SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:
MACLEODS LAMIVUDINE 150 (Film-coated tablets)

COMPOSITION:
Each film-coated tablet contains 150 mg lamivudine.
Excipients: magnesium stearate, microcrystalline cellulose, and sodium starch glycolate.

PHARMACOLOGICAL CLASSIFICATION:
A.20.2.8 Antiviral agents

PHARMACOLOGICAL ACTION:
Pharmacodynamic properties:
Lamivudine, a nucleoside reverse transcriptase inhibitor (NRTI), is a selective inhibitor of HIV-1 and HIV-2. Lamivudine is also active against zidovudine-resistant clinical isolates of HIV. Lamivudine has been shown to be synergistic with other anti-HIV agents, particularly zidovudine, inhibiting the replication of HIV in cell culture.
Lamivudine is metabolised intracellularly to the 5'-triphosphate which has an intracellular half-life of 16 - 19 hours. Lamivudine 5'-triphosphate is a weak inhibitor of the RNA- and DNA-dependent activities of HIV reverse transcriptase, its mode of action is a chain terminator of HIV reverse transcription.
Lamivudine does not interfere with cellular deoxynucleotide metabolism and has little effect on mammalian cell and mitochondrial DNA content.
Pharmacokinetic properties:
Absorption:
Lamivudine is well absorbed from the gastrointestinal tract, and the bioavailability of oral lamivudine in adults is normally between 80 and 85 %. Following oral administration, the mean time (T_{max}) to maximum serum concentration (C_{max}) is about an hour. At therapeutic dose levels i.e. 4 mg/kg/day (as two 12-hourly doses), C_{max} is in the order of 1 – 1,5 µg/ml.
Distribution:
From intravenous studies, the mean volume of distribution is 1,3 l/kg and the mean terminal half-life of elimination is 5 to 7 hours.
Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays limited binding to the major plasma protein albumin.
Metabolism and elimination:
The mean systemic clearance of lamivudine is approximately 0,32 l/kg/h, with predominantly renal clearance (> 70 %) via active tubular secretion, but little (< 10 %) hepatic metabolism.
Lamivudine elimination will be affected by renal impairment, whether it is disease or age-related. A recommended dosage regimen for patients with creatinine clearance below 50 ml/min is shown in the dosage section.
No dose adjustment is needed when co-administered with food as lamivudine bioavailability is not altered, although a delay in T_{max} and reduction in C_{max} have been observed.
Co-administration of zidovudine results in an increase in zidovudine exposure and an increase in peak plasma levels. This is not considered to be of significance to patient safety and therefore no dosage adjustments are necessary.
The likelihood of adverse interactions with lamivudine is low due to the limited metabolism and plasma protein binding and almost complete renal clearance. An interaction with trimethoprim, a constituent of co-trimoxazole, causes a 40 % increase in lamivudine exposure at therapeutic doses. This does not require dose adjustment unless the patient also has renal impairment. Administration of co-trimoxazole with the lamivudine/zidovudine combination in patients with renal impairment should be carefully assessed.

INDICATIONS:
MACLEODS LAMIVUDINE 150 in combination with zidovudine is indicated in the treatment of:
- HIV infected adults with progressive immunodeficiency (CD4 count < 500 cells/mm³) who have no prior antiretroviral therapy.
- HIV infected adults with progressive immunodeficiency who have been previously treated with zidovudine.

MACLEODS LAMIVUDINE 150 is indicated as part of antiretroviral combination therapy for the treatment of HIV infected children.

CONTRA-INDICATIONS:
The use of **MACLEODS LAMIVUDINE 150** is contra-indicated in patients with known hypersensitivity to lamivudine or to any ingredient of the preparation.
There is a known interaction between lamivudine and zalcitabine. The concomitant use of **MACLEODS LAMIVUDINE 150** and zalcitabine should be avoided (see INTERACTIONS).

WARNINGS AND SPECIAL PRECAUTIONS
Lactic Acidosis/hyperlactatesemia
Use of **MACLEODS LAMIVUDINE 150** can result in potentially fatal lactic acidosis as a consequence of mitochondrial dysfunction.
Clinical features are non-specific, and include nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss.
In patients with suspicious symptoms or biochemistry, measure the venous lactate level (normal < 2 mmol/ℓ) and the serum bicarbonate and respond as follows:
- Lactate 2 – 5 mmol/ℓ with minimum symptoms: switch to agents that are less likely to cause lactic acidosis.
- Lactate 5 – 10 mmol/ℓ with symptoms and/or with reduced bicarbonate: Stop NRTIs and change treatment option. Once lactate has settled, use medicines that are less likely to cause lactic acidosis. Exclude other causes, (e.g sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis and hyperthyroidism).
- Lactate > 10 mmol/ℓ: STOP all therapy (80 % mortality).

The above lactate values may not be applicable to paediatric patients.
Caution should be exercised when administering **MACLEODS LAMIVUDINE 150** to patients with known factors for liver disease.
Treatment with **MACLEODS LAMIVUDINE 150** should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

Mitochondrial dysfunction
Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed *in utero* and/or post-natally to nucleoside analogues. Apart from lactic acidosis/hyperlactataemia (see above) other manifestations of mitochondrial dysfunction include haematological disorders (anaemia, neutropenia), and peripheral neuropathy. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). It is not known whether the neurological disorders are transient or permanent. Any foetus exposed *in utero* to nucleoside and nucleotide analogues, even HIV negative infants/children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms.

Pancreatitis
Pancreatitis has been observed in some patients receiving **MACLEODS LAMIVUDINE 150**. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of **MACLEODS LAMIVUDINE 150** until diagnosis of pancreatitis is excluded

Patients with moderate to severe renal impairment
In patients with moderate to severe renal impairment, the terminal half-life of **MACLEODS LAMIVUDINE 150** is increased due to decreased clearance. The dose of **MACLEODS LAMIVUDINE 150** should therefore be adjusted (see DOSAGE AND DIRECTION FOR USE).

Liver disease
Use of **MACLEODS LAMIVUDINE 150** can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of **MACLEODS LAMIVUDINE 150** has not been established in patients with significant underlying liver disorders/diseases. In case of concomitant antiviral therapy for hepatitis B or C, please also consult the relevant package inserts for these medicines.
Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored. If there is evidence of worsening liver disease in such patients, temporary or permanent discontinuation of treatment must be considered.

Patients with HIV and hepatitis B or C virus co-infection
Patients with chronic hepatitis B or C and treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions.
Medical practitioners should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV).
In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant package inserts for these medicines.
Patients co-infected with HIV and HBV who discontinue **MACLEODS LAMIVUDINE 150** should be closely monitored with both clinical and laboratory follow-up after stopping treatment. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.
Discontinuation of **MACLEODS LAMIVUDINE 150** therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis.

Lipodystrophy and metabolic abnormalities
Combination antiretroviral therapy has been associated with the redistribution/accumulation of body fat, including central obesity, dorso-cervical fat, enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and elevated serum lipid and glucose levels in HIV patients. Clinical examination should include evaluation for physical signs of fat redistribution. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment.

Immune Reconstitution Inflammatory Syndrome
Immune reconstitution inflammatory syndrome (IRIS) is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses to pre-existing antigens combined with immune dysregulation, which occurs shortly after starting combination Anti-Retroviral Therapy (cART). Typically it presents by paradoxical deterioration of opportunistic infections being treated or with unmasking of a asymptomatic opportunistic disease, often with an atypical inflammatory presentation. IRIS usually develops within the first three months of initiation of ART and occurs more commonly in patients with low CD4 counts. Common examples of IRIS reactions to opportunistic diseases are tuberculosis, cytomegalovirus retinitis, and cryptococcal meningitis. Appropriate treatment of the opportunistic disease should be instituted or continued and ART continued. Inflammatory manifestations generally subside after a few weeks. Severe cases may respond to glucocorticoids, but there is only limited evidence for this in patients with tuberculosis IRIS. Autoimmune disorders (such as Graves' disease) have also been reported as IRIS reactions; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Osteonecrosis
Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported, particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (cART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Opportunistic infections
Patients receiving **MACLEODS LAMIVUDINE 150** should be advised that they may continue to develop opportunistic infections and other complications of HIV infection, and therefore they should remain under close observation by healthcare professionals experienced in the treatment of patients with associated HIV disease. Regular monitoring of viral load and CD4 counts needs to be done.

The risk of HIV transmission to others
Patients should be advised that current antiretroviral therapy, including **MACLEODS LAMIVUDINE 150**, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Effects on ability to drive and use machines
MACLEODS LAMIVUDINE 150 may cause dizziness, drowsiness and impaired concentration. Patients should be advised that if they experience these symptoms they should avoid potentially hazardous tasks such as driving or operating machinery.

INTERACTIONS
The likelihood of metabolic interactions with lamivudine is low due to limited metabolism and plasma protein binding, and almost complete renal clearance.
The possibility of interactions with other medicines administered concurrently with **MACLEODS LAMIVUDINE 150** must be considered particularly when the main route of elimination is active renal secretion especially via the cationic transport system e.g. trimethoprim. The nucleoside analogues (e.g. zidovudine, didanosine and zalcitabine) and other medicines (e.g. ranitidine, cimetidine) are eliminated only in part by this mechanism and were shown not to interact with lamivudine.
Trimethoprim:
Administration of prophylactic doses of co-trimoxazole results in a 40 % increase in lamivudine exposure, because of the trimethoprim component; the sulphamethoxazole component did not interact. However, unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary (see **DOSAGE AND DIRECTIONS FOR USE**).
When concomitant administration with co-trimoxazole is warranted patients should be monitored clinically. Co-administration of **MACLEODS LAMIVUDINE 150** with high doses of co-trimoxazole for the treatment of Pneumocystis jiroveci pneumonia (PCP) and toxoplasmosis should be avoided
Zalcitabine:
Lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the two medicinal products are used concurrently. **MACLEODS LAMIVUDINE 150** is therefore not recommended to be used in combination with zalcitabine (see **CONTRA-INDICATIONS**).
Other:
Co-administration of **MACLEODS LAMIVUDINE 150** with intravenous ganciclovir or foscarnet is not recommended.
Lamivudine metabolism does not involve CYP3A, making interactions with medicines metabolised by this system (e.g. protease inhibitors) unlikely.
Once daily triple nucleoside combinations of lamivudine and tenofovir with either abacavir or didanosine are associated with a high level of treatment failure and emergence of resistance and should therefore be avoided.
Zidovudine plasma levels are not significantly altered when co-administered with **MACLEODS LAMIVUDINE 150**. Zidovudine has no effect on the pharmacokinetics of lamivudine.

PREGNANCY AND LACTATION
Safety in human pregnancy and lactation has not been established.
Pregnancy
Consistent with passive transmission of the medicines across the placenta, lamivudine concentrations in infant serum at birth were similar to those in maternal and cord serum at delivery.
Reproductive studies in animals have not shown evidence of teratogenicity, and showed no effect on male or female fertility. There was some evidence of early embryolethality when administered to pregnant rabbits at exposure levels comparable to those achieved in information on placental transfer in humans.
Although animal reproductive studies are not always predictive of the human response, administration during pregnancy should only be considered if the expected benefit outweighs any possible risk.
There have been reports of mild and transient elevations in serum lactate levels which may be due to mitochondrial dysfunction, in neonates and infants exposed *in utero* or peripartum to nucleoside reverse transcriptase inhibitors (NRTIs). The clinical relevance of transient elevations in serum lactate is unknown. There have been very rare reports of developmental delay, seizures and other neurological disease. However, a causal relationship between these events and NRTI exposure *in utero* has not been established.
Lactation
A study in lactating rabbits showed that the following oral administration, lamivudine was excreted in breast milk. Following oral administration lamivudine was excreted in breast milk at similar concentrations to that found in serum. Therefore, mothers taking **MACLEODS LAMIVUDINE 150** should not breastfeed their infants.

DOSAGE AND DIRECTIONS FOR USE
Adults and adolescents > 12 years of age:
The recommended dose of lamivudine is 150 mg twice daily in combination with zidovudine. The package insert for zidovudine must be consulted for information on its dosage and administration.
For adults with low body weights (less than 50 kg), the recommended oral dose of lamivudine is 2 mg/kg twice daily, administered in combination with zidovudine. No data are available to support a dosage recommendation for adolescents with low body weights (less than 50 kg).
Renal and hepatic impairment:
Lamivudine plasma concentrations (AUC) are increased in patients with moderate to severe renal impairment due to decreased clearance. The doses should therefore be adjusted.
Adults and adolescents > 12 years of age:

Creatinine Clearance (ml/min)	Recommended dose of **MACLEODS LAMIVUDINE 150**
≥ 50	150 mg twice daily
30 – 49	150 mg once daily
15 – 29 *	150 mg first dose then 100 mg once daily
5 – 14 *	150 mg first dose then 50 mg once daily
<5 *	50 mg first dose then 25 mg once daily

* As doses below 150 mg are required, the use of an appropriate oral solution is recommended.

SIDE EFFECTS
The following side effects have been reported during therapy of HIV disease with **MACLEODS LAMIVUDINE 150** alone or in combination with other anti-retrovirals.
Infections and infestations
Frequent: Ear, nose and throat infections
Blood and lymphatic systems disorders
Less frequent: Anaemia, neutropenia, thrombocytopenia, pure red cell aplasia
Immune system disorders
Less frequent: Hypersensitivity/allergic reactions including angioedema, urticaria and anaphylaxis
Endocrine disorders
Frequency not known: Hyperglycaemia
Metabolism and nutritional disorders
Frequent: Hyperlactataemia
Less frequent: Lactic acidosis, lipodystrophy (redistribution/ accumulation of body fat (see **WARNINGS AND SPECIAL PRECAUTIONS**)
Psychiatric disorders
Frequent: Insomnia, other sleep disorders and depressive disorders
Nervous system disorders
Frequent: Peripheral neuropathy, paraesthesia, dizziness and headache
Ear and labyrinth disorders
Frequent: Ear discharge
Respiratory, thoracic and mediastinal disorders
Frequent: Nasal symptoms such as discharge or congestion, cough, wheezing and sore throat
Frequency not known: Abnormal breathing
Gastrointestinal disorders
Frequent: Pancreatitis, upper abdominal pain, nausea, vomiting, diarrhea, splenomegaly, anorexia or decreased appetite and stomatitis
Less frequent: Rises in serum amylase, dyspepsia
Hepato-biliary disorders
Less common: Transient rises in liver enzymes (AST, ALT), severe hepatomegaly with steatosis
Skin and subcutaneous tissue disorders
Frequent: Alopecia, rash and erythema, pain and swelling
Less frequent: Urticaria, pruritus
Musculoskeletal and connective tissue disorders
Frequent: Arthralgia, muscle disorders, musculoskeletal pain and myalgia
Less frequent: Rhabdomyolysis
General disorders
Frequent: Fatigue, malaise, fever, lymphadenopathy

Because adverse events may be attributable to the zidovudine component of the combination therapy, the complete prescribing information for zidovudine should be consulted before initiation of combination therapy.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT
The patient should be monitored for evidence of toxicity (see **SIDE EFFECTS**) and standard supportive treatment applied as necessary. Since lamivudine is dialysable, continuous haemodialysis could be used in the treatment of overdosage, although this has not been studied.

IDENTIFICATION
White coloured, capsule shaped, biconvex film coated tablets having score on one side and 'ML 1' debossed on the other side of the tablet.

PRESENTATION
Aluminium/PVC blister strips containing 10 tablets per strip, packed in a carton with 60 or 100 tablets or a white HDPE container with 56 or 60 tablets.

STORAGE INSTRUCTIONS
Store at or below 30 °C.
The blisters to be kept in the carton until required for use.
KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBER
45/20.2.8/0538

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION
MACLEODS PHARMACEUTICALS SA (PTY) LTD
Office block 1, Bassonia Estate Office,
Park (East), 1 Cussonia Drive,
Bassonia Rock, Ext. 12, Alberton.

DATE OF PUBLICATION OF THE PACKAGE INSERT
Date of registration: 20 April 2012
The date of the most recently revised package insert as approved by Council: 30 September 2016

Patient Information Leaflet

SCHEDULING STATUS:

S4

PROPRIETARY NAME, STRENGTH AND PHARMACEUTICAL FORM
MACLEODS LAMIVUDINE 150
Lamivudine 150 mg, Film-Coated Tablet.

READ ALL OF THIS LEAFLET CAREFULLY BEFORE YOU START TAKING MACLEODS LAMIVUDINE 150.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- **MACLEODS LAMIVUDINE 150** 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 MACLEODS LAMIVUDINE 150 CONTAINS
Each film-coated tablet contains lamivudine 150 mg:
Excipients: magnesium stearate, microcrystalline cellulose, sodium starch glycolate.

WHAT MACLEODS LAMIVUDINE 150 IS USED FOR
MACLEODS LAMIVUDINE 150 is used in antiretroviral combination therapy for the treatment of HIV infection and reduces the amount of HIV virus in your body and keeps it at a low level. It also increases CD4 cell counts. It reduces the risk of disease progression. Response to treatment with **MACLEODS LAMIVUDINE 150** varies between patients. Your doctor will be monitoring the effectiveness of your treatment.

BEFORE YOU TAKE MACLEODS LAMIVUDINE 150
Do not take MACLEODS LAMIVUDINE 150
It is important that you tell your doctor or healthcare professional if you suffer from any of the conditions mentioned below. If you are taking MACLEODS LAMIVUDINE 150 or have been prescribed MACLEODS LAMIVUDINE 150.
- If you are hypersensitive (allergic) to **MACLEODS LAMIVUDINE 150** or to any of the ingredients.
- If you are taking zalcitabine.

Take special care with MACLEODS LAMIVUDINE 150
Caution should be observed with the use of **MACLEODS LAMIVUDINE 150** in the following patients:
- If you have any kind of kidney or liver disease.
- Long term use of **MACLEODS LAMIVUDINE 150** may lead to an increase of acid in your body, and includes signs such as nausea, vomiting, stomach pain and cramps, weight loss, shortness of breath or fast breathing and fatigue. You may have a condition known as "lactic acidosis". Stop taking **MACLEODS LAMIVUDINE 150** and consult your doctor immediately.
- Take your child, if exposed during pregnancy or after birth to **MACLEODS LAMIVUDINE 150**, to your doctor immediately if your child appears pale, weak, sleepy all the time, is breathing faster, the heart is beating faster, the child does not appear to be putting on weight, is vomiting, has fever, sore throat, mouth ulcers, appears stiff, has convulsions (fits) or behaving abnormally. Your doctor will perform additional medical and laboratory tests on your child.
- **MACLEODS LAMIVUDINE 150** may cause inflammation of the pancreas. Inform your doctor if you experience severe upper stomach pain with nausea (feeling sick) and vomiting.
- Tell your doctor if you have had kidney disease, or if tests have shown problems with your kidneys. The dose of **MACLEODS LAMIVUDINE 150** may have to be adjusted.
- Inform your doctor if you have had any liver disease including hepatitis B or C, as treatment with **MACLEODS LAMIVUDINE 150** in patients with liver disease could cause severe side-effects affecting the liver including death. Your doctor will monitor your liver function by performing blood tests on a regular basis.
- If you have an ongoing hepatitis B infection, do not stop **MACLEODS LAMIVUDINE 150** without your doctor's advice, as your hepatitis may come back. The hepatitis may be more severe if you also have a serious liver disease.
- Inform your doctor, if you notice changes in body shape and weight including increase of weight around the waist, on the back of the neck between the shoulders and enlargement of the breasts or if you are losing weight in other areas of your body. **MACLEODS LAMIVUDINE 150** may also increase levels of sugar and fats (triglycerides and cholesterol) in the blood.
- You may experience an increase in other infections during initial treatment with **MACLEODS LAMIVUDINE 150** combined with other HIV medicine if your immune system is compromised. People with advanced HIV infection (AIDS) have weak immune systems, and are more likely to develop serious infections. When starting treatment you might find that old, hidden infections flare up, causing signs and symptoms of inflammation. These symptoms are probably caused by the body's immune system becoming stronger, so that the body starts to fight these infections. If you notice any symptoms of infection, please inform your doctor immediately.
- Long-term treatment with **MACLEODS LAMIVUDINE 150** in combination with other medicines to treat HIV may cause osteonecrosis which is bone death caused by poor blood supply to the area. It is most common in the hip and shoulder, but can affect other large joints such as knee, elbow, wrist and ankle.
- **MACLEODS LAMIVUDINE 150** is not a cure for HIV infection. **MACLEODS LAMIVUDINE 150** helps to control your condition and you need to keep taking it every day to stop your illness getting worse. You may still develop other infections and illnesses linked to HIV infection.
- Keep in touch with your doctor, and do not stop taking **MACLEODS LAMIVUDINE 150** without your doctor's advice.
- 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). **MACLEODS LAMIVUDINE 150** will not stop you passing your HIV infection on to other people.
- To protect other people from becoming infected with HIV:
  - Use a condom when you have oral or penetrative sex.
  - Do not risk blood transfer – for example, do not share needles.

Talk to your doctor if any of these applies to you. You may need extra check-ups, including blood tests, while you're taking your medication.

Taking MACLEODS LAMIVUDINE with food and drink
MACLEODS LAMIVUDINE 150 may be taken with or without food.

Pregnancy and breastfeeding

If you are pregnant or breastfeeding your baby, please consult your doctor, pharmacist or other healthcare professional for advice before taking **MACLEODS LAMIVUDINE 150.**

Pregnancy:
- It is important to tell your doctor if you are pregnant, and your doctor will give the appropriate medicine.

Breastfeeding:
- **MACLEODS LAMIVUDINE 150** is not recommended if you are breastfeeding. It is recommended that HIV infected women do not breastfeed their infants under any circumstances in order to avoid transmission of HIV.

Driving and the use of machinery
Dizziness, impaired concentration, and drowsiness have been reported during treatment with **MACLEODS LAMIVUDINE 150.** If you experience these symptoms, you should avoid potentially hazardous tasks such as driving or operating machinery.

Taking other medicines with MACLEODS LAMIVUDINE 150
When you are taking **MACLEODS LAMIVUDINE 150,** it is especially important to tell your doctor or healthcare professional if you are taking any of the following:
You should not take **MACLEODS LAMIVUDINE 150** with zalcitabine, high doses of co-trimoxazole, or infusions of ganciclovir or foscarnet.

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

HOW TO TAKE MACLEODS LAMIVUDINE 150

Do not share medicines prescribed for you with any other person.
Always take MACLEODS LAMIVUDINE 150 exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure. If you have the impression that the effect of MACLEODS LAMIVUDINE 150 is too strong or too weak talk to your doctor or pharmacist.

Adults and children over the age of 12 years and weighing more than 50 kg:
Always take **MACLEODS LAMIVUDINE 150** exactly as your doctor has told you. The recommended dose of **MACLEODS LAMIVUDINE 150** is one tablet twice daily administered with or without food. Therapy should be initiated by a medical doctor experienced in the management of HIV infection.
When **MACLEODS LAMIVUDINE 150** is used in combination with another anti-retroviral agent, the package insert of the particular agent should be consulted for information.

If you take more MACLEODS LAMIVUDINE 150 than you should
If you have accidently taken too much **MACLEODS LAMIVUDINE 150** get medical help immediately by calling your nearest doctor or healthcare professional.

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 MACLEODS LAMIVUDINE 150
If you have missed a dose of **MACLEODS LAMIVUDINE 150,** take it as soon as you remember. However if it is almost time for your next dose, skip the missed dose and go back to your regular scheduling. Never double your dose.

POSSIBLE SIDE EFFECTS
MACLEODS LAMIVUDINE 150 can have side effects.
Not all the side effects reported for **MACLEODS LAMIVUDINE 150** are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking **MACLEODS LAMIVUDINE 150,** please consult your doctor, pharmacist or healthcare professional for advice.

Get emergency medical help if you have any of these signs of an allergic reaction:
- Hives; difficulty breathing; swelling of your face, lips, tongue, or throat.

Call your doctor at once if you have any of these serious side effects:
- Lactic acidosis (severe increase of lactic acid in the blood, a 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.
- Liver damage – nausea; stomach pain; low fever; loss of appetite; dark urine; clay-coloured stools; jaundice (yellowing of the skin or eyes).
- Fever, chills, sore throat, cough, or other signs of infection.
- Changes in body shape because of changes in fat distribution.
- Stiffness in the joints, aches and pains (especially in the hip, knee or shoulder), difficulty moving as these are signs of osteonecrosis **[see TAKE SPECIAL CARE WITH MACLEODS LAMIVUDINE 150).**

Tell your doctor if you notice any of the following side effects and they worry you or if any of these symptoms are severe or do not go away:
- Headache
- Feeling sick (nausea), being sick (vomiting)
- Diarrhoea
- Tiredness, lack of energy, general feeling of being unwell
- Fever
- Muscle pain and discomfort, breakdown of muscle tissue
- Joint pain
- Sleep problems (inability to sleep)
- Feeling depressed
- Problems with nerves; numbness, tingling, pins and needles
- Dizziness
- Ear discharge
- Hair loss (alopecia)
- Rashes (including red spots or blotches sometimes with blistering and swelling of the skin), which may be allergic reactions, itching, changes in skin colour including darkening of the skin in patches
- Runny or blocked nose
- Cough, wheezing, abnormal breathing and sore throat
- Loss of appetite, lack of appetite; pancreas problems, enlarged spleen, heartburn and feeling bloated (dyspepsia), stomach pains, mouth ulcers and cold sores.

Less frequent side effects that may show up in blood tests are:
- a decrease in the number of cells involved in blood clotting (thrombocytopenia)
- a low red blood cell count (anaemia) or low white blood cell count (neutropenia)
- a failure of the bone marrow to produce new red blood cells
- an increase in the level of liver enzymes
- an increase in an enzyme called amylase
- an increase in blood glucose levels (hyperglycaemia)

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

STORING AND DISPOSING OF MACLEODS LAMIVUDINE 150
Store at or below 30 °C.
The blisters to be kept in the carton until required for use.
Any expired or outdated medicines and unused medicines can be returned to your nearest pharmacy.
STORE ALL MEDICINES OUT OF REACH OF CHILDREN.

PRESENTATION OF MACLEODS LAMIVUDINE 150
Aluminium/PVC blister strips containing 10 tablets per strip, packed in a carton with 60 or 100 tablets or a white HDPE container with 56 or 60 tablets.

IDENTIFICATION OF MACLEODS LAMIVUDINE 150
White coloured, capsule shaped, biconvex film coated tablets having score on one side and 'ML 1' debossed on the other side of the tablet.

REGISTRATION NUMBER
45/20.2.8/0538

NAME AND ADDRESS OF REGISTRATION HOLDER
MACLEODS PHARMACEUTICALS SA (PTY) LTD
Office block 1, Bassonia Estate Office,
Park (East), 1 Cussonia Drive,
Bassonia Rock, Ext. 12, Alberton.

DATE OF PUBLICATION
Date of registration: 20 April 2012
The date of the most recently revised package insert as approved by Council: 30 September 2016

MACLEODS PHARMACEUTICALS
MACLEODS LAMIVUDINE 150
PM029485001

SKEDULERINGSTATUS

S4

EIENDOMSNAAM EN DOSEERVORM
MACLEODS LAMIVUDINE 150 (Filmbedekte tablette)

SAMESTELLING
Elke filmbedekte tablet bevat 150 mg lamivudien.
Eksipiënte: magnesiumstearaat, mikrokristallyne sellulose en natriumstysel-glikolaat.

FARMAKOLOGIESE KLASSIFIKASIE
A 20.2.8 Antivirusmiddels

FARMAKOLOGIESE WERKING
Farmakodinamiese eienskappe:
Lamivudien, 'n nukleosied trutranskriptase-inhibeerder (NTTI), is 'n selektiewe inhibeerder van MIV-1 en MIV-2. Lamivudien is ook aktief teen sidovudien-weerstandbiedende kliniese isolate van MIV. Dit is aangetoon dat lamivudien sinergisties met ander anti-MIV middels, veral sidovudien, in die inhibisie van die replisering van MIV in selkultuur is.
Lamivudien word intrasellulêr na die 5'-trifosfaat gemetaboliseer, wat 'n intrasellulêre halfleeftyd van 16 – 19 ure het. Lamivudien 5'-trifosfaat is 'n swak inhibeerder van die RNA- en DNA-afhanklike aktiwiteite van MIV-trutranskriptase, en sy metode van werking is as 'n kettingbreker van MIV-trutranskripsie.
Lamivudien meng nie in met sellulêre deoksienukleotiedmetabolisme nie en het min effek op soogdiersel- en mitochondriale DNA-inhoud.
Farmakokinetiese eienskappe:
Absorpsie:
Lamivudien word goed vanuit die maagdermkanaal geabsorbeer en die biobeskikbaarheid van orale lamivudien in volwassenes is gewoonlik tussen 80 en 85 %. Na orale toediening is die gemiddelde tyd (T_{maks}) tot maksimum serumkonsentrasie (K_{maks}) ongeveer een uur. Teen terapeutiese dosisvlakke, d.i. 4 mg/kg/dag (as twee 12-uurlikse dosisse), is K_{maks} ongeveer 1 – 1,5 g/mℓ.
Verspreiding:
Intraveneuse studies toon aan dat die gemiddelde volume van verspreiding 1,3 ℓ/kg en die gemiddelde halfleeftyd van eliminasie 5 tot 7 ure is.
Lamivudien toon lineêre farmakokinetika oor die terapeutiese dosisreikwydte en toon beperkte binding aan die belangrike plasmaproteïen, albumien.
Metabolisme en eliminasie:
Die gemiddelde sistemiese suiwering van lamivudien is ongeveer 0,32 ℓ/kg/uur, hoofsaaklik niersuiwering (> 70 %) via buissekresie en min (< 10 %) lewermetabolisme.
Die eliminasie van lamivudien sal deur siekte- of ouderdomsverwante ingekorte nierfunksie beïnvloed word. 'n Aanbevole dosregimen vir pasiënte met kreatiniensuiwering van minder as 50 mℓ/min word in die doseringsafdeling aangetoon.
Geen dosisaanpassing is nodig wanneer dit saam met voedsel toegedien word nie, aangesien die biobeskikbaarheid van lamivudien nie verander nie. 'n Vertraging in T_{maks} en 'n afname in K_{maks} is egter waargeneem
Die medetoediening van sidovudien lei tot 'n toename in sidovudien-blootstelling en 'n toename in piek plasmavlakke. Dit word nie as betekenisvol vir pasiëntveiligheid beskou nie en daarom is aanpassing van die dosis onnodig.
Die waarskynlikheid van nadelige interaksies met lamivudien is laag weens die beperkte metabolisme, plasmaproteïenbinding en byna totale niersuiwering daarvan. 'n Interaksie met trimetoprim, 'n bestanddeel van kotrimoksasool, veroorsaak 'n 40 % toename in lamivudienblootstelling teen terapeutiese dosisse. Dit vereis geen dosisaanpassing nie, tensy die pasiënt ook aan ingekorte nierfunksie lei. Die toediening van kotrimoksasool tesame met die lamivudien/sidovudien kombinasie in pasiënte met ingekorte nierfunksie behoort noukeurig geëvalueer te word.

INDIKASIES
MACLEODS LAMIVUDINE 150 in kombinasie met sidovudien word aangedui in die behandeling van:
- MIV-besmette volwassenes met 'n gevorderde immuuntekort (CD4-telling < 500 selle/mm³) met geen vorige antiretrovirusterapie nie.
- MIV-besmette volwassenes met 'n gevorderde immuuntekort wat voorheen met sidovudien behandel is.

MACLEODS LAMIVUDINE 150 word aangedui as deel van antiretrovirus kombinasieterapie in die behandeling van MIV-besmette kinders.

KONTRA-INDIKASIES
Die gebruik van **MACLEODS LAMIVUDINE 150** word teenaangedui in pasiënte met 'n bekende hipersensitiwiteit teen lamivudien of enige bestanddeel van die preparaat. Daar bestaan 'n bekende interaksie tussen lamivudien en salsitabien. Die gelyktydige gebruik van **MACLEODS LAMIVUDINE 150** en salsitabien behoort vermy te word (sien **INTERAKSIES**).

WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS
Melksuurasidose/hiperlaktatemie:
Die gebruik van **MACLEODS LAMIVUDINE 150** kan weens mitochondriale wanfunksie tot potensieel fatale melksuurasidose lei.
Kliniese eienskappe is nie-spesifiek en sluit naarheid, braking, buikpyn, dispnee, moegheid en massaverlies in.
In pasiënte met verdagte simptome of biochemie, behoort die veneuse laktaatvlak (normaal < 2 mmol/ℓ) en serumbikarbonaat gemeet en as volg opgetree te word.
- **Laktaat 2 - 5 mmol/ℓ met minimum simptome:** Skakel oor na medisyne wat minder waarskynlik melksuurasidose sal veroorsaak.
- **Laktaat 5 - 10 mmol/ℓ met simptome en/of laer bikarbonaat:** Staak NTTIs en verander die behandeling. Wanneer die laktaatvlak gestabiliseer het, gebruik medisyne wat minder waarskynlik melksuurasidose sal veroorsaak. Sluit ander oorsake uit (bv. sepsis, uremie, diabetiese ketoasidose, tirotoksikose en hipertiroïedisme).
- **Laktaat > 10 mmol/ℓ: STAAK** alle terapie (80 % mortaliteit).

Die bogenoemde laktaatvlakke is moontlik nie in pediaters van toepassing nie.
Sorg behoort aan die dag gelê te word wanneer **MACLEODS LAMIVUDINE 150** aan pasiënte met bekende faktore vir lewersiekte toegedien word.
Behandeling met **MACLEODS LAMIVUDINE 150** behoort opgeskort te word in enige pasiënt wat kliniese of laboratorium bevindings ontwikkel wat op melksuurasidose of hepatotoksisiteit dui.

Mitochondriale disfunksie:
Daar is *in vitro* en *in vivo* aangetoon dat nukleosied- en nukleotiedanaloë 'n wisselende graad van mitochondriale beskadiging veroorsaak. Daar bestaan vermeldings van mitochondriale disfunksie in MIV-negatiewe babas wat *in utero* en/of post-nataal aan nukleosiedanaloë blootgestel is. Behalwe vir melksuurasidose/hiperlaktatemie (sien hierbo) sluit ander manifesterings van mitochondriale disfunksie hematologiese afwykings (anemie, neutropenie) en perifere neuropatie in. Sommige neurologiese afwykings wat eers later ontwikkel is aangemeld (hipertonie, stuipaanvalle, abnormale gedrag). Dit is nie bekend of die neurologiese afwykings van verbygaande aard of permanent is nie. Enige fetus wat *in utero* aan nukleosied- en nukleotiedanaloë blootgestel is, selfs MIV-negatiewe babas/kinders, behoort kliniese en laboratoriumopvolg te ondergaan en behoort in die geval van relevante tekens of simptome ten volle vir mitochondriale disfunksie ondersoek te word.

Pankreatitis:
Pankreatitis is in sommige pasiënte wat **MACLEODS LAMIVUDINE 150** ontvang, waargeneem.
Pankreatitis moet oorweeg word wanneer 'n pasiënt buikpyn, naarheid, braking of verhoogde biochemiese merkers ontwikkel. Staak die gebruik van **MACLEODS LAMIVUDINE 150** totdat 'n diagnose van pankreatitis uitgesluit is.

Pasiënte met matige tot ernstige nierversaking:
In pasiënte met matige tot ernstige nierversaking, word die terminale halfleeftyd van **MACLEODS LAMIVUDINE 150** verhoog as gevolg van verminderde klaring. Die dosis van **MACLEODS LAMIVUDINE 150** moet dus aangepas word (sien DOSIS EN GEBRUIKSAANWYSING).

Lewersiekte:
Weens nie-alkoholiese vetlewersiekte (lewersteatose) kan die gebruik van **MACLEODS LAMIVUDINE 150** tot hepatomegalie lei. Die veiligheid en effektiwiteit van **MACLEODS LAMIVUDINE 150** is nie in pasiënte met beduidende onderliggende lewerafwykings/-siekte vasgestel nie. In die geval van meegaande antivirusterapie vir hepatitis B of C, moet die relevante voubiljette vir hierdie medisyne geraadpleeg word.
Pasiënte met reeds bestaande lewerdisfunksie, insluitende chroniese, aktiewe hepatitis toon 'n toename in die frekwensie van lewerfunksie-abnormaliteite gedurende kombinasie antiretrovirusterapie en behoort gemonitor te word. As daar bewys van agteruitgang van die lewersiekte in sulke pasiënte is, behoort tydelike of permanente staking van behandeling oorweeg te word.

Pasiënte met beide MIV en hepatitis B of C infeksie:
Pasiënte met chroniese hepatitis B of C en wat met antiretrovirus terapie behandel word, het 'n groter risiko vir erge en potensieel fatale newe-effekte van die lewer.
Mediese praktisyns behoort na die huidige MIV-behandelingsriglyne te verwys vir die optimale bestuur van MIV-infeksie in pasiënte wat ook met hepatitis B virus (HBV) besmet is.
In die geval van meegaande antivirusterapie vir hepatitis B of C, moet ook na die relevante voubiljette vir hierdie medisyne verwys word.
Pasiënte wat mede besmet is met MIV en HBV wat **MACLEODS LAMIVUDINE 150** stop, moet noukeurig gemoniteer word met beide kliniese en laboratoriumopvolg na behandeling gestaak is.
In pasiënte met gevorderde lewersiekte of -sirrose, word die staking van terapie nie aanbeveel nie, aangesien die agteruitgang van hepatitis na behandeling tot lewerdekompensering kan lei.
Die staking van **MACLEODS LAMIVUDINE 150** in pasiënte wat met beide MIV en HBV besmette, kan met erge agteruitgang van hepatitis geassosieer word.

Lipodistrofie en metaboliese abnormaliteite:
Kombinasie antiretrovirusterapie is met die herverspreiding/akkumulasie van liggaamsvet, insluitende sentrale vetsug, dorsoservikale vetvergroting (buffelskof), perifere vermaering, gesigsvermaering, borsvergroting en verhoogde serumlipied- en glukosevlakke in MIV-pasiënte geassosieer. 'n Kliniese ondersoek behoort die evaluering van fisiese tekens van die herverspreiding van vet in te sluit. Pasiënte met bewys van lipodistrofie behoort 'n deeglike kardiovaskulêre risiko-evaluering te ondergaan.

Immuunherinstelling en inflammatoriese sindroom:
Immuunherinstelling en inflammatoriese sindroom (IRIS) is 'n immunopatologiese respons wat volg op die vinnige herstel van patogeenspesifieke immuunresponse tot reeds bestaande immuun-disregulering wat kort na die begin van kombinasie antiretrovirusterapie (kART) voorkom. Dit presenteer tipies met paradoksale agteruitgang van opportunistiese infeksies wat behandel word of met ontmaskering van 'n asimptomatiese opportunistiese infeksie, dikwels met 'n atipiese inflammatoriese presentering. IRIS ontwikkel gewoonlik binne die eerste drie maande na inisiëring van ART en kom meer dikwels in pasiënte met lae CD4 tellings voor. Algemene voorbeelde van IRIS reaksies teen opportunistiese siektes is tuberkulose, sitomegalovirusretinitis en kriptokokmeningitis. Toepaslike behandeling van die opportunistiese siekte behoort ingestel en voortgesit te word en ART behoort ook voortgesit te word. Inflammatoriese manifesterings verdwyn gewoonlik na 'n paar weke. Erge gevalle mag op kortikosteroïede reageer, maar daar is slegs beperkte bewys hiervan in pasiënte met tuberkulose IRIS. Outo-immuunafwykings (soos Graves se siekte) is ook as IRIS reaksies aangemeld. Die aangemelde tyd tot aanvangs wissel egter meer en hierdie episodes kan 'n aantal maande na aanvangs van behandeling voorkom.

Osteonekrose:
Alhoewel die etiologie as multifaktoriaal beskou word (insluitende die gebruik van kortikosteroïede, alkoholinname, erge immuunonderdrukking en hoër liggaamsmassa-indeks), is gevalle van osteonekrose aangemeld, veral in pasiënte met gevorderde MIV-siekte en/of langtermyn blootstelling aan kombinasie antiretrovirusterapie (KART). Pasiënte behoort aangeraai te word om mediese advies in te win wanneer hulle gewrigspyn, gewrigstyfheid of moeite met beweging.

Opportunistiese infeksies:
Pasiënte wat **MACLEODS LAMIVUDINE 150** ontvang behoort daarop ingelig te word dat hulle mag voortgaan om opportunistiese infeksies en ander komplikasies van MIV-siekte op te doen en behoort daarom onder noukeurige waarneming deur professionele gesondheidswerkers met ondervinding in die behandeling van pasiënte met verwante MIV-siekte gehou te word. Die viruslading en CD4 tellings behoort gereeld gemonitor te word.

Die risiko van oordraging van MIV na ander:
Pasiënte behoort in kennis gestel te word dat die huidige antiretrovirusterapie, insluitende **MACLEODS LAMIVUDINE 150**, nie die risiko van oordraging van MIV na ander deur seksuele kontak of bloedkontaminasie verminder nie. Toepaslike voorsorgmaatreëls behoort getref te word.

Effek op die vermoë om te bestuur of met masjinerie te werk:
MACLEODS LAMIVUDINE 150 kan tot duiseligheid, ingekorte konsentrasievermoë en/of lomerigheid lei. Pasiënte behoort aangeraai te word dat wanneer hulle hierdie simptome ontwikkel, hulle potensieel gevaarlike take soos om te bestuur en met masjinerie te werk, moet vermy.

INTERAKSIES
Weens die beperkte metabolisme en plasmaproteïenbinding van lamivudien, asook die byna totale niersuiwering daarvan, is die waarskynlikheid van metaboliese interaksies daarmee klein.
Die moontlikheid van interaksies met ander medisyne wat saam met **MACLEODS LAMIVUDINE 150** toegedien word, moet in ag geneem word, veral wanneer die hoofroete van eliminasie aktiewe niersekresie is, en dan veral via die kationtransportsisteem, bv. trimetoprim. Die nukleosiedanaloë (bv. sidovudien, didanosien en salsitabien) en ander medisyne (bv. ranitidien, simetidien) word slegs gedeeltelik deur hierdie meganisme geëlimineer en dit is aangetoon dat hulle geen interaksie met lamivudien het nie.
Trimetoprim:
Die toediening van profilaktiese kotrimoksasool dosisse lei weens die trimetoprimkomponent, tot 'n 40 % toename in lamivudienblootstelling. Die sulfametoksasoolkomponent het geen interaksie getoon nie. Tensy die pasiënt aan ingekorte nierfunksie ly, is geen dosisaanpassing van lamivudien nodig nie (sien **DOSIS EN GEBRUIKSAANWYSINGS**).
Wanneer die gelyktydige toediening saam met kotrimoksasool dit regverdig, behoort pasiënte klinies gemonitor te word. Die medetoediening van **MACLEODS LAMIVUDINE 150** saam met hoë dosisse kotrimoksasool vir die behandeling van Pneumocystis jirovecii pneumonie (PCP) en toksoplasmose behoort vermy te word.
Salsitabien:
Salsitabien mag die intrasellulêre fosforilering van salsitabien inhibeer wanneer die twee medisinale produkte saam gebruik word. Dit word daarom aanbeveel dat **MACLEODS LAMIVUDINE 150** nie in kombinasie met salsitabien gebruik word nie (sien **KONTRA-INDIKASIES**).
Ander:
Die medetoediening van **MACLEODS LAMIVUDINE 150** saam met intraveneuse gansiklovir of foskarnet word nie aanbeveel nie.
CYP3A is nie by die metabolisme van lamivudien betrokke nie. Interaksies met medisyne wat deur hierdie sisteem gemetaboliseer word (bv. proteaseïnhibeerders), is daarom onwaarskynlik.
Een keer daaglikse drievoudige nukleosiedkombinasies van lamivudien en tenofovir saam met abasavir of didanosien word met 'n hoë vlak van behandelingsmislukking en die ontwikkeling van weerstand geassosieer en behoort derhalwe vermy te word.
Die plasmavlakke van sidovudien word nie noemenswaardig verander wanneer dit saam met **MACLEODS LAMIVUDINE 150** toegedien word nie. Sidovudien het geen effek op die farmakokinetika van lamivudien nie.

SWANGERSKAP EN LAKTASIE
Die veiligheid in menslike swangerskap en laktasie is nie vasgestel nie.
Swangerskap
Ooreenstemmend met die passiewe oordrag van medisyne deur die plasenta, was lamivudienkonsentrasies in babaserum met geboorte soortgelyk aan dié van materale en naelstringserum met geboorte.
Reproduksiestudies in diere het geen bewys van teratogeniteit, asook geen effek op manlike of vroulike vrugbaarheid getoon nie. Daar was enkele bewyse van vroeë embriodood wanneer aan dragtige konyne toegedien is teen blootstellingsvlakke vergelykbaar met dié bereik in mense.
Alhoewel reproduksiestudies in diere nie altyd die menslike respons voorspel nie, behoort die toediening gedurende swangerskap slegs oorweeg te word wanneer die verwagte voordeel opweeg teen enige moontlike risiko.
Daar bestaan vermeldings van geringe en verbygaande verhogings in serumlaktaatvlakke, moontlik weens mitochondriale disfunksie, in neonate en babas wat *in utero* of peripartum aan nukleosied trutranskriptase-inhibeerders (NTTI) blootgestel is. Die kliniese betekenis van verbygaande verhogings in serumlaktaat is onbekend. Daar bestaan slegs 'n paar vermeldings van vertraagde ontwikkeling, stuiptrekkings en ander neurologiese siektes. 'n Oorsaaklike verwantskap tussen hierdie gebeurtenisse en die *in utero* blootstelling aan NTTI's is egter nie vasgestel nie.
Laktasie
'n Studie in lakterende konyne, na orale toediening, het aangetoon dat lamivudien in die borsmelk uitgeskei is. Na orale toediening is lamivudien in die borsmelk in soortgelyke konsentrasies as dié wat in serum gevind is, uitgeskei. Dus, moeders wat **MACLEODS LAMIVUDINE 150** neem, nie hul babas borsvoed nie.

DOSIS EN GEBRUIKSAANWYSINGS
Volwassenes en adolessente > 12 jaar:
Die aanbevole lamivudiendosis is 150 mg twee keer per dag in kombinasie met sidovudien. Die voubiljet vir sidovudien moet geraadpleeg word vir inligting oor die dosis en toediening daarvan.
Vir volwassenes met 'n lae liggaamsmassa (minder as 50 kg) is die aanbevole orale lamivudiendosis 2 mg/kg twee keer per dag, toegedien in kombinasie met sidovudien. Daar is geen data beskikbaar om 'n dosisaanbeveling vir adolessente met 'n liggaamsmassa van minder as 50 kg te maak nie.
Ingekorte nier- en lewerfunksie:
Weens 'n afname in suiwering is plasmakonsentrasies van lamivudien (AOK) hoër in pasiënte met matig tot erg ingekorte nierfunksie. Die dosis behoort daarom aangepas te word
Volwassenes en adolessente > 12 jaar:

Kreatiniensuiwering (mℓ/min)	Aanbevole MACLEODS LAMIVUDINE 150 dosis
≥ 50	150 mg twee keer per dag
30 – 49	150 mg een keer per dag
15 – 29 *	Eerste dosis 150 mg, daarna 100 mg een keer per dag
5 – 14 *	Eerste dosis 150 mg, daarna 50 mg een keer per dag
< 5 *	Eerste dosis 50 mg, daarna 25 mg een keer per dag

*As dosisse van minder as 150 mg benodig word, word die gebruik van 'n toepaslike orale oplossing aanbeveel.

NEWE-EFFEKTE
Die volgende newe-effekte is gedurende die terapie van MIV-siekte met **MACLEODS LAMIVUDINE 150** alleen of in kombinasie met ander antiretrovirusmiddels aangemeld.
Infeksies en infestasies
Algemeen: Oor-, neus- en keelinfeksies
Afwykings van die bloed- en limfsisteem
Minder algemeen: Anemie, neutropenie, trombositopenie, suiwer rooiselaplasie
Afwykings van die immuunstelsel
Minder algemeen: Hipersensitiewe/Allergiese reaksies insluitend angioëdeem, urtikarie en anafilaksie
Endokriene afwykings
Frekwensie onbekend: Hiperglukemie
Metabolisme en voedingsafwykings
Algemeen: Hiperlaktatemie
Minder algemeen: Melksuurasidose, lipodistrofie (herverspreiding/ aansameling van liggaamsvet) (sien **WAARSKUWINGS EN SPESIALE VOORSORGSMAATREËLS**)
Psigiatriese afwykings
Algemeen: Slapeloosheid, ander slaapafwykings en depressiewe afwykings
Afwykings van die senuweestelsel
Algemeen: Perifere neuropatie, parestesie, duiseligheid en hoofpyn
Oor- en labirintafwykings
Algemeen: Oorsuising
Respiratoriese, torakale en mediastinale afwykings
Algemeen: Neussimptome soos uitskeiding of verstopping, hoes, hyg en seer keel
Frekwensie onbekend: Abnormale asemhaling
Gastrointestinale afwykings
Algemeen: Pankreatitis, bo-buikpyn, naarheid, braking, diarree, splenomegalie, anoreksie of verlies aan eetlus en stomatitis
Minder algemeen: Toename in serumamilase, dispepsie
Hepatobiliêre afwykings
Minder algemeen: Verbygaande toenames in lewerensieme (AST, ALT), erge hepatomegalie met steatose
Afwykings van die vel en subkutane weefsel
Algemeen: Alopesia, uitslag en eritreem, pyn en swelling
Minder algemeen: Urtikarie, pruritus
Muskuloskeletale en bindweefselafwykings
Algemeen: Artralgie, spierafwykings, muskuloskeletale pyn en mialgie
Minder algemeen: Rabdomiolise
Algemene afwykings
Algemeen: Moegheid, malaise, koors, limfadenopatie

Aangesien newe-effekte aan die sidovudienkomponent van die kombinasieterapie toegeskryf kan word, behoort die volledige voorskrifinligting geraadpleeg te word alvorens daar met kombinasieterapie begin word.

BEKENDE SIMPTOME VAN OORDOSERING EN BESONDERHEDE VAN DIE BEHANDELING DAARVAN
Die pasiënt moet vir enige tekens van toksisiteit gemonitor te word (sien **NEWE-EFFEKTE**), en behoort standaard ondersteuningsbehandeling waar nodig, toegepas te word. Aangesien lamivudien dialiseerbaar is, kan aanhoudende hemodialise moontlik gebruik word in die behandeling van oordosering. Laasgenoemde is egter nog nie bestudeer nie.

IDENTIFIKASIE
Wit, kapsuulvormige, bikonvekse, filmbedekte tablette met 'n breeklyn aan die een kant, en 'ML 1' op die ander kant van die tablet gedruk.

AANBIEDING
Aluminium/PVC stolpverpakkings met 10 tablette per strokie, gepak in 'n kartonhouer met 60 of 100 tablette, of in 'n HDPE houer met 56 of 60 tablette.

BERGINGSAANWYSINGS
Berg teen of onder 30 °C.
Die strokies behoort in die karton gehou te word totdat hulle vir gebruik benodig word.
HOU BUITE BEREIK VAN KINDERS

REGISTRASIENOMMER
45/20.2.8/0538

NAAM EN BESIGHEIDSADRES VAN DIE HOUER VAN DIE REGISTRASIESERTIFIKAAT
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SKEDULERINGSTATUS

S4

EIENDOMSNAAM, STERKTE EN FARMASEUTIESE VORM
MACLEODS LAMIVUDINE 150
Lamivudien 150 mg, Filmbedekte Tablet

LEES DIE HELE BLAADJIE SORGVULDIG VOORDAT U BEGIN OM MACLEODS LAMIVUDINE 150 TE GEBRUIK
- Hou die blaadjie. U mag dit moontlik weer wil lees.
- Indien u enige verdere vrae het, raadpleeg u dokter of apteker.
- **MACLEODS LAMIVUDINE 150** is vir u persoonlik voorgeskryf en u moet nie u medisyne met ander deel nie. Dit mag hulle skade aandoen, ook al toon hulle dieselfde simptome as u.

WAARUIT BESTAAN MACLEODS LAMIVUDINE 150
Elke filmbedekte tablet bevat lamivudien 150 mg.
Eksipiënte: magnesiumstearaat, mikrokristallyne sellulose, natriumstysel-glikolaat.

WAARVOOR MACLEODS LAMIVUDINE 150 GEBRUIK WORD
MACLEODS LAMIVUDINE 150 word in antiretrovirusterapie gebruik vir die behandeling van MIV-infeksie, verminder die hoeveelheid MIV viruses in u liggaam en hou dit op 'n lae vlak. Dit verhoog ook CD4-tellings. Dit verminder die risiko van siektevordering. Die respons op behandeling met **MACLEODS LAMIVUDINE 150** wissel tussen pasiënte. U dokter sal die effektiwiteit van u behandeling monitor.

VOORDAT U BEGIN OM MACLEODS LAMIVUDINE 150 TE GEBRUIK
Moenie MACLEODS LAMIVUDINE 150 gebruik nie:
Indien u **MACLEODS LAMIVUDINE 150** gebruik, of indien **MACLEODS LAMIVUDINE 150** aan u voorgeskryf is, is dit belangrik dat u u dokter of gesondheidsorgprofessioneel daarvoor inlig as u aan enige van die kondisies hieronder genoem, ly:
- Indien u hipersensitief (allergies) teen **MACLEODS LAMIVUDINE 150** of enige van die eksipiënte is.
- Indien u salsitabien gebruik.

Neem spesiale sorg met MACLEODS LAMIVUDINE 150
Sorg moet aan die dag gelê word met die gebruik van **MACLEODS LAMIVUDINE 150** in die volgende pasiënte:
- Indien u aan enige soort nier- of lewersiekte ly.
- Die langtermyn gebruik van **MACLEODS LAMIVUDINE 150** mag tot 'n toename van suur in u liggaam ly. Dit sluit tekens soos naarheid, braking, maagpyn en -krampe, gewigsverlies, kortasemheid of vinnige asemhaling en moegheid in. U mag aan 'n kondisie genaamd "melksuurasidose" ly. Stop met die gebruik van **MACLEODS LAMIVUDINE 150** en raadpleeg u dokter onmiddellik.
- Neem u kind, indien gedurende swangerskap aan **MACLEODS LAMIVUDINE 150** blootgestel is, onmiddellik na u dokter indien hy/sy bleek lyk, swak is, aanhoudend slaperig is, vinniger asemhaal, as die hart vinniger klop, as dit lyk of hy/sy nie gewig aansit nie, as hy/sy braak, koors, seer keel of mondulkusse het, as hy/sy styf is, stuiptrekkings het of abnormale gedrag toon. U dokter sal bykomende mediese en laboratoriumtoetse op u kind doen.
- **MACLEODS LAMIVUDINE 150** kan inflammasie van die pankreas veroorsaak. Stel u dokter in kennis indien u enige maagpyn ervaar met siekte en braking.
- Vertel jou dokter as ju nier siekte gehad het, of as toetse probleme met jou niere getoon het. Die dosis van **MACLEODS LAMIVUDINE 150** sal moontlik aangepas moet word.
- Stel u dokter in kennis as u aan 'n lewersiekte ly insluitende hepatitis B of C, want behandeling met **MACLEODS LAMIVUDINE 150** in pasiënte met lewersiekte ernstige newe-effekte wat die lewer effek, insluitend die dood, kan veroorsaak. Jou dokter sal jou lewerfunksie monitor deur gereeld bloedtoetse te doen.
- As u 'n voortdurende hepatitis B-infeksie het, moet nie **MACLEODS LAMIVUDINE 150** stop sonder u dokter se advies nie, aangesien u hepatitis mag terugkom. Die hepatitis kan erger wees as jy ook 'n ernstige lewersiekte het.
- Stel u dokter in kennis indien u enige veranderinge in u liggaamsvorm en -gewig waarneem, insluitende 'n gewigstoename om die middel, op die agterkant van die nek tussen die skouers en vergroting van die borste opmerk, of indien u gewig op ander plekke van u liggaam verloor. **MACLEODS LAMIVUDINE 150** kan ook vlakke van suiker en vette (trigliseriede en cholesterol) in die bloed verhoog.
- Wanneer u immuunstelsel onderdruk is, mag u 'n toename in ander infeksies gedurende die aanvanklike behandeling met **MACLEODS LAMIVUDINE 150** gekombineer met ander MIV medisyne ondervind. Mense met gevorderde MIV-infeksie (VIGS) het swak immuunstelsels, en is meer geneig om ernstige infeksies te ontwikkel. By die aanvang van behandeling kan u vind dat ou, verborge infeksies flikker, wat tekens en simptome van inflammasie veroorsaak. Hierdie simptome word waarskynlik veroorsaak deurdat die liggaam se immuunstelsel sterker word, sodat die liggaam hierdie infeksies begin beveg. As u enige simptome van infeksie ervaar, moet u asseblief u dokter dadelik in kennis stel.
- Die langtermyn behandeling met **MACLEODS LAMIVUDINE 150** in kombinasie met ander medisyne om MIV mee te behandel, mag osteonekrose, of beendood, weens swak bloedtoevoer na die area veroorsaak. Dit kom mees algemeen in die heup en skouer voor, maar kan enige ander groot gewrigte soos die knie, elmboog, pols of enkel aantas.
- **MACLEODS LAMIVUDINE 150** is nie 'n genesing vir MIV-infeksie nie. **MACLEODS LAMIVUDINE 150** help om u kondisie te beheer en u moet dit elke dag neem om te verhoed dat u siekte erger word. U mag aanhou om ander infeksies en siektes wat met MIV geassosieer word, op te doen. Bly in kontak met u dokter en moenie ophou om **MACLEODS LAMIVUDINE 150** te neem sonder om u dokter te raadpleeg nie.
- MIV-infeksie word deur seksuele kontak met iemand wat die infeksie het, versprei, of deur oordraging van besmette bloed (bv. die deel van spuitnaalde). **MACLEODS LAMIVUDINE 150** sal nie verhoed dat u MIV-infeksie na ander oordra nie. Om te voorkom dat ander mense met MIV besmet raak:
  - o Gebruik 'n kondoom wanneer u orale of penetrerende seks het.
  - o Wees versigtig vir bloedoordraging – bv. moenie naalde deel nie.

Praat met u dokter indien enige van die volgende op u van toepassing is. U mag moontlik bykomende ondersoeke benodig terwyl u die medikasie gebruik, insluitende bloedtoetse.

Die neem van MACLEODS LAMIVUDINE 150 met voedsel en vloeistof:
MACLEODS LAMIVUDINE 150 mag met of sonder voedsel geneem word.

Swangerskap en borsvoeding:

Indien u swanger is of u baba borsvoed, moet u asseblief u dokter, apteker of ander gesondheidsbeampte raadpleeg voordat u **MACLEODS LAMIVUDINE 150** neem.

Swangerskap:
- Dit is belangrik dat u u dokter daaroor inlig as u swanger is, en hy/sy sal vir u die toepaslike medisyne gee.

Borsvoeding:
- **MACLEODS LAMIVUDINE 150** word nie aanbeveel terwyl u borsvoed nie. Daar word aanbeveel dat MIV-besmette vroue onder geen omstandighede hul babas borsvoed nie om sodoende oordraging van MIV te vermy.

Bestuur en die gebruik van masjinerie:
Duiseligheid, ingekorte konsentrasie en lomerigheid is gedurende die behandeling met **MACLEODS LAMIVUDINE 150** aangemeld. Indien u hierdie simptome ondervind, behoort u potensieel gevaarlike take soos bestuur en om met masjinerie te werk, te vermy.

Die neem van ander medisyne saam met MACLEODS LAMIVUDINE 150:
Wanneer u **MACLEODS LAMIVUDINE 150** neem is dit veral belangrik dat u u dokter of gesondheidsprofessioneel inlig indien u enige van die volgende neem:
Moet nie **MACLEODS LAMIVUDINE 150** saam met salsitabien, hoë dosisse kotrimoksasool of saam met infusies van gansiklovir of foskarnet neem nie.

Laat altyd u gesondheidsbeampte weet as u ander medisyne gebruik (dit sluit komplementêre of tradisionele medisyne in.

HOE OM MACLEODS LAMIVUDINE 150 TE NEEM

Moenie medisyne wat vir u voorgeskryf is, met enige ander persoon deel nie.
Neem altyd MACLEODS LAMIVUDINE 150 presies soos wat u dokter voorgeskryf het. Indien u onseker is, raadpleeg u dokter of apteker. Raadpleeg u dokter of apteker indien u van mening is dat die effek van MACLEODS LAMIVUDINE 150 te sterk of te swak is.

Volwassenes en kinders ouer as 12 jaar en wat meer as 50 kg weeg:
Neem altyd **MACLEODS LAMIVUDINE 150** presies soos wat u dokter voorgeskryf het. Die aanbevole dosis van **MACLEODS LAMIVUDINE 150** is een tablet twee keer per dag, toegedien met of sonder voedsel. Terapie behoort deur 'n dokter met ondervinding in die bestuur van MIV-infeksie, geïnisieer te word.
Wanneer **MACLEODS LAMIVUDINE 150** in kombinasie met 'n ander antiretrovirusmiddel gebruik word, behoort die voubiljet van die spesifieke middel vir inligting geraadpleeg te word.

As u te veel MACLEODS LAMIVUDINE 150 geneem het:
Indien u per ongeluk te veel **MACLEODS LAMIVUDINE 150** geneem het, moet u onmiddellik mediese hulp kry deur u naaste dokter of gesondheid-sorgprofessioneel te skakel.

In die geval van oordosering moet u u dokter of apteker raadpleeg. Indien hulle nie beskikbaar is nie, kontak u naaste hospitaal of gifbeheersentrum.

As u vergeet om MACLEODS LAMIVUDINE 150 te neem:
Indien u 'n **MACLEODS LAMIVUDINE 150** oorgeslaan het, moet u dit so gou moontlik neem wanneer u onthou. Indien dit egter reeds naby u volgende dosis is, moet u nie die oorgeslane dosis neem nie en terugkeer na die normale skedule. Moet nooit die dosis verdubbel nie.

MOONTLIKE NEWE-EFFEKTE
MACLEODS LAMIVUDINE 150 mag newe-effekte veroorsaak.
Nie al die newe-effekte van **MACLEODS LAMIVUDINE 150** word nie in hierdie blaadjie genoem nie. As u algemene gesondheid sou verswak terwyl u **MACLEODS LAMIVUDINE 150** gebruik, moet u asseblief u dokter, apteker of gesondheidsprofessioneel vir advies raadpleeg.

Ontbied onmiddellik nood mediese hulp indien u enige van hierdie **tekens of 'n allergiese reaksie toon:**
- Veluitslag; moeite met asemhaling; swelling van die gesig, lippe, tong of keel.

Ontbied onmiddellik u dokter wanneer u enige van die volgende newe-effekte ondervind:
- Melksuurasidose (erge toename van melksuur in die bloed, 'n ernstige newe-effekte wat fataal mag wees). Die volgende newe-effekte mag tekens van melksuurasidose wees: diep, vinnige asemhaling, lomerigheid, naarheid, braking en maagpyn.
- Lewerbeskadiging – naarheid; maagpyn; afferse koors; verlies aan eetlus; donker urien, grys verkleuring van die stoelgang; geelsug (geel verkleuring van die vel of oë).
- Koors, koue rillings, seer keel, hoes of ander tekens van infeksie.
- Veranderinge in liggaamsvorm weens veranderinge in vet-verspreiding.
- Styfheid van die gewrigte, algemene pyn (veral in die heup, knie of skouer), moeite met beweging aangesien die bogenoemde tekens van osteonekrose is (sien **WEES VERSIGTIG MET MACLEODS LAMIVUDINE 150**).

Lig u dokter daaroor in as u enige van die volgende newe-effekte waarneem en hulle u kwel, of indien enige van hierdie newe-effekte erg is of nie verdwyn nie:
- Hoofpyn
- Naarheid, braking
- Diarree
- Moegheid, tekort aan energie, algemene "voel nie lekker nie"
- Koors
- Spierpyn en ongemak, afbraak van spierweefsel
- Gewrigspyn
- Slaapafwykings (slapeloosheid)
- Gevoel van depressie
- Senuweeprobleme; gevoelloosheid, prikkeling, tinteling
- Duiseligheid
- Oorsuising
- Haarverlies (alopesia)
- Uitslag (insluitende rooi kolletjies of vlekke, soms met blaasvorming en swelling van die vel) wat allergiese reaksies mag wees, jeuk, veranderinge in velkleur, insluitende verdonkering in plekke.
- Loop- of verstopte neus
- Hoes, hyging, abnormale asemhaling en seer keel
- Verlies aan eetlus, geen eetlus, probleme met die pankreas, sooibrand en 'n gevoel van opgeblasenheid (dispepsie), maagpyn, mondulkusse en koue sere.

Minder gereelde newe-effekte wat in bloedtoetse uitgewys mag word:
- 'n afname in die aantal selle wat by bloedstolling betrokke is (trombositopenie)
- 'n lae rooibloedseltelling (anemie), of 'n lae witbloedseltelling (neutropenie)
- 'n onvermoë van die beenmurg om nuwe rooibloedselle te vervaardig
- 'n toename in lewerensiemvlakke
- 'n toename in die ensiem genaamd amilase
- 'n toename in bloedglukosevlakke

OPBERGING EN WEGDOEN VAN MACLEODS LAMIVUDINE 150
Berg teen of onder 30 °C.
Hou die strokies in die karton tot voor gebruik.
Enige vervalde of ou en ongebruikte medisyne kan aan u apteker teruggegee word.
HOU ALLE MEDISYNE BUITE DIE BEREIK VAN KINDERS

AANBIEDING VAN MACLEODS LAMIVUDINE 150
Aluminium/PVC stolpverpakking met 10 tablette per strokie, verpak in 'n karton met 60 of 100 tablette, of in 'n HDPE houer met 56 of 60 tablette.

IDENTIFIKASIE VAN MACLEODS LAMIVUDINE 150
Wit, kapsuulvormige, bikonvekse, filmbedekte tablette met 'n breeklyn aan die een kant en "ML 1" op die ander kant.

REGISTRASIENOMMER
45/20.2.8/0538

NAAM EN BESIGHEIDSADRES VAN DIE HOUER VAN DIE REGISTRASIESERTIFIKAAT
Macleods Pharmaceuticals SA (Edms.) Bpk.
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Alberton.

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PACKAGING RESEARCH & DEVELOPMENT

MACLEODS

Restricted Circulation

(Front Page)

ARTWORK / PRINTPROOF APPROVAL FORM

1. Product : MACLEODS LAMIVUDINE 150	
2. Country: South Africa	3. Packaging component: Package Insert & Patient Information Leaflet
4. No. of Colours: 1 Colour	5. Pantone Shade No.: Black
6. Specification: 40 gsm bible paper	
7. Machine Layout No.: NA	8. Dimensions: 426 x 400 mm
9. Design / Style: NA	10. Item code No.: PM02946001
11. Artwork has been made: Actual Size	12. Pharma code No.: 21325 mini
13. Barcode/NDC no: NA	14. Supersedes Item code No: NA
15. Revision no: 00	16. File Name : E:\ANDA Regulatory\South Africa\Lamivudine 150\63\Lamivudine 150 mg leaflet PM02946001.cdr
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PRD	M.A. HOLDER	MEDICAL/RAD	QC	PRODN	QA
07/12/18	Rashmi Gosai	07/12/18	07/12/18	07/12/18	Dyadov 10/12/18

Note: 1. To follow overleaf checklist for approval of Artwork / Print proof.

Instructions to Vendor :

1. Before processing, please ensure First pull out / Commercial supply should match with approved Artwork with respect to Design, Size, Fonts & Text.
2. Print proof to represent full printing area with Station Numbers.

FRM/CQA/021/04-01

Reason for revision :	Item code	Artwork Release Date	Artwork Implementation Date
1) New Artwork for South Africa	PM02946001		