SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Lamivudine and Zidovudine Tablets 150 mg/300 mg*

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150 mg lamivudine and 300 mg zidovudine.

For a full list of excipients see 6.1.

3. PHARMACEUTICAL FORM

White, film-coated, modified capsule-shaped tablets with a breakline on both sides of the tablet.
"D" is debossed on one side of the breakline and "02" is debossed on the other side of the breakline on both tablet faces such that when broken in half, "D" and "02" are present on each half tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Lamivudine and Zidovudine Tablets 150 mg/300 mg is indicated in combination with another antiretroviral agent for the treatment of human immunodeficiency virus (HIV) infection in adults, adolescents and children weighing over 25 kg.

Consideration should be given to official treatment guidelines for HIV-1 infection (e.g. those of the WHO).

4.2 Posology and method of administration

Oral use.

The therapy should be initiated by a health care provider experienced in the management of HIV infection.

Adults, adolescents and children (weighing at least 25 kg):

The recommended dose of Lamivudine and Zidovudine Tablets 150 mg/300 mg is one tablet twice a day, leaving approximately 12 hours between each dose (see section 4.4).

Children weighing less than 25 kg

This product should not be used in children weighing < 25 kg since appropriate dose adjustments cannot be made. For these patients another formulation should be used, e.g. a tablet which can be used to give smaller doses of lamivudine and zidovudine.

Lamivudine and Zidovudine Tablets 150 mg/300 mg may be taken with food or between meals.

To ensure administration of the entire dose, the tablet should be swallowed whole. For patients who are unable to swallow tablets, the tablets may be crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately.

* Trade names are not prequalified by WHO. This is the national medicines regulatory authority's (NMRA) responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

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

Elderly

Special care is advised in the elderly because of age-associated changes such as decrease in renal function and alteration of haematological parameters.

Renal impairment

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

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. Health care providers should refer to the individual prescribing information for these medicinal products.

Haematological adverse reactions

Dosage adjustment of zidovudine may be necessary if the haemoglobin level falls below 9 g/dl or 5.59 mmol/l or the neutrophil count falls below 1.0 x 10^9/l (see sections 4.3 and 4.4). As dosage adjustment of Lamivudine and Zidovudine Tablets 150 mg/300 mg is not possible, separate preparations of zidovudine and lamivudine should be used. Health care providers should refer to the individual prescribing information for these medicinal products.

4.3 Contraindications

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

- Hypersensitivity to lamivudine, zidovudine or to any excipient in the formulation,
- Abnormally low neutrophil count (< 0.75 x 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

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 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 B_{12} deficiency, and usually after at least 4–6 weeks of therapy.

Therefore, monitoring of haematological parameters is recommended in patients receiving Lamivudine and Zidovudine Tablets 150 mg/300 mg, 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 and Zidovudine Tablets 150 mg/300 mg 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 hyperlactataemia) include benign digestive symptoms (nausea, vomiting and abdominal pain) non-specific malaise, loss of appetite, weight loss, respiratory symptoms (rapid and/or deep breathing) or neurological symptoms (including motor weakness).

Lactic acidosis has a high mortality and may be associated with pancreatitis, liver failure, or renal failure.

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

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

Caution should be exercised when administering 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

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 reactions 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. 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. 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, 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* pneumonia) may arise and cause serious clinical conditions or aggravation of symptoms. 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

Caution should be exercised when administering Lamivudine and Zidovudine Tablets 150 mg/300 mg 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 and Zidovudine Tablets 150 mg/300 mg 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

Cases of osteonecrosis have been reported, particularly in patients with advanced HIV-disease or long-term exposure to combination antiretroviral therapy. Additional risk factors for this condition include corticosteroid use, alcohol consumption, severe immunosuppression and higher body mass index Patients should be advised to seek medical advice if they develop joint aches and pain, joint stiffness or difficulty in movement.

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

4.5 Interaction with other medicinal products and other forms of interaction

As Lamivudine and Zidovudine Tablets 150 mg/300 mg 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 and Zidovudine Tablets 150 mg/300 mg.
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 and Zidovudine Tablets 150 mg/300 mg.
Anti-infectives		
Clarithromycin/Zidovudine (500 mg twice daily/100 mg every 4 hours)	Zidovudine AUC ↓12%	Administration of Lamivudine and Zidovudine Tablets 150 mg/300 mg 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 and Zidovudine Tablets 150 mg/300 mg is necessary, unless patient has renal impairment (section 4.2). When concomitant administration with trimethoprim + sulfamethaxazole is warranted, patients should be monitored clinically. High doses of trimethoprim + sulfamethoxazole for treating *Pneumocystis jirovecii* (*Pneumocystis carinii*) 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).
Cytotoxics		
Cladribine/Lamivudine	Interaction not studied *In vitro* lamivudine inhibits the intracellular phosphorylation of cladribine leading to a potential risk of cladribine loss of efficacy in case of combination in the clinical setting. Some clinical findings also support a possible interaction between lamivudine and cladribine	Therefore the concomitant use of lamivudine with cladribine is not recommended (see section 4.4)
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).
Miscellaneous		
Sorbitol solution (3.2g, 10.2g, 13.4g) /Lamivudine	Single dose lamivudine oral solution 300mg Lamivudine: AUC ↓ 14%; 32%; 36% Cmax ↓ 28%; 52%: 55%	When possible, avoid chronic coadministration of Lamivudine and Zidovudine Tablets 150 mg/300 mg with medicinal products containing sorbitol or other osmotic acting poly-alcohols (e.g. xylitol, mannitol, lactitol, maltitol). Consider more frequent monitoring of HIV-1 viral load when chronic coadministration cannot be avoided
Abbreviations	↑ = Increase ↔ = no significant change	↓ = decrease 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 and Zidovudine Tablets 150 mg/300 mg 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, flucytosine, ganciclovir, interferon, vincristine, vinblastine and doxorubicin) and zidovudine may increase the risk of adverse reactions. If concomitant therapy with Lamivudine and Zidovudine Tablets 150 mg/300 mg 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. 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. Current recommendations on HIV and breastfeeding (e.g. those from the WHO) should be consulted before advising patients on this matter. Preferred options may vary depending on the local circumstances.

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

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

4.7 Effects on ability to drive and use machines

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 and Zidovudine Tablets 150 mg/300 mg should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

As Lamivudine and Zidovudine Tablets 150 mg/300 mg 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 (≥ 1/10), common (1/100–1/10), uncommon (1/1000–1/100), rare (1/10 000–1/1000) or very rare (≤ 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').

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: Lipoatrophy, weight increase, hypertriglyceridaemia, hypercholesterolaemia, hyperglycaemia, (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

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health care professionals are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

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 and zidovudine in combination with a third antiretroviral agent reduce HIV-1 viral load and increases CD4 cell count. 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.

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

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 was conducted with the fixed-dose combination product Lamivudine and Zidovudine tablets USP 150 mg/300 mg of Shanghai Desano Bio-Pharmaceutical Co., Ltd., China and with Combivir® (lamivudine and zidovudine tablets 150 mg/300 mg) of GlaxoSmithKline Research Triangle Park, NC 27709 in healthy adults under fasting condition.

The mean (CV) lamivudine and zidovudine C_{max} values were 1702 ± 547 ng/ml and 1898 ± 920 ng/ml, respectively and the corresponding values for AUC were 7450 ± 1792 ng·h/ml and 2583 ± 833 ng·h/ml respectively. The median (range) lamivudine and zidovudine t_{max} values were 1.35 ± 0.62 hours and 0.71 ± 0.42 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 ≤ 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 and zidovudine pharmacokinetics in paediatric patients is similar to adults. However, for lamivudine 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.

.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. The vaginal tumours were the result of long-term local exposure of the rodent vaginal epithelium to high concentrations of unmetabolised zidovudine in urine.

In addition, two transplacental carcinogenicity studies have been conducted in mice. In one study zidovudine 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) were seen.

In a second study, mice were administered zidovudine at doses up to 40 mg/kg for 24 months. The second study thus provided no evidence that zidovudine acts as a transplacental carcinogen.

While the clinical relevance of these findings is unknown, these data suggest that a carcinogenic risk to humans is outweighed by the potential clinical benefit.

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

Tablet core:

Microcrystalline cellulose
Sodium starch glycolate
Colloidal silicon dioxide
Magnesium stearate

Film coating (Opadry 13B58802 White):

Hypromellose
Titanium dioxide
Macrogol / polyethylene glycol
Polysorbate 80

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C. Protect from light and moisture.

6.5 Nature and contents of container

Tablets are available in white opaque HDPE bottle pack of 60’s.
The HDPE bottle closure is a white opaque polypropylene, round cylindrical 38 mm child resistant closure with induction sealing liner.

6.6 Instructions for use and handling and disposal

No special requirements.

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

7. SUPPLIER

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8. WHO REFERENCE NUMBER (PREQUALIFICATION PROGRAMME)

HA655

9. DATE OF FIRST PREQUALIFICATION/RENEWAL OF PREQUALIFICATION

21 June 2017

10. DATE OF REVISION OF THE TEXT

July 2018

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The main reference source for this text is the European SmPC for Combivir, available at:
http://www.emea.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000190/WC500032326.pdf (accessed on July 10, 2018)

Further references relevant to sections of the SmPC include:

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