Applicant: Ranbaxy Pharmaceuticals (Pty) Ltd
Product name: Sonke Lamivudine 150 tablets
Dosage form: Film- coated Tablets
Strength: Lamivudine 150 mg/tablet

APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

SONKE LAMIVUDINE 150 tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains lamivudine 150 mg.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated Tablets

White to off-white, oval shaped, biconvex film-coated tablets with 'RX919' debossed on one side and a score line on the other side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

Adults and adolescents more than 12 years of age

The recommended dose of **SONKE LAMIVUDINE 150** is 300 mg daily. This may be administered as either 300 mg once daily or 150 mg twice daily.

The professional information for zidovudine must be consulted for information on its dosage and administration when co-administered.

For patients with low body weights (less than 50 kg), the recommended oral dose of SONKE LAMIVUDINE 150 is 2 mg/kg twice daily.

Special populations

Paediatric population

Children weighing between 14 kg < 20 kg:

The recommended dose is 150 mg once daily.

Children weighing at least 25 kg:

The adult dosage of 150 mg twice daily or 300 mg once daily should be taken

Children < 3 months of age:

There are limited data to propose specific dosage recommendations (see section 5.2).

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 weighing atleast 25 Kg. :

Creatinine Clearance (ml/min)	**Recommended dose of SONKE LAMIVUDINE 150**
≥ 50	150 mg twice daily.
30 – 49	150 mg once daily.

Hepatic Impairment:

No dose adjustment is necessary in patients with moderate or severe hepatic impairment unless accompanied by renal impairment.

Method of administration

Oral use.

SONKE LAMIVUDINE 150 can be taken with or without food.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Patients receiving **SONKE LAMIVUDINE 150** and another antiretroviral agent may continue to develop opportunistic infections and other complications of HIV infection. Patients should therefore remain under close supervision by medical practitioners experienced in the treatment of patients with HIV-associated diseases.

Current antiretroviral therapy including **SONKE LAMIVUDINE 150**, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination

Lamivudine is not recommended for use as monotherapy.

Lactic acidosis/severe hepatomegaly with steatosis

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

Long-term use of **SONKE LAMIVUDINE 150** can result in potentially fatal lactic acidosis. Symptomatic hyperlactataemia and lactic acidosis are uncommon. Clinical features are non-specific and include nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss. Suspicious biochemical features include mild raised transaminases, raised lactate dehydrogenase (LDH) and/or creatine kinase. In patients with suspicious symptoms or biochemistry, measure the venous lactate level (normal <2 mmol/l) and respond as follows:

Lactate 2-5 mmol/l	Monitor regularly and be alert for clinical signs.
Lactate 5-10 mmol/l without symptoms	Monitor closely.
Lactate 5-10 mmol/l with symptoms	STOP all therapy. Exclude other causes e.g. sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis, lymphoma.
Lactate >10 mmol/l	STOP all therapy. (80 % mortality)

Diagnosis of lactic acidosis is confirmed by demonstrating metabolic acidosis with an increased anion gap and raised lactate level. Therapy should be stopped in any acidotic patient with a raised lactate level. Blood for lactate assays should be heparinised and stored on ice.

After recovery, NRTI's should be avoided. Seek expert advice on medicine selection

The above lactate values may not be applicable to paediatric patients.

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of lamivudine alone or in combination, in the treatment of HIV infection. Most cases were women. Caution should be exercised when administering **SONKE LAMIVUDINE 150** to patients with known risk factors for liver disease (See section 4.4). Treatment with **SONKE LAMIVUDINE 150** should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

SONKE LAMIVUDINE 150 should be used with caution in patients with advanced cirrhotic liver disease due to chronic Hepatitis B infection as there is a small risk of rebound hepatitis post treatment

Pancreatitis

Pancreatitis has been observed in some patients receiving **SONKE LAMIVUDINE 150**. However, it is unclear whether this is due to **SONKE LAMIVUDINE 150** or to underlying HIV disease. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of **SONKE LAMIVUDINE 150** until diagnosis of pancreatitis is excluded.

Opportunistic infections

Patients receiving **SONKE LAMIVUDINE 150** may continue to develop opportunistic infections and other complications of HIV infection and, therefore, they should remain under close observation by medical practitioners experienced in the treatment of patients with associated HIV disease (See section 4.4).

The risk of HIV transmission to others

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

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 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.

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.

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 sign and symptoms.

Patients with moderate to severe renal impairment

In patients with moderate to severe renal impairment, the terminal half-life of SONKE LAMIVUDINE 150 TABLETS is increased due to decreased clearance. The dose of SONKE LAMIVUDINE 150 TABLETS should therefore be adjusted (see section 4.2).

Liver disease

Use of SONKE LAMIVUDINE 150 TABLETS can result in hepatomegaly due to nonalcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of SONKE LAMIVUDINE 150 TABLETS 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.

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 professional information for these medicines.

Patients co-infected with HIV and HBV who discontinue SONKE LAMIVUDINE 150 TABLETS 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 SONKE LAMIVUDINE 150 TABLETS therapy in patients co-infected with HIV and HBV may be associated with severe, acute exacerbations of hepatitis.

4.5 Interaction with other medicines and other forms of interaction

Zidovudine plasma levels are not significantly altered when co-administered with **SONKE LAMIVUDINE 150**, (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 **SONKE LAMIVUDINE 150** in patients with renal impairment should be carefully assessed.

SONKE LAMIVUDINE 150 may inhibit the intracellular phosphorylation of zalcitabine when the two medicinal products are used concurrently. **SONKE LAMIVUDINE 150** is, therefore, not recommended to be used in combination with zalcitabine.

Due to similarities, **SONKE LAMIVUDINE 150** 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 **SONKE LAMIVUDINE 150** 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

Safety in pregnancy and lactation has not been established.

Pregnancy

As a general rule, when deciding to use antiretroviral agents 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 reported outcomes from first trimester and more than reported 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.

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

Tabulated list of adverse reactions

MedDRA System organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Less frequent	Neutropenia, thrombocytopenia, anaemia, pure red cell aplasia.
Metabolism and nutrition disorders	Less frequent	Lactic acidosis.
Nervous system disorders	Frequent	Peripheral neuropathy, paraesthesia, headache, insomnia.
Respiratory, thoracic and mediastinal disorders	Frequent	Cough, nasal symptoms

Gastro-intestinal disorders	Frequent	Pancreatitis, upper abdominal pain or cramps, nausea, vomiting and diarrhoea.
	Frequency unknown	Rises in serum amylase
Hepato-biliary disorders	Less frequent	Hepatitis.
	Frequency unknown	Transient rises in serum liver enzymes (AST, ALT)
Skin and subcutaneous tissue disorders	Frequent	Skin rash (hypersensitivity reaction).
	Less frequent	Angioedema.
	Frequency unknown	Alopecia.
Musculoskeletal, connective tissue and bone disorders	Frequent	Arthralgia and muscle disorders.
	Less frequent	Rhabdomyolysis.
General disorders and administration site conditions	Frequent	Malaise fatigue and fever.

Reporting of suspected adverse reactions

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 "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Class & Category: A 20.2.8 Antiviral agents.

Lamivudine is a selective inhibitor of HIV-1 and HIV-2 replication in in vitro, including zidovudine-resistant clinical isolates of the human immunodeficiency virus (HIV). Lamivudine is metabolised intracellularly to

the active 5'-triphosphate which inhibits the RNA- and DNA-dependent activities of HIV reverse transcriptase by termination of the viral DNA chain. 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 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 (Tmax) to maximum serum concentration (C max) is about an hour. At therapeutic dose levels of 4 mg/kg/day (as two 12-hourly doses), Cmax is in the order of 1-1,5 µg/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 is 5 to 7 hours. The mean systemic clearance of lamivudine is approximately 0,32 l/kg/hr, 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 Cmax 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. Co-administration 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 show that 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 are similar to adults. However, the 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Magnesium stearate

Microcrystalline cellulose

Sodium starch glycollate

Film-coat

Hypromellose

Titanium dioxide

Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C in the original package, protected from moisture.

6.5 Nature and contents of container

10 tablets are packed in blister strips of clear, transparent, PVC film with an aluminium foil backing.

Cartons contain 10, 30 or 60 tablets.

56 or 60 Tablets packed in securitainers or in white opaque HDPE bottles.

7. HOLDER OF CERTIFICATE OF REGISTRATION

RANBAXY PHARMACEUTICALS (PTY) LTD

a Sun Pharma company

14 Lautre Road, Stormill Ext 1

Roodepoort, 1724

South Africa

8. REGISTRATION NUMBER:

A40/20.2.8/0272

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 August 2007

10. DATE OF REVISION OF THE TEXT

25 January 2023

Botswana: S2 Reg. no.: BOT0801207

Namibia: NS2 Reg. no.: 05/20.2.8/0416

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