Patient Information Leaflet

Information for the Patient about

TRIPLAVAR TABLETS

Read this entire leaflet carefully before you start taking TRIPLAVAR.

- Keep this leaflet; you may need to read it again.

- If you have further questions, please ask your doctor or your pharmacist.

- TRIPLAVAR 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.

SCHEDULING STATUS:

S4

PROPRIETARY NAME (AND DOSAGE FORM):

TRIPLAVAR (Film-coated tablets)

WHAT TRIPLAVAR TABLETS CONTAIN:

The active substances are nevirapine, lamivudine and zidovudine. Each tablet contains 150 mg lamivudine, 300 mg zidovudine and 200 mg nevirapine.

Inactive ingredients include microcrystalline cellulose, corn starch, sodium starch glycolate, povidone, magnesium stearate, and opadry white.

WARNING:

THE FIRST 18 WEEKS OF THERAPY WITH NEVIRAPINE, AND THEREFORE TRIPLAVAR, IS A CRITICAL PERIOD AND YOUR DOCTOR

WILL MONITOR YOU INTENSIVELY TO IDENTIFY THE POTENTIAL APPEARANCE OF SEVERE AND LIFE-THREATENING SKIN REACTIONS (INCLUDING CASES OF STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS, WHICH ARE BLISTER-FORMING SKIN RASHES THAT MAY RESULT IN DEATH) OR SERIOUS INFLAMMATION OF THE LIVER OR LIVER FAILURE. THE GREATEST RISK OF LIVER EVENTS AND SKIN REACTIONS OCCURS IN THE FIRST 6 WEEKS OF THERAPY. HOWEVER, THE RISK OF ANY LIVER EVENT CONTINUES PAST THIS PERIOD AND YOU WILL BE MONITORED AT FREQUENT INTERVALS FOR THESE POSSIBLE ADVERSE EVENTS.

If you experience a severe rash or a rash accompanied by constitutional symptoms, such as fever, blistering, lesions inside the mouth, conjunctivitis (inflammation of the membrane covering the eye), swelling of the face, muscle or joint aches or generally feeling unwell, you should stop taking your medication and immediately seek help from your doctor. You should also not restart therapy with TRIPLAVAR.

The safety and efficacy of TRIPLAVAR in patients infected with both human immunodeficiency virus (HIV) and hepatitis B virus (HBV) have not been established. TRIPLAVAR should not be used for the treatment of chronic HBV infection. You should be closely monitored for several months if you are also infected with HBV and have discontinued the use of TRIPLAVAR.

Liver reactions:

If clinical inflammation of the liver (hepatitis) occurs, characterised by loss of appetite, nausea, vomiting, jaundice (yellow discolouration of the skin and whites of the eyes), and laboratory findings (such as moderate or severe liver function test abnormalities), nevirapine, and therefore TRIPLAVAR, must be permanently stopped. You should not receive TRIPLAVAR ever again if you required permanent discontinuation of treatment because of clinical hepatitis due to nevirapine.

WHAT TRIPLAVAR IS USED FOR:

TRIPLAVAR is a combination of three medicines that all belong to a class of medicines called antiretroviral agents. Antiretroviral agents are used to treat Human Immunodeficiency Virus (HIV) infection.

TRIPLAVAR is used to treat HIV infected adults and children over 12 years of age and is only given to patients once they have completed a two (2) week lead-in period on the three (3) individual components. Alternatively, **TRIPLAVAR** is also given to patients who have been stabilised on the individual components at the same doses.

BEFORE YOU USE TRIPLAVAR:

Do NOT take TRIPLAVAR if any of the following applies to you:

- Hypersensitivity or allergy to lamivudine, zidovudine, nevirapine or any other component of the preparation.
- Abnormally low white cell counts or abnormally low red blood cell counts. Your doctor will determine this with a blood test.

- Age below 12 years due to insufficient data, and because the dose (in a fixed dose combination, such as **TRIPLAVAR**) cannot be adjusted for this patient population.
- Concomitant use of either ribavirin or stavudine (other antiretrovirals for the treatment of HIV infection).
- Impairment of liver function, including abnormal liver function test results. Your doctor will perform blood tests before and during treatment to evaluate your liver function.
- Kidney dysfunction or impairment.
- Previous discontinuation of treatment due to severe skin rash, rash accompanied by constitutional symptoms (such as fever, blistering, lesions in the mouth, swelling of lymph glands, etc.), hypersensitivity (allergy) syndrome, or clinical hepatitis (inflammation of the liver) due to nevirapine, one of the active ingredients in **TRIPLAVAR**.

Take special care with TRIPLAVAR:

WARNING:

The first 18 weeks of therapy with nevirapine (and therefore **TRIPLAVAR**) is a critical period and you will have to undergo intensive monitoring to identify the potential appearance of severe and life-threatening skin reactions (including cases of Stevens-Johnson syndrome and toxic epidermal necrolysis) or serious hepatitis (inflammation of the liver) or liver failure. The greatest risk of liver events and skin reactions occurs in the first 6 weeks of therapy (see initial boxed **"WARNING"**).

The major toxicity of nevirapine, one of the active ingredients in TRIPLAVAR, is skin rash and you must promptly notify your doctor of any rash. The majority of rashes associated with nevirapine, as contained in **TRIPLAVAR**, occur within the first 6 weeks of therapy; therefore, you will be carefully monitored for the appearance of any rash during this period. During the first two weeks of therapy you will receive separate preparations of the three components of **TRIPLAVAR** and nevirapine will be administered at a lower dose (this is known as the lead-in dosing period). You should only receive **TRIPLAVAR** if you have successfully completed the lead-in dosing period or if you have already been stabilised on the three components of **TRIPLAVAR** at the same doses. Your dose of nevirapine should not be increased if any rash occurs during the lead-in dosing period, until the rash has resolved.

If you experience a severe rash or a rash accompanied by constitutional symptoms, such as fever, blistering, mouth lesions, inflammation of the membrane covering the eyes, swelling of the face, muscle or joint aches, or generally feeling unwell, you should stop TRIPLAVAR and consult a doctor. You should never restart therapy with nevirapine, and therefore TRIPLAVAR, again.

If you develop a hypersensitivity syndrome, characterised by rash with constitutional symptoms, such as fever, joint pain, muscle pain and swelling of lymph glands, plus internal organ involvement, such as hepatitis (liver inflammation), abnormal white cell counts, and kidney

dysfunction, you must permanently stop taking nevirapine, and therefore TRIPLAVAR, and never reintroduce treatment with these medicines at a later stage.

Liver reactions:

If you have a severe underlying liver disorder, you should not take nevirapine (and therefore **TRIPLAVAR**). If you have chronic hepatitis B or C infection and you are receiving treatment with combination antiretroviral therapy, you are at an increased risk for severe and potentially fatal liver adverse events. If you have pre-existing liver dysfunction, including chronic active hepatitis, you will have an increased frequency of liver function abnormalities during treatment with **TRIPLAVAR** and your doctor will monitor you for possible adverse events. Your doctor may decide to interrupt or stop treatment if there is evidence of worsening liver disease.

If clinical inflammation of the liver occurs, characterised by loss of appetite, nausea, vomiting, jaundice and laboratory findings, such as moderate or severe liver function test abnormalities, you must permanently stop taking nevirapine, and therefore TRIPLAVAR. In these circumstances you should never receive nevirapine, and therefore TRIPLAVAR, again.

TRIPLAVAR is not a cure for HIV infection. You may continue to develop opportunistic infections and other complications of HIV infection. Treatment with **TRIPLAVAR** has not been shown to reduce the incidence or frequency of

such illnesses. You should therefore remain under close supervision of your doctor.

*Currently prescribed antiretroviral therapy, including **TRIPLAVAR**, has not been proven to prevent the risk of transmitting HIV to others through sexual contact or blood contamination. You need to continue to take appropriate precautions against transmitting the virus to other people (such as the use of condoms during sexual intercourse).*

***Blood disorders*:**

Low red blood and white blood cell counts can be expected to occur in patients on zidovudine (and therefore **TRIPLAVAR**) and who have advanced symptomatic HIV disease. Your doctor will therefore carefully monitor your blood counts through the use of blood tests at least every 2 weeks for the first 3 months of therapy and at least monthly thereafter. Blood adverse reactions do not occur frequently in patients with early HIV disease. Blood tests may be performed less frequently (e.g. every one to three months) depending on your overall condition. Depending on your results, your doctor may also decide to monitor blood parameters more frequently.

If you develop very low red blood cell counts or suppression of your bone marrow (where blood cells are made), your doctor may decide to reduce the dosage of the medicines you are taking. This will require the use of separate preparations of the active ingredients in **TRIPLAVAR**. Your doctor will instruct you on the use of these medicines.

Gastrointestinal (gut):

Cases of pancreatitis (inflammation of the pancreas) have occurred less frequently in patients treated with zidovudine and lamivudine. Should clinical signs, symptoms (such as loss of appetite, nausea, vomiting, and severe stomach pain with distension of the stomach) or laboratory abnormalities, suggestive of pancreatitis, occur, **TRIPLAVAR** therapy should be stopped immediately.

Metabolic:

Zidovudine, one of the active ingredients in **TRIPLAVAR**, may cause a condition known as lactic acidosis as well as an enlarged liver with fatty degeneration of the liver. This rare, but serious, side-effect has occasionally been fatal. Symptoms of lactic acidosis include deep, rapid breathing, drowsiness, and non-specific symptoms, such as nausea, vomiting and stomach pain. Your treating doctor will monitor you closely for the development of lactic acidosis. Please report any of the symptoms listed here to him/her. Your doctor may decide to stop treatment with **TRIPLAVAR** in these circumstances.

Lactic acidosis and severe enlargement of the liver with fatty degeneration of the liver, including fatal cases, have been reported with the use of lamivudine alone or in combination in the treatment of HIV infection.

The long-term effects of **TRIPLAVAR** are not known at this time.

Oral contraceptives and other methods of birth control that make use of hormone (oestrogen and progesterone) should not be used as the sole method of contraception in women taking **TRIPLAVAR**, since the nevirapine in **TRIPLAVAR** may lower blood levels of such hormones. For this reason, and to reduce the risk of HIV transmission, barrier contraception (e.g. condoms) is recommended (please see **"Taking other medicines with TRIPLAVAR"**).

Taking TRIPLAVAR with food and drink:

TRIPLAVAR can be taken without regard to meals.

Pregnancy and breast feeding:

The safe and effective use of **TRIPLAVAR** during pregnancy has not been demonstrated. The use of **TRIPLAVAR** during pregnancy is therefore not recommended. Adequate contraceptive measures should be taken (please see **"Take special care with TRIPLAVAR"**). Please discuss the use of barrier contraception with your doctor or pharmacist.

It is also recommended not to breast feed your baby while taking **TRIPLAVAR**. It is further recommended that HIV infected women do not breast feed their infants under any circumstances in order to avoid transmission of HIV from mother to child.

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

Driving and using machinery:

Although the effects of **TRIPLAVAR** on the ability to drive and operate machinery have not been studied, patients should be cautioned to refrain from driving or performing other hazardous tasks where dizziness or sleepiness (potential side-effects of **TRIPLAVAR**) may lead to accidents.

Taking other medicines with TRIPLAVAR?

If you are taking other medicines on a regular basis, including over-the-counter, complementary or traditional medicines, concomitant use of such medicines with TRIPLAVAR may cause undesirable interactions. Please consult your doctor or pharmacist, or other healthcare professional for advice.

In particular, please inform your doctor or pharmacist if you are taking any of the following as it may require dosage adjustments or special monitoring:

- Any other medicine for the treatment of HIV infection.
- Ketoconazole for the treatment of fungal infections.
- Fluconazole for the treatment of fungal infections.
- Warfarin, a blood thinner, since you will have to undergo more frequent blood tests to monitor the efficacy of warfarin.
- Rifampicin or rifabutin for the treatment of tuberculosis, since this may require dose adjustments.
- St. John's wort for the treatment of depression, as this may make **TRIPLAVAR** less effective.

- Antibiotics, specifically clarithromycin or co-trimoxazole.
- Cimetidine, a medicine to reduce the amount of stomach acid.
- Oral contraceptives, since the nevirapine in **TRIPLAVAR** will significantly reduce oestrogen levels, making the oral contraceptive less effective or ineffective (please see **"Take special care with TRIPLAVAR"**). Please discuss the use of barrier methods of contraception with your doctor or pharmacist.
- Methadone.
- Ganciclovir or foscarnet.
- Phenytoin for the treatment of epilepsy, since this will require careful monitoring of blood phenytoin concentrations.
- Paracetamol, as this may increase the risk of certain side-effects.
- Codeine (for pain), morphine (for pain), aspirin (for pain and inflammation), indomethacin (for pain and inflammation), ketoprofen (for pain and inflammation), naproxen (for pain and inflammation), clofibrate (for high blood cholesterol levels), dapsone (for the prevention of pneumonia), oxazepam (for the relief of anxiety), lorazepam (for the relief of anxiety), and isoprinosine (for cancer, as immune system modulator and for AIDS – Acquired Immune Deficiency Syndrome).
- Pentamidine (for the treatment of parasitic infections), pyrimethamine (for the treatment of parasitic infections, such as toxoplasmosis), amphotericin (for fungal infections), interferon (a medicine acting on the immune system), flucytosine (for fungal infections), vincristine (for certain types of cancer), vinblastine (for certain types of cancer), and

doxorubicin (for certain types of cancer), as combination of any of these medicines with **TRIPLAVAR** may increase the risk of adverse events.

- Probenecid for gout.

HOW TO TAKE TRIPLAVAR:

You should only take TRIPLAVAR once you have been stabilised on the individual components at the same doses or once you have completed an initial two (2) week lead-in period on the three individual components at the following doses:

- **Lamivudine 300 mg daily, administered as either 300 mg once daily or 150 mg twice daily.**
- **Zidovudine 300 mg twice daily.**
- **Nevirapine 200 mg once daily.**

Following this lead-in dose, your doctor may increase your nevirapine dose to 200 mg twice a day and you may proceed with taking TRIPLAVAR, a fixed-dose combination of these three active ingredients.

The recommended dose is one **TRIPLAVAR** tablet twice daily, with or without food (see **"Taking TRIPLAVAR with food and drink"**).

If your doctor decides to change the dosages of the three active ingredients for any reason, you will be given separate preparations of each of these agents.

You should take **TRIPLAVAR** every day as prescribed. You should not alter the dose without consulting your doctor.

You will be required to undergo blood tests before and regularly during therapy with **TRIPLAVAR**.

Your doctor will stop treatment with TRIPLAVAR if you experience severe rash or a rash accompanied by constitutional findings (see initial boxed "WARNING"). If you experience a rash during the 14-day lead-in period, you should not have your nevirapine dose increased until the rash has resolved (see initial boxed "WARNING").

If you or your doctor interrupt **TRIPLAVAR** dosing for more than 7 days, you should restart the recommended dosing of nevirapine using 200 mg daily for the first 14 days (lead-in) followed by 200 mg twice daily .

If you suffer from impairment of kidney or liver function, you require treatment with separate preparations of lamivudine, zidovudine, and nevirapine.

If you have poor bone marrow reserve prior to treatment, particularly if you have advanced HIV disease, you will be more prone to side-effects involving blood cells and blood cell counts. Separate preparations of zidovudine, lamivudine, and nevirapine should be used, as **TRIPLAVAR** dosage cannot be adjusted.

Elderly patients may also require dosage adjustments. Your doctor will decide on the most appropriate dosage for you.

If you have the feeling that **TRIPLAVAR** is too strong or too weak for you, please discuss this with your treating doctor.

If you take more TRIPLAVAR than you should:

In the event of an overdosage, or if someone else has taken your medicine by mistake, you, or this other person, may experience side-effects such as those listed below. **In the event of overdosage, consult your doctor or pharmacist. If neither is available, immediately seek help at the nearest hospital or poison control centre.**

If you forget to take TRIPLAVAR:

Always take **TRIPLAVAR** as prescribed. If you miss a dose, take it as soon as you remember. If you do not remember the missed dose until the next dose is due, skip the missed dose and go back to your regular dosing schedule. Do not take a double dose to compensate for the forgotten individual dose. It is important to take **TRIPLAVAR** regularly, because irregular intake may increase the risk of the virus developing resistance to your medication.

Effects when treatment with TRIPLAVAR is stopped:

If you had to stop treatment with **TRIPLAVAR** for any reason, but particularly because of side-effects, such as skin rash or liver complications, it is important

that you obtain your doctor's opinion before restarting. If **TRIPLAVAR** was stopped due to an allergic or hypersensitivity reaction, skin rash, or because of liver damage or potential liver damage due to nevirapine, you should never take **TRIPLAVAR** or any other medicine containing nevirapine again.

POSSIBLE SIDE-EFFECTS:

Not all side-effects reported for TRIPLAVAR are included in this leaflet. Should your general health worsen while taking TRIPLAVAR, please consult your doctor, pharmacist or other healthcare professional for advice.

One of the most serious, and potentially life-threatening, side-effects of TRIPLAVAR is an allergic or hypersensitivity reaction presenting with a skin rash. Please see the initial boxed **"Warning"**. You should report any skin rash to your doctor as a matter of urgency.

Other side-effects that you should report to your doctor as a matter of urgency include:

- Deep, rapid breathing, drowsiness, and non-specific symptoms, such as nausea, vomiting and stomach pain, as this may indicate a condition known as lactic acidosis (see **"Take special care with TRIPLAVAR"**).
- Severe abdominal pain, loss of appetite, vomiting, fever and generally feeling unwell, as this may indicate inflammation of the pancreas.

- Allergic reactions presenting with skin rash, hives, itching, difficulty breathing, shortness of breath, and nausea.
- Loss of appetite, nausea, vomiting, pain over the liver area with or without jaundice (yellow discolouration of the whites of the eyes or skin) as this may indicate inflammation of the liver or liver failure.
- Pallor accompanied by tiredness, shortness of breath, and chest pain, as this may indicate low red blood cell counts, which may be severe and require blood transfusions.
- Pinpoint red spots on the skin, easy bruising or bleeding from the gums, as this may be due to low platelet counts.
- Pins and needles or pain and abnormal sensation experienced with normal stimulation, as this may indicate nerve damage.
- Epileptic fits or convulsions.

Other side-effects that you should report to your doctor as soon as possible include:

- Shortness of breath.
- Changes in body shape due to changes in fat distribution (lipodystrophy). These may include loss of fat from the legs, arms and face, increased fat in the abdomen (belly) and other internal organs, breast enlargement and fatty lumps on the back of the neck ('buffalo hump').

The most serious side-effects due to **TRIPLAVAR** include serious skin reactions (such as Stevens-Johnson syndrome and toxic epidermal necrolysis), liver damage, including liver failure, and a hypersensitivity

syndrome characterised by rash, fever, joint pain, muscle pain and swelling of lymph glands as well as inflammation of the liver, abnormal blood cell counts and kidney dysfunction. The first 18 weeks of treatment is a critical period, which requires close monitoring.

Please report the following side-effects to your doctor if they continue or become bothersome:

- Headache, insomnia, loss of mental acuity, sleepiness, dizziness, anxiety and depression.
- Taste perversion (abnormal taste).
- Nasal (relating to the nose) symptoms, cough.
- Nausea, vomiting, stomach pain or cramps, diarrhoea (runny stomach), loss of appetite, poor digestion (dyspepsia), and flatulence.
- Hives, itching, and sweating.
- Muscle, joint, and bone pain.
- Frequent urination.
- Fatigue, fever, generally feeling unwell, and excessive tiredness or weakness.
- Flu-like syndrome, chills, generalised pain, and chest pain.
- Skin and nail pigmentation as well as pigmentation inside the mouth.

Other side-effects of **TRIPLAVAR** for which you will be monitored, include:

- Increased blood amylase levels, which may indicate inflammation of the pancreas.
- Increased blood lactate levels.

- Changes in liver enzyme levels.
- Changes in blood cell counts.

Not all side-effects reported for **TRIPLAVAR** are included in this leaflet. Please tell your doctor or pharmacist of any other undesirable effects you think may be due to taking **TRIPLAVAR**, especially if not mentioned in this leaflet.

STORAGE AND DISPOSING OF TRIPLAVAR:

Store at or below 30 °C.

KEEP OUT OF REACH OF CHILDREN.

Keep well closed.

Do not use after the expiry date stated on the packaging material.

Return all unused medicine to your pharmacist. Do not dispose of unused medicine in drains or sewerage systems, for example toilets.

PRESENTATION OF TRIPLAVAR:

White HDPE plastic container containing 30 tablets or 60 tablets.

IDENTIFICATION OF TRIPLAVAR:

White to off-white, capsule-shaped, biconvex, film-coated tablets, with central breakline on one side and plain on the other.

REGISTRATION NUMBER:

To be allocated.

NAME AND BUSINESS ADDRESS OF THE HOLDER CERTIFICATE OF REGISTRATION:

CIPLA MEDPRO (PTY) LTD

Rosen Heights

Pasita Street

Rosen Park

Bellville

7530

DATE OF PUBLICATION OF THIS PATIENT LEAFLET:

To be allocated.