

1. NAME OF THE MEDICINAL PRODUCT

Lamivudine/Zidovudine Tablets USP 150 mg/300 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150 mg Lamivudine USP and 300 mg Zidovudine USP.

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 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

The fixed combination of lamivudine and zidovudine is indicated in combination with another antiretroviral agent for the treatment of Human Immunodeficiency Virus (HIV) infected adults and adolescents over 12 years of age.

4.2 Posology and method of administration

Posology and method of administration

Oral use.

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

The recommended dose of Lamivudine/Zidovudine 150/300 mg Tablets adults and adolescents over 12 years of age is: One tablet twice daily.

For situations where discontinuation of therapy with one of the active substances of Lamivudine/Zidovudine 150/300 mg Tablets, or dose reduction is necessary, separate preparations of lamivudine and zidovudine are available as tablets and oral solutions.

Lamivudine/Zidovudine 150/300 mg Tablets may be taken with or without food (1).

Children: Lamivudine/Zidovudine 150/300 mg Tablets is not indicated for children < 12 years of age, as appropriate dose reduction for the weight of the child cannot be made.

Elderly: Special care is advised in this age group due to associated changes such as decrease in renal function and alteration of haematological parameters.

Dose adjustment

Renal Impairment: Since dose adjustment may be necessary in patients with renal impairment (creatinine clearance ≤ 50 ml/min), it is recommended that separate preparations of lamivudine and zidovudine be administered (see section 4.4) (2, 3).

Hepatic impairment: No dose adjustments are necessary for mild to moderate hepatic impairment. In patients with severe hepatic impairment, dose adjustment for zidovudine may be necessary. Therefore, it is recommended that separate preparations of lamivudine and zidovudine be administered in these patients (see section 4.4).

Haematological adverse reactions: Since substitution or dose reductions of zidovudine should be considered in patients whose haemoglobin concentrations or neutrophil counts fall to clinically significant levels, it is recommended that separate preparations of lamivudine and (if appropriate) zidovudine be administered (see section 4.4).

4.3 Contraindications

Lamivudine/Zidovudine 150 mg/300 mg Tablets is contraindicated in patients with:

- Hypersensitivity to lamivudine, zidovudine or to any excipient in the formulation,
- Abnormally low neutrophil count ($< 0.75 \times 10^9$ /litre) (see section 4.4),
- Abnormally low haemoglobin (< 7.5 g/dl or 4.65 mmol/litre) (see section 4.4).

4.4 Special warnings and special precautions for use

Lamivudine and zidovudine should only be used with abacavir in the treatment of antiretroviral-naïve patients when a regimen based on a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI) cannot be used. Concomitant use of stavudine with zidovudine should be avoided (see section 4.5).

Dose adjustment

It is recommended that separate preparations of lamivudine and zidovudine be administered when any dosage adjustment is necessary (see section 4.2). In these cases the health care provider should refer to the individual prescribing information for each of the products.

Opportunistic infections

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

Transmission of HIV

Patients should be advised that current antiretroviral therapy has not been proven to prevent the transmission of HIV to others through sexual contact or contamination with blood. Appropriate precautions should continue to be taken to prevent transmission.

Haematological adverse reactions

Anaemia, neutropenia and leucopenia have been reported in patients receiving zidovudine-containing preparations, especially in patients with advanced HIV disease (poor bone-marrow reserve) or with vitamin B12 deficiency, and usually after at least 4–6 weeks of therapy.

Therefore, monitoring of haematological parameters is recommended in patients receiving Lamivudine/Zidovudine 150 mg/300 mg Tablets, e.g. as follows:

- In advanced HIV disease: at least every 2 weeks during the first 3 months of therapy, and monthly thereafter.
- In early (non-symptomatic) HIV disease, at a frequency depending on the overall condition of the patient: e.g. every 1–3 months.

Since substitution, dose reduction or interruption of zidovudine therapy may be necessary in patients whose haemoglobin concentration or neutrophil count fall to clinically significant levels, separate preparations of lamivudine and (if appropriate) zidovudine should be administered (refer to the Summary of Product Characteristics of zidovudine-only containing products).

Pancreatitis

Treatment with Lamivudine/Zidovudine 150 mg/300 mg Tablets should be stopped immediately if clinical signs, symptoms or laboratory abnormalities suggestive of pancreatitis occur.

Lactic acidosis

Lactic acidosis is a rare but severe, potentially life-threatening complication associated with nucleoside reverse transcriptase inhibitors (NRTI) use. It may occur after a few to several months of treatment. Patients with hyperlactataemia may be asymptomatic, critically ill, or may have non-specific symptoms such as dyspnoea, fatigue, nausea, vomiting, diarrhoea and abdominal pain. Risk factors for NRTI-related lactic acidosis include female gender and obesity. Patients co-infected with hepatitis C and treated with interferon alfa and ribavirin may constitute a special risk. Patients at increased risk should be closely monitored clinically. Screening for hyperlactataemia in asymptomatic patients treated with NRTIs, however, is not recommended. Symptomatic patients usually have lactic acid levels > 5 mmol/litre and require discontinuation of all NRTIs, including zidovudine and lamivudine. Lactic acid level > 10 mmol/litre is usually a medical emergency.

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 to nucleoside analogues *in utero* or postnatally. The main adverse events reported are haematological disorders (anaemia and neutropenia), metabolic disorders (hyperlactataemia, hyperlipasaemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether these 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 considerations, however, do not affect 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. A higher risk of lipodystrophy has been associated with, for example, older age, longer duration of ART and related metabolic disturbances. Clinical examination should

include evaluation for physical signs of fat redistribution. Measurement of fasting serum lipids and blood glucose as well as appropriate management of lipid disorders should be considered (see section 4.8).

Immune reactivation syndrome

In HIV-infected patients with severe immune deficiency, typically in the first few weeks or months of initiating combination antiretroviral therapy, an inflammatory reaction to asymptomatic or residual opportunistic pathogens (e.g. CMV retinitis, mycobacterial infections, *Pneumocystis jirovecii* (*Pneumocystis carinii*) pneumonia) may arise and cause serious clinical conditions or aggravation of symptoms. Treatment should be instituted when necessary.

Liver disease

Caution should be exercised when administering Lamivudine/Zidovudine 150 mg/300 mg Tablets to any patient with chronic hepatitis B infection. Lamivudine is a potent inhibitor of hepatitis B virus (HBV) replication and discontinuation of lamivudine or virological failure after development of resistance to lamivudine by HBV may cause hepatic deterioration and a hepatitis flare. If Lamivudine/Zidovudine 150 mg/300 mg Tablets is discontinued in a patient with HBV infection, the patient should be periodically monitored, both clinically and by assessment of liver function tests (ALT and bilirubin levels) and markers of HBV replication, for at least 4 months, and then as clinically indicated.

Patients with chronic hepatitis B or C who are treated with combination antiretroviral therapy, have an increased risk of severe and potentially fatal hepatic adverse events.

Patients with liver dysfunction have an increased risk of liver function abnormalities during combination antiretroviral therapy, and should be monitored according to standard practice. If liver disease worsens in such patients, interruption or discontinuation of therapy should be considered.

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 or long-term exposure to combination antiretroviral therapy. Patients should be advised to seek medical advice if they develop joint aches and pain, joint stiffness or difficulty in movement.

4.5 Interaction with other medicinal products and other forms of interaction

As Lamivudine/Zidovudine 150 mg/300 mg Tablets contains lamivudine and zidovudine, any interactions that have been identified with these agents individually may occur.

Whereas lamivudine undergoes limited metabolism and is almost completely eliminated via the kidneys, zidovudine is primarily eliminated by hepatic conjugation, to form an inactive glucuronide metabolite. Lamivudine and zidovudine are not significantly metabolised by cytochrome P450 enzymes (such as CYP3A4, CYP2C9 or CYP2D6) and do not 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.

The following list of interactions is not exhaustive, but is representative of the classes of medicinal products where caution should be exercised.

Drugs	Interaction Geometric mean change (%) (Possible mechanism)	Recommendation concerning co-administration
Antiretrovirals		
Emtricitabine/Lamivudine	Overlapping resistance and lack of additive antiretroviral effects.	Emtricitabine should not be co-administered with Lamivudine/Zidovudine 150 mg/300 mg Tablets.
Stavudine/Zidovudine	In vitro antagonism of anti-HIV activity between stavudine and zidovudine could result in decreased efficacy of both drugs.	Stavudine should not be co-administered with Lamivudine/Zidovudine 150 mg/300 mg Tablets.
Anti-infectives		
Clarithromycin/Zidovudine (500 mg twice daily/100 mg every 4 hours)	Zidovudine AUC ↓12%	Administration of Lamivudine/Zidovudine 150 mg/300 mg Tablets and clarithromycin should be separated by at least 2 hours.
Rifampicin/Zidovudine (600 mg once daily/200 mg three times daily)	Zidovudine AUC ↓48% (UGT induction)	Insufficient data to recommend dosage adjustment.
Trimethoprim + sulfamethoxazole/Lamivudine (160 mg/800 mg once daily for 5 days/300 mg single dose)	Lamivudine: AUC ↑40% Trimethoprim: AUC ↔ Sulfamethoxazole: AUC ↔ (Organic cation transporter inhibition)	No dosage adjustment of Lamivudine/Zidovudine 150 mg/300 mg Tablets is necessary, unless patient has renal impairment (section 4.2). When concomitant administration with trimethoprim + sulfamethoxazole is warranted, patients should be monitored clinically. High doses of trimethoprim + sulfamethoxazole for treating <i>Pneumocystis jirovecii</i> (<i>Pneumocystis carinii</i>) pneumonia and toxoplasmosis have not been studied and should be avoided.
Antifungal		
Fluconazole/Zidovudine (400 mg once daily/200 mg three times daily)	Zidovudine AUC ↑74% (UGT inhibition)	The clinical significance is not known. Monitor for signs of zidovudine toxicity (section 4.8).

Antimalarial		
Atovaquone/Zidovudine (750 mg twice daily with food/200 mg three times daily)	Zidovudine AUC ↑33% Atovaquone AUC ↔	The clinical significance is not known.
Anticonvulsants		
Phenobarbital/Zidovudine	Interaction not studied. Potential to slightly decrease zidovudine plasma concentrations through UGT induction.	Insufficient data to recommend dosage adjustment.
Phenytoin/Zidovudine	Phenytoin AUC ↑↓	Monitor phenytoin concentration.
Valproic acid/Zidovudine (250 mg or 500 mg three times daily/100 mg three times daily)	Zidovudine AUC ↑80% (UGT inhibition)	The clinical significance is not known. Monitor for signs of zidovudine toxicity (section 4.8).
Opioids		
Methadone/Zidovudine (30–90 mg once daily/200 mg every 4 hours)	Zidovudine AUC ↑43% Methadone AUC ↔	The clinical significance is not known. Monitor for signs of zidovudine toxicity (section 4.8). Methadone dosage adjustment may be required only occasionally.
Uricosuric		
Probenecid/Zidovudine(500 mg four times daily/2 mg/kg three times daily)	Zidovudine AUC ↑106% (UGT inhibition)	The clinical significance is not known. Monitor for signs of zidovudine toxicity(section 4.8).
Abbreviations ↑ = Increase, ↔ = no significant change, ↓ = decrease and AUC = area under the concentration versus time curve		

Exacerbation of anaemia due to ribavirin has been reported when zidovudine is part of the regimen used to treat HIV. Therefore, concomitant use of ribavirin with Lamivudine/Zidovudine 150 mg/300 mg Tablets is not recommended (see section 4.4), particularly in patients with a history of zidovudine-induced anaemia.

Concomitant treatment, especially acute therapy, with potentially nephrotoxic or myelosuppressive medicines (e.g. systemic pentamidine, dapsone, pyrimethamine, trimethoprim + sulfamethoxazole, amphotericin, ganciclovir, clozapine, flucytosine, interferon, vincristine, vinblastine and doxorubicin) and zidovudine may increase the risk of adverse reactions. If concomitant therapy with Lamivudine/Zidovudine 150 mg/300 mg Tablets and any of these medicines is necessary then extra care should be taken to monitor renal function and haematological parameters and, if required, the dose of one or more agents should be reduced.

4.6 Pregnancy and breastfeeding

Pregnancy

No increased risk of birth defects have been reported for lamivudine or for zidovudine (www.apregistry.com). However, risks to the fetus cannot be ruled out.

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

Breastfeeding

Both lamivudine and zidovudine are present in breast milk at concentrations similar to those in the serum. It is recommended that HIV-infected mothers should not breast-feed in order to avoid the transmission of HIV. Only under specific circumstances the benefits of breast-feeding might be considered to outweigh the risks. The most recent official treatment guidelines (e.g. those issued by WHO) should be consulted before advising mothers on breastfeeding.

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. Nevertheless, the clinical status of the patient and the adverse reaction profile of Lamivudine/Zidovudine 150 mg/300 mg Tablets should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

As Lamivudine/Zidovudine 150 mg/300 mg Tablets 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 with concurrent administration of the two compounds.

The most frequently reported adverse reactions are headache and nausea. The most common serious adverse reactions include anaemia (which may require transfusions), neutropenia and leucopenia (see section 4.4).

Adverse events considered to be at least possibly related to treatment with zidovudine and lamivudine, are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common ($\geq 1/10$), common ($1/100$ – $1/10$), uncommon ($1/1000$ – $1/100$), rare ($1/10\ 000$ – $1/1000$) or very rare ($\leq 1/10\ 000$). In addition, adverse events identified during post-approval use of lamivudine, zidovudine, and lamivudine/zidovudine as a fixed-dose combination are listed. Since they are reported voluntarily from a population of unknown size, the frequency cannot be estimated (frequency category: 'unknown'). These events have been included on the basis of their seriousness, number of reports, or potential causal connection to lamivudine, zidovudine, and lamivudine/zidovudine as fixed-dose combination.

Blood and lymphatic systems disorders

Common: Anaemia, neutropenia, leucopenia

Uncommon: Thrombocytopenia, pancytopenia

Rare: Pure red cell aplasia

Very rare: Aplastic anaemia

Metabolic and nutrition disorders

Rare: Lactic acidosis, anorexia

Unknown: changes in distribution of body fat, hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, hyperlactataemia (see section 4.4)

Psychiatric disorders

Rare: anxiety, depression

Nervous system disorders

Very common: Headache

Common: Dizziness, insomnia

Rare: Paraesthesia, somnolence, loss of mental acuity, convulsions

Cardiac disorders

Rare: Cardiomyopathy

Respiratory, thoracic and mediastinal disorders

Common: Cough, nasal symptoms

Uncommon: Dyspnoea

Gastrointestinal disorders

Very common: Nausea

Common: Vomiting, abdominal pain or cramps, diarrhoea

Uncommon: Flatulence

Rare: Pancreatitis, raised serum amylase, oral mucosa pigmentation, taste perversion, dyspepsia

Hepatobiliary disorders

Common: Elevated liver enzymes and bilirubin

Rare: Hepatitis, severe hepatomegaly with steatosis

Skin and subcutaneous tissue disorders

Common: Rash, hair loss

Uncommon: Pruritus

Rare: Nail and skin pigmentation, urticaria, sweating, angioedema

Musculoskeletal and connective tissue disorders

Common: Arthralgia, myalgia

Uncommon: Myopathy

Rare: Rhabdomyolysis

Unknown: osteonecrosis

Renal and urinary disorders

Rare: Urinary frequency

Reproductive system and breast disorders

Rare: Gynaecomastia

General disorders and administration site disorders:

Common: Malaise, fatigue, fever

Uncommon: Asthenia, generalised pain

Rare: Chest pain, influenza-like syndrome, chills

Unknown: Immune reconstitution syndrome (see section 4.4)

See also sections 4.4 and 4.5

4.9 Overdose

There is limited experience of overdosage with lamivudine/zidovudine. No specific signs and symptoms have been identified following acute overdose with zidovudine or lamivudine apart from those listed as undesirable effects. No fatalities occurred and the patients recovered. If overdose occurs patients should be monitored for toxicity (see section 4.8), and standard supportive treatment given as necessary. Since elimination of lamivudine and the glucuronide metabolite of zidovudine are enhanced by haemodialysis, continuous haemodialysis could be used in the treatment of overdosage (but this has not been studied).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group

Antivirals for treatment of HIV infections, combinations, ATC Code J05AR01

Mechanism of action:

Lamivudine and zidovudine are nucleoside analogues that are active against HIV. Additionally, lamivudine has activity against hepatitis B virus (HBV). Both compounds are metabolised intracellularly to their active moieties, lamivudine 5'-triphosphate (TP) and zidovudine 5'-triphosphate 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.

Clinical efficacy:

In clinical trials, lamivudine in combination with zidovudine reduces HIV-1 viral load and increases 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. In a trial of zidovudine and lamivudine in combination with efavirenz, 68% of subjects achieved plasma HIV RNA < 50 copies/ml after 48 weeks, by intention-to-treat analysis. 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 (protease inhibitors, non-nucleoside reverse transcriptase inhibitors).

Resistance:

In the great majority of cases when combination antiretroviral therapy comprising zidovudine and lamivudine fails virologically, the M184V mutation will be selected for at an early stage. M184V causes high-level resistance to lamivudine (> 300-fold reduced susceptibility). *In vitro* data suggest that 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, available clinical data are very limited and preclude any reliable

conclusion in the field. Therefore, maintaining lamivudine therapy despite emergence of M184V mutation should be considered only when the activity of the best available NRTI backbone is significantly compromised.

On virological failure, resistance to zidovudine is developed along two separate, though not mutually exclusive, pathways. The first of these include M41L, L210W and T215F/Y. The second includes D67N, K70R and K219E/Q. Collectively these mutations are termed 'thymidine analogue mutations' (TAM). In viruses with M184V, two to three TAMs are generally required for phenotypically detectable and clinically significant zidovudine resistance. M41L, L210W, and T215Y have a greater effect on zidovudine susceptibility and cross-resistance to other NRTIs than the other TAMs. Other important mutations selected for by zidovudine include T69 insertion mutations and the Q151M complex, where this mutation appears in combination with mutations at positions 75, 77, and 116. Both of these patterns confer high-level resistance to zidovudine and all other presently available NRTIs.

The likelihood of a gradual accumulation of mutations conferring resistance to the entire class of NRTI, upon virological failure with combination therapy including zidovudine and lamivudine, underscores the importance of early detection of virological failure. Delayed detection of virological failure may severely limit the options for second-line therapy.

The combination of lamivudine and zidovudine has not been specifically investigated in HIV patients co-infected with HBV.

5.2 Pharmacokinetic properties

No pharmacokinetic data are available for Lamivudine/Zidovudine 150 mg/300 mg Tablets. As Lamivudine/Zidovudine 150 mg/300 mg Tablets met the WHO criteria for a BCS based biowaiver, a bioequivalence study was not conducted.

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%.

Following single dose of Lamivudine/Zidovudine Tablets 150/300 mg in healthy volunteers, mean $\pm$ SD of lamivudine and zidovudine C_{max} values were 1.75 ± 0.50 μ g/ml and 3.02 ± 2.07 μ g/ml, respectively and the corresponding values for AUC _{∞} were 6.81 ± 1.58 μ g·hour/ml and 2.86 ± 0.71 μ g·hour/ml, respectively. The mean lamivudine and zidovudine t_{max} values were 1.3 hours and 0.5 hours respectively.

The extent of lamivudine and zidovudine absorption (AUC_T) and estimates of half-life following administration of a respective fixed combination product (Combivir®, GSK) 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 150/300 mg may be administered with food or between meals.

Administration of crushed tablets with a small amount of semi-solid food or liquid would not be expected to affect 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 ingests the full dose immediately after crushing the tablets.

Distribution

Intravenous studies with lamivudine and zidovudine showed that the mean apparent volume of distribution is 1.3 litre/kg and 1.6 litre/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 34–38%. Drug interactions involving binding site displacement are not anticipated with Lamivudine and Zidovudine Tablets 150/300 mg.

Metabolism

Metabolism of lamivudine is a minor route of elimination. Lamivudine is predominantly 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 protein 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 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 half-life of intracellular lamivudine triphosphate has been estimated to be approximately 22 hours. The mean systemic clearance of lamivudine is approximately 0.32 litre/hour/kg, with predominantly renal clearance (> 70%), including tubular secretion through the organic cationic transport system. Studies in patients with renal impairment show that lamivudine elimination is affected by renal dysfunction. Dose reduction is recommended for patients with creatinine clearance $\leq$ 50 ml/minute (see section 4.2).

In studies with intravenous zidovudine, the mean terminal plasma half-life was 1.1 hours and the mean systemic clearance was 1.6 litre/hour/kg. The half-life of intracellular zidovudine triphosphate has been estimated to be around 7 hours. Renal clearance of zidovudine is estimated to be 0.34 litre/hour/kg, indicating glomerular filtration and active tubular secretion by the kidneys. Zidovudine concentrations are increased in patients with advanced renal failure.

Special populations:

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

Children: In general, lamivudine pharmacokinetics in paediatric patients are similar to adults. However, absolute bioavailability (approximately 55–65%) was reduced in paediatric patients aged below 12 years. In addition, systemic clearance values were greater in younger paediatric patients and decreased with age, approaching adult values at around 12 years of age.

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%.

5.3 Preclinical safety data

Neither lamivudine nor zidovudine is mutagenic in bacterial tests, but like many nucleoside analogues they show activity in mammalian *in vitro* tests such as the mouse lymphoma assay. Lamivudine has not shown any genotoxic activity in *in vivo* studies at doses that produced 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.

A transplacental genotoxicity study in monkeys compared zidovudine alone with the combination of zidovudine and lamivudine at exposures equivalent to those in humans. That study demonstrated that fetuses exposed *in utero* to the combination sustained a higher level of nucleoside analogue-DNA

incorporation into multiple fetal 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 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. No other zidovudine-related tumours were observed in either sex of either species.

In addition, two transplacental carcinogenicity studies have been conducted in mice. In one study 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.

In reproductive toxicity studies lamivudine has demonstrated evidence of increasing 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 fetal abnormalities was observed at lower doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose,
Colloidal anhydrous silica,
Sodium starch glycolate,
Magnesium stearate,
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

Blister pack

Blister pack comprises of clear PVdC coated PVC film with backing of aluminium foil coated with heat seal lacquer Pack of 10s.

HDPE bottle pack

HDPE bottle comprises of white opaque HDPE bottle with screw cap. Bottle of 60s.

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. SUPPLIER

Marketing Authorization Holder

HEALTHLINE LIMITED

Manufactured by

Mylan Laboratories Limited

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References