## 1. NAME OF THE MEDICINAL PRODUCT

Epivir 10 mg/ml oral solution

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of oral solution contains 10 mg of lamivudine.

Excipient(s) with known effect:

Each 15 ml dose contains 3 g sucrose (20% w/v).
Methyl parahydroxybenzoate
Propyl parahydroxybenzoate
Each 15 ml dose contains 300 mg propylene glycol.
Each 15 ml dose contains 39 mg sodium.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Oral solution

Clear, colourless to pale yellow solution.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Epivir is indicated as part of antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infected adults and children.

### 4.2 Posology and method of administration

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

Epivir may be administered with or without food.

Epivir is also available as a tablet formulation for patients who weigh at least 14 kg (see section 4.4).

Patients changing between lamivudine tablets and lamivudine oral solution should follow the dosing recommendations that are specific for the formulation (see section 5.2).

For patients who are unable to swallow tablets, the tablet(s) may be crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately (see section 5.2).

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

The recommended dose of Epivir is 300 mg daily. This may be administered as either 150 mg (15 ml) twice daily or 300 mg (30 ml) once daily (see section 4.4).

*Children (weighing less than 25 kg):*

*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 sections 4.4 and 4.5).

*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 sections 4.4, 5.1 and 5.2).

*Children less than three months of age:* The limited data available are insufficient to propose specific dosage recommendations (see section 5.2).

Patients changing from the twice daily dosing regimen to the once daily dosing regimen should take the recommended once daily dose (as described above) approximately 12 hours after the last twice daily dose, and then continue to take the recommended once daily dose (as described above) approximately every 24 hours. When changing back to a twice daily regimen, patients should take the recommended twice daily dose approximately 24 hours after the last once daily dose.

*Special populations:*

*Older people:* 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.

*Renal impairment:* Lamivudine concentrations are increased in patients with moderate - severe renal impairment due to decreased clearance. The dose should therefore be adjusted (see tables).

*Dosing recommendations – Adults, adolescents and children (weighing at least 25 kg):*

| **Creatinine clearance (ml/min)** | **First dose** | **Maintenance dose** |
|---|---|---|
| ≥50 | 300 mg (30 ml)<br>or<br>150 mg (15 ml) | 300 mg (30 ml) once daily<br>or<br>150 mg (15 ml) twice daily |
| 30 to<50 | 150 mg (15 ml) | 150 mg (15 ml) once daily |
| 15 to <30 | 150 mg (15 ml) | 100 mg (10 ml) once daily |
| 5 to <15 | 150 mg (15 ml) | 50 mg (5 ml) once daily |
| <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. Based on the assumption that creatinine clearance and lamivudine clearance are correlated similarly in children as in adults; it is recommended that the dosage in children with renal impairment be reduced according to their creatinine clearance by the same proportion as in adults. The Epivir 10 mg/mL oral solution may be the most appropriate formulation to achieve the recommended dose in children with renal impairment aged at least 3 months and weighing less than 25kg.

*Dosing recommendations – Children aged at least 3 months and weighing less than 25 kg:*

| **Creatinine clearance (ml/min)** | **First dose** | **Maintenance dose** |
|---|---|---|
| ≥50 | 10 mg/kg<br>or<br>5 mg/kg | 10 mg/kg once daily<br>or<br>5 mg/kg twice daily |
| 30 to<50 | 5 mg/kg | 5 mg/kg once daily |
| 15 to <30 | 5 mg/kg | 3.3 mg/kg once daily |
| 5 to <15 | 5 mg/kg | 1.6 mg/kg once daily |
| <5 | 1.6 mg/kg | 0.9 mg/kg once daily |

*Hepatic impairment:* Data obtained in patients with moderate to severe hepatic impairment shows that lamivudine pharmacokinetics are not significantly affected by hepatic dysfunction. Based on these data, no dose adjustment is necessary in patients with moderate or severe hepatic impairment unless accompanied by renal impairment.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

## 4.4 Special warnings and precautions for use

Epivir is not recommended for use as monotherapy.

*Renal impairment:* In patients with moderate –to- severe renal impairment, the terminal plasma half-life of lamivudine is increased due to decreased clearance, therefore the dose should be adjusted (see section 4.2).

*Triple nucleoside therapy:* There have been reports of a high rate of virological failure and of emergence of resistance at an early stage when lamivudine was combined with tenofovir disoproxil fumarate and abacavir as well as with tenofovir disoproxil fumarate and didanosine as a once daily regimen.

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

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

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

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

*Immune Reactivation Syndrome:* In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or

months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterium infections, and *Pneumocystis jirovecii* pneumonia (often referred to as PCP). Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

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

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

If Epivir is discontinued in patients co-infected with hepatitis B virus, periodic monitoring of liver function tests and markers of HBV replication is recommended, as withdrawal of lamivudine may result in an acute exacerbation of hepatitis (see Zeffix SPC).

Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy, and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered (see section 4.8).

*Excipients:* Diabetic patients should be advised that each dose (150 mg = 15 ml) contains 3 g of sucrose.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Epivir contains methyl parahydroxybenzoate and propyl parahydroxybenzoate. These may cause allergic reactions (possibly delayed).

This medicinal product contains 39 mg sodium per 15 ml, equivalent to 1.95% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

*Paediatric Population:* In a study performed in paediatric patients (see section 5.1 ARROW study), lower rates of virologic suppression and more frequent viral resistance were reported in children receiving the oral solution of Epivir as compared to those receiving the tablet formulation.

Whenever possible in children, an all-tablet regimen should preferably be used. 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 [e.g. Ziagen oral solution]. Although not studied, the same effect would be expected with other osmotic acting poly-alcohols or monosaccharide alcohols (e.g. xylitol, mannitol, lactitol, maltitol (see section 4.5)).

*Osteonecrosis:* Although the etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

*Drug Interactions:* Epivir should not be taken with any other medicinal products containing lamivudine or medicinal products containing emtricitabine (see section 4.5).

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

Interaction studies have only been performed in adults.

The likelihood of metabolic interactions is low due to limited metabolism and plasma protein binding and almost complete renal clearance.

Administration of trimethoprim/sulfamethoxazole 160 mg/800 mg results in a 40 % increase in lamivudine exposure, because of the trimethoprim component; the sulfamethoxazole component did not interact. However, unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary (see section 4.2). Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole. When concomitant administration is warranted, patients should be monitored clinically. Co-administration of lamivudine with high doses of co-trimoxazole for the treatment of *Pneumocystis jirovecii* pneumonia (PCP) and toxoplasmosis should be avoided.

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

A modest increase in $C_{max}$ (28 %) was observed for zidovudine when administered with lamivudine, however overall exposure (AUC) is not significantly altered. Zidovudine has no effect on the pharmacokinetics of lamivudine (see section 5.2).

Due to similarities, Epivir should not be administered concomitantly with other cytidine analogues, such as emtricitabine. Moreover, Epivir should not be taken with any other medicinal products containing lamivudine (see section 4.4).

*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).

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

Coadministration 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 ($AUC_{\infty}$) and 28%, 52%, and 55% in the $C_{max}$ of lamivudine in adults. When possible, avoid chronic coadministration of Epivir with medicinal products containing sorbitol or other osmotic acting poly-alcohols or monosaccharide alcohols (e.g. xylitol, mannitol, lactitol, maltitol). Consider more frequent monitoring of HIV-1 viral load when chronic coadministration cannot be avoided (see section 4.4).

## 4.6 Fertility Pregnancy and lactation

Pregnancy

As a general rule, when deciding to use antiretroviral agents for the treatment of HIV infection in pregnant women and consequently for reducing the risk of HIV vertical transmission to the newborn, the animal data as well as the clinical experience in pregnant women should be taken into account.

Animal studies with lamivudine showed an increase in early embryonic deaths in rabbits but not in rats (see section 5.3). Placental transfer of lamivudine has been shown to occur in humans.

More than 1000 outcomes from first trimester and more than 1000 outcomes from second and third trimester exposure in pregnant women indicate no malformative and foeto/neonatal effect. Epivir can be used during pregnancy if clinically needed. The malformative risk is unlikely in humans based on those data.

For patients co-infected with hepatitis who are being treated with lamivudine and subsequently become pregnant, consideration should be given to the possibility of a recurrence of hepatitis on discontinuation of lamivudine.

*Mitochondrial dysfunction:* Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in infants exposed *in utero* and/or post-natally to nucleoside analogues (see section 4.4).

Breast-feeding

Following oral administration lamivudine was excreted in breast milk at similar concentrations to those found in serum. Based on more than 200 mother/child pairs treated for HIV, serum concentrations of lamivudine in breastfed infants of mothers treated for HIV are very low (< 4% of maternal serum concentrations) and progressively decrease to undetectable levels when breastfed infants reach 24 weeks of age. There are no data available on the safety of lamivudine when administered to babies less than three months old. It is recommended that women living with HIV do not breast-feed their infants in order to avoid transmission of HIV.

Fertility
Studies in animals showed that lamivudine had no effect on fertility (see section 5.3).

### 4.7 Effects on ability to drive and use machines

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

### 4.8 Undesirable effects

The following adverse reactions have been reported during therapy for HIV disease with Epivir.

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

Blood and lymphatic systems disorders
*Uncommon*: Neutropenia and anaemia (both occasionally severe), thrombocytopenia
*Very rare*: Pure red cell aplasia

Metabolism and nutrition disorders
*Very rare:* Lactic acidosis

Nervous system disorders
*Common:* Headache, insomnia
*Very rare:* Peripheral neuropathy (or paraesthesia)

Respiratory, Thoracic and mediastinal disorders
*Common:* Cough, nasal symptoms

Gastrointestinal disorders
*Common:* Nausea, vomiting, abdominal pain or cramps, diarrhoea
*Rare:* Pancreatitis, elevations in serum amylase

Hepatobiliary disorders
*Uncommon:* Transient elevations in liver enzymes (AST, ALT)
*Rare:* Hepatitis

Skin and subcutaneous tissue disorders
*Common:* Rash, alopecia
*Rare:* Angioedema

Musculoskeletal and connective tissue disorders
*Common:* Arthralgia, muscle disorders
*Rare:* Rhabdomyolysis

General disorders and administration site conditions
*Common:* Fatigue, malaise, fever

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4)

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) 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 (see section 4.4).

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term combined antiretroviral exposure (CART). The frequency of which is unknown (see section 4.4).

Paediatric population

1206 HIV-infected paediatric patients aged 3 months to 17 years were enrolled in the ARROW Trial (COL105677), 669 of whom received abacavir and lamivudine either once or twice daily (see section 5.1). No additional safety issues have been identified in paediatric subjects receiving either once or twice daily dosing compared to adults.

Reporting of suspected adverse reactions
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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

## 4.9 Overdose

Administration of lamivudine at very high dose levels in acute animal studies did not result in any organ toxicity. No specific signs or symptoms have been identified following acute overdose with lamivudine, apart from those listed as undesirable effects.

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.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: nucleoside analogue, ATC Code: J05AF05.

Mechanism of action

Lamivudine is a nucleoside analogue which has activity against human immunodeficiency virus (HIV) and hepatitis B virus (HBV). It is metabolised intracellularly to the active moiety, lamivudine 5'- triphosphate. Its main mode of action is as a chain terminator of viral reverse transcription. The triphosphate has selective inhibitory activity against HIV-1 and HIV-2 replication *in vitro*; it is also active against zidovudine-resistant clinical isolates of HIV. No antagonistic effects *in vitro* were seen with lamivudine and other anti retrovirals (tested agents: abacavir, didanosine, nevirapine and zidovudine).

Resistance

HIV-1 resistance to lamivudine involves the development of a M184V amino acid change close to the active site of the viral reverse transcriptase (RT). This variant arises both *in vitro* and in HIV-1 infected patients treated with lamivudine-containing antiretroviral therapy. M184V mutants display greatly reduced susceptibility to lamivudine and show diminished viral replicative capacity *in vitro*. *In vitro* studies indicate that zidovudine-resistant virus isolates can become zidovudine sensitive when they simultaneously acquire resistance to lamivudine. The clinical relevance of such findings remains, however, not well defined.

*In vitro* data tend to suggest that the continuation of lamivudine in anti-retroviral regimen despite the development of M184V might provide residual anti-retroviral activity (likely through impaired viral fitness). The clinical relevance of these findings is not established. Indeed, the available clinical data are very limited and preclude any reliable conclusion in the field. In any case, initiation of susceptible NRTI's should always be preferred to maintenance of lamivudine therapy. Therefore, maintaining lamivudine therapy despite emergence of M184V mutation should only be considered in cases where no other active NRTI's are available.

Cross-resistance conferred by the M184V RT is limited within the nucleoside inhibitor class of antiretroviral agents. Zidovudine and stavudine maintain their antiretroviral activities against lamivudine-resistant HIV-1. Abacavir maintains its antiretroviral activities against lamivudine-resistant HIV-1 harbouring only the M184V mutation. The M184V RT mutant shows a <4-fold decrease in susceptibility to didanosine; the clinical significance of these findings is unknown. *In vitro* susceptibility testing has not been standardised and results may vary according to methodological factors.

Lamivudine demonstrates low cytotoxicity to peripheral blood lymphocytes, to established lymphocyte and monocyte-macrophage cell lines, and to a variety of bone marrow progenitor cells *in vitro*.

Clinical efficacy and safety

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

Evidence from clinical studies shows 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 (NRTIs) or different classes (PIs, non-nucleoside reverse transcriptase inhibitors).

Clinical trial evidence from paediatric patients receiving lamivudine 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 lamivudine oral solution concomitantly with other antiretroviral oral solutions in clinical trials developed viral resistance more frequently than children receiving tablets (see the description of the clinical experience in paediatric population (ARROW study) and section 5.2).

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

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

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

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

*Once daily dosing (300 mg once a day):* a clinical study has demonstrated the non inferiority between Epivir once a day and Epivir twice a day containing regimens. These results were obtained in an antiretroviral naïve-population, primarily consisting of asymptomatic HIV infected patients (CDC stage A).

*Paediatric population:*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. 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. Of note, from this study clinical data were not available for children under one year old. 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 | |

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 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 (<200c/ml, <400c/ml, <1000c/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 lamivudine 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.

## 5.2 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. Based on data derived from a study in healthy volunteers, at a therapeutic dose of 150 mg twice daily, mean (CV) steady-state $C_{max}$ and $C_{min}$ of lamivudine in plasma are 1.2 µg/ml (24%) and 0.09 µg/ml (27%), respectively. The mean (CV) AUC over a dosing interval of 12 hours is 4.7 µg.h/ml (18%). At a therapeutic dose of 300 mg once daily, the mean (CV) steady-state $C_{max}$, $C_{min}$ and 24h AUC are 2.0 µg/ml (26%), 0.04 µg/ml (34%) and 8.9 µg.h/ml (21%), respectively.

Co-administration of lamivudine with food results in a delay of $t_{max}$ and a lower $C_{max}$ (decreased by 47 %). However, the extent (based on the AUC) of lamivudine absorbed is not influenced.

Administration of crushed tablets with a small amount of semi-solid food or liquid would not be expected to have an impact on the pharmaceutical quality, and would therefore not be expected to alter the clinical effect. This conclusion is based on the physiochemical and pharmacokinetic data assuming that the patient crushes and transfers 100% of the tablet and ingests immediately.

Co-administration of zidovudine results in a 13% increase in zidovudine exposure and a 28% increase in peak plasma levels. This is not considered to be of significance to patient safety and therefore no dosage adjustments are necessary.

Distribution

From intravenous studies, the mean volume of distribution is 1.3 l/kg. The mean systemic clearance of lamivudine is approximately 0.32 l/h/kg, with predominantly renal clearance (>70 %) via the organic cationic transport system.

Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays limited binding to the major plasma protein albumin (< 16% - 36% to serum albumin in *in vitro* studies).

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

Biotransformation

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

Lamivudine is predominately cleared unchanged by renal excretion. The likelihood of metabolic interactions of lamivudine with other medicinal products is low due to the small extent of hepatic metabolism (5-10%) and low plasma protein binding.

Elimination

Studies in patients with renal impairment show lamivudine elimination is affected by renal dysfunction. A recommended dosage regimen for patients with creatinine clearance below 50 ml/min is shown in the dosage section (see section 4.2).

An interaction with trimethoprim, a constituent of co-trimoxazole, causes a 40 % increase in lamivudine exposure at therapeutic doses. This does not require dose adjustment unless the patient also has renal impairment (see sections 4.5 and 4.2). Administration of co-trimoxazole with lamivudine in patients with renal impairment should be carefully assessed.

Special 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 given concomitantly with other antiretroviral tablets delivered higher plasma lamivudine $AUC_{\infty}$ and $C_{max}$ than oral solution given concomitantly with other antiretroviral oral solutions. 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 section 4.2). 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 suggests 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 Stead-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% Cl) | Lamivudine 4 mg/kg Twice-Daily Dosing Geometric Mean (95% Cl) | Once-Versus Twice-Daily Comparison GLS Mean Ratio (90% Cl) |
|---|---|---|---|---|
| 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 section 5.1) 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.

*Pregnancy:* Following oral administration, lamivudine pharmacokinetics in late-pregnancy were similar to non-pregnant women.

### 5.3 Preclinical safety data

Administration of lamivudine in animal toxicity studies at high doses was not associated with any major organ toxicity. At the highest dosage levels, minor effects on indicators of liver and kidney function were seen together with occasional reductions in liver weight. The clinically relevant effects noted were a reduction in red blood cell count and neutropenia.

Lamivudine was not mutagenic in bacterial tests but, like many nucleoside analogues, showed activity in an *in vitro* cytogenetic assay and the mouse lymphoma assay. Lamivudine was not genotoxic *in vivo* at doses that gave plasma concentrations around 40-50 times higher than the anticipated clinical plasma levels. As the *in vitro* mutagenic activity of lamivudine could not be confirmed in *in vivo* tests, it is concluded that lamivudine should not represent a genotoxic hazard to patients undergoing treatment.

A transplacental genotoxicity study conducted in monkeys compared zidovudine alone with the combination of zidovudine and lamivudine at human-equivalent exposures. The study demonstrated that foetuses exposed *in utero* to the combination sustained a higher level of nucleoside analogue-DNA incorporation into multiple foetal organs, and showed evidence of more telomere shortening than in those exposed to zidovudine alone. The clinical significance of these findings is unknown.

The results of long-term carcinogenicity studies in rats and mice did not show any carcinogenic potential relevant for humans.

A fertility study in rats has shown that lamivudine had no effect on male or female fertility.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sucrose 20 % w/v (3 g/15 ml)
Methyl parahydroxybenzoate
Propyl parahydroxybenzoate
Citric acid Anhydrous
Propylene glycol
Sodium citrate
Artificial strawberry flavour
Artificial banana flavour
Purified water

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

2 years

Discard the oral solution one month after first opening.

### 6.4 Special precautions for storage

Do not store above 25°C.

### 6.5 Nature and contents of container

Cartons containing 240 ml oral solution in a white high density polyethylene (HDPE) bottle, with a child resistant closure. The pack also includes a polyethylene syringe-adapter, and a 10 ml oral dosing syringe comprised of a polypropylene barrel (with ml graduations) and a polyethylene plunger.

The oral dosing syringe is provided for accurate measurement of the prescribed dose of the oral solution. Instructions for use are included in the pack.

### 6.6 Special precautions for disposal

No special requirements for disposal.

## 7. MARKETING AUTHORISATION HOLDER

ViiV Healthcare UK Limited
980 Great West Road
Brentford
Middlesex
TW8 9GS
United Kingdom

## 8. MARKETING AUTHORISATION NUMBER

PLGB 35728/0031

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01 January 2021

## 10. DATE OF REVISION OF THE TEXT

21 April 2023