1. Name of the medicinal product

INN Name **:** Lamivudine and Zidovudine Tablets USP 150mg/300mg

Propriority Name **:** Lamivudine and Zidovudine Tablets USP 150mg/300 mg

Strength **:** 150mg/300 mg

Pharmaceutical form: film coated Tablet

2. Qualitative and quantitative composition

Each tablet contains 150 mg of Lamivudine USP and 300 mg of Zidovudine USP.

3. Pharmaceutical form

Dosage form: Tablet

Description: White, film coated, Capsule shaped tablets debossed with 'H' and score line on one side and '2' on other side

4. Clinical particulars

4.1 Therapeutic indications

Lamivudine and Zidovudine Tablets is indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection**.**

4.2 Posology and method of administration

Posology

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

Lamivudine and Zidovudine Tablets 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 Lamivudine and Zidovudine Tablets is one tablet twice daily.

Children weighing between 21 kg and 30 kg*:* the recommended oral dose of Lamivudine and Zidovudine Tablets 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 Lamivudine and Zidovudine Tablets is one-half tablet taken twice daily.

The dosing regimen for paediatric patients weighing 14-30 kg is based primarily on pharmacokinetic modelling and supported by data from clinical studies using the individual components Lamivudine and Zidovudine. 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.

Lamivudine and Zidovudine Tablets should not be used for children weighing less than 14 kg, since doses can not 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 Lamivudine and Zidovudine Tablets, 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 $\leq$ 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 x 10^9/l. As dosage adjustment of Lamivudine and Zidovudine Tablets 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.

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). Lamivudine and Zidovudine Tablets is therefore contra-indicated in these patients

4.4 Special warnings and precautions for use

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 Lamivudine and Zidovudine Tablets.

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 Lamivudine and Zidovudine Tablets 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.

Transmission of HIV: Patients should be advised that current antiretroviral therapy, including Lamivudine and Zidovudine Tablets, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or contamination with blood. Appropriate precautions should continue to be taken.

Haematological adverse reactions: Anaemia, neutropenia and leucopenia 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 Lamivudine and Zidovudine Tablets. 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 Lamivudine and Zidovudine Tablets, 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. As dosage adjustment of Lamivudine and Zidovudine Tablets 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 Lamivudine and Zidovudine Tablets 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 nucleoside analogues. 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 nucleoside analogues 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 nucleoside analogues 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*:* 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. The main adverse events reported are haematological disorders (anaemia, neutropenia), metabolic disorders (hyperlactatemia, hyperlipasemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether the neurological disorders are transient or permanent is currently unknown. Any child exposed *in utero* to nucleoside and nucleotide analogues, even HIV-negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. These findings do

not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Lipodystrophy: Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) 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 drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. 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 jiroveci pneumonia (*formerly known as *Pneumocystis carinii pneumonia)*. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

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 SPC.

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 Lamivudine and Zidovudine Tablets 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.

4.5 Interaction with other medicinal products and other forms of interaction

As Lamivudine and Zidovudine Tablets contain Lamivudine and Zidovudine, any interactions that have been identified with these agents individually may occur with Lamivudine and Zidovudine Tablets. The likelihood of metabolic interactions with Lamivudine is low due to limited metabolism and plasma protein binding, and almost complete renal clearance. Zidovudine is primarily eliminated by hepatic conjugation to an inactive glucuronidated metabolite. Medicinal products which are primarily eliminated by hepatic metabolism especially via glucuronidation may have the potential to inhibit metabolism of Zidovudine. The interactions listed below should not be considered exhaustive but are representative of the classes of medicinal products where caution should be exercised.

Lamivudine and Zidovudine metabolism do not involve CYP3A, making interactions with medicinal products metabolised by this system (e.g. PIs) unlikely.

Interactions relevant to Lamivudine

The possibility of interactions with other medicinal products administered concurrently with Lamivudine and Zidovudine Tablets should be considered, particularly when the main route of elimination is active renal secretion, especially via the cationic transport system e.g. trimethoprim. Nucleoside analogues (e.g. zidovudine, didanosine and zalcitabine) and other medicinal products (e.g. ranitidine, cimetidine) are eliminated only in part by this mechanism and were shown not to interact with Lamivudine.

Administration of trimethoprim/sulfamethoxazole 160 mg/800 mg results in a 40% increase in Lamivudine exposure, because of the trimethoprim component; the sulfamethoxazole component does not interact. However, unless the patient has renal impairment, no dosage adjustment of Lamivudine is necessary. Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole. When concomitant administration with co-trimoxazole is warranted, patients should be monitored clinically. Co-administration of Lamivudine and Zidovudine Tablets with high doses of co-trimoxazole for the treatment of Pneumocystis jiroveci pneumonia *(*formerly known as Pneumocystis carinii pneumoni*a* [PCP]) and toxoplasmosis should be avoided.

Co-administration of Lamivudine with intravenous ganciclovir or foscarnet is not recommended

Interactions relevant to Zidovudine

Limited data suggest that co-administration of Zidovudine and rifampicin decreases the AUC of Zidovudine by 48% ± 34%. However the clinical significance of this is unknown. Dose modifications of Zidovudine in this situation have not been formally evaluated.

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. Patients receiving both medicinal products should be closely monitored for haematological toxicity.

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 Lamivudine and Zidovudine Tablets and phenytoin.

In a pharmacokinetic study co-administration of Zidovudine and atovaquone tablets showed a decrease in Zidovudine clearance after oral dosing leading to a 35% ± 23% increase in plasma Zidovudine AUC. The mode of interaction is unknown and as higher concentrations of atovaquone can be achieved with atovaquone suspension it is possible that greater changes in AUC values for Zidovudine might be induced when atovaquone is administered as a suspension. Given the limited data available the clinical significance of this is unknown.

Valproic acid, fluconazole or methadone when co-administered with Zidovudine have been shown to increase the AUC of Zidovudine, with a corresponding decrease in its clearance. As only limited data are available the clinical significance is not known. If Zidovudine is used concurrently with either valproic acid, fluconazole or methadone, patients should be monitored closely for potential toxicity of Zidovudine.

Zidovudine and stavudine in combination are antagonistic *in vitro*, therefore the concomitant use of stavudine with Lamivudine and Zidovudine Tablets should be avoided.

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 Lamivudine and Zidovudine Tablets 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.

Since some patients receiving Lamivudine and Zidovudine Tablets may continue to experience opportunistic infections, concomitant use of prophylactic antimicrobial therapy may have to be considered. Limited data from clinical trials do not indicate a significantly increased risk of adverse reactions to Zidovudine with co-trimoxazole (see interaction information above relating to lamivudine and co-trimoxazole), aerosolised pentamidine, pyrimethamine and acyclovir at doses used in prophylaxis.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of Lamivudine in human pregnancy has not been established. No data are available for the treatment with a combination of Lamivudine and Zidovudine in humans or animals. The use in pregnant women of Zidovudine alone, with subsequent treatment of the newborn infants, has been shown to reduce the rate of maternal-foetal transmission of HIV. However, no such data are available for Lamivudine.

In humans, consistent with passive transmission of Lamivudine across the placenta, Lamivudine concentrations in infant serum at birth were similar to those in maternal and cord serum at delivery. Zidovudine was measured in plasma and gave similar results to those observed for Lamivudine.

As the active ingredients of Lamivudine and Zidovudine Tablets may inhibit cellular DNA replication, any use, especially during the first trimester of pregnancy, presents a potential risk to the foetus. Consequently the administration of Lamivudine and Zidovudine Tablets during pregnancy should only be considered if expected benefits outweigh any possible risks.

Pregnant women considering using Lamivudine and Zidovudine Tablets during pregnancy should be

made aware of the findings from animal carcinogenicity and mutagenicity studies.

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

Lactation: Both Lamivudine and Zidovudine are excreted in breast milk at similar concentrations to those found in serum. It is recommended that mothers taking Lamivudine and Zidovudine Tablets do not breast-feed their infants. It is recommended that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

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 Lamivudine and Zidovudine Tablets contain 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 nucleoside analogues.

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia.

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.

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.

Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥ 1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Blood and lymphatic systems disorders

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

Very rare: Pure red cell aplasia

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

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/mm^3.

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.

The adverse reactions considered at least possibly related to the treatment are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥ 1/1000 to <1/100), rare (≥ 1/10,000 to <1/1000), very rare (<1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Blood and lymphatic system disorders

Common: Anaemia, neutropenia and leucopenia

Uncommon: Thrombocyopenia 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

The available data from both placebo-controlled and open-label studies indicate that the incidence of nausea and other frequently reported clinical adverse events consistently decreases over time during the first few weeks of therapy with Zidovudine.

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4.9 Overdose

There is limited experience of over dosage with Lamivudine and Zidovudine Tablets. 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 over dosage 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. 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. Lamivudine in combination with Zidovudine exhibits synergistic anti-HIV activity against clinical isolates in cell culture.

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 vitro* studies indicate that Zidovudine-resistant virus isolates can become Zidovudine sensitive when they simultaneously acquire resistance to Lamivudine. The clinical relevance of such findings remains, however, not well defined.

In vitro data tend to suggest that the continuation of Lamivudine in anti-retroviral regimen despite the development of M184V might provide residual anti-retroviral 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 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. The M184V RT mutant shows a <4-fold decrease in susceptibility to didanosine and zalcitabine; 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.

Clinical Experience

In clinical trials, Lamivudine in combination with Zidovudine has been shown to reduce HIV-1 viral load and increase CD4 cell count. Clinical end-point data indicate that Lamivudine in combination with Zidovudine, results in a significant reduction in the risk of disease progression and mortality.

Lamivudine and Zidovudine have been widely used as components of antiretroviral combination therapy with other antiretroviral agents of the same class (NRTIs) or different classes (PIs, non-nucleoside reverse transcriptase inhibitors).

Multiple drug antiretroviral therapy containing Lamivudine has been shown to be effective in antiretrovirally-naive patients as well as in patients presenting with viruses containing the M184V mutations.

Evidence from clinical studies shows that Lamivudine plus Zidovudine delays the emergence of zidovudine resistant isolates in individuals with no prior antiretroviral therapy. Subjects receiving Lamivudine and Zidovudine with or without additional concomitant antiretroviral therapies and who already present with the M184V mutant virus also experience a delay in the onset of mutations that confer resistance to zidovudine and stavudine (Thymidine Analogue Mutations; TAMs).

The relationship between *in vitro* susceptibility of HIV to Lamivudine and Zidovudine and clinical response to lamivudine/zidovudine containing therapy remains under investigation.

Lamivudine at a dose of 100 mg once daily has also been shown to be effective for the treatment of adult patients with chronic HBV infection (for details of clinical studies, see the prescribing information for Zeffix). However, for the treatment of HIV infection only a 300 mg daily dose of Lamivudine (in combination with other antiretroviral agents) has been shown to be efficacious.

Lamivudine has not been specifically investigated in HIV patients co-infected with HBV.

5.2 Pharmacokinetic properties

Absorption: Lamivudine and Zidovudine are well absorbed from the gastrointestinal tract. The bioavailability of oral Lamivudine in adults is normally between 80–85% and for Zidovudine 60–70%.

A bioequivalence study compared Lamivudine and Zidovudine Tablets with Lamivudine 150 mg and Zidovudine 300 mg tablets taken together. The effect of food on the rate and extent of absorption was also studied. Lamivudine and Zidovudine Tablets was shown to be bioequivalent to Lamivudine 150 mg and Zidovudine 300 mg given as separate tablets, when administered to fasting subjects.

Following single dose Lamivudine and Zidovudine Tablets administration in healthy volunteers, mean (CV) Lamivudine and Zidovudine C_{max} values were 1.6 µg/ml (32%) and 2.0 µg/ml (40%), respectively and the corresponding values for AUC were 6.1 µg h/ml (20%) and 2.4 µg h/ml (29%) 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 of Lamivudine and Zidovudine absorption (AUC ∞) and estimates of half-life following administration of Lamivudine and Zidovudine Tablets with food were similar when compared to fasting subjects, although the rates of absorption ($C_{max,}$ t_{max}) were slowed. Based on these data Lamivudine and Zidovudine Tablets may be administered with or without food.

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. This conclusion is based on the physiochemical and pharmacokinetic data assuming that the patient crushes and transfers 100% of the tablet and ingests immediately.

Distribution: Intravenous studies with Lamivudine and Zidovudine showed that the mean apparent volume of distribution is 1.3 and 1.6 l/kg respectively. Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays limited binding to the major plasma protein albumin (<36% serum albumin *in vitro*). Zidovudine plasma protein binding is 34% to 38%. Interactions involving binding site displacement are not anticipated with Lamivudine and Zidovudine Tablets.

Data show that Lamivudine and Zidovudine penetrate the central nervous system (CNS) 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 CNS penetration of Lamivudine and its relationship with any clinical efficacy is unknown.

Metabolism: 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 (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 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. Studies in patients with renal impairment show Lamivudine elimination is affected by renal dysfunction. Dose reduction is required for patients with creatinine clearance $\leq$ 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 in children: In children over the age of 5-6 months, the pharmacokinetic profile of Zidovudine is similar to that in adults. Zidovudine is well absorbed from the gut and at all dose levels studied in adults and children, the bioavailability was between 60-74% with a mean of 65%. Css_{max} levels were 4.45 μM (1.19 μg/ml) following a dose of 120 mg Zidovudine (in solution)/m^2 body surface area and 7.7 μM (2.06 μg/ml) at 180 mg/m^2 body surface area. Dosages of 180 mg/m^2 four times daily in children produced similar systemic exposure (24 hour AUC 40.0 h μM or 10.7 h μg/ml) as doses of 200 mg six times daily in adults (40.7 h μM or 10.9 h μg/ml).

In six HIV-infected children from 2 to 13 years of age, Zidovudine plasma pharmacokinetics were evaluated while subjects were receiving 120 mg/m^2 Zidovudine three times daily and again after switching to 180 mg/m^2 twice daily. Systemic exposures (daily AUC and C_{max}) in plasma from the twice daily regimen appeared equivalent to those from the same total daily dose given in three divided doses [Bergshoeff, 2004].

In general, Lamivudine pharmacokinetics in paediatric patients are similar to adults. However, absolute bioavailability (approximately 55-65%) was reduced in paediatric patients below 12 years of age. In addition, systemic clearance values were greater in younger paediatric patients and decreased with age, approaching adult values around 12 years of age. Due to these differences, 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. This dose will achieve an average AUC_{0-12} ranging from approximately 3,800 to 5,300 ng h/ml. Recent findings indicate that exposure in children <6 years of age may be reduced by about 30% compared with other age groups. Further data addressing this issue are currently awaited. At present, the available data do not suggest that Lamivudine is less efficacious in this age group.

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.

Neither Lamivudine nor Zidovudine are mutagenic in bacterial tests, but like many nucleoside analogues they show activity in *in vitro* mammalian tests such as the mouse lymphoma assay.

Lamivudine has not shown any genotoxic activity in *in vivo* studies at doses that gave plasma concentrations up to 40-50 times higher than clinical plasma levels. Zidovudine showed clastogenic effects in an oral repeated dose micronucleus test in mice. Peripheral blood lymphocytes from AIDS patients receiving Zidovudine treatment have also been observed to contain higher numbers of chromosome breakages.

A pilot study has demonstrated that Zidovudine is incorporated into leukocyte nuclear DNA of adults, including pregnant women, taking Zidovudine as treatment for HIV-1 infection, or for the prevention of mother to child viral transmission. Zidovudine was also incorporated into DNA from cord blood leukocytes of infants from Zidovudine-treated mothers. A transplacental genotoxicity study conducted in monkeys compared Zidovudine alone with the combination of Zidovudine and Lamivudine at human-equivalent exposures. The study demonstrated that foetuses exposed *in utero* to the combination sustained a higher level of nucleoside analogue-DNA incorporation into multiple foetal organs, and showed evidence of more telomere shortening than in those exposed to Zidovudine alone. The clinical significance of these findings is unknown.

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

In long-term oral carcinogenicity studies in rats and mice, lamivudine did not show any carcinogenic potential.

In oral carcinogenicity studies with zidovudine in mice and rats, late appearing vaginal epithelial tumours were observed. A subsequent intravaginal carcinogenicity study confirmed the hypothesis that the vaginal tumours were the result of long term local exposure of the rodent

vaginal epithelium to high concentrations of unmetabolised zidovudine in urine. There were no other zidovudine-related tumours observed in either sex of either species.

In addition, two transplacental carcinogenicity studies have been conducted in mice. In one study, by the US National Cancer Institute, zidovudine was administered at maximum tolerated doses to pregnant mice from day 12 to 18 of gestation. One year post-natally, there was an increase in the incidence of tumours in the lung, liver and female reproductive tract of offspring exposed to the highest dose level (420 mg/kg term body weight).

In a second study, mice were administered zidovudine at doses up to 40 mg/kg for 24 months, with exposure beginning prenatally on gestation day 10. Treatment related findings were limited to late-occurring vaginal epithelial tumours, which were seen with a similar incidence and time of onset as in the standard oral carcinogenicity study. The second study thus provided no evidence that zidovudine acts as a transplacental carcinogen.

It is concluded that as the increase in incidence of tumours in the first transplacental carcinogenicity study represents a hypothetical risk, this should be balanced against the proven therapeutic benefit.

In reproductive toxicity studies lamivudine has demonstrated evidence of causing an increase in early embryonic deaths in the rabbit at relatively low systemic exposures, comparable to those achieved in man, but not in the rat even at very high systemic exposure. Zidovudine had a similar effect in both species, but only at very high systemic exposures. Lamivudine was not teratogenic in animal studies. At maternally toxic doses, zidovudine given to rats during organogenesis resulted in an increased incidence of malformations, but no evidence of foetal abnormalities was observed at lower doses.

6. Pharmaceutical particulars

6.1 List of excipients

Microcrystalline Cellulose, Sodium Starch Glycolate, Colloidal Silicon Dioxide, Magnesium Stearate, Opadry White and purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Store below 30°C and protect from moisture.

6.5 Nature and contents of container

HDPE container pack of 60's count

6.6 Special precautions for disposal and other handling

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

7. Marketing Authorisation Holder and Manufacturing Site Addresses

Marketing authorization Holder:

Name: **Hetero Labs Limited**

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8. Marketing authorization number

9. Date of first registration/renewal of the registration

10. Date of revision of the text