PATIENT INFORMATION LEAFLET

SCHEDULING STATUS

S4

NUVACO, 300 mg, 300 mg, 50 mg, film-coated tablets

Lamivudine, Tenofovir, Dolutegravir sodium

Contains sugar (140,4 mg mannitol per tablet)

Read all of this leaflet carefully before you start taking NUVACO

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor, pharmacist, nurse or other healthcare provider.
- NUVACO 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 NUVACO is and what it is used for
2. What you need to know before you take NUVACO
3. How to take NUVACO
4. Possible side effects
5. How to store NUVACO
6. Contents of the pack and other information

WARNING:

Lactic acidosis (build-up of acid in the blood); Hepatomegaly with steatosis (swollen and fatty liver):

Two components NUVACO (Tenofovir and lamivudine) belong to a class of medicines (NRTIs) that can cause a condition called lactic acidosis (excess of lactic acid in your blood), together with an enlarged liver. Signs and symptoms of lactic acidosis include deep, rapid breathing; drowsiness, nausea, vomiting and stomach pain.

If you have liver disease you may also be more at risk of getting this condition. While you are being treated with NUVACO your doctor will monitor you closely for any signs that you may be developing lactic acidosis.

Worsening of hepatitis B virus infection in people who have HIV-1 infection:
NUVACO is not indicated for the treatment of long-term (chronic) hepatitis B virus infection.
Patients with liver disease including chronic hepatitis B virus infection, who are treated with combination antiretrovirals, have a higher risk of severe and potentially life-threatening liver problems.
If you have hepatitis B virus infection, you should not stop NUVACO without instructions from your doctor, as you may have recurrence of your hepatitis. This may occur due to you suddenly stopping lamivudine, a component of NUVACO. Your doctor may conduct blood tests in order to check how well your liver is working or may switch you to another medicine.

1. What NUVACO is and what it is used for

NUVACO is used to treat HIV (‘human immunodeficiency virus’) infection. It belongs to a group of medicines called ‘antiretroviral medicines’. NUVACO contains the active substances: lamivudine, tenofovir and dolutegravir sodium.

NUVACO is used in the treatment of human immunodeficiency virus (HIV) infection in adults and adolescents over 18 years of age.

2. What you need to know before you take NUVACO

Do not take NUVACO:

- If you are hypersensitive (allergic) to lamivudine, tenofovir, dolutegravir or any of the other ingredients of NUVACO (listed in section 6.1).
- If you have moderate or severe liver problems.
- If you have kidney problems (see Take special care with NUVACO).
- If you are planning to become pregnant.
- If you are pregnant or breastfeeding your baby (see Pregnancy, breastfeeding and fertility).
- If you are a woman of childbearing age and are not using highly effective contraception.
- If you are currently taking adefovir dipivoxil (used to treat hepatitis B infection), dofetilide or pilsicainide (used to treat heart conditions), didanosine (used to treat HIV infection) or metformin (used to treat high sugar levels) (see Other medicines and NUVACO).
- If you or your child is younger than 18 years old.

Warnings and precautions

Take special care with NUVACO:

- If you experience any of the following signs or symptoms of a hypersensitivity (allergic) reaction: severe rash, fever, general feeling of discomfort, unusual weakness or tiredness, muscle or joint pain, blisters, mouth sores (oral lesions), pink eye (conjunctivitis), swelling of your face, swelling in other parts of your body due to fluid build-up (oedema), blood disorder (eosinophilia) or urticaria (hives), stop taking NUVACO tablets and consult your doctor immediately.
- If you have lipodystrophy (a problem with the way your body uses and stores fat). This condition is characterised by being overweight (obesity), build-up of fat on the back of the neck between the shoulders (buffalo hump), loss of fat under the skin (making the face look thin), breast enlargement and high levels of fat and glucose (sugar) in the blood. If you have

any of these signs, you should be thoroughly examined by your doctor.

- If you have advanced HIV infection, your immune system is weak, and you are more likely to develop serious infections (opportunistic infections). Such infections may have been "silent" and not detected by the weakened immune system before treatment was started. After starting treatment, the immune system becomes stronger, and may attack the infections, which can cause symptoms of infection or inflammation. Symptoms usually include fever, plus some of the following: headache, stomach ache or difficulty breathing.
- In rare cases, as your immune system becomes stronger, it can also attack healthy body tissue (autoimmune disorders). The symptoms of autoimmune disorders may develop many months after you start taking medicine to treat your HIV infection.
- Talk to your doctor or healthcare provider if you have a history of liver disease, including hepatitis. HIV-infected patients with liver disease including chronic hepatitis B or C, who are treated with antiretrovirals, have a higher risk of severe and potentially fatal liver complications. If you are infected with HIV and hepatitis B virus your doctor will carefully consider the best treatment for you. If you have a history of liver disease or chronic hepatitis B infection, your doctor may conduct blood tests to monitor your liver function.
- If you have a condition called osteonecrosis (where parts of the bone tissue die, because of reduced blood supply to the bone). You are more likely to get this condition:
  - if you are also taking corticosteroids (anti-inflammatory medicine)
  - if you drink alcohol
  - if your immune system is very weak
  - if you are overweight.

  Tell your doctor if you notice any of these symptoms of osteonecrosis: joint aches and pain, joint stiffness or difficulty in movement.
- Bone problems (sometimes resulting in fractures) may also occur due to damage to the kidney cells. The growth of bone could be affected when adolescents that are not fully-grown use NUVACO tablets.

- If you are taking other medicine (prescription and non-prescription). Some medicines can affect how NUVACO works or make it more likely that you will have side effects. NUVACO can also affect how some other medicines work. Tell your doctor if you are taking, have recently taken or are planning to take any other medicines (see Other medicines and NUVACO).
- If you develop opportunistic infections and other complications of HIV infection. You should remain under close observation by your healthcare provider, where regular monitoring of viral load and CD4 counts will be done.
- HIV infection is spread by sexual contact with someone who has the infection, or by transfer of infected blood (for example, by sharing injection needles). You can still pass on HIV while taking NUVACO, although the risk is lowered by effective antiretroviral therapy. Discuss with your doctor the precautions needed to avoid infecting other people.
- Look out for possible signs and symptoms of lactic acidosis (excess of lactic acid in your blood) once you start taking NUVACO tablets. Possible signs and symptoms of lactic acidosis are:
  - Deep, rapid breathing
  - Drowsiness
  - Nausea, vomiting and stomach pain.

  This does not occur frequently, but this serious side effect can cause enlargement of the liver and has occasionally been fatal. Lactic acidosis occurs more often in women and in patients that are very overweight. If you have liver disease you may also be more at risk of getting this condition. While you are being treated with NUVACO tablets, your doctor will monitor you closely for any signs that you may be developing lactic acidosis. If you think you may have lactic acidosis, contact your doctor immediately.
- NUVACO may affect your kidneys. Before starting treatment with NUVACO you may need blood tests to check how well your kidneys are working. Blood tests may also be required during treatment to check the health of your kidneys. NUVACO is not usually taken with

other medicines that can damage your kidneys (see Other medicines and NUVACO). If this is unavoidable, you may need regular tests to check how well your kidneys are working.

- NUVACO may cause pancreatitis (inflammation of the pancreas). Contact your doctor if you develop any of these symptoms: stomach pain, nausea (feeling sick), vomiting (being sick).
- You will need to take NUVACO tablets every day. NUVACO helps to control your condition, but it is not a cure for HIV infection. You may continue to develop other infections and other illnesses associated with HIV disease. You should keep in regular contact with your doctor or healthcare provider. Do not stop taking NUVACO without first talking to your doctor or healthcare provider.
- NUVACO is not a cure for HIV infection. While taking NUVACO tablets you may still develop infections or other diseases associated with HIV infection.
- During HIV therapy there may be an increase in weight and in levels of blood lipids, lactate and glucose. Your doctor will test for these changes.
- Do not take NUVACO if you are already taking medicines that contain lamivudine, tenofovir and emtricitabine because these medicines contain the same or similar active ingredients. Discuss this with your doctor if you are not sure.

Children

Special medical care (clinical and laboratory follow up) should be taken in infants, babies and children that were exposed to antiretroviral medicines that belong in the classes of medicines called nucleoside and nucleotide analogues during pregnancy. These medicines (nucleoside and nucleotide analogues) include abacavir, didanosine, emtricitabine, lamivudine, stavudine and tenofovir. Your doctor may want to do tests to check your child for any signs of anaemia (low red blood cell count); neutropenia (decrease in the main type of the white blood cells); peripheral neuropathy (weakness and numbness associated with nerve damage in the hands and feet) and neurological disorders (disease that affect the nervous system) such as seizures;

hypertonia (medical condition associated with muscle stiffness and uncontrolled muscle movement).

Other medicines and NUVACO

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

Some medicines can affect how NUVACO works, or make it more likely that you will have side effects. NUVACO can also affect how some other medicines work.

Tell your doctor, pharmacist or other healthcare provider if you are taking any of the medicines in the following list:

- Other medicines containing tenofovir, dolutegravir, emtricitabine, lamivudine as they contain same or similar active ingredients.
- Cladribine (used to treat a certain type of cancer). NUVACO may affect activity of cladribine.
- Dofetilide and pilsicainide (used to treat heart conditions). Dolutegravir, a component of NUVACO, may increase the amount of dofetilide and pilsicainide in your blood, which could result in life-threatening toxicity of these medicines.
- Adefovir dipivoxil may increase the amount of NUVACO in your blood, which could result in more side effects.
- Didanosine (used to treat HIV infection (AIDS)). Tenofovir disoproxil fumarate, a component of NUVACO, may increase the amount of didanosine in your blood, which could result in more side effects.
- Zalcitabine, abacavir, and indinavir (used to treat HIV infection (AIDS)) may increase the amount of tenofovir disoproxil fumarate, a component of NUVACO, in your blood, which could result in more side effects.

- Etravirine (used to treat HIV infection (AIDS)) may decrease the amount of dolutegravir, a component of NUVACO, in your blood, which may result in loss of virologic response and possible resistance to dolutegravir.
- Atazanavir, atazanavir/ritonavir (used to treat HIV infection (AIDS)) may increase the amount of dolutegravir, a component of NUVACO, in your blood, which could result in more side effects.
- Metformin (used to treat diabetes (high blood sugar)). Dolutegravir, a component of NUVACO, may increase the amount of metformin in your blood, which could result in more side effects.
- Antacids containing calcium, magnesium or aluminium (used to treat indigestion and heartburn). NUVACO is recommended to be administered 2 hours before or 6 hours after taking these antacids.
- Calcium supplements, iron supplements or multivitamins. NUVACO is recommended to be administered 2 hours before or 6 hours after taking these supplements.
- Rifampicin and/or isoniazid (used to treat tuberculosis (TB) and other bacterial infections) may decrease the amount of dolutegravir, a component of NUVACO, in your blood, which may require dose adjustment of dolutegravir.
- Phenytoin, phenobarbitone, oxcarbazepine and carbamazepine (used to treat epilepsy) may decrease the amount of dolutegravir, a component of NUVACO, in your blood.
- St John's wort (*Hypericum perforatum*) (a herbal remedy, used to treat depression) may decrease the amount of dolutegravir, a component of NUVACO, in your blood.
- Ethinyl oestradiol and norgestromin (oral contraceptives, used to prevent unplanned pregnancies).
- Methadone (used for opiate addiction and as a pain reliever).
- Co-trimoxazole (used to treat certain bacterial infections) may increase the amount of NUVACO) in your blood, which could result in more side effects.

- Medicines (usually liquids) containing sorbitol and other sugar alcohols (such as xylitol, mannitol, lactitol or maltitol), if taken regularly.
- Efavirenz, nevirapine, tipranavir/ritonavir (used to treat HIV infection (AIDS)) may decrease the amount of dolutegravir, a component of NUVACO, in your blood, which may require adjustment of dolutegravir by your doctor.
- Other medicines such as ranitidine, cimetidine, fosamprenavir/ritonavir (FPV + RTV), nelfinavir, saquinavir/ritonavir, lopinavir/ritonavir (LPV + RTV), darunavir/ritonavir (DRV + RTV), lopinavir/ritonavir + etravirine (LPV/RTV + ETR), darunavir/ritonavir + etravirine (DRV/RTV + ETR) have not shown to have any effect on NUVACO.

NUVACO with food and drink

NUVACO tablets can be taken with or without food.

Pregnancy, breastfeeding and fertility

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 healthcare provider for advice before taking NUVACO.

Women of childbearing potential

Women of childbearing potential should be counselled about the potential risk of neural tube defects with dolutegravir (see below), including consideration of using effective contraceptive measures.

Perform pregnancy testing before initiation of NUVACO in women of childbearing potential to exclude inadvertent (unintentional) use of NUVACO during the first trimester of pregnancy.

If a woman plans pregnancy, the benefits and the risks of starting or continuing treatment with dolutegravir versus using another antiretroviral regimen should be discussed with her.

Pregnancy

Use of dolutegravir during pregnancy was associated with a small increase in the prevalence of neural tube defects (0,19 %) compared to non-dolutegravir regimens (0,11 %). Most neural tube defects occur within the first 4 weeks of embryonic development after conception (approximately 6 weeks after the last menstrual period).

If a pregnancy is confirmed in the first trimester while on dolutegravir, the benefits and risks of continuing dolutegravir versus switching to another antiretroviral regimen should be discussed with the patient, taking the gestational age and the critical time period of neural tube defect development into account.

Dolutegravir may be used during the second and third trimester of pregnancy when the expected benefit outweighs the potential risk to the foetus. Dolutegravir was shown to cross the placenta in humans, leading to significant exposure to the foetus, but the implications of such exposure are not yet known.

Breastfeeding

HIV infected women should not breast-feed their infants in order to avoid transmission of HIV or follow appropriate guidelines.

Dolutegravir is excreted in human breast milk, and there is significant exposure to the neonate/infants due to slow elimination; the half-life of dolutegravir in the new born was 33 hr compared to 14 hr in the adults. There is insufficient information on the effects of dolutegravir in neonates/infants.

Fertility

There are no data on the effects of dolutegravir on human male or female fertility. Animal studies indicate no effects of dolutegravir on male or female fertility.

Driving and using machines

NUVACO may make you dizzy, drowsy or impair your concentration. If you experience these symptoms you should avoid potentially hazardous tasks such as driving or operating machinery.

3. HOW TO TAKE NUVACO

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

NUVACO therapy should be initiated by a healthcare provider experienced in the management of HIV infection.

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

Adults and adolescents (aged 18 years and older)

The usual dose of NUVACO is one (1) tablet taken orally, once daily with or without food.

Paediatrics

NUVACO is not recommended for use if you or your child is younger than18 years of age.

Your doctor will tell you how long your treatment with NUVACO will last. Do not stop treatment early because it may worsen your condition and make your body resistant to NUVACO. Your doctor will prescribe a dose according to your condition.

If you have the impression that the effect of NUVACO is too strong or too weak, talk to your doctor or pharmacist.

If you take more NUVACO than you should

In the event of overdosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison centre. Take the tablet container with you so that the doctor can see what you have taken.

If you forget to take NUVACO

It is important that you do not miss a dose. If you do miss a dose, take it as soon as possible unless it is nearly time for your next dose.

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

If you throw up the tablet (just after taking your NUVACO tablet) you should take another tablet. Do not wait until your next dose is due.

If you stop taking NUVACO

Do not stop taking treatment unless your doctor tells you to. This is very important because the virus may become resistant to NUVACO which may worsen you condition and make it more difficult to treat.

If NUVACO tablets are stopped, speak to your doctor before you restart taking NUVACO tablets.

Your doctor may consider giving you the components of NUVACO tablets separately if you are having problems or need your dose adjusted.

4. POSSIBLE SIDE EFFECTS

NUVACO can have side effects.

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

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

- Skin rash accompanied by a high temperature (fever), lack of energy (fatigue) swelling of the face or mouth which may cause difficulty in swallowing or breathing, muscle or joint pain. You may have a less frequently occurring, serious allergic reaction to dolutegravir, a component of NUVACO.
- Swelling with a red coloured rash (itchy or not itchy) beneath the surface of the skin, in area on or near the feet, hands, eyes, or lips; swollen throat, hoarseness, and difficulty breathing; abdominal cramps. You could be experiencing serious, less frequently occurring allergic reaction, angioedema.
- Deep rapid breathing; drowsiness, feeling sick (nausea), being sick (vomiting) and stomach pain; a general feeling of discomfort and unusual sleepiness, tiredness, or weakness. These are symptoms of a less frequently occurring, but serious condition called lactic acidosis (see Take special care with NUVACO).

These are all very serious side effects. If you have them, you may have had a serious reaction to NUVACO. 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 upper stomach pain, often with nausea and vomiting. These side effects may be due to a less frequently occurring condition called pancreatitis.
- Suicidal thoughts (especially if you have had depression or mental problems before), suicide attempt.
- Kidney problems, including kidney failure. Symptoms may include nausea and fatigue, but also passing a lot of urine and feeling thirsty. This may also lead to softening of the bones (with bone pain and sometimes resulting in fractures).

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

Tell your doctor, pharmacist or other healthcare provider if you are pregnant; think you may be pregnant or if you are planning to have a baby as NUVACO may cause abnormalities to the unborn baby (see Pregnancy, breastfeeding and fertility).

Tell your doctor if you notice any of the following:

Frequent side effects:

- Sleeping problems (insomnia).
- Headache, dizziness, abnormal dreams.
- Anorexia (an eating disorder).
- Feeling of dizziness or spinning (vertigo).
- Nausea (feeling sick), diarrhoea, vomiting, flatulence (wind), pain in the upper stomach area.
- Unusual weakness or tiredness, fever.

- Coughing, nasal symptoms.
- Hair loss (temporary).
- Rash, itching (pruritis).
- Joint pain, muscle disorders, muscle pain.

Less frequent side effects:

- Blood disorders (bleeding or bruising more easily than normal).
- Appearance of symptoms of infection as part of the “immune reconstitution inflammatory syndrome” (see Take special care with NUVACO).
- Anxiety depression, paranoia.
- Stomach pain, stomach discomfort, gastritis.
- Hepatitis (yellowing of the skin and eyes, also called jaundice).
- Hepatomegaly (enlarged liver, characterised by jaundice (yellowing of skin), abnormal liver function test results, blood in stools).
- Severe skin rash (erythema multiforme, Stevens-Johnson syndrome).
- Muscle breakdown (rhabdomyolysis), muscle spasms.
- Osteonecrosis (a bone disease that may cause pain or limit physical activity).
- Increase in amount of fat and sugar in the blood.
- Increase in enzymes (chemical that speed up chemical reactions in the body) produced by the pancreas (amylase), produced by muscles (creatine phosphokinase), produced by the liver (AST, ALT, gamma-GT).
- Test may show abnormal results for cholesterol, fat, enzyme creatine phosphokinase, white blood cells, blood and sugar (glucose) in the urine.
- Difficulty in breathing (dyspnoea), pneumonia (serious lung infection with fever, chills, shortness of breath, cough, phlegm.
- Changes in body shape due to changes in fat distribution. These may include loss of fat from legs, arms and face, increased fat in the abdomen and internal organs, breast

enlargement and fatty lumps on the back of the neck ('buffalo hump'), high levels of fat, cholesterol, glucose, lactate or lipase in the blood, low levels of potassium.

- Anorexia (an eating disorder characterised by a loss of appetite and a decrease in body mass).
- Abnormal behaviour.
- Nerve injury causing weakness and sensations of tingling, prickling, or numbness of the skin, especially in the feet and hands (peripheral neuropathy).
- Seizures (convulsions).
- Disorders of the nervous system, e.g. the brain, spinal cord or nerves (which may develop at a later stage in children, who were exposed to NUVACO while still developing in the womb).
- Breast enlargements in males (gynaecomastia).
- Inflammation of the kidney (nephritis), passing a lot of urine and feeling thirsty (nephrogenic diabetes insipidus).

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 safety of NUVACO.

5. How to store NUVACO

- Store all medicines out of reach of children.
- Store at or below 30 °C.

- Keep the container tightly closed.
- Keep in the original container until required for use.
- Protect from light and moisture.
- Do not store in a bathroom.
- Do not use after the expiry date stated on the label / 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 NUVACO contains

The active substances in each film-coated tablet is:

Lamivudine 300 mg

Tenofovir disoproxil fumarate 300 mg

Dolutegravir sodium equivalent to dolutegravir 50 mg

The other ingredients are:

Tablet core: croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, mannitol, microcrystalline cellulose, povidone, sodium starch glycolate and sodium stearyl fumarate

Film coating: iron oxide red, iron oxide yellow, macrogol/polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide.

What NUVACO looks like and contents of the pack

Orange coloured, modified capsule shaped, biconvex film-coated tablets debossed with 'H' on one side, and 'D 17' on the other side.

Pack sizes 28, 30, 56, 60, 84, 90, 100, 180 and 750 film-coated tablets:

NUVACO tablets are packed in white opaque high density polyethylene (HDPE) container, with a cotton or rayon coil wadding and a desiccant canister containing silica gel. The HDPE container is closed with a white polypropylene, child-resistant cap with heat seal induction liner or pulp liner. Pack size of 30's is packed in an outer carton.

Not all pack sizes may be marketed.

Holder of certificate of registration

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