

ZOVILAM

(Lamivudine and Zidovudine Tablets USP 150 mg/300 mg)

1. NAME OF THE MEDICINAL PRODUCT

Zovilam
(Lamivudine and Zidovudine Tablets USP 150 mg/300 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains Lamivudine USP 150 mg and Zidovudine USP 300 mg.
For a full list of excipients see 6.1.

3. PHARMACEUTICAL FORM

A white to off white, film-coated, capsule shaped, biconvex tablet debossed with **M** on one side of the score and **2** on other side of score on one side of the tablet and **L** on one side of the score and **Z** on other side of the score on the other side.

4. Clinical particulars

4.1 Therapeutic indications

ZOVILAM is indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection .

4.2 Posology and method of administration

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

ZOVILAM may be administered with or without food.

To ensure administration of the entire dose, the tablet(s) should ideally be swallowed without crushing. For patients who are unable to swallow tablets, tablets may be crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately

Adults and adolescents weighing at least 30 kg: the recommended dose of ZOVILAM is one tablet twice daily.

Children weighing between 21 kg and 30 kg: the recommended oral dose of ZOVILAM is one-half tablet taken in the morning and one whole tablet taken in the evening.

Children weighing from 14 kg to 21 kg: the recommended oral dose of ZOVILAM is one-half tablet taken twice daily.

A pharmacokinetic overexposure of zidovudine can occur, therefore close safety monitoring is warranted in these patients. If gastrointestinal intolerance occurs in patients weighing 21-30 kg, an

alternative dosing schedule with one-half tablet taken thrice daily can be applied in attempt to improve tolerability.

ZOVILAM tablets should not be used for children weighing less than 14 kg, since doses cannot be appropriately adjusted for the weight of the child. In these patients, lamivudine and zidovudine should be taken as separate formulations according to the prescribed dosing recommendations for these products. For these patients and for patients, who are unable to swallow tablets, oral solutions of lamivudine and zidovudine are available.

For situations where discontinuation of therapy with one of the active substances of ZOVILAM, or dose reduction is necessary separate preparations of lamivudine and zidovudine are available in tablets/capsules and oral solution.

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). Physicians should refer to the individual prescribing information for these medicinal products.

Hepatic impairment: Limited data in patients with cirrhosis suggest that accumulation of zidovudine may occur in patients with hepatic impairment because of decreased glucuronidation. Data obtained in patients with moderate to severe hepatic impairment show that lamivudine pharmacokinetics are not significantly affected by hepatic dysfunction. However, 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. Physicians should refer to the individual prescribing information for these medicinal products.

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 $1.0 \times 10^9/l$. As dosage adjustment of ZOVILAM is not possible, separate preparations of zidovudine and lamivudine should be used. Physicians should refer to the individual prescribing information for these medicinal products.

Dosage in the elderly: 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.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in.

Zidovudine is contraindicated in patients with abnormally low neutrophil counts ($<0.75 \times 10^9/l$), or abnormally low haemoglobin levels (<7.5 g/dl or 4.65 mmol/l). ZOVILAM is therefore contraindicated in these patients .

4.4 Special warnings and precautions for use

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

The special warnings and precautions relevant to both lamivudine and zidovudine are included in this section. There are no additional precautions and warnings relevant to the combination ZOVILAM.

It is recommended that separate preparations of lamivudine and zidovudine should be administered in cases where dosage adjustment is necessary. In these cases the physician should refer to the individual prescribing information for these medicinal products.

The concomitant use of stavudine with zidovudine should be avoided.

Opportunistic infections: Patients receiving ZOVILAM or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection. Therefore patients should remain under close clinical observation by physicians experienced in the treatment of HIV infection.

Haematological adverse reactions: Anaemia, neutropenia and leucopenia (usually secondary to neutropenia) can be expected to occur in patients receiving zidovudine. These occurred more frequently at higher zidovudine dosages (1200-1500 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 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. 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 10⁹/l. As dosage adjustment of ZOVILAM is not possible separate preparations of zidovudine and lamivudine should be used. Physicians should refer to the individual prescribing information for these medicinal products.

Pancreatitis: Cases of pancreatitis have occurred rarely in patients treated with lamivudine and zidovudine. However it is not clear whether these cases were due to the antiretroviral treatment or to the underlying HIV disease. Treatment with ZOVILAM should be stopped immediately if clinical signs, symptoms or laboratory abnormalities suggestive of pancreatitis occur.

Lactic acidosis: Lactic acidosis usually associated with hepatomegaly and hepatic steatosis has been reported with the use of zidovudine. Early symptoms (symptomatic hyperlactatemia) 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 zidovudine should be discontinued if there is symptomatic hyperlactatemia and

metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels. Caution should be exercised when administering zidovudine to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease and hepatic steatosis (including certain medicinal products 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.

Mitochondrial dysfunction following exposure in utero: Nucleoside and nucleotide analogues may impact mitochondrial function to a variable degree, which is most pronounced with stavudine, didanosine and zidovudine. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed *in utero* and/or post-natally to nucleoside analogues; these have predominantly concerned treatment with regimens containing zidovudine. The main adverse reactions reported are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactatemia, hyperlipasemia). These events have often been transitory. Late-onset neurological disorders have been reported rarely (hypertonia, convulsion, abnormal behaviour). Whether such neurological disorders are transient or permanent is currently unknown. These findings should be considered for any child exposed *in utero* to nucleoside and nucleotide analogues, who presents with severe clinical findings of unknown etiology particularly neurologic findings. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Lipoatrophy: Treatment with zidovudine has been associated with loss of subcutaneous fat, which has been linked to mitochondrial toxicity. The incidence and severity of lipoatrophy are related to cumulative exposure. This fat loss, which is most evident in the face, limbs and buttocks, may not be reversible when switching to a zidovudine-free regimen. Patients should be regularly assessed for signs of lipoatrophy during therapy with zidovudine and zidovudine-containing products (ZOVILAM and Trizivir). Therapy should be switched to an alternative regimen if there is suspicion of lipoatrophy development.

Weight and metabolic parameters: An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Immune Reactivation Syndrome: In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterium infections, and *Pneumocystis jirovecii pneumonia* (formerly known as *Pneumocystis carinii pneumonia*). Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease) 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.

Liver disease: If lamivudine is being used concomitantly for the treatment of HIV and HBV, additional information relating to the use of lamivudine in the treatment of hepatitis B infection is available in the Zeffix SmPC.

The safety and efficacy of zidovudine has not been established in patients with significant underlying liver disorders.

Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk of severe and potentially fatal hepatic adverse events. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

If ZOVILAM is discontinued in patients co-infected with hepatitis B virus, periodic monitoring of both liver function tests and markers of HBV replication for 4 months is recommended, as withdrawal of lamivudine may result in an acute exacerbation of hepatitis.

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 according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Patients co-infected with hepatitis C virus: The concomitant use of ribavirin with zidovudine is not recommended due to an increased risk of anaemia.

Osteonecrosis: Although the etiology 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 medicinal products containing lamivudine or medicinal products containing emtricitabine.

The combination of lamivudine with cladribine is not recommended.

4.5 Interaction with other medicinal products and other forms of interaction

ZOVILAM contains lamivudine and zidovudine, therefore any interactions identified for these individually are relevant to ZOVILAM.

Zidovudine is primarily metabolised by UGT enzymes; co-administration of inducers or inhibitors of UGT enzymes could alter zidovudine exposure. Lamivudine is cleared renally. Active renal secretion of lamivudine in the urine is mediated through organic cation transporters (OCTs); co-administration of lamivudine with OCT inhibitors or nephrotoxic drugs may increase lamivudine exposure.

Lamivudine and zidovudine are not significantly metabolised by cytochrome P₄₅₀ enzymes (such as CYP 3A4, CYP 2C9 or CYP 2D6) nor do they inhibit or induce this enzyme system. Therefore, there is little potential for interactions with antiretroviral protease inhibitors, non-nucleosides and other medicinal products metabolised by major P₄₅₀ enzymes.

Interaction studies have only been performed in adults. The list below should not be considered exhaustive but is representative of the classes studied.

Drugs by Therapeutic Area	Recommendation concerning co-administration
ANTIRETROVIRAL MEDICINAL PRODUCTS	
Didanosine/Lamivudine	No dosage adjustment necessary.
Didanosine /Zidovudine	
Stavudine/Lamivudine	Combination not recommended. This combination will decreased efficacy of both drugs.
Stavudine/Zidovudine	
ANTI-INFECTIVE PRODUCTS	
Atovaquone/Lamivudine	As only limited data available the clinical significance is unknown.
Atovaquone/Zidovudine (750 mg twice daily with food/200 mg thrice daily)	
Clarithromycin/Lamivudine	Separate administration of ZOVILAM and clarithromycin by at least 2 hours
Clarithromycin/Zidovudine (500 mg twice daily/100 mg every 4 hours)	
Trimethoprim/sulfamethoxazole (Co-trimoxazole)/Lamivudine (160 mg/800 mg once daily for 5 days/300 mg single dose)	No ZOVILAM dosage adjustment necessary, unless patient has renal impairment. When concomitant administration with co-trimoxazole is warranted, patients should be monitored clinically. High doses of trimethoprim/ sulfamethoxazole for the treatment of <i>Pneumocystis jirovecii</i> pneumonia (PCP) and toxoplasmosis have not been studied and should be avoided.
Trimethoprim/sulfamethoxazole (Co-trimoxazole)/Zidovudine	
ANTIFUNGALS	
Fluconazole/Lamivudine	As only limited data are available the clinical significance is not known. Monitor for signs of zidovudine toxicity.
Fluconazole/Zidovudine (400 mg once daily/200 mg thrice daily)	
ANTIMYCOBACTERIALS	
Rifampicin/Lamivudine	Insufficient data to recommend dosage adjustment.
Rifampicin/Zidovudine (600 mg once daily/200 mg thrice daily)	
ANTICONSULSANTS	
Phenobarbital/Lamivudine	Insufficient data to recommend dosage adjustment.
Phenobarbital/Zidovudine	
Phenytoin/Lamivudine	Monitor phenytoin concentrations.
Phenytoin/Zidovudine	
Valproic acid/Lamivudine	As only limited data are available the clinical significance is not known. Monitor for signs of zidovudine toxicity .
Valproic acid/Zidovudine (250 mg or 500 mg thrice daily/100 mg thrice daily)	
ANTIHISTAMINES (HISTAMINE H1 RECEPTOR ANTAGONISTS)	
Ranitidine/Lamivudine	No dosage adjustment necessary.
Ranitidine/Zidovudine	
Cimetidine/Lamivudine	No dosage adjustment necessary.

Cimetidine/Zidovudine	
CYTOTOXICS	
Cladribine/Lamivudine	Therefore the concomitant use of lamivudine with cladribine is not recommended
OPIOIDS	
Methadone/Lamivudine	As only limited data are available the clinical significance is not known. Monitor for signs of zidovudine toxicity . Methadone dosage adjustment unlikely in majority of patients; occasionally methadone re-titration may be required.
Methadone/Zidovudine (30 to 90 mg once daily/200 mg every 4 hours)	
URICOSURIC	
Probenecid/Lamivudine	As only limited data are available the clinical significance is not known. Monitor for signs of zidovudine toxicity .
Probenecid/Zidovudine (500 mg four times daily/2mg/kg thrice daily)	

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

Consideration should be given to replacing zidovudine in a combination ART regimen if this is already established. This would be particularly important in patients with a known history of zidovudine induced anaemia.

Concomitant treatment, especially acute therapy, with potentially nephrotoxic or myelosuppressive medicinal products (e.g. systemic pentamidine, dapsone, pyrimethamine, co-trimoxazole, amphotericin, flucytosine, ganciclovir, interferon, vincristine, vinblastine and doxorubicin) may also increase the risk of adverse reactions to zidovudine. If concomitant therapy with ZOVILAM and any of these medicinal products is necessary then 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.

Limited data from clinical trials do not indicate a significantly increased risk of adverse reactions to zidovudine with cotrimoxazole (see interaction information above relating to lamivudine and co-trimoxazole), aerosolised pentamidine, pyrimethamine and acyclovir at doses used in prophylaxis.

4.6 Fertility, pregnancy and lactation

Pregnancy

As a general rule, when deciding to use antiretroviral agents for the treatment of HIV infection in pregnant women and consequently for reducing the risk of HIV vertical transmission to the newborn, the animal data as well as the clinical experience in pregnant women should be taken into account. 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 3000 outcomes from first trimester exposure each, of which over 2000 outcomes involved exposure to both lamivudine and zidovudine). The malformative risk is unlikely in humans based on the mentioned large amount of data.

For patients co-infected with hepatitis who are being treated with lamivudine containing medicinal products 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 .

Breast-feeding

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 are 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 mothers infected by HIV do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

Fertility

There are no data on their affect 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

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

4.8 Undesirable effects

Adverse reactions have been reported during therapy for HIV disease with lamivudine and zidovudine separately or in combination. For many of these events, it is unclear whether they are related to lamivudine, zidovudine, the wide range of medicinal products used in the management of HIV disease, or as a result of the underlying disease process.

As ZOVILAM 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 added toxicity following concurrent administration of the two compounds.

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

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.

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy

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) 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 .

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

Lamivudine:

The adverse reactions considered at least possibly related to the treatment are listed below by body system, organ class and absolute frequency.

Blood and lymphatic systems disorders

Uncommon: Neutropenia and anaemia (both occasionally severe), thrombocytopenia

Very rare: Pure red cell aplasia

Metabolism and nutrition disorders

Very Rare: Lactic acidosis

Nervous system disorders

Common: Headache, insomnia

Very rare: Peripheral neuropathy (or paraesthesiae)

Respiratory, thoracic and mediastinal disorders

Common: Cough, nasal symptoms

Gastrointestinal disorders

Common: Nausea, vomiting, abdominal pain or cramps, diarrhoea

Rare: Pancreatitis, rises in serum amylase

Hepatobiliary disorders

Uncommon: Transient rises in liver enzymes (AST, ALT)

Rare: Hepatitis

Skin and subcutaneous tissue disorders

Common: Rash, alopecia

Rare: Angioedema

Musculoskeletal and connective tissue disorders

Common : Arthralgia, muscle disorders

Rare: Rhabdomyolysis

General disorders and administration site conditions

Common: Fatigue, malaise, fever

Zidovudine:

The adverse reactions profile appears similar for adults and adolescents. The most serious adverse reactions include anaemia (which may require transfusions), neutropenia and leucopenia. These

occurred more frequently at higher dosages (1200-1500 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/mm³.

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.

The adverse reactions considered at least possibly related to the treatment are listed below by body system, organ class and absolute frequency.

Blood and lymphatic system disorders

Common : Anaemia, neutropenia and leucopenia

Uncommon: Thrombocytopenia and pancytopenia (with marrow hypoplasia)

Rare : Pure red cell aplasia

Very rare : Aplastic anaemia

Metabolism and nutrition disorders

Rare : Lactic acidosis in the absence of hypoxaemia, anorexia

Psychiatric disorders

Rare: Anxiety and depression

Nervous system disorders

Very common : Headache

Common : Dizziness

Rare : Insomnia, paraesthesiae, somnolence, loss of mental acuity, convulsions

Cardiac disorders

Rare :Cardiomyopathy

Respiratory, thoracic and mediastinal disorders

Uncommon: Dyspnoea

Rare : Cough

Gastrointestinal disorders

Very common : Nausea

Common : Vomiting, abdominal pain and diarrhoea

Uncommon : Flatulence

Rare : Oral mucosa pigmentation, taste perversion and dyspepsia. Pancreatitis

Hepatobiliary disorders

Common : Raised blood levels of liver enzymes and bilirubin

Rare : Liver disorders such as severe hepatomegaly with steatosis

Skin and subcutaneous tissue disorders

Uncommon : Rash and pruritus

Rare : Nail and skin pigmentation, urticaria and sweating

Musculoskeletal and connective tissue disorders

Common : Myalgia

Uncommon : Myopathy

Renal and urinary disorders

Rare: Urinary frequency

Reproductive system and breast disorders

Rare : Gynaecomastia

General disorders and administration site conditions

Common : Malaise

Uncommon : Fever, generalised pain and asthenia

Rare :Chills, chest pain and influenza-like syndrome

4.9 Overdose

No specific symptoms or signs have been identified following acute overdose with zidovudine or lamivudine apart from those listed as undesirable effects. No fatalities occurred, and all patients recovered.

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. Haemodialysis and peritoneal dialysis appear to have a limited effect on elimination of zidovudine, but enhance the elimination of the glucuronide metabolite. For more details physicians should refer to the individual prescribing information for lamivudine and zidovudine.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for treatment of HIV infections, combinations, ATC Code: J05AR01

Lamivudine and zidovudine are nucleoside analogues which have activity against HIV. Additionally, lamivudine has activity against hepatitis B virus (HBV). Both medicinal products are metabolised intracellularly to their active moieties, lamivudine 5'-triphosphate (TP) and zidovudine 5'-TP respectively. Their main modes of action are as chain terminators of viral reverse transcription. 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 agents: abacavir, didanosine and nevirapine). No antagonistic effects *in vitro* were seen with zidovudine and other antiretrovirals (tested agents: abacavir, didanosine and interferon-alpha).

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). M184V mutants display greatly reduced susceptibility to lamivudine and show diminished viral replicative capacity *in vitro*.

The continuation of lamivudine in antiretroviral regimen despite the development of M184V might provide residual antiretroviral activity (likely through impaired viral fitness). In any case, initiation of susceptible NRTI's 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

Cross-resistance conferred by the M184V RT is limited within the nucleoside inhibitor class of antiretroviral agents. 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.

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 gastrointestinal tract.

Administration of crushed tablets with a small amount of semi-solid food or liquid would not be expected to have an impact on the pharmaceutical quality, and would therefore not be expected to alter the clinical effect..

Distribution

Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays limited binding to the major plasma protein albumin (<36% serum albumin *in vitro*). Interactions involving binding site displacement are not anticipated with ZOVILAM.

The true extent of CNS penetration of lamivudine and its relationship with any clinical efficacy is unknown.

Biotransformation

Metabolism of lamivudine is a minor route of elimination. Lamivudine is predominately cleared unchanged by renal excretion. The likelihood of metabolic drug interactions with lamivudine is low due to the small extent of hepatic metabolism and low plasma binding.

The 5'-glucuronide of zidovudine is the major metabolite in both plasma and urine, Majority of the administered dose eliminated by renal excretion. Elimination

The observed lamivudine half-life of elimination is 5 to 7 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.

Renal clearance of zidovudine is indicating glomerular filtration and active tubular secretion by the kidneys. Zidovudine concentrations are increased in patients with advanced renal failure.

Pharmacokinetics in children: In children over the age of 5-6 months, the pharmacokinetic profile of zidovudine is similar to that in adults.

The recommended dose for lamivudine in children (aged more than three months and weighing less than 30 kg) is 4 mg/kg twice a day. Recent findings indicate that exposure in children <6 years of age may be reduced by about 30% compared with other age groups.

Pharmacokinetics in pregnancy: The pharmacokinetics of lamivudine and zidovudine were similar to that of non-pregnant women.

5.3 Preclinical safety data

The clinically relevant effects of lamivudine and zidovudine in combination are anaemia, neutropenia and leucopenia.

The carcinogenic potential of a combination of lamivudine and zidovudine has not been tested.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet:

Microcrystalline cellulose,
Colloidal silicon dioxide,
Sodium starch glycolate,
Magnesium stearate,

Film coat:

Hypromellose,
Titanium dioxide and
Propylene glycol.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 months

6.4 Special precautions for storage

Do not store above 30°C. Store in the original container.

6.5 Nature and contents of container

HDPE bottle pack

HDPE bottle pack (marketable pack) comprises of round wide mouth white high density polyethylene (HDPE) bottle with white opaque polypropylene (PP) screw cap with induction sealing liner.

Bottle of 60's.

6.6 Instructions for use and handling and disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Manufactured By

Mylan Laboratories Limited
F-4 & F-12, MIDC, Malegaon, Sinnar,
Nashik - 422 113, Maharashtra, INDIA

8. Product Registration Holder

Pahang Pharmacy Sdn. Bhd.
Lot 5979, Jalan Teratai, 5 ½ Miles off Jalan Meru,
41050 Klang, Selangor, MALAYSIA.

9. DATE OF REVISION OF THE TEXT

January 2018