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SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

LAMILEOD 10 mg/mL (oral solution)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

LAMILEOD 10 mg/mL: Each mL of oral solution contains Lamivudine 10 mg

Contains sugar (200 mg of sucrose). Preservative (1,50 mg of methyl hydroxybenzoate), (0,18 mg of propyl hydroxybenzoate) and solvent (20 mg of propylene glycol).
Each mL of oral solution contains 200 mg of sucrose, 1,50 mg of Methyl hydroxybenzoate, 0,18 mg of Propyl hydroxybenzoate and 20 mg of Propylene Glycol.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Oral solution

LAMILEOD 10 mg/mL: Clear, colourless to pale yellow, flavoured liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LAMILEOD 10 mg/mL is indicated as part of antiretroviral combination therapy for the treatment of HIV infected adults and children.

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4.2 Posology and method of administration

Posology

The professional information for zidovudine must be consulted for information on its dosage and administration.

Adults, and adolescents more than 12 years of age

The recommended dose of **LAMILEOD 10 mg/mL** is 300 mg daily. This may be administered as 300 mg once daily or 150 mg twice daily.

For patients with low body weights (less than 50 kg), the recommended oral dose of **LAMILEOD 10 mg/mL** is 2 mg/kg twice daily.

Children

***Children < 3 months of age*:**

The limited data available are insufficient to propose specific dosage recommendations (see section 5.2).

***For Children aged ≥ 3 months* to 12 years of age:**

The recommended dose is 4 mg/kg twice daily up to a maximum of 300 mg daily.

Special populations

Renal and hepatic impairment:

Renal impairment , whether disease- or age-related, affects lamivudine elimination. For recommended dosage regimens in patients with a creatinine clearance below 50 mL/min see table below.

Adults and adolescents > 12 years of age:

Creatinine clearance (mL/min)	Recommended dose
≥ 50	150 mg twice daily
30 – 49	150 mg twice 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

Children > 3 months to 12 years:

Creatinine clearance (mL/min)	Recommended dose
≥ 50	4 mg/kg first dose, then 4 mg/kg twice daily
30 – 49	4 mg/kg first dose, then 4 mg/kg twice daily
15 – 29	4 mg/kg first dose, then 2,6 mg/kg twice daily
5 – 14	4 mg/kg first dose, then 1,3 mg/kg twice daily
< 5	1,3 mg/kg first dose, then 0,7 mg/kg twice daily

Method of administration

For oral use.

LAMILEOD 10 mg/mL can be taken with food or without food.

4.3 Contraindications

Hypersensitivity to lamivudine or any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Lactic acidosis/hyperlactataemia:

Use of **LAMILEOD 10 mg/mL** 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.

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- Lactate 5 - 10 mmol/ℓ with symptoms and/or with reduced standard 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 **LAMILEOD 10 mg/mL** to patients with known risk factors for liver disease. Treatment with **LAMILEOD 10 mg/mL** 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 these 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 sign and symptoms.

Lipodystrophy and metabolic abnormalities:

Redistribution/accumulation of body fat, including central obesity, dorsocervical fat, enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, elevated serum lipid and glucose levels have been observed in some patients receiving combination antiretroviral therapy (see section 4.8).

Clinical examination should include evaluation for physical signs of fat redistribution. Patients with

evidence of lipodystrophy should have a thorough cardiovascular assessment.

***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.

Patients with Moderate to severe renal impairment:

In patients with moderate to severe renal impairment, the terminal half-life of **LAMILEOD 10 mg/mL** is increased due to decreased clearance. The dose of **LAMILEOD 10 mg/mL** should therefore be adjusted (see section 4.2).

Liver disease:

Use of **LAMILEOD 10 mg/mL** can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of **LAMILEOD 10 mg/mL** 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 professional information 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.

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, such reaction presents by paradoxical deterioration of opportunistic infections being treated or with unmasking of an 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.

Pancreatitis:

Pancreatitis has been observed in patients receiving lamivudine. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of **LAMILEOD 10 mg/mL** until diagnosis of pancreatitis is excluded.

Opportunistic infections:

Patients receiving **LAMILEOD 10 mg/mL** or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore they should remain under close observation by physicians 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 **LAMILEOD 10 mg/mL**, has not been shown to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Patients with HIV and hepatitis B or C 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 professional information for these medicines.

Patients co-infected with HIV and HBV who discontinue **LAMILEOD 10 mg/mL** should be closely

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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 **LAMILEOD 10 mg/mL** therapy in patients co-infected with HIV and HBV may be associated with severe, acute exacerbations of hepatitis.

Information about excipients

LAMILEOD 10 mg/mL contains sucrose. This should be taken into account in patients with diabetes mellitus. Sucrose may be harmful to teeth.

Patients with rare hereditary problems of fructose intolerance, total lactase deficiency or glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free".

This medicine contains 300 mg propylene glycol in each 15 mL which is equivalent to 20 mg/mL.

If your baby is less than 4 weeks old, talk to your doctor or pharmacist before giving them this medicine, in particular if the baby is given other medicines that contain propylene glycol or alcohol.

4.5 Interaction with other medicines and other forms of interaction

Zidovudine plasma levels are not significantly altered when co-administered with **LAMILEOD 10 mg/mL** (see section 5.2).

An interaction with trimethoprim, a constituent of co-trimoxazole, causes a 40 % increase in lamivudine plasma concentrations at therapeutic doses. This does not require dose adjustment unless the patient also has renal impairment.

Administration of co-trimoxazole with the **LAMILEOD 10 mg/mL** /zidovudine combination in patients with renal impairment should be carefully assessed.

LAMILEOD 10 mg/mL may inhibit the intracellular phosphorylation of zalcitabine when the two medicinal products are used concurrently. Use of **LAMILEOD 10 mg/mL** in combination with

zalcitabine is therefore not recommended.

Due to similarities, **LAMILEOD 10 mg/mL** should not be administered concomitantly with other cytidine analogues, such as emtricitabine. *In vitro* lamivudine inhibits the intracellular phosphorylation of cladribine leading to a potential risk of cladribine loss of efficacy in case of combination in the clinical setting. Some clinical findings also support a possible interaction between lamivudine and cladribine. Therefore, the concomitant use of lamivudine with cladribine is not recommended. Coadministration of sorbitol solution (3,2 g, 10,2 g, 13,4 g) with a single 300 mg dose of lamivudine oral solution resulted in dose-dependent decreases of 14 %, 32 %, and 36 % in lamivudine exposure (AUC∞) and 28 %, 52 %, and 55 % in the Cmax of lamivudine in adults. When possible, avoid chronic coadministration of **LAMILEOD 10 mg/mL** with medicinal products containing sorbitol or other osmotic acting poly-alcohols or monosaccharide alcohols (e.g. xylitol, mannitol, lactitol, maltitol). Consider more frequent monitoring of HIV-1 viral load when chronic coadministration cannot be avoided

4.6 Fertility, pregnancy and lactation

Pregnancy

As a general rule, when deciding to use antiretroviral medicines for the treatment of HIV infection in pregnant women and consequently for reducing the risk of HIV vertical transmission to the newborn, the animal data as well as the clinical experience in pregnant women should be taken into account.

Animal studies with lamivudine showed an increase in early embryonic deaths in rabbits but not in rats.

Placental transfer of lamivudine has been shown to occur in humans.

More than 1000 outcomes from first trimester and more than 1000 outcomes from second and third trimester exposure in pregnant women indicate no malformative and foeto/neonatal effect. Lamivudine can be used during pregnancy if clinically needed. The malformative risk is unlikely in humans based on those data.

For patients co-infected with hepatitis who are being treated with lamivudine and subsequently become pregnant, consideration should be given to the possibility of a recurrence of hepatitis on discontinuation of lamivudine.

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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 infants exposed in utero and/or post-natally to nucleoside analogues (see section 4.4).

Breastfeeding

Following oral administration lamivudine was excreted in breast milk at similar concentrations to those found in serum.

Based on more than 200 mother/child pairs treated for HIV, serum concentrations of lamivudine in breastfed infants of mothers treated for HIV are very low (< 4 % of maternal serum concentrations) and progressively decrease to undetectable levels when breastfed infants reach 24 weeks of age. There are no data available on the safety of lamivudine when administered to babies less than three months old. It is recommended that HIV infected women do not breastfeed their infants under any circumstances in order to avoid transmission of HIV.

Fertility

Studies in animals showed that lamivudine had no effect on fertility.

4.7 Effects on ability to drive and use machines

No data available.

4.8 Undesirable effects

Summary of the safety profile

Tabulated summary of adverse reactions

System organ class	Frequent	Less frequent	Frequency unknown
Blood and lymphatic system disorders		Neutropenia, anaemia, thrombocytopenia, pure red cell aplasia	

Metabolism and nutrition disorders		Lactic acidosis	
Nervous system disorders	Headache, peripheral neuropathy, paraesthesia, insomnia		
Respiratory, thoracic and mediastinal disorders	Cough, nasal symptoms		
Gastrointestinal disorders	nausea, vomiting, upper abdominal pain or cramps, diarrhoea, pancreatitis	rises in serum amylase	
Hepatobiliary disorders		Hepatitis	transient rises in liver enzymes (AST, ALT)
Skin and subcutaneous disorders	Skin Rash	angioedema	alopecia
Musculoskeletal connective tissue and bone disorders	arthralgia, muscle disorders		rhabdomyolysis
General disorders and administrative site conditions	Fatigue, malaise, fever		

Reporting of suspected adverse reactions

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Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website or to Macleods Pharmaceuticals SA (Pty) Ltd. at safety@macleodspharma.com

4.9 Overdose

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A.20.2.8 Antiviral agents

Pharmacotherapeutic group: antivirals for systemic use. ATC code: J05AF05

Mechanism of action

Lamivudine is a selective inhibitor of HIV-1 and HIV-2 replication *in vitro*. It is also active against zidovudine-resistant clinical isolates of HIV.

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.

In vitro, lamivudine demonstrates low cytotoxicity to peripheral blood lymphocytes, to established lymphocyte and monocyte-macrophage cell lines, and to a variety of bone marrow progenitor cells.

In vitro, lamivudine therefore has a high therapeutic index. Reduced in vitro sensitivity to lamivudine has been reported for HIV isolated from patients who have received lamivudine therapy before.

Lamivudine has been shown to act additively or synergistically with other anti-HIV agents, particularly zidovudine, inhibiting the replication of HIV in cell culture. In vitro studies indicate that zidovudine-

resistant virus isolates can become zidovudine-sensitive when they acquire resistance to lamivudine.

5.2 Pharmacokinetic properties

Pharmacokinetics in adults:

Following oral administration, lamivudine is well absorbed with bioavailability of approximately 80 %.

The mean time (T_{max}) to maximum serum concentration (C_{max}) is about an hour. At therapeutic dose levels of 4 mg/kg/day (as two 12-hourly doses), C_{max} is in the order of 1 - 1,5 ug/mL.

The mean volume of distribution from intravenous studies has been reported as 1,3 L/kg and the mean terminal half-life of elimination as 5 to 7 hours. The mean systemic clearance of lamivudine is approximately 0,32 L/kg/h, with predominantly renal clearance of more than 70 % via active tubular secretion, but little hepatic metabolism, at less than 10 %. The intracellular half-life of the lamivudine triphosphate active metabolite is prolonged, averaging over 10 hours in peripheral blood lymphocytes.

A delay in Tmax and reduction in C_{max} have been observed when co-administered with food, but no dose adjustment is needed, as lamivudine bioavailability is not altered. Lamivudine displays limited binding to albumin and exhibits linear pharmacokinetics over the therapeutic dose range. Coadministration of zidovudine results in a 13 % increase in zidovudine exposure and a 28 % increase in peak plasma levels. No dosage adjustments are necessary, as this is not considered to be of significance to patient safety.

Limited data shows lamivudine penetrates the central nervous system and reaches the cerebrospinal fluid (CSF). The true extent of penetration or relationship with any clinical efficacy is unknown.

Pharmacokinetics in children:

In general, lamivudine pharmacokinetics in paediatric patients is similar to adults. However, absolute bioavailability is reduced to approximately 65 % in paediatric patients, with an increased clearance of 0,52 L/kg/hr.

There are limited pharmacokinetic data for patients < 3 months of age.

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6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose, Methyl hydroxybenzoate, Propyl hydroxybenzoate, Citric acid anhydrous, Sodium citrate, Propylene glycol, Strawberry flavour wild TP, Banana flavour, Sodium hydroxide, Purified water.

Flavourants:

i) Strawberry flavour wild TP: Flavouring ingredients approved for use in a regulation of FDA or in a reliable, published industry list, Propylene Glycol, Water.

ii) Banana flavour: Flavouring ingredients approved for use in a regulation of FDA or in a reliable, published industry list, Propylene Glycol.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months for HDPE bottle pack

6.4 Special precautions for storage

Store at or below 30°C.

Keep the bottles tightly closed.

Discard oral solution one month after first opening.

KEEP REACH OUT OF CHILDREN

6.5 Nature and contents of container

For HDPE bottle pack:

Solution is packed in a round white HDPE Bottle and closed with 28 mm white cap made up of Polypropylene with Induction Sealing Wad and packed in a pre-printed carton.

Pack sizes include 240 mL Bottle Pack.

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6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

MACLEODS PHARMACEUTICALS SA (PTY) LTD

Ground floor, Block 1,

Bassonia estate office park (east),

1 Cussonia drive,

Bassonia rock ext 12

Alberton Gauteng

8. REGISTRATION NUMBERS

LAMILEOD 10 mg/mL: 61/20.2.8/0316

9. DATE OF FIRST AUTHORISATION

LAMILEOD 10 mg/mL: 28/07/2026

10. DATE OF REVISION OF THE TEXT

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