APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

SONKE-LAMIVUDINE+ZIDOVUDINE Film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Lamivudine 150 mg

Zidovudine 300 mg

Sugar free.

For the full list of excipients, see section 6.1.

WARNING:

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION WITH OTHER ANTIRETROVIRALS (SEE SECTION 4.4).

EARLY SYMPTOMS (SYMPTOMATIC HYPERLACTATAEMIA) INCLUDE BENIGN DIGESTIVE SYMPTOMS (NAUSEA, VOMITING AND ABDOMINAL PAIN), NON-SPECIFIC MALAISE, LOSS OF APPETITE, WEIGHT LOSS, RESPIRATORY SYMPTOMS (RAPID AND/OR DEEP BREATHING) OR NEUROLOGICAL SYMPTOMS (INCLUDING MOTOR WEAKNESS).

LACTIC ACIDOSIS HAS A HIGH MORTALITY AND MAY BE ASSOCIATED WITH PANCREATITIS, LIVER FAILURE OR RENAL FAILURE.

LACTIC ACIDOSIS GENERALLY OCCURRED AFTER A FEW OR SEVERAL MONTHS OF TREATMENT.

TREATMENT WITH SONKE-LAMIVUDINE+ZIDOVUDINE SHOULD BE DISCONTINUED IN THE SETTING OF SYMPTOMATIC HYPERLACTATAEMIA AND METABOLIC/LACTIC ACIDOSIS, PROGRESSIVE HEPATOMEGALY, OR RAPIDLY ELEVATING AMINOTRANSFERASE LEVELS.

CAUTION SHOULD BE EXERCISED WHEN ADMINISTERING SONKE-LAMIVUDINE+ZIDOVUDINE TO ANY PATIENT (PARTICULARLY OBESE WOMEN) WITH HEPATOMEGALY, HEPATITIS OR OTHER KNOWN RISK FACTORS FOR LIVER DISEASE AND HEPATIC STEATOSIS (INCLUDING CERTAIN MEDICINES AND ALCOHOL).

PATIENTS CO-INFECTED WITH HEPATITIS C AND TREATED WITH ALPHA-INTERFERON AND RIBAVIRIN MAY CONSTITUTE A SPECIAL RISK.

PATIENTS AT INCREASED RISK SHOULD BE FOLLOWED CLOSELY.

SONKE-LAMIVUDINE+ZIDOVUDINE IS NOT INDICATED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION AND THE SAFETY AND EFFICACY OF SONKE-LAMIVUDINE+ZIDOVUDINE HAS NOT BEEN ESTABLISHED IN PATIENTS CO-INFECTED WITH HBV AND HIV. SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO ARE CO-INFECTED WITH HBV AND HIV AND HAVE DISCONTINUED SONKE LAMIVUDINE+ZIDOVUDINE. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE SONKE- LAMIVUDINE+ZIDOVUDINE AND ARE CO-INFECTED WITH HIV AND HBV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE SECTION 4.4).

3. PHARMACEUTICAL FORM

Film-coated tablets

White to off-white, film-coated capsule shaped tablets debossed with “RX923” on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Sonke-Lamivudine+Zidovudine is indicated as part of anti-retroviral therapy for the treatment of HIV infected adults and children over 12 years of age, with progressive immunodeficiency (CD4+ Count ≤ 500 cells/mm3).

Post Exposure Prophylaxis in Adults following Occupational Exposure

The best prophylaxis against occupational exposure is adherence to universal precautions including, amongst others, careful disposal of sharp objects e.g. needles and scalpels and the use of protective barriers (e.g. gloves, eyeglasses etc). Sonke-Lamivudine+Zidovudine is indicated for initial prophylactic treatment (until results of serology tests are available) in HIV negative adults whenever there has been exposure to material known to be, or strongly suspected to be, infected with HIV. This includes

- percutaneous injury (from needles, instruments, bone fragments, etc);
- exposure of broken skin (abrasions, cuts, eczema etc);
- exposure of mucous membranes including the eye.

No randomised clinical studies on the use of Sonke-Lamivudine+Zidovudine following occupational exposure have been performed. It has been reported that a retrospective case-controlled study has concluded that the use of zidovudine for post exposure prophylaxis reduces the rate of infection. Reports have shown that the use of zidovudine and lamivudine in combination has demonstrated a greater reduction in viral load than either medicine used alone.

The addition of a protease inhibitor to the combination regimen is recommended in the following cases:

- when a large volume of inoculation has occurred;
- when the source material has a high viral titre; or
- when inoculation has occurred from a patient with HIV resistant to Sonke-Lamivudine+Zidovudine, zidovudine and/or lamivudine.

4.2 Posology and method of administration

Posology

Adults and children over the age of 12 years

The recommended dose: One tablet twice daily.

Sonke-Lamivudine+Zidovudine may be administered with or without food.

A medical practitioner experienced in the management of HIV infection should initiate therapy. During combination therapy with other anti-retroviral agents, the package insert of the particular agent should be consulted for information.

For situations where discontinuation of therapy with one of the active constituents of Sonke-Lamivudine+Zidovudine, or dose reduction, is necessary, separate preparations of lamivudine and zidovudine are available in tablets/capsules and oral solution.

Post Exposure Prophylaxis following Exposure:

The course of medication should be begun as soon as possible (preferably within 1 - 2 hours) after the exposure has occurred and continue until confirmation of HIV-status of source material. In cases where the source material is confirmed to be infected with HIV, it is recommended that the prophylactic course be continued for a period of 4 weeks.

The following dosing guidelines are based on the recommendations of the CDC (Centres for Disease Control) in the USA:

Duration	Sonke-Lamivudine+Zidovudine Dosage
Days 1-3	1 Sonke-Lamivudine+Zidovudine tablet taken twice daily. This equates to a daily dose of 600 mg zidovudine and 300 mg lamivudine.
Days 4-28	1 Sonke-Lamivudine+Zidovudine tablet taken twice daily. This equates to a daily dose of 600 mg zidovudine and 300 mg lamivudine.

If the use of a protease inhibitor is necessary (see section 4.1) the CDC guidelines should be consulted for dosing requirements. Treatment should be discontinued as soon as the source material is confirmed not to be infected with HIV.

Special populations

Renal impairment

Due to decreased clearance in patients with renal impairment, the concentrations of lamivudine and zidovudine are elevated. Therefore, as dosage adjustment of these may be required, it is advised that separate preparations of lamivudine and zidovudine be administered to patients with reduced renal function (creatinine clearance ≤ 50 ml/min). The package inserts of the separate preparations should be consulted for full details of these dosage adjustments.

Hepatic impairment

The influence of hepatic impairment on lamivudine levels has not been fully elucidated. Lamivudine clearance is largely renal. Based on preliminary safety data, no dosage adjustment is necessary. Lamivudine

should be used with caution in patients with hepatomegaly or other risk factors for hepatic disease. Limited data in patients with cirrhosis suggest that accumulation of zidovudine may occur in patients with hepatic impairment because of decreased glucuronidation. Therefore, as dosage adjustments for zidovudine may be necessary, it is recommended that separate preparations of lamivudine and zidovudine be administered to patients with severe hepatic impairment. The package inserts of the separate preparations should be consulted for full details of the dosage adjustments.

Dose adjustments in patients with haematological adverse reactions

Dosage adjustment of zidovudine may be necessary if the haemoglobin level falls below 9 g/dl or 5,59 mmol/l or the neutrophil count falls below 1,0 x 10^9/l (see section 4.3). This is more likely in patients with poor bone marrow reserve prior to treatment, particularly in patients with advanced HIV disease. As dosage adjustment may be necessary, separate preparations of lamivudine and zidovudine should be used. Medical practitioners should refer to the individual package inserts of these medicines**.**

Dosage in the elderly

Special care is advised in geriatric patients due to age-related changes such as the decrease in renal function and alteration of haematological parameters.

4.3 Contraindications

- Hypersensitivity to lamivudine and zidovudine or to any of the excipients listed in section 6.1.
- Patients with abnormally low neutrophil counts (less than 0,75 x 10^9/l) or abnormally low haemoglobin levels (less than 7,5 g/dl or 4,65 mmol/l).
- Children below the age of 12 years as appropriate dose reduction for the weight of the child cannot be made. Insufficient data available.
- The combination of zidovudine with either ribavirin or stavudine is antagonistic in vitro. The concomitant use of either ribavirin or stavudine with Sonke-Lamivudine+Zidovudine should be avoided.
- Concomitant use with zalcitabine.

4.4 Special warnings and special precautions for use

Opportunistic infections

Opportunistic infections and other complications of HIV infection may continue to develop in patients receiving Sonke-Lamivudine+Zidovudine**.** Patients should, therefore, remain under close clinical supervision by physicians experienced in the treatment of HIV infection. Regular monitoring of viral load and CD4 counts needs to be done.

Sonke-Lamivudine+Zidovudine should not be taken with any other medicines containing lamivudine or medicines containing emtricitabine.

The risk of HIV transmission to others

Sonke-Lamivudine+Zidovudine have not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Patients should be advised that appropriate precautions should continue to be employed.

Haematological: Anaemia, neutropenia and leucopenia (usually secondary to neutropenia) can be expected to occur in patients with advanced symptomatic HIV disease receiving zidovudine, therefore, haematological parameters should be carefully monitored (see section 4.3 and 4.8) in patients receiving Sonke-Lamivudine+Zidovudine. These haematological effects are not usually observed before four to six week's therapy. It is generally recommended that blood test be performed for patients with advanced symptomatic HIV disease on at least a bi-weekly basis for the first three months of therapy and thereafter at least monthly. In patients with early HIV disease, haematological adverse reactions are infrequent. Blood tests may be performed less often, for example, every one to three months depending on the overall condition of the patient. If haemoglobin levels are decreased by more than 25 % from baseline and falls in the neutrophil count of more than 50 % from baseline, more monitoring may be required.

If severe anaemia or myelosuppression occurs during treatment with Sonke-Lamivudine+ Zidovudine or in patients with pre-existing bone marrow compromise e.g. haemoglobin <9 g/dl (5,59 mmol/l) or neutrophil count less than 1,0 x 10^9/l (see section 4.2), dosage adjustment of zidovudine may be required. As dosage adjustment of Sonke-Lamivudine+ Zidovudine is not possible, separate preparations of zidovudine and

lamivudine should be used. Medical practitioners should refer to the individual package inserts of these agents for dosage specifications.

Sero-conversion to HIV-positive status may still occur despite the prompt use of Sonke-Lamivudine+ Zidovudine. The recommended prophylactic dose must be strictly adhered to (see section 4.2).

Pancreatitis

Pancreatitis has been observed in some patients receiving Sonke-Lamivudine+ Zidovudine.

Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of Sonke-Lamivudine+Zidovudine until diagnosis of pancreatitis is excluded.

Both lamivudine and zidovudine were shown to cross the placenta in reproductive animal studies and have demonstrated evidence of causing an increase in early embryonic deaths in the rabbit (lamivudine) or rat and rabbit (zidovudine). Lamivudine was not teratogenic in animal studies. Zidovudine given to rats during organogenesis at maternally toxic doses resulted in an increased incidence of malformations. Foetal abnormalities did not occur at lower doses.

A carcinogenic risk to humans cannot be excluded due to the animal carcinogenicity and mutagenicity data (see Special Precautions). Although the results of rodent carcinogenicity studies cannot always be extrapolated to humans, late-occurring vaginal tumours (appearing after 19 months of continuous daily oral dosing) have been seen in rodents following lifetime dosing with zidovudine. The relevance of these findings to both infected and uninfected infants exposed to zidovudine is unknown. However, pregnant women considering using Sonke-Lamivudine+Zidovudine during pregnancy should be informed of these findings.

Lactic acidosis / hyperlactataemia

Use of Sonke-Lamivudine+Zidovudine 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/) and the serum bicarbonate and respond as follows:

- Lactate 2-5 mmol/ with minimum symptoms: switch to medicines that are less likely to cause lactic acidosis.
- Lactate 5-10 mmol/ 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/: STOP all therapy (80 % mortality).

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

Caution should be exercised when administering Sonke-Lamivudine+Zidovudine to patients with known risk factors for liver disease.

Treatment with Sonke-Lamivudine+Zidovudine 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 postnatally 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+ Zidovudine is increased due to decreased clearance. The dose of Sonke-Lamivudine+ Zidovudine should therefore be adjusted (see section 4.2).

Liver disease

Use of Sonke-Lamivudine+ Zidovudine can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of Sonke-Lamivudine+ Zidovudine 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+ Zidovudine 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+ Zidovudine 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, including Sonke-Lamivudine+Zidovudine has been associated with hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia.

Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, elevated serum lipid and blood glucose levels have been observed either separately or together in some patients receiving combination antiretroviral therapy which includes Sonke-Lamivudine+Zidovudine (see section 4.8).

In addition, the lipodystrophy syndrome has a multi-factorial aetiology; with for example HIV disease status, older age and duration of antiretroviral treatment all playing important, possibly synergistic roles. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate**.**

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, atypical mycobacterial infections, cytomegalovirus, retinitis, Pneumocystis jirovecii (carinii) pneumonia 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.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and 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.

Use with Interferon- and Ribavirin-Based Regimens

In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine and zidovudine. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when ribavirin was co-administered with lamivudine or zidovudine in HIV-1/HCV co-infected patients, hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin. Patients receiving interferon alfa with or without ribavirin and Sonke-Lamivudine+Zidovudine should be closely monitored for treatment-associated toxicities, especially hepatic decompensation, neutropenia, and anaemia. Discontinuation of Sonke-Lamivudine+Zidovudine should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Child-Pugh greater than 6).

Exacerbation of anaemia has been reported in HIV-1/HCV co-infected patients receiving ribavirin and zidovudine. Co-administration of ribavirin and zidovudine is not advised (see section 4.5).

4.5 Interaction with other medicines and other forms of interaction

Any interactions that have been identified with lamivudine and zidovudine individually may occur with Sonke-Lamivudine+Zidovudine.

The interactions listed below should not be considered exhaustive but are representative of the classes of medicines where caution should be exercised.

Interactions relevant to lamivudine

The likelihood of metabolic interactions with lamivudine is low due to limited metabolism and plasma protein binding, and almost complete renal clearance. Possible interactions with other medicines administered

concurrently with Sonke-Lamivudine+ Zidovudine should be investigated, 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 other medicines (e.g. ranitidine, cimetidine) are eliminated partly by this mechanism and were shown not to interact with lamivudine.

Please refer to the Pharmacokinetics section for full details on the interaction of lamivudine with other anti-retroviral agents.

Trimethoprim:

Administration of prophylactic doses of co-trimoxazole results in a 40 % increase in lamivudine exposure, because of trimethoprim component; the sulphamethoxazole component did not interact. However, unless the patient has renal impairment, no dosage adjustment of lamivudine (see section 4.2).

When concomitant administration with co-trimoxazole is warranted, patients should be monitored clinically. Co-administration of Sonke-Lamivudine+ Zidovudine with high doses of co-trimoxazole for the treatment of Pneumocystis carinii pneumonia (PCP) and toxoplasmosis should be avoided. Lamivudine has no effect on the pharmacokinetics of co-trimoxazole at doses studied.

Zalcitabine:

Lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the two medicines are used concurrently. Sonke-Lamivudine+ Zidovudine is therefore not recommended to be used in combination with zalcitabine (see section 4.3).

Miscellaneous:

Until further information is available, co-administration of lamivudine 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.

Cladribine:

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.

Medicines containing sorbitol or other osmotic acting poly-alcohols or monosaccharide alcohols (e.g. xylitol, mannitol, lactitol, maltitol):

Avoid chronic co-administration of Sonke-Lamivudine+Zidovudine with medicines containing sorbitol or other osmotic acting poly-alcohols or monosaccharide alcohols (e.g. xylitol, mannitol, lactitol, maltitol).

Interactions relevant to zidovudine:

Zidovudine has limited protein binding but is eliminated primarily by hepatic conjugation to an inactive glucuronidated metabolite.

Lamivudine:

Zidovudine has no effect on the pharmacokinetics of lamivudine. A slight increase in C_{max} (28 %) was observed for zidovudine when administered with lamivudine, however, overall exposure (AUC) was not significantly changed.

Rifampicin:

The co-administration of zidovudine and rifampicin decreases the AUC of zidovudine by 48 % ± 34 %. However, the clinical significance of this is unknown.

Valproic acid:

The co-administration of zidovudine and valproic acid increases the AUC of zidovudine by 80 %. Monitor for signs of zidovudine toxicity.

Phenytoin:

In some patients receiving zidovudine, the phenytoin blood levels have been reported to be low, while in one patient a high level was noted. These observations imply that phenytoin concentrations should be carefully monitored in patients receiving Sonke-Lamivudine+Zidovudine in combination with phenytoin.

Probenecid:

Limited data suggest that probenecid increases the mean half-life and area under the plasma concentration curve of zidovudine by decreasing glucuronidation. Renal excretion of the glucuronide (and possibly zidovudine itself) is reduced in the presence of probenecid.

Ribavirin:

Zidovudine in combination with ribavirin is antagonistic in vitro. The concomitant use of ribavirin with Sonke-Lamivudine+Zidovudine should be avoided.

Stavudine:

Zidovudine may inhibit the intracellular phosphorylation of stavudine when the two medicinal products are used concurrently. Stavudine is therefore not recommended to be used in combination with Sonke-Lamivudine+Zidovudine (see section 4.3).

Paracetamol:

Paracetamol use during treatment with zidovudine in a placebo-controlled trial was associated with an increased incidence of neutropenia especially following chronic therapy. However, the available pharmacokinetic data indicate that paracetamol at the doses studied does not increase plasma levels of zidovudine nor of its glucuronide metabolite.

Atovaquone:

The co-administration of zidovudine (750 mg twice daily with food / 200 mg three times per day) and atovaquone increases the AUC of zidovudine by 33 %.

Miscellaneous:

The following medicines, including but not limited to, may alter the metabolism of zidovudine by competitively inhibiting glucuronidation or directly inhibiting hepatic microsomal metabolism: Aspirin, codeine, morphine, indomethacin, ketoprofen, naproxen, oxazepam, lorazepam, cimetidine, clofibrate, dapsone and isoprinosine. The possibilities of medicine interaction before using such medicines, particularly for chronic therapy, in combination with Sonke-Lamivudine+Zidovudine, should be considered.

The risk of adverse reactions to zidovudine may also increase, with concomitant treatment, especially acute therapy, with potentially nephrotoxic or myelosuppressive medicines (e.g. systemic pentamidine, dapsone, pyrimethamine, co-trimoxazole, amphotericin, flucytosine, ganciclovir, interferon, vincristine, vinblastine and doxorubicin). Extra care should be taken in monitoring renal function and haematological parameters and, if required, the dosage of one or more agents should be reduced if concomitant therapy with Sonke-Lamivudine+Zidovudine and any of these medicines is necessary.

The concomitant use of prophylactic antimicrobial therapy may have to be considered, since some patients receiving Sonke-Lamivudine+Zidovudine may continue to experience opportunistic infections. This named prophylaxis has included pyrimethamine, co-trimoxazole, aerolised pentamidine and aciclovir. The limited data from clinical trials do not indicate a significantly increased risk of adverse reactions to zidovudine with these medicines.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of lamivudine in human pregnancy has not been established. Therefore, the use of Sonke-Lamivudine+Zidovudine during pregnancy is not recommended.

The use of zidovudine in pregnant women, with subsequent treatment of the newborn infants, has been shown to reduce the rate of maternal-foetal transmission of HIV. However, no such data are available for lamivudine.

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 peri-partum to nucleoside reverse transcriptase inhibitors (NRTIs), such as Sonke-Lamivudine+Zidovudine. The clinical relevance of transient elevations in serum lactate is unknown. There have also been reports of developmental delay and seizures. However, a causal relationship between these events and NRTI exposure in utero or peri-partum has not been established.

Late onset of neurological disorders relating to mitochondrial dysfunction have been observed in children who have been exposed in utero and/or postnatally to nucleoside analogues as contained in Sonke-Lamivudine+Zidovudine.

Breastfeeding

Both lamivudine and zidovudine are excreted into human milk at similar concentrations to those found in serum.

Since lamivudine, zidovudine and HIV pass into breast milk it is recommended that mothers taking Sonke-Lamivudine+Zidovudine do not breastfeed their infants.

Fertility

With regard to fertility studies in male and female rats, neither zidovudine nor lamivudine have shown evidence of impairment. No data is available on their effect of this combination on human female fertility. Sperm count, morphology or motility has not been affected in men as a result of zidovudine.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

Sonke-Lamivudine+Zidovudine can cause dizziness, fatigue, loss of mental acuity and drowsiness.

Patients should be advised not to drive a vehicle or use machines until they know how they are affected.

4.8 Undesirable effects

During therapy for HIV disease with lamivudine and zidovudine separately or in combination, adverse events have been reported. With many of these events, it is unclear whether they are related to lamivudine, zidovudine or to the wide range of medicines used in the management of HIV disease or are as a result of the underlying disease process.

As Sonke-Lamivudine+Zidovudine contains lamivudine and zidovudine, the type and severity of adverse reactions associated with each of the compounds may be expected. There is no evidence of synergistic toxicity following concomitant administration of the two compounds.

Side effects related to Lamivudine:

MedDRA System organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Less frequent	Neutropenia and anaemia, (both occasionally severe), thrombocytopenia, pure red cell aplasia
Immune system disorders	Frequent	Angioedema, immune reconstitution inflammatory syndrome
Metabolism and nutrition disorders	Frequent	Hyperlactatemia
	Less frequent	Lactic acidosis, lipodystrophy (redistribution/ accumulation of body fat (see section 4.4).
Nervous system disorders	Frequent	iInsomnia and headache.
	Less frequent	Paraesthesia. Peripheral neuropathy has been reported although a causal relationship to treatment is uncertain. Late-onset neurological disorders.

Respiratory, thoracic and mediastinal disorders	Frequent	Cough, nasal symptoms.
Gastro-intestinal disorders	Frequent	Abdominal pain or cramps, nausea, vomiting and diarrhoea.
	Less frequent	Pancreatitis
Hepato-biliary disorders	Less frequent	Transient rises in liver enzymes (AST, ALT), hepatitis
Skin and subcutaneous tissue disorders	Frequent	Rash, alopecia
Musculoskeletal, connective tissue and bone disorders	Frequent	Arthralgia, muscle disorders including musculoskeletal pain
	Less frequent	Rhabdomyolysis
General disorders and administrative site conditions	Frequent	Malaise and fatigue

Side effects related to Zidovudine:

Blood and lymphatic system disorders	Frequent	Anaemia (which may require transfusions), leucopenia and neutropenia.
These occur more frequently at higher dosages (1 200 – 1 500 mg/day) and in patients with advanced HIV disease (especially when there is poor bone marrow reserve prior to treatment), and particularly in patients with CD4+ cell counts < 100/mm^3. Dosage reduction or cessation of therapy may become necessary (see section 4.2). The incidence of neutropenia was also increased in those patients whose neutrophil counts, haemoglobin levels and serum vitamin B_{12} levels were low at the start of zidovudine therapy, and in those patients taking paracetamol concurrently (see section 4.5).		
Blood and lymphatic system disorders	Less frequent	Aplastic anaemia, pure red cell aplasia, pancytopenia (with marrow hypoplasia), and thrombocytopenia.

Immune system disorders	Frequent	Immune reconstitution inflammatory syndrome
Metabolism and nutrition disorders	Frequent	Hyperlactatemia
	Less frequent	Lactic acidosis anorexia, lipodystrophy (redistribution/ accumulation of body fat (see section 4.4).
Psychiatric disorders	Less frequent	Anxiety and depression.
Nervous system disorders	Frequent	Headache, dizziness
	Less frequent	Insomnia, paraesthesia, somnolence, loss of mental acuity and convulsions. Late-onset neurological disorders
Cardiac disorders	Less frequent	Cardiomyopathy
Respiratory, thoracic and mediastinal disorders	Less frequent	Dyspnoea, cough
Gastro-intestinal disorders	Frequent	Nausea, vomiting abdominal pain and diarrhoea
	Less frequent	Flatulence, oral mucosa pigmentation, taste disturbance, dyspepsia and pancreatitis
Hepatobiliary disorders	Frequent	Raised blood levels of liver enzymes and bilirubin
	Less frequent	Liver disorders such as severe hepatomegaly with steatosis.
Skin and subcutaneous tissue disorders	Less frequent	Nail and skin pigmentation, rash, pruritus, urticaria and sweating
Musculoskeletal, connective tissue and bone disorders	Frequent	Myalgia,
	Less frequent	Myopathy
Renal and urinary disorders	Less frequent	Urinary frequency.

Reproductive system and breast disorders	Less frequent	Gynaecomastia
General disorders and administrative site conditions	Frequent	Malaise.
	Less frequent	Fever, asthenia, chest pain, generalised pain, chills, influenza-like syndrome

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

See section 4.8.

There is no experience of overdosage with Sonke-Lamivudine+Zidovudine. Limited data is available on the consequences of ingestion of acute overdoses of lamivudine and zidovudine in humans. All patients recovered, no fatalities occurred. Following such overdosage, no specific signs or symptoms have been identified.

Treatment of overdose

In the event of overdosage, the patient should be monitored for evidence of toxicity (see section 4.8) and standard supportive treatment be applied as necessary. Continuous haemodialysis could be used in the treatment of overdosage since lamivudine is dialysable, although this has not been studied. Haemodialysis and peritoneal dialysis appear to have a limited effect on the elimination of zidovudine but enhance the elimination of the glucuronide metabolite. Medical practitioners should refer to the individual package inserts of lamivudine and zidovudine for more details. Patients, in whom intentional overdose is confirmed or suspected, should be referred for psychiatric consultation.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Class & Category: A 20.2.8 Antiviral agents.

Lamivudine and zidovudine are selective inhibitors of human immunodeficiency virus HIV-1 and HIV-2. Lamivudine has been shown to be synergistic with zidovudine, inhibiting the replication of HIV in cell culture. Both agents are metabolised, sequentially by intracellular kinases to 5'-triphosphate (TP). Lamivudine-TP and zidovudine-TP are substrates for and competitive inhibitors of the HIV reverse transcriptase. However, their main antiviral activity is through incorporation of the mono-phosphate form into the viral DNA chain, resulting in chain termination. Lamivudine and zidovudine triphosphates show significantly less affinity for host cell DNA polymerases. Individually, lamivudine and zidovudine therapy has resulted in HIV clinical isolates which show reduced sensitivity in vitro to the nucleoside analogue to which they have been exposed. However, in vitro studies also indicate that zidovudine- resistant virus isolates can become zidovudine sensitive when they simultaneously acquire resistance to lamivudine. Furthermore, in vivo there is clinical evidence that lamivudine plus zidovudine delays the emergence of zidovudine resistance in anti-viral naïve patients.

5.2 Pharmacokinetic properties

Absorption

Lamivudine and zidovudine are well absorbed from the gastro-intestinal tract. The bioavailability of oral lamivudine in adults is normally between 80-85 % and for zidovudine 60-70 %. Absorption of lamivudine is delayed, but not reduced, by ingestion with food. Binding to plasma protein is reported to be less than 36 %.

Bioavailability in neonates up to 14 days old is approximately 89 %, and in neonates over 14 days, it decreases to approximately 61 %. Administration with a high-fat meal may decrease the rate and extent of absorption. Lamivudine and zidovudine penetrate the central nervous system and reach the cerebrospinal fluid (CSF).

Metabolism

Metabolism of lamivudine is a minor route of elimination. Lamivudine is mainly cleared by renal excretion of unchanged substance. Interactions with lamivudine are low due to the small extent of hepatic metabolism (5-10 %) and low plasma binding.

Elimination

The 5'-glucoronide of zidovudine is the major metabolite in both plasma and urine, accounting for approximately 50-80 % of the administered dose eliminated by renal excretion. 3'-amino3'-deoxythymidine (AMT) has been identified as a metabolite of zidovudine following intravenous dosing.

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Pharmacokinetics of the lamivudine and zidovudine combination when used in combination with other anti-retroviral agents:

Zidovudine

Pharmacokinetic interaction studies indicate that there were no clinically significant alterations to zidovudine pharmacokinetics when given concomitantly with the following antiretroviral agents:

Nucleoside reverse transcriptase inhibitors (NRTI's) – zalcitabine, didanosine and abacavir;

Non-nucleoside reverse transcriptase inhibitors (NNRTI's) – nevirapine and efavirenz; and

Protease inhibitors – indinavir sulphate, saquinavir mesylate, ritonavir, amprenavir and nelfinavir.

There is a known interaction between zidovudine and stavudine (d4T) (see Interactions). The concomitant use of these two agents should be avoided.

Lamivudine

Pharmacokinetic interaction studies indicate that there were no clinically significant alterations to lamivudine pharmacokinetics when given concomitantly with the following antiretroviral agents:

Non-nucleoside reverse transcriptase inhibitors (NNRTI's) – efavirenz; and

Protease inhibitors – indinavir sulphate, ritonavir and nelfinavir.

Pharmacokinetics of the lamivudine and zidovudine combination when used in combination with other tuberculostatic agents:

Zidovudine

Co-administration of zidovudine and rifampicin decreases the AUC of zidovudine by approximately 48 %, however the clinical significance of this is unknown.

Lamivudine

Metabolism of lamivudine is a minor route of elimination. Lamivudine is mainly cleared by renal excretion of unchanged substance. The likelihood of metabolic drug interactions e.g. rifampicin with lamivudine is low due to the small extent of hepatic metabolism (5-10 %) and low plasma binding.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Colloidal silicon dioxide

Magnesium stearate

Microcrystalline cellulose

Sodium starch glycollate

Film-coat:

Opadry White 03H58900 consisting of:

Hypromellose

Propylene glycol

Titanium dioxide

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, 60 or 100 tablets.

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:

A40/20.2.8/0254

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

7 April 2006

10. DATE OF REVISION OF THE TEXT

21 November 2022

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This product is for use only in South Africa, Namibia, Botswana, Swaziland and Lesotho, is not for resale and any other use is not authorised.

Namibia: NS2 Reg. no.: 05/20.2.8/0523

Botswana: S2 Reg. no.: BOT 0701041