**PROPOSED PROFESSIONAL INFORMATION**

**SCHEDULING STATUS:** S4

## 1. NAME OF THE MEDICINE

**ZOVILAM film-coated tablets**

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

Lamivudine 150 mg

Zidovudine 300 mg

Sugar free.

**WARNINGS:**

**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).**

**ZOVILAM IS NOT INDICATED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION. SAFETY AND EFFICACY OF ZOVILAM 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 ZOVILAM. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE ZOVILAM 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

**Tablets**

A white to off-white, film-coated, capsule shaped, biconvex tablet debossed with M on the left of the

score and 2 on the right of the score on one side of the tablet and L on the left of the score and Z on the right of the score on the other side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

ZOVILAM is indicated as part of antiretroviral combination therapy for the treatment of HIV-infection in adults and children over 12 years of age, with progressive immunodeficiency (CD4+ count ≤ 500 cells/$mm^3$).

**Post exposure prophylaxis in adults following occupational exposure**

The best prophylaxis against occupational exposure is adherence to universal precautions including, amongst other, careful disposal of sharp objects e.g. needles and scalpels and the use of protective barriers (e.g. gloves, eyeglasses etc). ZOVILAM 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.

Randomised studies on the use of lamivudine 150 mg/zidovudine 300 mg following occupational exposure have not been performed. However, a retrospective case-controlled study has concluded that the use of zidovudine for post exposure prophylaxis reduces the rate of infection. The use of zidovudine and lamivudine in combination has demonstrated a greater reduction in viral load than when either medicine is 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 ZOVILAM, zidovudine and/or lamivudine.

### 4.2 Posology and method of administration

Patients should be stabilised on individual medicines before being switched over to ZOVILAM.

Therapy should be initiated by a medical practitioner experienced in the management of HIV infection.

**Posology**

**Adults and children over the age of 12 years**

The recommended dose of ZOVILAM is one tablet twice daily.

When ZOVILAM is used in combination with another antiretroviral medicine, the professional information of that medicine should be consulted for information.

Where discontinuation of therapy with one of the active ingredients of ZOVILAM or a dose reduction is necessary, separate preparations of lamivudine and zidovudine are available.

**Post exposure prophylaxis following exposure**

The course of treatment should be begun as soon as possible (preferably within 1 to 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.

***Recommended dose***

*Duration: ZOVILAM dosage*

Days 1 – 3: One (1) ZOVILAM tablet taken twice daily.

This equates to a daily dose of 600 mg zidovudine and 300 mg lamivudine.

Days 4 – 28: One (1) ZOVILAM 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 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***

Lamivudine and zidovudine concentrations are increased in patients with renal impairment due to decreased clearance. Therefore, as dosage adjustment of these may be necessary, it is recommended that separate preparations of lamivudine and zidovudine be administered to patients with reduced renal function (creatinine clearance ≤ 50 mL/min). Medical practitioners should refer to the individual professional information for these medicines.

***Hepatic impairment***

Lamivudine clearance is largely renal. Based on preliminary safety data no dosage adjustment is necessary. However, 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. Medical practitioners should refer to the individual professional information for these medicines.

***Dosage 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. It is more likely in patients with poor bone marrow reserve prior to treatment, particular in patients with advanced HIV disease. As dosage adjustment of ZOVILAM is not possible, separate preparations of zidovudine and lamivudine should be used.

Medical practitioners should refer to the individual professional information for these medicines.

**Elderly population**

No specific data are available. However, special care is advised in this age group due to age associated changes such as the decrease in renal function and alteration of haematological parameters.

**Paediatric population**

ZOVILAM is not indicated for children below the age of 12 years as appropriate dose reduction for the weight of the child cannot be made (see section 4.3).

**Method of administration**

ZOVILAM can be taken with or without food.

**4.3 Contraindications**

- Hypersensitivity to lamivudine or zidovudine or any of the excipients of ZOVILAM (listed in section 6.1).
- Zidovudine is contraindicated in patients with abnormally low neutrophil counts (< 0,75 x $10^9$/L) or abnormally low haemoglobin levels (< 7,5 g/dL or 4,65 mmol/L). ZOVILAM is therefore contraindicated in these patients.
- ZOVILAM is not indicated for children below the age of 12 years as appropriate dose reduction for the weight of the child cannot be made.
- There is a known interaction between zidovudine and stavudine. The concomitant use of ZOVILAM

and stavudine should be avoided (see section 4.5).

- There is a known interaction between lamivudine and zalcitabine. The concomitant use of ZOVILAM and zalcitabine should be avoided (see section 4.5).
- Concomitant use of ZOVILAM and ribavirin should be avoided (see section 4.5).
- ZOVILAM should not be taken with any other medicines containing lamivudine or medicines containing emtricitabine (see sections 4.4 and 4.5).

**4.4 Special warnings and precautions for use**

It is recommended that separate preparations of lamivudine and zidovudine should be administered in cases where dosage adjustment is necessary. In these cases, the medical practitioner should refer to the individual professional information for these medicines.

**Haematological adverse reactions**

Anaemia, neutropenia and leukopenia (usually secondary to neutropenia) can be expected to occur in patients receiving zidovudine and therefore, ZOVILAM. These occurred more frequently at higher zidovudine dosages (1 200 – 1 500 mg/day) and in patients with poor bone marrow reserve prior to treatment, particularly with advanced HIV disease. Haematological parameters should therefore be carefully monitored (see section 4.3) in patients receiving ZOVILAM. These haematological effects are not usually observed before four to six weeks therapy. For patients with advanced symptomatic HIV disease, it is generally recommended that blood tests are performed at least every two weeks for the first three months of therapy and at least monthly thereafter.

In patients with early HIV disease, haematological adverse reactions are infrequent. Depending on the overall condition of the patient, blood tests may be performed less often, for example every one to three months. Decreases in the haemoglobin level of more than 25 % from baseline and falls in the neutrophil count of more than 50 % from baseline may require more frequent monitoring.

Additionally, dosage adjustment of zidovudine may be required if severe anaemia or myelosuppression occurs during treatment with ZOVILAM, or in patients with pre-existing bone marrow compromise e.g. haemoglobin < 9 g/dL (5,59 mmol/L) or neutrophil count < 1,0 x $10^9$/L (see section 4.2). As dosage adjustment of ZOVILAM is not possible, separate preparations of zidovudine and lamivudine should be used. Medical practitioners should refer to the individual professional information for these medicines.

Sero-conversion to HIV-positive status may still occur despite the prompt use of ZOVILAM. The

recommended prophylactic dose must be strictly adhered to (see section 4.2).

**Pancreatitis**

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

**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 (see below). A majority of these cases have been in women. Clinical features which may be indicative of the development of lactic acidosis include generalised weakness, anorexia and sudden unexplained weight loss, gastrointestinal symptoms and respiratory symptoms (dyspnoea and tachypnoea).

**Lactic acidosis/ hyperlactataemia**

Use of ZOVILAM 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, 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, hepatic failure or renal failure.

Lactic acidosis generally occurred after a few or several months of treatment.

Treatment with ZOVILAM should be discontinued if there is symptomatic hyperlactataemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels.

Caution should be exercised when administering ZOVILAM 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 (HCV) and treated with alpha interferon and ribavirin may constitute a special risk.

Patients at increased risk should be followed closely.

Suspicious biochemical features include 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 the serum bicarbonate and respond as follows:

- Lactate 2 – 5 mmol/L: with minimum symptoms: switch to medicines that are less likely to cause lactic acidosis.
- 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 ZOVILAM to patients with known risk factors of liver disease.

Treatment with ZOVILAM should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

**Liver disease**

Use of ZOVILAM can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis).

The safety and efficacy of 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.

In patients co-infected with hepatitis C virus (HCV), the concomitant use of ribavirin with zidovudine is not recommended due to an increased risk of anaemia (see sections 4.3 and 4.5).

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

**Patients with moderate to severe renal impairment**

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

Patients with a creatinine clearance between 30 and 49 mL/min receiving ZOVILAM may experience a 1,6- to 3,3- fold higher lamivudine exposure (AUC) than patients with a creatinine clearance ≥ 50 mL/min.

Patients with a sustained creatinine clearance between 30 and 49 mL/min who receive ZOVILAM should be monitored for lamivudine-related adverse events, notably haematologic toxicities. If new or worsening neutropenia or anaemia develop, a dose adjustment of lamivudine, per lamivudine prescribing information, is indicated, which cannot be achieved with ZOVILAM. ZOVILAM should be discontinued, and the individual components should be used to construct the treatment regimen.

**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, other manifestations of mitochondrial dysfunction include haematological disorders (anaemia, neutropenia), metabolic disorders (hyperlactataemia, hyperlipasaemia) and peripheral neuropathy. These events have often been transitory. 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.

**Lipodystrophy and metabolic abnormalities**

Combination antiretroviral therapy has been associated with the redistribution/accumulation of body fat, including central obesity, dorsocervical fat, enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement and elevated serum lipid and glucose levels in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors (PIs) and lipoatrophy and nucleoside reverse transcriptase inhibitors (NRTIs) has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with medicine related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances.

Clinical examination should include evaluation for physical signs of fat redistribution. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment. Consideration should be given to the measurement of fasting 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 (generalised and/or focal mycobacterium infections), cytomegalovirus retinitis, cryptococcal meningitis and *Pneumocystis jirovecii* pneumonia (often referred to as PCP).

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 and autoimmune hepatitis) 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.

**Patients co-infected with hepatitis C virus**

ZOVILAM is not recommended due to an increased risk of anaemia.

**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.

ZOVILAM should not be taken with any other medicines containing lamivudine or medicines containing emtricitabine.

The combination of lamivudine with cladribine is not recommended (see section 4.5).

**Opportunistic infections**

Patients receiving ZOVILAM should be advised that they may continue to develop opportunistic infections and other complications of HIV infection, and therefore they should remain under close clinical 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 ZOVILAM, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be taken.

**Excipient information**

*Sodium*

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

**4.5 Interaction with other medicines and other forms of interaction**

**Lamivudine and zidovudine**

As ZOVILAM contains lamivudine and zidovudine, any interactions that have been identified with these medicines individually may occur with ZOVILAM.

The likelihood of metabolic interactions with lamivudine is low due to limited metabolism and plasma

protein binding, and almost complete renal clearance.

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

*Effect of lamivudine on the pharmacokinetics of other medicines*

*In vitro,* lamivudine demonstrates no or weak inhibition of the medicine transporters organic anion transporter 1B1 (OATP1B1), OATP1B3, breast cancer resistance protein (BCRP) or P-glycoprotein (Pgp), multidrug and toxin extrusion protein 1 (MATE1), MATE2-K or organic cation transporter 3 (OCT3). Lamivudine is therefore not expected to affect the plasma concentrations of medicines that are substrates of these medicine transporters.

Lamivudine is an inhibitor of OCT1 and OCT2 *in vitro* with IC50 values of 17 and 33 µM, respectively, however lamivudine has low potential to affect the plasma concentrations of OCT1 and OCT2 substrates at therapeutic medicine exposures (up to 300 mg).

*Effect of other medicines on the pharmacokinetics of lamivudine*

Lamivudine is a substrate of MATE1, MATE2-K and OCT2 *in vitro.* Trimethoprim (an inhibitor of these medicine transporters) has been shown to increase lamivudine plasma concentrations; however this interaction is not considered clinically significant as no dose adjustment of lamivudine is needed.

Lamivudine is a substrate of the hepatic uptake transporter OCT1. As hepatic elimination plays a minor role in the clearance of lamivudine, medicine interactions due to inhibition of OCT1 are unlikely to be of clinical significance.

Lamivudine is a substrate of Pgp and BCRP, however due to its high bioavailability it is unlikely that these transporters play a significant role in the absorption of lamivudine.

Therefore, co-administration of medicines that are inhibitors of these efflux transporters is unlikely to affect the disposition and elimination of lamivudine.

**Interactions relevant to lamivudine**

The possibility of other medicines administered concurrently with ZOVILAM should 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 other medicines (e.g. ranitidine, cimetidine) are eliminated only in part by this mechanism and were shown not to interact with lamivudine; see section 5.2 for full details on the interaction of lamivudine with other antiretroviral

medicines.

*Sorbitol*

Co-administration 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 % (9 – 20 %), 32 % (28 – 37 %), and 36 % (32 – 41 %) in lamivudine exposure (AUC∞) and 28 % (20 – 34 %), 52 % (47 – 57 %), and 55 % (50 – 59 %) in the $C_{max}$ of lamivudine in adults. When possible, avoid chronic co-administration of sorbitol-containing medicines with lamivudine. Consider more frequent monitoring of HIV-1 viral load when chronic co-administration cannot be avoided.

*Trimethoprim*

Administration of trimethoprim, as trimethoprim/sulfamethoxazole 160 mg/800 mg, causes a 40 % increase in lamivudine plasma levels, due to the trimethoprim component; the sulfamethoxazole component does not interact. However, unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary (see section 4.2). Lamivudine has no effect on the pharmacokinetics of trimethoprim/sulfamethoxazole. Administration of lamivudine in patients with renal impairment should be assessed carefully.

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

*Zalcitabine*

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

*Miscellaneous*

Co-administration of lamivudine with intravenous ganciclovir or foscarnet is not recommended until further information is available.

In *in vitro* studies, ciprofloxacin and pentamidine reduced the anti-HIV activity of lamivudine. The clinical significance of this is not known.

Lamivudine metabolism does not involve CYP3A, making interactions with medicines metabolised by this system (e.g. ~~PIs~~ protease inhibitors) unlikely.

Lamivudine may inhibit the intracellular phosphorylation of emtricitabine when the two medicines are used concurrently. Additionally, the mechanism of viral resistance for both lamivudine and emtricitabine is mediated via mutation of the same viral reverse transcriptase gene (M184V) and therefore the therapeutic efficacy of these medicines in combination therapy may be limited. Lamivudine is not recommended for use in combination with emtricitabine or emtricitabine-containing fixed-dose combinations.

*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 (see section 4.4).

**Interactions relevant to zidovudine**

*Lamivudine*

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

*Atovaquone*

Zidovudine does not appear to affect the pharmacokinetics of atovaquone. However, pharmacokinetic data have shown that atovaquone appears to decrease the rate of metabolism of zidovudine to its glucuronide metabolite (steady state AUC of zidovudine was increased by 33 % and peak plasma concentration of the glucuronide was decreased by 19 %). At zidovudine dosages of 500 or 600 mg/day it would seem unlikely that a three-week, concomitant course of atovaquone for the treatment of acute PCP would result in an increased incidence of adverse reactions attributable to higher plasma concentrations of zidovudine. Extra care should be taken in monitoring patients receiving prolonged atovaquone therapy.

*Clarithromycin*

Clarithromycin tablets reduce the absorption of zidovudine. This can be avoided by separating the administration of zidovudine and clarithromycin by at least two hours.

*Rifampicin*

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

*Phenytoin*

Phenytoin blood levels have been reported to be low in some patients receiving zidovudine, while in one patient a high level was noted. These observations suggest that phenytoin concentrations should be carefully monitored in patients receiving ZOVILAM and phenytoin since many patients with advanced HIV infections have CNS conditions which may predispose to seizure activity.

*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*. Exacerbation of anaemia due to ribavirin has been reported when zidovudine is part of the regimen used to treat HIV although the exact mechanism remains to be elucidated. The concomitant use of ribavirin with ZOVILAM is not recommended due to an increased risk of anaemia (see section 4.3).

*Stavudine*

Zidovudine may inhibit the intracellular phosphorylation of stavudine when the two medicines are used concurrently. Stavudine is therefore not recommended to be used in combination with ZOVILAM (see section 4.3).

*Paracetamol*

Paracetamol use during treatment with zidovudine in a placebo-controlled study 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 the plasma levels of zidovudine nor of its glucuronide metabolite.

*Miscellaneous*

Other medicines, including but not limited to, acetylsalicylic acid (aspirin), codeine, morphine, methadone, indomethacin, ketoprofen, naproxen, oxazepam, lorazepam, cimetidine, clofibrate, dapsone and inosine pranobex, may alter the metabolism of zidovudine by competitively inhibiting glucuronidation or directly inhibiting hepatic microsomal metabolism. Careful thought should be given to the possibility of interactions before using such medicines in combination with ZOVILAM (lamivudine plus zidovudine), particularly for chronic therapy.

Some experimental nucleoside analogues affecting DNA replication antagonise the *in vitro* antiviral activity of zidovudine against HIV and thus, concomitant use of such medicines should be avoided.

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, adriamycin and doxorubicin) may also increase the risk of adverse reactions to zidovudine.

If concomitant therapy with ZOVILAM and any of these medicines is necessary, then extra care should be taken in monitoring renal function and haematological parameters and, if required, the dosage of one or more medicines should be reduced. See section 5.2 for full details on the interaction of zidovudine with other antiretroviral medicines.

Since some patients receiving ZOVILAM may continue to experience opportunistic infections, concomitant use of prophylactic antimicrobial therapy may have to be considered. Such prophylaxis has included co-trimoxazole, aerosolised pentamidine, pyrimethamine and aciclovir. Limited data from clinical trials do not indicate a significantly increased risk of adverse reactions to zidovudine with these medicines. However, there is one published report of neurotoxicity (profound lethargy) associated with concomitant use of zidovudine and aciclovir.

Valproic acid or methadone when co-administered with zidovudine have been shown to increase the AUC. As only limited data are available the clinical significance is not known.

**4.6 Fertility, pregnancy and lactation**

**Pregnancy**

The safety of ZOVILAM in human pregnancy has not been established.

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. In the present case, the use in pregnant women of zidovudine, with subsequent treatment of the newborn infants, has been shown to reduce the rate of maternal-foetal transmission of HIV. A large amount of data on pregnant women taking lamivudine or zidovudine indicate no malformative toxicity (more than 3 000 outcomes from first trimester exposure each, of which over 2 000 outcomes involved exposure to both lamivudine and zidovudine). The malformative risk is unlikely in humans based on the mentioned

large amount of data.

Lamivudine and zidovudine may inhibit cellular DNA replication, and zidovudine has been shown to be transplacental carcinogen in one animal study. The clinical relevance of these findings is unknown.

For patients co-infected with hepatitis who are being treated with lamivudine containing medicines such as ZOVILAM 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 HIV-negative infants exposed *in utero* and/or post-natally to nucleoside analogues (see section 4.4).

There have also been reports of developmental delay, seizures and other neurological disease.

**Breastfeeding**

Both lamivudine and zidovudine are 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 is no data available on the safety of lamivudine when administered to babies less than three months old.

After administration of a single dose of 200 mg zidovudine to HIV-infected women, the mean concentration of zidovudine was similar in human milk and serum.

It is recommended that women living with HIV do not breastfeed their infants in order to avoid transmission of HIV.

**Fertility**

Neither zidovudine nor lamivudine have shown evidence of impairment of fertility in studies in male and female rats. There is no data on their effect on human female fertility.

In men, zidovudine has not been shown to affect sperm count, morphology or motility.

**4.7 Effects on ability to drive and use machines**

ZOVILAM can cause dizziness and may have other side effects that will make the patient less alert. Patients should not drive or operate machines unless they are feeling well.

**4.8 Undesirable effects**

Adverse events have been reported during therapy for HIV disease with lamivudine and zidovudine separately or in combination.

As ZOVILAM contains lamivudine and zidovudine, the type and severity of adverse reactions associated with each of the medicines may be expected. There is no evidence of added toxicity following concurrent administration of the two medicines.

Cases of lactic acidosis, sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis, have been reported with the use of zidovudine (see section 4.4).

Treatment with zidovudine has been associated with loss of subcutaneous fat which is most evident in the face, limbs and buttocks. Patients receiving ZOVILAM should be frequently examined and questioned for signs of lipoatrophy. When such development is found, treatment with ZOVILAM should not be continued (see section 4.4).

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4).

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (cART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to (cART). The frequency of this is unknown (see section 4.4).

**Lamivudine**

*Tabulated summary of adverse reactions*

| **System Organ Class** | **Frequency** | **Adverse events** |
|---|---|---|
| *Blood and lymphatic system disorders* | Less frequent | Anaemia and neutropenia (both occasionally severe), thrombocytopenia, pure red cell aplasia. |
| *Infections and infestations* | Frequent | Ear, nose and throat infections. |

| | | |
|---|---|---|
| *Metabolism and nutrition disorders* | Frequent | Hyperlactataemia, anorexia. |
| | Less frequent | Lactic acidosis, lipodystrophy (redistribution/accumulation of body fat). |
| | Frequency not known | Hyperglycaemia. |
| *Immune system disorders* | Frequency not known | Anaphylaxis. |
| *Nervous system disorders* | Frequent | Headache, insomnia, dizziness. |
| | Less frequent | Paraesthesia, peripheral neuropathy. |
| *Respiratory, thoracic and mediastinal disorders* | Frequent | Cough, nasal symptoms. |
| | Frequency not known | Abnormal breathing, sore throat. |
| *Gastrointestinal disorders* | Frequent | Nausea, vomiting, abdominal pain or cramps, diarrhoea. |
| | Less frequent | Pancreatitis, splenomegaly, stomatitis, rises in serum amylase, dyspepsia. |
| *Hepatobiliary disorders* | Less frequent | Transient rises in liver enzymes (AST, ALT), hepatitis, hepatomegaly with steatosis. |
| *Skin and subcutaneous tissue disorders* | Frequent | Rash, alopecia, erythema, pain. |
| | Less frequent | Angioedema. |
| | Frequency not known | Urticaria, pruritus. |
| *Musculoskeletal and connective tissue disorders* | Frequent | Arthralgia, muscle disorders including musculoskeletal pain, myalgia. |
| | Less frequent | Rhabdomyolysis, osteonecrosis. |
| *General disorders and administration site conditions* | Frequent | Fatigue, malaise, fever. |
| | Frequency not known | Weakness. |

**Zidovudine**

*Summary of the safety profile*

The adverse reactions profile appears similar for adults and adolescents. The most serious adverse reactions include anaemia (which may require transfusions), neutropenia and leukopenia. These occurred 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 less than 100/mm$^3$ (see section 4.4).

The incidence of neutropenia was also increased in those patients whose neutrophil counts, haemoglobin levels and serum vitamin B12 levels were low at the start of zidovudine therapy.

*Tabulated summary of adverse reactions*

| **System Organ Class** | **Frequency** | **Adverse events** |
|---|---|---|
| *Blood and lymphatic system disorders* | Frequent | Anaemia (which may require transfusions), neutropenia and leukopenia. 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). |
| | Less frequent | Thrombocytopenia and pancytopenia (with marrow hypoplasia), pure red cell aplasia, aplastic anaemia. |
| *Metabolism and nutrition* | Frequent | Hyperlactataemia. |

| | | |
|---|---|---|
| *disorders* | Less frequent | Lactic acidosis in the absence of hypoxaemia, anorexia, lipodystrophy (redistribution/accumulation of body fat). |
| *Psychiatric disorders* | Less frequent | Anxiety, depression. |
| *Nervous system disorders* | Frequent | Headache, dizziness. |
| | Less frequent | Insomnia, paraesthesia, somnolence, loss of mental acuity, convulsions. |
| *Cardiac disorders* | Less frequent | Cardiomyopathy. |
| *Respiratory, thoracic and mediastinal disorders* | Less frequent | Dyspnoea, cough. |
| *Gastrointestinal disorders* | Frequent | Nausea, vomiting, abdominal pain, diarrhoea. |
| | Less frequent | Flatulence, oral mucosa pigmentation, taste perversion, dyspepsia, 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 | Rash, pruritus, nail and skin pigmentation, urticaria and sweating. |
| *Musculoskeletal~~,~~ and connective tissue 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 administration site conditions* | Frequent | Malaise. |
| | Less frequent | Fever, generalised pain, asthenia, chills, chest pain, influenza-like syndrome. |

The incidence of nausea and other frequently reported clinical adverse events consistently decreases over time during the first few weeks of therapy with zidovudine.

If the severity of the symptoms warrants it, a reduction of zidovudine therapy may assist in the

assessment and management of these conditions. In this situation, ZOVILAM should be discontinued, and separate preparations of zidovudine and lamivudine should be administered (see sections 4.2 and 4.4).

**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 requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

**4.9 Overdose**

There are limited data available on the consequences of ingestion of acute overdoses of lamivudine and zidovudine in humans. No specific signs or symptoms have been identified following acute overdose with zidovudine or lamivudine apart from those listed as undesirable effects.

If overdosage occurs the patient should be monitored for evidence of toxicity 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. Haemodialysis and peritoneal dialysis appear to have a limited effect on elimination of zidovudine but enhance the elimination of the glucuronide metabolite.

**5. PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Category and class: A 20.2.8 Antiviral agents

**Mechanism of action**

Lamivudine and zidovudine are nucleoside reverse transcriptase inhibitors (NRTIs) and are potent selective inhibitors of human immunodeficiency virus (HIV-1 and HIV-2). Lamivudine has been shown to be highly synergistic with zidovudine, inhibiting the replication of HIV in cell culture.

Both medicines are metabolised sequentially by intracellular kinases to the 5'-triphosphate (TP).

Lamivudine-TP and zidovudine-TP are substrates for and competitive inhibitors of HIV reverse transcriptase. However, their main antiviral activity is through incorporation of the monophosphate form into the viral DNA chain, resulting in chain termination. Lamivudine and zidovudine triphosphates show

significantly less affinity for host cell DNA polymerases.

Lamivudine in combination with zidovudine reduces HIV-1 viral load and increases CD4+ cell counts. Clinical end-point data indicate that lamivudine in combination with zidovudine and lamivudine/zidovudine-containing treatment regimens result in a significant reduction in the risk of disease progression and mortality.

Lamivudine-TP and zidovudine-TP have selective inhibitory activity against HIV-1 and HIV-2 replication *in vitro*; lamivudine is also active against zidovudine-resistant clinical isolates of HIV. No antagonistic effects *in vitro* were seen with lamivudine and other antiretrovirals (tested medicines: abacavir, didanosine and nevirapine). No antagonistic effects *in vitro* were seen with zidovudine and other antiretrovirals (tested medicines: abacavir, didanosine and interferon-alpha).

**Resistance**

HIV-1 resistance to lamivudine involves the development of a M184V amino acid change close to the active site of the viral reverse transcriptase (RT). This variant arises both *in vitro* and in HIV-1 infected patients treated with lamivudine-containing antiretroviral therapy. M184V mutants display greatly reduced susceptibility to lamivudine and show diminished viral replicative capacity *in vitro*.

In patients receiving lamivudine monotherapy or combination therapy with lamivudine plus zidovudine, HIV-1 isolates from most patients became phenotypically and genotypically resistant to lamivudine within 12 weeks. In some patients harbouring zidovudine-resistant virus at baseline, phenotypic sensitivity to zidovudine was restored by 12 weeks of treatment with lamivudine and zidovudine. Combination therapy with lamivudine plus zidovudine delayed the emergence of mutations conferring resistance to zidovudine.

*In vitro* data tend to suggest that the continuation of lamivudine in antiretroviral regimen despite the development of M184V might provide residual antiretroviral activity (likely through impaired viral fitness). The clinical relevance of these findings is not established. Indeed, the available clinical data are very limited and preclude any reliable conclusion in the field. In any case, initiation of susceptible nucleoside analogue reverse-transcriptase inhibitors (NRTIs) should always be preferred to maintenance of lamivudine therapy. Therefore, maintaining lamivudine therapy despite emergence of M184V mutation should only be considered in cases where no other active NRTIs are available.

HIV-1 strains resistant to both lamivudine and zidovudine have been isolated from patients after prolonged lamivudine/zidovudine therapy. Dual resistance required the presence of multiple mutations,

the most essential of which may be at codon 333 (Gly → Glu). The incidence of dual resistance and the duration of combination therapy required before dual resistance occurs are unknown.

Lamivudine-resistant isolates of HIV-1 have been selected *in vitro* and have also been recovered from patients treated with lamivudine or lamivudine plus zidovudine. Genotypic analysis of the resistant isolates showed that the resistance was due to mutations in the HIV-1 reverse transcriptase gene at codon 184 from methionine to either isoleucine or valine.

HIV isolates with reduced susceptibility to zidovudine have been selected *in vitro* and were also recovered from patients treated with zidovudine. Genotypic analyses of the resistant isolates showed mutations which result in 5 amino acid substitutions (Met41→ Leu, Asp67→ Asn, Lys70 → Arg, Thr215 →Tyr or Phe, and Lys219 → Gln) in the HIV-1 reverse transcriptase gene. In general, higher levels of resistance were associated with greater number of mutations.

**Cross-resistance**

Cross-resistance conferred by the M184V RT is limited within the nucleoside inhibitor class of antiretroviral medicines. Zidovudine and stavudine maintain their antiretroviral activities against lamivudine-resistant HIV-1. Abacavir maintains its antiretroviral activities against lamivudine-resistant HIV-1 harbouring only the M184V mutation. The M184V RT mutant shows a < 4-fold decrease in susceptibility to didanosine; the clinical significance of these findings is unknown. *In vitro* susceptibility testing has not been standardised and results may vary according to methodological factors.

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*. Resistance to thymidine analogues (of which zidovudine is one) is well characterised and is conferred by the stepwise accumulation of up to six specific mutations in the HIV reverse transcriptase at codons 41, 67, 70, 210, 215 and 219. Viruses acquire phenotypic resistance to thymidine analogues through the combination of mutations at codons 41 and 215 or by the accumulation of at least four of the six mutations. These thymidine analogue mutations alone do not cause high-level cross-resistance to any of the other nucleosides, allowing for the subsequent use of any of the other approved reverse transcriptase inhibitors.

Two patterns of multi-drug resistance mutations, the first characterised by mutations in the HIV reverse transcriptase at codons 62, 75, 77, 116 and 151 and the second involving a T69S mutation plus a 6-base pair insert at the same position, result in phenotypic resistance to AZT as well as to the other

approved NRTIs. Either of these two patterns of multinucleoside resistance mutations severely limits future therapeutic options.

**5.2 Pharmacokinetic properties**

**Absorption**

Lamivudine and zidovudine are well absorbed from the gut. The bioavailability of oral lamivudine in adults is normally between 80 – 85 % and for zidovudine 60 – 70 %.

Following lamivudine 150 mg/zidovudine 300 mg combination administration, lamivudine and zidovudine $C_{max}$ values were 1,5 (1,3 – 1,8) mg/mL and 1,8 (1,5 – 2,2) mg/mL, respectively. The median (range) lamivudine and zidovudine $t_{max}$ values were 0,75 (0,50 – 2,00) hours and 0,50 (0,25 – 2,00) hours, respectively. The extent (AUC∞) of lamivudine and zidovudine absorption and estimates of half-life following administration of lamivudine 150 mg/ zidovudine 300 mg combination with food were similar when compared to fasting subjects, although the rate of absorption ($C_{max}$, $t_{max}$) was slowed. Based on these data lamivudine 150 mg/zidovudine 300 mg combination may be administered with or without food.

**Distribution**

Intravenous studies with lamivudine and zidovudine showed that the mean apparent volume of distribution is 1,3 and 1,6 L/kg, respectively.

Zidovudine plasma protein binding is 34 % to 38 %. Interactions involving binding site displacement are not anticipated with lamivudine 150 mg/ zidovudine 300 mg combination. Data show that lamivudine and zidovudine penetrate the central nervous system and reach the cerebrospinal fluid (CSF). The mean ratios of CSF/serum lamivudine and zidovudine concentrations 2 – 4 hours after oral administration were approximately 0,12 and 0,5, respectively. The true extent of penetration of lamivudine or relationship with any clinical efficacy is unknown.

**Biotransformation**

Metabolism of lamivudine is a minor route of elimination. Lamivudine is predominantly cleared by renal excretion of unchanged ~~substance~~ medicine. The likelihood of metabolic interactions with lamivudine are low due to the small extent of hepatic metabolism (5 – 10 %) and low plasma binding.

The 5'-glucuronide 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'-amino-3'-

deoxythymidine (AMT) has been identified as a metabolite of zidovudine following intravenous dosing.

**Elimination**

The observed lamivudine half-life of elimination is 18 to 19 hours. The mean systemic clearance of lamivudine is approximately 0,32 L/h/kg, with predominantly renal clearance (> 70 %) via the organic cationic transport system.

**Linearity/non-linearity**

Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays limited binding the major plasma protein albumin (< 36 % serum albumin *in vitro*).

**Special populations**

***Renal impairment***

Studies in patients with renal impairment show lamivudine elimination is affected by renal dysfunction. Dose reduction is required for patients with creatinine clearance ≤ 50 mL/min (see section 4.2).

From studies with intravenous zidovudine, the mean terminal plasma half-life was 1,1 hours and the mean systemic clearance was 1,6 L/h/kg. Renal clearance of zidovudine is estimated to be 0,34 L/h/kg, indicating glomerular filtration and active tubular secretion by the kidneys. Zidovudine concentrations are increased in patients with advanced renal failure.

***Pharmacokinetics of the lamivudine and zidovudine combination when used in combination with other antiretroviral medicines***

*Zidovudine*

Pharmacokinetic/interaction studies indicate that there were no clinically significant alterations to zidovudine pharmacokinetics when given concomitantly with the following antiretroviral medicines: 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 section 4.5). The concomitant use of these two medicines 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 medicines: non-nucleoside reverse transcriptase inhibitors (NNRTI's): efavirenz; and protease inhibitors: indinavir

sulphate, ritonavir, emprenavir and nelfinavir.

***Pharmacokinetics of lamivudine and zidovudine combination when used in combination with other tuberculostatic medicines***

*Zidovudine*

Co-administration of zidovudine and rifampicin decreases the AUC of zidovudine by approximately 48 % ± 34 %. 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 interactions e.g. rifampicin with lamivudine is low due to the small extent of hepatic metabolism (5 – 10 %) and low plasma binding.

***Pharmacokinetics in pregnancy***

The pharmacokinetics of lamivudine and zidovudine were similar to that of non-pregnant women.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

**Tablet core**

Cellulose microcrystalline

Colloidal anhydrous silica

Magnesium stearate

Sodium starch glycolate

**Tablet coating**

Hypromellose

Propylene glycol

Titanium dioxide

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

48 months

**6.4 Special precautions for storage**

Store at or below 30 °C. Store in the original container. Do not remove from the carton until required for use. Keep the bottles tightly closed.

**6.5 Nature and contents of container**

ZOVILAM is packed in an HDPE bottle pack (marketable pack) comprised of round wide-mouth white high-density polyethylene bottle and 33 mm white opaque screw cap with induction sealing liner packed in an outer carton in pack size of 60's and 100's.

ZOVILAM is packed in an HDPE bottle pack (marketable pack) comprised of white opaque polypropylene screw cap with aluminium induction sealing liner wad in an outer carton in a pack size of 56's.

ZOVILAM is packed in an HDPE bottle pack (marketable pack) comprised of blue opaque HDPE bottle with blue opaque polypropylene screw closure with wad containing aluminium induction sealing liner packed in an outer carton in pack sizes of 56's and 60's.

ZOVILAM is packed in a polybag LDPE plain 150 micron 330 mm x 485 mm IND-DMF (non-marketable pack) in a 50's pack size with a 10 g silica gel bag desiccant or a canister/sachet desiccant.

Not all pack sizes may be marketed.

**7. HOLDER OF CERTIFICATE OF REGISTRATION**

Viatris Healthcare (Pty) Ltd

4 Brewery Street

Isando, Gauteng

Republic of South Africa

**8. REGISTRATION NUMBER**

45/20.2.8/0170

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

05 June 2014

**10. DATE OF REVISION OF THE TEXT**

27 January 2025