately if you have any unusual aches or pains in your muscles which go on for longer than you might expect.

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

Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:

Lactic acidosis (excess lactic acid in the blood) is a rare (may affect up to 1 in every 1,000 patients) 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 doctor immediately.

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 changes, if you feel motionless or speechless for a period (catatonia).

Pain in the stomach, caused by inflammation of the pancreas.

Forgetfulness, confusion, fitting (seizures), incoherent speech, tremor (shaking).

Yellow skin or eyes, itching or pain the stomach caused by inflammation of the liver.

Damage to kidney tubules.

Psychiatric side effects in addition to those listed above include delusions (false beliefs), neurosis. Some patients have 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.

Side effects to the liver: If you are also infected with hepatitis B virus, you may experience a worsening of hepatitis after discontinuation of treatment (see section 3).

The following serious side effects can occur less frequently

- liver failure, in some cases leading to death or liver transplant. Most cases occurred in patients who already had liver disease, but there have been a few reports in patients without any existing liver disease;
- inflammation of the kidney, passing a lot of urine and feeling thirsty;
- back pain caused by kidney problems, including kidney failure. Your doctor may do blood tests to see if your kidneys are working properly;
- softening of the bones (with bone pain and sometimes resulting in fractures) which may occur due to damage to the kidney tubule cells;
- fatty liver.

If you think that you may have any of these serious side effects, talk to your doctor.

Most frequent side effects

- dizziness, headache, 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;
- increased levels of creatine kinase in the blood that may result in muscle pain and weakness.

The following side effects occur frequently

- allergic reactions;
- disturbances of coordination and balance;
- feeling worried or depressed;
- difficulty sleeping, abnormal dreams, difficulty concentrating, drowsiness;
- pain, stomach pain;
- problems with digestion resulting in discomfort after meals, feeling bloated, wind (flatulence);
- loss of appetite;
- tiredness;
- itching;
- changes in skin colour including darkening of the skin in patches often starting on hands and soles of feet.

Tests may also show:

- low white blood cell count (a reduced white blood cell count can make you more prone to infection);
- liver and pancreas problems;
- increased fatty acids (triglycerides), bilirubin or sugar levels in the blood.

The following side effects occur less frequently

- breakdown of muscle, muscle pain or weakness;
- anaemia (low red blood cell count);
- a feeling of spinning or tilting (vertigo), whistling, ringing or other persistent noise in the ears;
- blurred vision;
- chills;
- breast enlargement in males;

- flushing;
- itchy rash to the skin caused by a reaction to sunlight.

Tests may also show

- decreases in potassium in the blood;
- increases in creatinine in the blood;
- proteins in urine;
- increased cholesterol in the blood.

The breakdown of muscle, softening of the bones (with bone pain and sometimes resulting in fractures), muscle pain, muscle weakness and decreases in potassium or phosphate in the blood may occur due to damage to kidney tubule cells.

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 you 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 safety of CITENVIR

5. How to store CITENVIR

Store at or below 30 °C.

Keep HDPE containers tightly closed.

STORE ALL MEDICINES OUT OF REACH OF CHILDREN.

Return all unused medicine to your pharmacist.

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

6. Content of the pack and other information

What CITENVIR contains

The active substances are efavirenz, emtricitabine and tenofovir disoproxil fumarate.

CITENVIR 600/200/300:

Each film-coated tablet contains efavirenz 600 mg, emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg. Contains titanium dioxide.

CITENVIR is sugar free.

The other ingredients are croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, Opadry II white and sodium lauryl sulphate.

Opadry II white contains macrogol, polyvinyl alcohol, talc and titanium dioxide (C.I. No: 77891).

What CITENVIR looks like and contents of the pack

White to off white, oval shaped, biconvex, film-coated tablets debossed with 'I48' on one side and plain on the other side.

HDPE Container Pack:

Tablets are packed in a white opaque round 100 ml HDPE containers with 38 mm neck finish, closed with 38 mm-400 CR white opaque polypropylene child resistant closure with a wad having an induction sealing liner. Each HDPE container shall contain a 3 g silica gel sachet.

Pack size: 30's - One HDPE container contains 30 tablets.

Holder of Certificate of Registration

Novagen Pharma (Pty) Ltd

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FOR NAMIBIA ONLY:

Schedule: NS2

Registration Number:

Citenvir: 13/20.2.8/0240

Professional Information for Citenvir tablets is available on the Novagen Pharma website:

http://www.novagenpharma.co.za/products/antiretroviral /