EPIVIR Tablets

EPIVIR Oral Solution (alcohol free)

QUALITATIVE AND QUANTITATIVE COMPOSITION

EPIVIR oral solution contains 10 mg/mL lamivudine in a solution containing 20% (w/v) sucrose. It is a clear, colourless to pale yellow solution.

EPIVIR tablets contain 150 mg of lamivudine.

EPIVIR 150 mg tablets are white, diamond shaped, scored and engraved with the code "GX CJ7" on both faces.

CLINICAL INFORMATION

Indications

EPIVIR, in combination with other antiretroviral agents, is indicated for the treatment of HIV-infected adults and children.

Dosage and Administration

Pharmaceutical Form:

Oral Solution.

Film-coated tablets.

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

EPIVIR can be taken 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, lamivudine is available as an oral solution. Alternatively, the tablets may be crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately (see *Pharmacokinetics*).

- **Adults, adolescents and children weighing at least 25 kg**

The recommended dose of *EPIVIR* is 300 mg daily. This may be administered as 150 mg (15 mL oral solution, 1 x 150 mg tablet) twice daily or 300 mg (30 mL oral solution, 2 x 150 mg tablets) once daily (see *Warnings and Precautions*).

Patients changing to the once daily regimen should take 150 mg twice a day and switch to 300 mg once a day the following morning. When an evening once a day regimen is preferred, 150 mg of *EPIVIR* should be taken on the first morning only, followed by 300 mg in the

evening. When changing back to a twice daily regimen, patients should complete the day's treatment and start 150 mg twice a day the following morning.

- **Children weighing less than 25 kg**

Oral Solution

Children from one year of age: The recommended dose is 0.5 mL/kg (5 mg/kg) twice daily or 1 mL/kg (10 mg/kg) once daily (see *Warnings and Precautions*).

Children from three months to one year of age: The recommended dose is 0.5 mL/kg (5 mg/kg) twice daily. If a twice daily regimen is not feasible, a once daily regimen (10 mg/kg/day) could be considered. It should be taken into account that data for the once daily regimen are very limited in this population (see *Clinical Studies*).

150 mg Scored Tablets

Since an accurate dosing cannot be achieved with this formulation, dosing according to weight bands is recommended for *EPIVIR* tablets.

Children weighing ≥ 20 kg to < 25 kg: The recommended dose is 225 mg daily. This may be administered as either 75 mg (one-half of a 150 mg tablet) taken in the morning and 150 mg (one whole 150 mg tablet) taken in the evening, or 225 mg (one and a half 150 mg tablets) taken once daily.

Children weighing 14 kg to < 20 kg: The recommended dose is 150 mg daily. This may be administered as 75 mg (one-half of a 150 mg tablet) taken twice daily, or 150 mg (one whole 150 mg tablet) taken once daily.

Patients changing between lamivudine oral solution and lamivudine tablets should follow the dosing recommendations that are specific for the formulation (see *Pharmacokinetics*).

- **Children less than three months of age**

The limited data available are insufficient to propose specific dosage recommendations (see *Pharmacokinetics*).

- **Renal impairment**

Lamivudine plasma concentrations (AUC) are increased in patients with moderate to severe renal impairment due to decreased clearance (see *Pharmacokinetics*). The dosage should therefore be reduced for patients with a creatinine clearance of < 30 mL/minute as shown in the table below.

Dosing Recommendations - Adults, adolescents and children weighing at least 25 kg:

Creatinine clearance (mL/min)	First Dose	Maintenance Dose
15 to less than 30	150 mg (15 mL)	100 mg (10 mL) once daily
5 to less than 15	150 mg (15 mL)	50 mg (5 mL) once daily
less than 5	50 mg (5 mL)	25 mg (2.5 mL) once daily

There are no data available on the use of lamivudine in children with renal impairment.

A reduction in the dose and/or increase in the dosing interval should be considered in children aged at least three months and weighing less than 25 kg with a creatinine clearance of less than 50 mL/min.

Dosing Recommendations - Children aged ≥ three months and weighing less than 25 kg

Creatinine clearance (mL/min)	First dose	Maintenance dose
≥ 50	5 mg/kg	5 mg/kg twice daily
30 to < 50	5 mg/kg	5 mg/kg once daily
15 to < 30	5 mg/kg	3.25 mg/kg once daily
5 to < 15	5 mg/kg	1.63 mg/kg once daily
< 5	1.63 mg/kg	0.88 mg/kg once daily

- **Hepatic impairment**

No dose adjustment is necessary in patients with moderate or severe hepatic impairment unless accompanied by renal impairment (see *Pharmacokinetics*).

- **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.

Contraindications

The use of *EPIVIR* is contraindicated in patients with known hypersensitivity to lamivudine or to any ingredient of the preparation.

Warnings and Precautions

EPIVIR is not recommended for use as monotherapy.

- **Opportunistic infections**

Patients receiving *EPIVIR* or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore they should remain under close clinical observation by physicians experienced in the treatment of patients with associated HIV diseases.

- **Renal impairment**

Lamivudine plasma concentrations (AUC) are increased in patients with moderate to severe renal impairment due to decreased clearance. The dose should therefore be adjusted (see *Dosage and Administration*).

- **Pancreatitis**

Pancreatitis has been observed in some patients receiving *EPIVIR*. However it is unclear whether this was due to treatment with the medicinal product or to the underlying HIV disease. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of *EPIVIR* until diagnosis of pancreatitis is excluded.

- **Lactic acidosis/severe hepatomegaly with steatosis**

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues either alone or in combination, including *EPIVIR*. A majority of these cases have been in women.

Clinical features which may be indicative of the development of lactic acidosis include generalised weakness, anorexia, and sudden unexplained weight loss, gastrointestinal symptoms and respiratory symptoms (dyspnoea and tachypnoea).

Caution should be exercised when administering *EPIVIR* particularly to those with known risk factors for liver disease. Treatment with *EPIVIR* should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

- **Serum lipids and blood glucose**

Serum lipid and blood glucose levels may increase during antiretroviral therapy. Disease control and lifestyle changes may also be contributing factors. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

- **Immune reconstitution syndrome**

In HIV-infected patients with severe immune deficiency at the time of initiation of antiretroviral therapy (ART), an inflammatory reaction to asymptomatic or residual opportunistic infections 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 ART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and *Pneumocystis jiroveci* pneumonia (often referred to as PCP). Any inflammatory symptoms must be evaluated without delay and treatment

initiated when necessary. Autoimmune disorders (such as Graves' disease, polymyositis and Guillain-Barre syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable, and can occur many months after initiation of treatment and sometimes can be an atypical presentation.

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

Clinical trial and marketed use of *EPIVIR*, have shown that some patients with chronic hepatitis B virus (HBV) disease may experience clinical or laboratory evidence of recurrent hepatitis upon discontinuation of *EPIVIR*, which may have more severe consequences in patients with decompensated liver disease. If *EPIVIR* is discontinued in a patient with HIV and HBV co-infection, periodic monitoring of both liver function tests and markers of HBV replication should be considered.

Oral solution:

Diabetic patients should be advised that an adult dose contains 3 g of sucrose.

Trough levels of lamivudine in plasma and of intracellular lamivudine triphosphate were lower with once daily dosing than with twice daily dosing. The clinical significance of this observation is not known.

- **Special patient population**

Children

Children who at anytime received *EPIVIR* oral solution concomitantly with other antiretroviral oral solutions in clinical trials experienced lower rates of virological suppression, had lower plasma lamivudine exposure and developed viral resistance more frequently than children receiving tablets (see *Clinical Studies* and *Pharmacokinetics*).

An all-tablet regimen should be used when possible. *EPIVIR* oral solution given concomitantly with sorbitol-containing medicines should be used only when an all-tablet regimen cannot be used and the benefits of treatment outweigh possible risks including lower virological suppression. Consider more frequent monitoring of HIV-1 viral load when *EPIVIR* is used with chronically-administered, sorbitol-containing medicines (see *Interactions*).

Interactions

The likelihood of interactions is low due to limited metabolism and plasma protein binding and almost complete renal elimination of unchanged lamivudine.

Lamivudine is predominantly eliminated by active organic cationic secretion. The possibility of interactions with other medicinal products administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system e.g. trimethoprim. Other active substances (e.g. ranitidine, cimetidine) are eliminated only in part by this mechanism and were shown not to interact with lamivudine.

Active substances shown to be predominantly excreted either via the active organic anionic pathway, or by glomerular filtration are unlikely to yield clinically significant interactions with lamivudine.

Effect of lamivudine on the pharmacokinetics of other agents

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

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

Effect of other agents on the pharmacokinetics of lamivudine

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

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

Lamivudine is a substrate of Pgp and BCRP, however due to its high bioavailability it is unlikely that these transporters play a significant role in the absorption of lamivudine. Therefore co-administration of drugs that are inhibitors of these efflux transporters is unlikely to affect the disposition and elimination of lamivudine.

Interactions relevant to lamivudine

Sorbitol: Co-administration of sorbitol solution (3.2 g, 10.2 g, 13.4 g) with a single 300 mg dose of lamivudine oral solution resulted in dose-dependent decreases of 14%, 32%, and 36% in lamivudine exposure (AUC_∞) and 28%, 52%, and 55% in the C_{max} of lamivudine in adults. When possible, avoid use of *EPIVIR* with sorbitol-containing medicines or consider more frequent monitoring of HIV-1 viral load when chronic co-administration cannot be avoided (see *Warnings and Precautions*).

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

Trimethoprim/sulphamethoxazole: Administration of trimethoprim/sulphamethoxazole 160 mg/800 mg (co-trimoxazole) causes a 40% increase in lamivudine exposure because of the trimethoprim component. However, unless the patient has renal impairment, no dosage adjustment of *EPIVIR* is necessary (see *Dosage and Administration*). Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulphamethoxazole. The effect of co-

administration of *EPIVIR* with higher doses of co-trimoxazole for the treatment of *Pneumocystis jiroveci* pneumonia and toxoplasmosis has not been studied.

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

Pregnancy and Lactation

Pregnancy:

Lamivudine has been evaluated in the Antiretroviral Pregnancy Registry in over 11,000 women during pregnancy and postpartum. Available human data from the Antiretroviral Pregnancy Registry do not show an increased risk of major birth defects for lamivudine compared to the background rate (see *Clinical Studies*). However, there are no adequate and well-controlled trials in pregnant women and the safe use of lamivudine in human pregnancy has not been established. Studies in humans have confirmed that lamivudine crosses the placenta. Use in pregnancy should be considered only if the benefit outweighs the risk. Although the results of animal studies are not always predictive of human response, the findings in rabbits suggest a potential risk of early embryonic loss.

Reproductive studies in animals have not shown evidence of teratogenicity and showed no effect on male or female fertility. Lamivudine produced small increases in early embryonic loss when administered to pregnant rabbits, at exposure levels comparable to those achieved in man. However, there was no evidence of embryonic loss in rats at exposure levels of approximately 35 times the clinical exposure (based on C_{max}).

There have been reports of mild, transient elevations in serum lactate levels, which may be due to mitochondrial dysfunction, in neonates and infants exposed *in utero* or *peri-partum* to nucleoside reverse transcriptase inhibitors (NRTIs). The clinical relevance of transient elevations in serum lactate is unknown. There have also been very rare reports of developmental delay, seizures and other neurological disease. However, a causal relationship between these events and NRTI exposure *in utero* or *peri-partum* has not been established. These findings do not affect current recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Lactation:

Health experts recommend that where possible women infected with HIV do not breast feed their infants in order to avoid the transmission of HIV. Following oral administration lamivudine was excreted in human breast milk at similar concentrations to those found in serum (1 to 8 micrograms/mL). Since lamivudine and the virus pass into breast milk, it is recommended that mothers taking *EPIVIR* do not breast feed their infants.

Effects on Ability to Drive and Use Machines

There have been no studies to investigate the effect of *EPIVIR* on driving performance or the ability to operate machinery. Further, a detrimental effect on such activities cannot be predicted from the pharmacology of lamivudine. Nevertheless, the clinical status of the patient and the adverse event profile of *EPIVIR* should be borne in mind when considering the patient's ability to drive or operate machinery.

Adverse Reactions

The following events have been reported during therapy for HIV disease with *EPIVIR* alone and in combination with other antiretroviral agents. With many it is unclear whether they are related to medicinal products or are as a result of the underlying disease process.

The following convention has been utilised for the classification of undesirable effects: Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1,000, <1/100), rare (>1/10,000, <1/1,000), very rare (<1/10,000).

Blood and lymphatic systems disorders

Uncommon:	Neutropenia, anaemia, thrombocytopenia
Very rare:	Pure red cell aplasia

Metabolism and nutrition disorders

Common:	Hyperlactataemia
Rare:	Lactic acidosis (see *Warnings and Precautions*)

Nervous system disorders

Common:	Headache
Very rare:	Paraesthesia. Peripheral neuropathy has been reported although a causal relationship to treatment is uncertain.

Gastrointestinal disorders

Common:	Nausea, vomiting, upper abdominal pain, diarrhoea
Rare:	Pancreatitis, although a causal relationship to treatment is uncertain. Rises in serum amylase

Hepatobiliary disorders

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

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

Paediatric population

The safety database to support lamivudine once daily dosing in paediatric patients comes from the ARROW Trial (COL105677) in which 669 HIV-1 infected paediatric subjects received abacavir and lamivudine either once or twice daily (see *Clinical Studies*). No additional safety issues have been identified in paediatric subjects receiving either once or twice daily dosing compared to adults.

Overdose

Symptoms and Signs

No specific signs or symptoms have been identified following acute overdose with lamivudine, apart from those listed as undesirable effects.

Treatment

If overdosage occurs the patient should be monitored, and standard supportive treatment applied as required. Since lamivudine is dialysable, continuous haemodialysis could be used in the treatment of overdosage, although this has not been studied.

PHARMACODYNAMIC PROPERTIES

Lamivudine is a potent, selective inhibitor of HIV-1 and HIV-2 replication *in vitro*. It is also active against zidovudine-resistant clinical isolates of HIV. Lamivudine is metabolised intracellularly to the 5'-triphosphate, the active moiety, which has an intra-cellular half-life of 16-19 hours. Lamivudine 5'-triphosphate is a weak inhibitor of the RNA and DNA dependant activities of HIV reverse transcriptase, its main mode of action is as a chain terminator of HIV reverse transcription. No antagonistic effects *in vitro* were seen with lamivudine and other antiretrovirals (tested agents: abacavir, didanosine, nevirapine, zalcitabine, and zidovudine). Lamivudine does not interfere with cellular deoxynucleotide metabolism and has little effect on mammalian cell and mitochondrial DNA content.

In vitro, 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*. Lamivudine therefore has, *in vitro*, a high therapeutic index.

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.

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 less than 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.

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

Reduced *in vitro* sensitivity to lamivudine has been reported for HIV isolates from patients who have received *EPIVIR* therapy.

Evidence from clinical studies show that lamivudine plus zidovudine delays the emergence of zidovudine-resistant isolates in individuals with no prior antiretroviral therapy.

Lamivudine has been widely used as a component of antiretroviral combination therapy with other antiretroviral agents of the same class (nucleoside reverse transcriptase inhibitors) or different classes (protease inhibitors, non-nucleoside reverse transcriptase inhibitors).

Clinical trial evidence from paediatric patients receiving *EPIVIR* with other antiretroviral drugs (abacavir, nevirapine/efavirenz or zidovudine) has shown that the resistance profile observed in paediatric patients is similar to that observed in adults, in terms of the genotypic substitutions detected and their relative frequency.

Children receiving *EPIVIR* oral solution concomitantly with other antiretroviral oral solutions in clinical trials developed viral resistance more frequently than children receiving tablets (see *Clinical Studies* and *Pharmacokinetics*).

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

The relationship between *in vitro* susceptibility of HIV to lamivudine and the clinical response to therapy remain under investigation.

Post-exposure prophylaxis (PEP):

Internationally recognised guidelines (Centre for Disease Control and Prevention - June 1998) recommend that in the event of accidental exposure to HIV infected blood, e.g. from a needlestick injury, a combination of zidovudine and lamivudine should be administered promptly (1 to 2 h). In cases of higher risk of infection, a protease inhibitor should be included in the regimen. It is recommended that antiretroviral prophylaxis be continued for four weeks. No controlled clinical studies have been carried out in post-exposure prophylaxis

and supporting data is limited. Seroconversion may still occur despite prompt treatment with antiretroviral agents.

Pharmacokinetic Properties

Absorption:

Lamivudine is well absorbed from the gastrointestinal tract, and the bioavailability of oral lamivudine in adults is normally between 80 and 85%. Following oral administration, the mean time (t_{max}) to maximal serum concentrations (C_{max}) is about an hour. At therapeutic dose levels i.e. 4 mg/kg/day (as two 12-hourly doses), C_{max} is in the order of 1-1.9 micrograms/mL.

Co-administration of lamivudine with food resulted in a delay of t_{max} and a lower C_{max} (decreased by up to 47%). However, the extent (based on the AUC) of lamivudine absorbed was not influenced. No dose adjustment is needed when co-administered with 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 characteristics of the active ingredient and the *in vitro* dissolution behaviour of lamivudine tablets in water, assuming that the patient crushes and transfers 100% of the tablet and ingests immediately.

Tablets:

Administration of two 150 mg tablets is bioequivalent to administration of one 300 mg tablet with respect to AUC_∞, C_{max}, and t_{max}. Administration of tablets is bioequivalent to oral solution with respect to AUC_∞ and C_{max} in adults.

Absorption differences have been observed between adult and paediatric populations, and between the tablet and oral solution formulations in the paediatric population (see *Special Patient Populations - Children*).

Distribution:

From i.v. studies, the mean volume of distribution is 1.3 L/kg.

Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays low plasma protein binding to albumin.

Limited data shows lamivudine penetrates the central nervous system and reaches the cerebro-spinal fluid (CSF). The mean lamivudine CSF/serum concentration ratio 2-4 hours after oral administration was approximately 0.12. The true extent of penetration or relationship with any clinical efficacy is unknown.

Metabolism and Elimination:

Lamivudine mean systemic clearance is approximately 0.32 L/h/kg, with predominantly renal clearance (greater than 70%) via the organic cationic transport system, and little (less than 10%) hepatic metabolism.

The plasma lamivudine half-life after oral dosing is (18 to 19 h) and the active moiety, intracellular lamivudine triphosphate, has a prolonged terminal half-life in the cell (16 to 19 h). In 60 healthy adult volunteers, lamivudine 300 mg once daily has been demonstrated to be pharmacokinetically equivalent at steady-state to lamivudine 150 mg twice daily with respect to intracellular triphosphate AUC_{24} and C_{max}.

The likelihood of adverse interactions between lamivudine and other medicinal products is low due to limited metabolism and plasma protein binding and almost complete renal elimination of unchanged lamivudine.

Special Patient Populations

- **Children**

The absolute bioavailability of lamivudine (approximately 58-66%) was reduced in paediatric patients below 12 years of age. In children, administration of tablets delivered higher plasma lamivudine AUC_{∞} and C_{max} than oral solution. Children receiving lamivudine oral solution according to the recommended dosage regimen achieve plasma lamivudine exposure within the range of values observed in adults. Children receiving lamivudine oral tablets according to the recommended dosage regimen achieve higher plasma lamivudine exposure than children receiving oral solution because higher mg/kg doses are administered with the tablet formulation and the tablet formulation has higher bioavailability (see *Dosage and Administration*). Paediatric pharmacokinetic studies with both oral solution and tablet formulations have demonstrated that once daily dosing provides equivalent AUC_{0-24} to twice daily dosing of the same total daily dose.

There are limited pharmacokinetic data for patients less than three months of age. In neonates one week of age, lamivudine oral clearance was reduced when compared to paediatric patients and is likely to be due to immature renal function and variable absorption. Therefore to achieve similar adult and paediatric exposure, an appropriate dose for neonates is 4 mg/kg/day. Glomerular filtration estimates suggest that to achieve similar adult and paediatric exposure, an appropriate dose for children aged six weeks and older could be 8 mg/kg/day.

Pharmacokinetic data were derived from 3 pharmacokinetic studies (PENTA 13, PENTA 15 and ARROW PK substudy) enrolling children under 12 years of age. The data are displayed in the table below:

Summary of Steady-State Plasma Lamivudine $AUC_{(0-24)}$ (µg.h/mL) and Statistical Comparisons for Once and Twice-Daily Oral Administration Across Studies

Study	Age Group	Lamivudine 8mg/kg Once-Daily Dosing Geometric Mean (95% CI)	Lamivudine 4 mg/kg Twice-Daily Dosing Geometric Mean (95% CI)	Once-Versus Twice-Daily Comparison GLS Mean Ratio (90% CI)
ARROW PK Substudy Part 1	3 to 12 years (N=35)	13.0 (11.4, 14.9)	12.0 (10.7, 13.4)	1.09 (0.979, 1.20)
PENTA 13	2 to 12 years (N=19)	9.80 (8.64, 11.1)	8.88 (7.67, 10.3)	1.12 (1.03, 1.21)
PENTA 15	3 to 36 months (N=17)	8.66 (7.46, 10.1)	9.48 (7.89, 11.40)	0.91 (0.79, 1.06)

In PENTA 15 study, the geometric mean plasma lamivudine $AUC_{(0-24)}$ (95% CI) of the four subjects under 12 months of age who switch from a twice daily to a once daily regimen (see *Clinical Studies*) are 10.31 (6.26, 17.0) µg.h/mL in the once-daily dosing and 9.24 (4.66, 18.3) µg.h/mL in the twice-daily dosing.

The mean C_{max} was approximately 80% to 90% higher with lamivudine once-daily dosing compared with twice-daily dosing.

- **Elderly**

No pharmacokinetic data are available in patients over 65 years of age.

- **Renal impairment**

Lamivudine plasma concentrations (AUC) are increased in patients with renal dysfunction due to decreased clearance. The dosage should therefore be reduced for patients with a creatinine clearance of less than 30 mL/min (see *Dosage and Administration*).

- **Hepatic impairment**

Data obtained in patients with moderate to severe hepatic impairment show that lamivudine pharmacokinetics are not significantly affected by hepatic dysfunction.

- **Pregnancy**

The pharmacokinetics of lamivudine are similar to that of non-pregnant adults. 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.

Clinical Studies

A randomised comparison of a regimen including once daily vs twice daily dosing of abacavir and lamivudine was undertaken within a randomised, multicentre, controlled study of HIV-infected, paediatric patients. Of note, from this study clinical data were not available for children under one year old. 1206 paediatric patients aged 3 months to 17 years enrolled in the ARROW Trial (COL105677) and were dosed according to the weight-band dosing recommendations in the World Health Organisation treatment guidelines (Antiretroviral therapy of HIV infection in infants and children, 2006). After 36 weeks on a regimen including twice daily abacavir and lamivudine, 669 eligible subjects were randomised to either continue twice daily dosing or switch to once daily abacavir and lamivudine for at least 96 weeks. The results are summarised in the table below:

Virological Response Based on Plasma HIV-1 RNA Less than 80 copies/mL at Week 48 and Week 96 in the Once Daily versus Twice Daily Abacavir + Lamivudine Randomisation of ARROW (Observed Analysis)

	Twice Daily n/N (%)	Once Daily n/N (%)
Week 0 (After ≥36 Weeks on Treatment)		
Plasma HIV-1 RNA <80 c/mL	250/331 (76)	237/335 (71)
Risk difference (once daily-twice daily)	-4.8% (95% CI -11.5% to +1.9%), p=0.16	
Week 48		
Plasma HIV-1 RNA <80 c/mL	242/331 (73)	236/330 (72)
Risk difference (once daily-twice daily)	-1.6% (95% CI -8.4% to +5.2%), p=0.65	
Week 96		
Plasma HIV-1 RNA <80 c/mL	234/326 (72)	230/331 (69)
Risk difference (once daily-twice daily)	-2.3% (95% CI -9.3% to +4.7%), p=0.52	

The abacavir/lamivudine once daily dosing group was demonstrated to be non-inferior to the twice daily group according to the pre-specified non-inferiority margin of -12%, for the primary endpoint of <80 c/mL at Week 48 as well as at Week 96 (secondary endpoint) and all other thresholds tested (<200 c/mL, <400 c/mL, <1000 c/mL), which all fell well within this non-inferiority margin. Subgroup analyses testing for heterogeneity of once vs twice daily demonstrated no significant effect of sex, age, or viral load at randomisation. Conclusions supported non-inferiority regardless of analysis method.

At the time of randomization to once daily vs twice daily dosing (Week 0), those patients who had received tablet formulations had a higher rate of viral load suppression than those who had received any solution formulations at any time. These differences were observed in each different age group studied. This difference in suppression rates between tablets and solutions remained through Week 96 with once daily dosing.

Proportions of Subjects in the Once Daily versus Twice Daily Abacavir + Lamivudine Randomisation of ARROW with Plasma HIV-1 RNA <80 copies/mL: Subgroup Analysis by Formulation

	Twice Daily **Plasma HIV-1 RNA <80 c/mL: n/N (%)**	**Once Daily** **Plasma HIV-1 RNA <80 c/mL: n/N (%)**
Week 0 (after 36 weeks on Treatment)		
Any solution regimen at any time	14/26 (54)	15/30 (50)
All tablet-based regimen throughout	236/305 (77)	222/305 (73)
Week 96		
Any solution regimen at any time	13/26 (50)	17/30 (57)
All tablet-based regimen throughout	221/300 (74)	213/301 (71)

Genotypic resistance analyses were conducted on samples with plasma HIV-1 RNA >1000 copies/mL. More cases of resistance were detected among patients who had received *EPIVIR* solution, in combination with other antiretroviral solutions, compared with those who received similar doses of tablet formulation. This is consistent with the lower rates of antiviral suppression observed in these patients.

In a pharmacokinetic study (PENTA 15), four virologically controlled subjects less than 12 months of age switched from abacavir plus lamivudine oral solution twice daily to a once daily regimen. Three subjects had undetectable viral load and one had plasmatic HIV-RNA of 900 copies/mL at Week 48. No safety concerns were observed in these subjects.

The Antiretroviral Pregnancy Registry has received reports of over 11,000 exposures to lamivudine during pregnancy resulting in live birth. These consist of over 4,200 exposures during the first trimester, over 6,900 exposures during the second/third trimester and included 135 and 198 birth defects respectively. The prevalence (95% CI) of defects in the first trimester was 3.2% (2.6, 3.7%) and in the second/third trimester, 2.8% (2.4, 3.2%). Among pregnant women in the reference population, the background rate of birth defects is 2.7%. The Antiretroviral Pregnancy Registry does not show an increased risk of major birth defects for lamivudine compared to the background rate.

Shelf Life

The expiry date is indicated on the packaging.

Storage

The storage conditions are indicated on the packaging.

Use and Handling

Oral solution:

Where supplied, the oral dosing syringe should be used for accurate measurement of the prescribed dose of *EPIVIR* oral solution.

1. Remove the plastic wrap from the syringe/adapter.
2. Remove the adapter from the syringe.
3. Remove the bottle cap and keep it safe.
4. Push the plastic adapter into the neck of the bottle, while holding the bottle firmly.
5. Insert the syringe firmly into the adapter.
6. Invert bottle.
7. Pull out syringe plunger until the correct amount is withdrawn.
8. Turn the bottle the correct way up and remove the syringe from the adapter.
9. Administer the dose into the mouth by placing the tip of the syringe against the inside of the cheek. Slowly depress the plunger, allowing time to swallow. Forceful squirting to the back of the throat may cause choking.
10. Repeat steps 5-9 if needed to administer the entire dose.
11. After use the syringe must not be left in the bottle and should be washed thoroughly in clean water.
12. Close the bottle tightly with the cap, leaving the adapter in place.

Discard oral solution one month after first opening.

Tablets:

There are no special requirements for use or handling for this formulation.

Product Registrant

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