ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Epivir 150 mg film-coated tablets

Epivir 300 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Epivir 150 mg film-coated tablets

Each film-coated tablet contains 150 mg lamivudine.

Epivir 300 mg film-coated tablets

Each film-coated tablet contains 300 mg lamivudine

Excipient(s) with known effect:
Each 150 mg tablet contains 0.378 mg sodium.
Each 300 mg tablet contains 0.756 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Epivir 150 mg film-coated tablets

Film-coated tablet

White, diamond shaped scored tablets engraved with "GX CJ7" on both faces.

Epivir 300 mg film-coated tablets

Film-coated tablet

Grey, diamond shaped and engraved with "GX EJ7" on one face

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.
To ensure administration of the entire dose, the tablet(s) should ideally be swallowed without crushing.

Epivir is also available as an oral solution for children over three months of age and who weigh less than 14 kg or for patients who are unable to swallow tablets (see section 4.4).
Patients changing between lamivudine oral solution and lamivudine tablets should follow the dosing recommendations that are specific for the formulation (see section 5.2)

Alternatively, 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 twice daily or 300 mg once daily (see section 4.4).

The 300 mg tablet is only suitable for the once a day regimen.

Children (weighing less than 25 kg):

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 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.

Children from three months of age: As an accurate dosage cannot be achieved with the 300 mg non-scored tablet formulation in this patient population, it is recommended that the Epivir 150 mg scored tablet formulation is used and the corresponding recommended dosage instructions are followed.

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, using oral solution presentation of Epivir for patients whose creatinine clearance falls below 30 ml/min (see tables).

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

Creatinine clearance (ml/min)	**First dose**	**Maintenance dose**
≥50	300 mg or 150 mg	300 mg once daily or 150 mg twice daily
30-<50	150 mg	150 mg once daily

<30 As doses below 150 mg are needed the use of the oral solution is recommended		
15 to <30	150 mg	100 mg once daily
5 to <15	150 mg	50 mg once daily
<5	50 mg	25 mg 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 or 5 mg/kg	10 mg/kg once daily or 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).

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, Epivir as tablet formulation should preferably be used.

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).

Excipients:
Sodium: This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

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_{∞}) 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.

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 national reporting system listed in Appendix V.

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 antiretrovirally-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 (%)	**Once Daily 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.

The 150 mg tablet is bioequivalent and dose proportional to the 300 mg tablet with respect to AUC_{∞}, C_{max}, and t_{max}. Administration of Epivir tablets is bioequivalent to Epivir oral solution with respect to AUC_{∞} and C_{max} in adults. Absorption differences have been observed between adult and paediatric populations (see Special populations).

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_{∞} 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

Epivir 150 mg Film-coated tablets

Tablet core:
Microcrystalline cellulose (E460),
Sodium starch glycollate
Magnesium stearate

Tablet film-coat:
Hypromellose (E464)
Titanium dioxide (E171),
Macrogol,
Polysorbate 80

Epivir 300 mg Film-coated tablets

Tablet core:
Microcrystalline cellulose (E460),
Sodium starch glycollate
Magnesium stearate

Tablet film-coat:
Hypromellose (E464),
Titanium dioxide (E171),

Black iron oxide (E172),
Macrogol, Polysorbate 80

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Epivir 150 mg Film-coated tablets

HDPE bottles: 5 years

PVC/aluminium foil blister packs: 2 years

Epivir 300 mg Film-coated tablets

HDPE bottles : 3 years

PVC/aluminium foil blister packs: 2 years

6.4 Special precautions for storage

Do not store above 30°C

6.5 Nature and contents of container

Epivir 150 mg Film-coated tablets

Child resistant HDPE bottles or PVC/aluminium foil blister packs each containing 60 tablets.

Epivir 300 mg Film-coated tablets

Child resistant HDPE bottles or PVC/aluminium foil blister packs each containing 30 tablets

6.6 Special precautions for disposal

No special requirements for disposal

7. MARKETING AUTHORISATION HOLDER

ViiV Healthcare BV
Van Asch van Wijckstraat 55H
3811 LP Amersfoort
Netherlands

8. MARKETING AUTHORISATION NUMBER

Epivir 150 mg Film-coated tablets

EU/1/96/015/001 (Bottle)
EU/1/96/015/004 (Blister pack)

Epivir 300 mg Film-coated tablets

EU/1/96/015/003 (Bottle)
EU/1/96/015/005 (Blister pack)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Epivir 150 mg Film-coated tablets

Date of first authorisation: 8 August 1996
Date of last renewal: 28 July 2006

Epivir 300 mg Film-coated tablets

Date of first authorisation: 15 November 2001
Date of last renewal: 28 July 2006

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

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) or 150 mg (15 ml)	300 mg (30 ml) once daily or 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 or 5 mg/kg	10 mg/kg once daily or 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_{∞}) 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 national reporting system listed in Appendix V.

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 (%)	**Once Daily 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_{∞} 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% 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 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 BV
Van Asch van Wijckstraat 55H
3811 LP Amersfoort
Netherlands

8. MARKETING AUTHORISATION NUMBER

EU/1/96/015/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8 August 1996
Date of last renewal: 28 July 2006

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Film-coated tablets:

Delpharm Poznań Spółka Akcyjna
ul. Grunwaldzka 189
60-322 Poznan
Poland

Oral solution:

ViiV Healthcare Trading Services UK Limited
12 Riverwalk,
Citywest Business Campus
Dublin 24,
Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2)

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

Periodic safety update reports (PSURs)

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.
An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

BOTTLE CARTON X 60 FILM-COATED TABLETS (150 mg)

1. NAME OF THE MEDICINAL PRODUCT

Epivir 150 mg film-coated tablets
Lamivudine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains lamivudine 150 mg

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 film-coated tablets
Scored tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ViiV Healthcare BV
Van Asch van Wijckstraat 55H
3811 LP Amersfoort
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/015/001

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

epivir 150 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

BOTTLE LABEL X 60 FILM-COATED TABLETS (150 mg)

1. NAME OF THE MEDICINAL PRODUCT

Epivir 150 mg film-coated tablets
Lamivudine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains lamivudine 150 mg

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 film-coated tablets
Scored tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ViiV Healthcare BV
Van Asch van Wijckstraat 55H
3811 LP Amersfoort
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/015/001

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BLISTER CARTON X 60 FILM-COATED TABLETS (150 mg)

1. NAME OF THE MEDICINAL PRODUCT

Epivir 150 mg film-coated tablets
Lamivudine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains
lamivudine 150 mg

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ViiV Healthcare BV
Van Asch van Wijckstraat 55H
3811 LP Amersfoort
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/015/004

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

epivir 150 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

Epivir 150 mg tablets

lamivudine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

ViiV Healthcare BV

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

BOTTLE CARTON FOR ORAL SOLUTION

1. NAME OF THE MEDICINAL PRODUCT

Epivir 10 mg/ml oral solution
Lamivudine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of oral solution contains 10 mg lamivudine

3. LIST OF EXCIPIENTS

This product also contains sugar, preservatives: methyl parahydroxybenzoate and propyl parahydroxybenzoate, propylene glycol and sodium.

4. PHARMACEUTICAL FORM AND CONTENTS

Bottle contents:
240 ml oral solution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C

Discard one month after first opening

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ViiV Healthcare BV
Van Asch van Wijckstraat 55H
3811 LP Amersfoort
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/015/002

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

epivir 10 mg/ml

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

BOTTLE LABEL FOR ORAL SOLUTION

1. NAME OF THE MEDICINAL PRODUCT

Epivir 10 mg/ml oral solution
Lamivudine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of oral solution contains 10 mg lamivudine

3. LIST OF EXCIPIENTS

This product also contains sugar, preservatives: methyl parahydroxybenzoate and propyl parahydroxybenzoate, propylene glycol and sodium.

4. PHARMACEUTICAL FORM AND CONTENTS

Bottle contents:
240 ml oral solution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C

Discard one month after first opening

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ViiV Healthcare BV
Van Asch van Wijckstraat 55H
3811 LP Amersfoort
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/015/002

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

BOTTLE CARTON X 30 FILM-COATED TABLETS (300 mg)

1. NAME OF THE MEDICINAL PRODUCT

Epivir 300 mg film-coated tablets
Lamivudine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains
Lamivudine 300 mg

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ViiV Healthcare BV
Van Asch van Wijckstraat 55H
3811 LP Amersfoort
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/015/003

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

epivir 300 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

BOTTLE LABEL X 30 FILM-COATED TABLETS (300 mg)

1. NAME OF THE MEDICINAL PRODUCT

Epivir 300 mg film-coated tablets
Lamivudine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains
Lamivudine 300 mg

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ViiV Healthcare BV
Van Asch van Wijckstraat 55H
3811 LP Amersfoort
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/015/003

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BLISTER CARTON X 30 FILM-COATED TABLETS (300 mg)

1. NAME OF THE MEDICINAL PRODUCT

Epivir 300 mg film-coated tablets
Lamivudine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains
lamivudine 300 mg

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ViiV Healthcare BV
Van Asch van Wijckstraat 55H
3811 LP Amersfoort
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/015/005

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

epivir 300 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

Epivir 300 mg tablet

lamivudine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

ViiV Healthcare BV

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Epivir 150 mg film-coated tablets
lamivudine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any of the side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Epivir is and what it is used for
2. What you need to know before you take Epivir
3. How to take Epivir
4. Possible side effects
5. How to store Epivir
6. Contents of the pack and other information

1. What Epivir is and what it is used for

Epivir is used to treat HIV (human immunodeficiency virus) infection in adults and children.

The active ingredient in Epivir is lamivudine. Epivir is a type of medicine known as an anti-retroviral. It belongs to a group of medicines called *nucleoside analogue reverse transcriptase inhibitors* (*NRTIs*).

Epivir does not completely cure HIV infection; it reduces the amount of virus in your body, and keeps it at a low level. It also increases the CD4 cell count in your blood. CD4 cells are a type of white blood cells that are important in helping your body to fight infection.

Not everyone responds to treatment with Epivir in the same way. Your doctor will monitor the effectiveness of your treatment.

2. What you need to know before you take Epivir

Do not take Epivir:

- if you are **allergic** to lamivudine or any of the other ingredients of this medicine (*listed in Section 6*).

  Check with your doctor if you think this applies to you.

Take special care with Epivir

Some people taking Epivir or other combination treatments for HIV are more at risk of serious side effects. You need to be aware of the extra risks:

- if you have ever had **liver disease,** including hepatitis B or C (if you have hepatitis B infection, do not stop Epivir without your doctor's advice, as your hepatitis may come back)
- if you are seriously **overweight** (especially if you are a woman)
- **if you or your child has a kidney problem**, your dose may be altered.

Talk to your doctor if any of these apply to you. You may need extra check-ups, including blood tests, while you are taking your medicine. **See Section 4 for more information**.

Look out for important symptoms

Some people taking medicines for HIV infection develop other conditions, which can be serious. You need to know about important signs and symptoms to look out for while you are taking Epivir.

Read the information 'Other possible side effects of combination therapy for HIV' in Section 4 of this leaflet.

Other medicines and Epivir

Tell your doctor or pharmacist if you are taking any other medicines, or if you have taken any recently, including herbal medicines or other medicines you bought without a prescription.

Remember to tell your doctor or pharmacist if you begin taking a new medicine while you are taking Epivir.

These medicines should not be used with Epivir:

- medicines (usually liquids) containing sorbitol and other sugar alcohols (such as xylitol, mannitol, lactitol or maltitol), if taken regularly
- other medicines containing lamivudine, (used to treat **HIV infection** or **hepatitis B infection**)
- emtricitabine (used to treat **HIV infection**)
- high doses of **co-trimoxazole**, an antibiotic
- cladribine (used to treat hairy cell leukaemia).

Tell your doctor if you are being treated with any of these.

Pregnancy

If you are pregnant, if you become pregnant, or are planning to become pregnant, talk to your doctor about the risks and benefits to you and your baby of taking Epivir.

Epivir and similar medicines may cause side effects in unborn babies. If you have taken Epivir during your pregnancy, your doctor may request regular blood tests and other diagnostic tests to monitor the development of your child. In children whose mothers took NRTIs during pregnancy, the benefit from the protection against HIV outweighed the risk of side effects.

Breast-feeding

Breast-feeding is **not recommended** in women living with HIV because HIV infection can be passed on to the baby in breast milk.

A small amount of the ingredients in Epivir can also pass into your breast milk.

If you are breast-feeding, or thinking about breast-feeding, you should **discuss it with your doctor as soon as possible**.

Driving and using machines

Epivir is unlikely to affect your ability to drive or use machines.

Epivir contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

3. How to take Epivir

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Swallow the tablets, with some water. Epivir can be taken with or without food.

If you cannot swallow the tablets whole, you may crush and combine them with a small amount of food or drink, and take all the dose immediately.

Stay in regular contact with your doctor

Epivir helps to control your condition. You need to keep taking it every day to stop your illness getting worse. You may still develop other infections and illnesses linked to HIV infection.

Keep in touch with your doctor, and do not stop taking Epivir without your doctor's advice.

How much to take

Adults, adolescents and children who weigh at least 25 kg:

The usual dose of Epivir is 300 mg a day. This can be taken as either one 150 mg tablet twice a day (leaving approximately 12 hours between each dose), or two 150 mg tablets once a day as advised by your doctor.

Children weighing at least 20 kg and less than 25 kg:

The usual dose of Epivir is 225 mg a day. This can be given as 75 mg (half a 150 mg tablet) in the morning and 150 mg (one whole 150 mg tablet) in the evening, or 225 mg (one and a half 150 mg tablets) once a day as advised by your doctor.

Children weighing at least 14 kg and less than 20 kg:

The usual dose of Epivir is 150 mg a day. This can be given as 75 mg (half a 150 mg tablet) twice a day (leaving approximately 12 hours between each dose), or 150 mg (one 150 mg tablet) once a day as advised by your doctor.

An oral solution is also available for the treatment of children over 3 months of age, or for people who need a lower dose than usual, or who cannot take tablets.

If you or your child has a kidney problem, your dose may be altered.
Talk to your doctor if this applies to you or your child.

If you take more Epivir than you should

If you take too much Epivir, tell your doctor or your pharmacist, or contact your nearest hospital emergency department for further advice. If possible, show them the Epivir pack.

If you forget to take Epivir

If you forget to take a dose, take it as soon as you remember. Then continue your treatment as before. Do not take a double dose to make up for a forgotten dose.

4. Possible side effects

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Like all medicines, this medicine can cause side effects, but not everyone gets them.

When you are being treated for HIV, it can be hard to tell whether a symptom is a side effect of Epivir or other medicines you are taking, or an effect of the HIV disease itself. **So it is very important to talk to your doctor about any changes in your health**.

As well as the side effects listed below for Epivir, other conditions can develop during combination therapy for HIV.

> It is important to read the information later in this section under 'Other possible side effects of combination therapy for HIV'.

Common side effects
These may affect **up to 1 in 10** people:

- headache
- feeling sick (*nausea*)
- being sick (*vomiting*)
- diarrhoea
- stomach pains
- tiredness, lack of energy
- fever (high temperature)
- general feeling of being unwell
- muscle pain and discomfort
- joint pain
- difficulty in sleeping (*insomnia*)
- cough
- irritated or runny nose
- rash
- hair loss (*alopecia*).

Uncommon side effects
These may affect **up to 1 in 100** people:

Uncommon side effects that may show up in blood tests are:

- a decrease in the number of cells involved in blood clotting (*thrombocytopenia*)
- a low red blood cell count (*anaemia*) or low white blood cell count (*neutropenia*)
- an increase in the level of liver enzymes.

Rare side effects
These may affect **up to 1 in 1000** people:

- serious allergic reaction causing swelling of the face, tongue or throat which may cause difficulty in swallowing or breathing
- inflammation of the pancreas (*pancreatitis*)
- breakdown of muscle tissue
- inflammation (*hepatitis*).

A rare side effect that may show up in blood tests is:

- an increase in an enzyme called amylase.

Very rare side effects
These may affect **up to 1 in 10,000** people:
- Lactic acidosis (excess lactic acid in the blood)
- tingling or numbness of the arms, legs, hands or feet.

A very rare side effect that may show up in blood tests is:
- a failure of the bone marrow to produce new red blood cells *(pure red cell aplasia)*.

If you get side effects

Tell your doctor or pharmacist if any of the side effects gets severe or troublesome, or if you notice any side effects not listed in this leaflet.

Other possible side effects of combination therapy for HIV

Combination therapy including Epivir may cause other conditions to develop during HIV treatment.

Old infections may flare up

People with advanced HIV infection (AIDS) have weak immune systems and are more likely to develop serious infections (opportunistic infections). When these people start treatment, they may find that old, hidden infections flare up, causing signs and symptoms of inflammation. These symptoms are probably caused by the body's immune system becoming stronger, so that the body starts to fight these infections.

In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.

If you get any symptoms of infection while you are taking Epivir:

Tell your doctor immediately. Do not take other medicines for the infection without your doctor's advice.

You may have problems with your bones

Some people taking combination therapy for HIV develop a condition called *osteonecrosis*. With this condition, parts of the bone tissue die because of reduced blood supply to the bone. People may be more likely to get this condition:
- if they have been taking combination therapy for a long time
- if they are also taking anti-inflammatory medicines called corticosteroids
- if they drink alcohol
- if their immune systems are very weak
- if they are overweight.

Signs of osteonecrosis include:
- stiffness in the joints
- aches and pains (especially in the hip, knee or shoulder)
- difficulty moving.

If you notice any of these symptoms:

Tell your doctor.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system

listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Epivir

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton.

Do not store Epivir above 30°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away the medicines you no longer use. These measures will help to protect the environment.

6 Contents of the pack and other information

What Epivir contains
The active substance is lamivudine.
The tablets also contain the following other ingredients:
Tablet core: microcrystalline cellulose, sodium starch glycollate (gluten free), magnesium stearate
Film-coat: hypromellose, titanium dioxide, macrogol, polysorbate 80

What Epivir looks like and the contents of the pack
Epivir 150 mg film-coated tablets are supplied in white polyethylene bottles or blister packs containing 60 tablets. They are white, diamond shaped, scored, film-coated tablets, marked with the code 'GXCJ7' on both sides.

Marketing Authorisation Holder and Manufacturer

Manufacturer	**Marketing Authorisation Holder**
Delpharm Poznań Spółka Akcyjna ul. Grunwaldzka 189 60-322 Poznan Poland	ViiV Healthcare BV Van Asch van Wijckstraat 55H 3811 LP Amersfoort Netherlands

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This leaflet was last revised in {MM/YYYY}
Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu.

Package leaflet: Information for the user

Epivir 10 mg/ml oral solution
lamivudine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you or for your child. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any of the side effects talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Epivir is and what it is used for
2. What you need to know before you take Epivir
3. How to take Epivir
4. Possible side effects
5. How to store Epivir
6. Contents of the pack and other information

1. What Epivir is and what it is used for

Epivir is used to treat HIV (human immunodeficiency virus) infection in adults and children.

The active ingredient in Epivir is lamivudine. Epivir is a type of medicine known as an anti-retroviral. It belongs to a group of medicines called *nucleoside analogue reverse transcriptase inhibitors* (*NRTIs*).

Epivir does not completely cure HIV infection; it reduces the amount of virus in your body and keeps it at a low level. It also increases the CD4 cell count in your blood. CD4 cells are a type of white blood cells that are important in helping your body to fight infection.

Not everyone responds to treatment with Epivir in the same way. Your doctor will monitor the effectiveness of your treatment.

2. What you need to know before you take Epivir

Do not take Epivir:

- if you are **allergic** to lamivudine or any of the other ingredients of this medicine (*listed in Section 6*).

  Check with your doctor if you think this applies to you.

Take special care with Epivir

Some people taking Epivir or other combination treatments for HIV are more at risk of serious side effects. You need to be aware of the extra risks:

- if you have ever had **liver disease,** including hepatitis B or C (if you have hepatitis B infection, do not stop Epivir without your doctor's advice, as your hepatitis may come back)
- if you are seriously **overweight** (especially if you are a woman)
- **if you or your child has a kidney problem**, your dose may be altered.

Talk to your doctor if any of these apply to you. You may need extra check-ups, including blood tests, while you are taking your medicine. **See Section 4 for more information**.

Look out for important symptoms

Some people taking medicines for HIV infection develop other conditions, which can be serious. You need to know about important signs and symptoms to look out for while you are taking Epivir.

Read the information 'Other possible side effects of combination therapy for HIV' in Section 4 of this leaflet.

Other medicines and Epivir

Tell your doctor or pharmacist if you are taking any other medicines, or if you have taken any recently, including herbal medicines or other medicines you bought without a prescription.

Remember to tell your doctor or pharmacist if you begin taking a new medicine while you are taking Epivir.

These medicines should not be used with Epivir:

- medicines (usually liquids) containing sorbitol and other sugar alcohols (such as xylitol, mannitol, lactitol or maltitol), if taken regularly
- other medicines containing lamivudine, (used to treat **HIV infection** or **hepatitis B infection**)
- emtricitabine (used to treat **HIV infection**)
- high doses of **co-trimoxazole**, an antibiotic
- cladribine (used to treat hairy cell leukaemia).

Tell your doctor if you are being treated with any of these.

Pregnancy

If you are pregnant, if you become pregnant, or are planning to become pregnant, talk to your doctor about the risks and benefits to you and your baby of taking Epivir.

Epivir and similar medicines may cause side effects in unborn babies. If you have taken Epivir during your pregnancy, your doctor may request regular blood tests and other diagnostic tests to monitor the development of your child. In children whose mothers took NRTIs during pregnancy, the benefit from the protection against HIV outweighed the risk of side effects.

Breast-feeding

Breast-feeding is **not recommended** in women living with HIV because HIV infection can be passed on to the baby in breast milk.

A small amount of the ingredients in Epivir can also pass into your breast milk.

If you are breast-feeding, or thinking about breast-feeding, you should **discuss it with your doctor as soon as possible**.

Driving and using machines

Epivir is unlikely to affect your ability to drive or use machines.

Important information about some of the ingredients of Epivir

If you are a diabetic, please note that each dose (150 mg = 15 ml) contains 3 g sugar.
Epivir contains sucrose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking Epivir. Sucrose may be harmful to the teeth.

Epivir also contains preservatives (*parahydroxybenzoates*) which may cause allergic reactions (possibly delayed).

Epivir contains sodium

This medicine contains 39 mg sodium in each 15 ml. This is equivalent to 1.95% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to take Epivir

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Epivir can be taken with or without food.

Stay in regular contact with your doctor

Epivir helps to control your condition. You need to keep taking it every day to stop your illness getting worse. You may still develop other infections and illnesses linked to HIV infection.

Keep in touch with your doctor, and do not stop taking Epivir without your doctor's advice.

How much to take

Adults, adolescents and children weighing at least 25 kg

The usual dose of Epivir is 30 ml (300 mg) a day. This can be taken either as 15 ml (150 mg) twice a day (leaving approximately 12 hours between each dose), or as 30 ml (300 mg) once a day.

Children from 3 months of age weighing less than 25 kg

The dose depends on the child's body weight. The usual dose of Epivir is 0.5 mL/kg (5 mg/kg) twice daily (leaving approximately 12 hours between each dose), or 1 mL/kg (10 mg/kg) once daily.

Use the oral dosing syringe supplied with the pack to measure your dose accurately.

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. Hold the bottle firmly. **Push the plastic adapter into the neck of the bottle**.
5. **Insert the syringe** firmly into the adapter.
6. Turn the bottle upside down.
7. **Pull out syringe plunger** until the syringe contains the first part of your full dose.
8. Turn the bottle the correct way up. **Remove the syringe** from the adapter.
9. **Put the syringe into your mouth,** placing the tip of the syringe against the inside of your cheek. **Slowly push the plunger in,** allowing time to swallow. **Do not** push too hard and squirt the liquid into the back of your throat or you may choke.
10. **Repeat steps 5 to 9** in the same way until you have taken your whole dose. *For example, if your dose is 15 ml, you need to take one and a half syringe-fulls of medicine.*
11. **Take the syringe out of the bottle** and **wash** it thoroughly in clean water. Let it dry completely before you use it again.
12. **Close the bottle tightly** with the cap, leaving the adapter in place.

Discard oral solution one month after first opening.

If you or your child has a kidney problem, the dose may be altered.
Talk to your doctor if this applies to you or your child.

If you take more Epivir than you should

If you take too much Epivir, tell your doctor or your pharmacist, or contact your nearest hospital emergency department for further advice. If possible, show them the Epivir pack.

If you forget to take Epivir

If you forget to take a dose, take it as soon as you remember. Then continue your treatment as before. Do not take a double dose to make up for a forgotten dose.

4. Possible side effects

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Like all medicines, this medicine can cause side effects, but not everyone gets them.

When you are being treated for HIV, it can be hard to tell whether a symptom is a side effect of Epivir or other medicines you are taking, or an effect of the HIV disease itself. **So it is very important to talk to your doctor about any changes in your health**.

As well as the side effects listed below for Epivir, other conditions can develop during combination therapy for HIV.

> It is important to read the information later in this section under 'Other possible side effects of combination therapy for HIV'.

Common side effects

These may affect **up to 1 in 10** people:

- headache
- feeling sick (*nausea*)
- being sick (*vomiting)*
- diarrhoea
- stomach pains
- tiredness, lack of energy
- fever (high temperature)
- general feeling of being unwell
- muscle pain and discomfort
- joint pain
- difficulty in sleeping (*insomnia*)
- cough
- irritated or runny nose
- rash
- hair loss (*alopecia*).

Uncommon side effects

These may affect **up to 1 in 100** people:

Uncommon side effects that may show up in blood tests are:

- a decrease in the number of cells involved in blood clotting (*thrombocytopenia*)
- a low red blood cell count (*anaemia*) or low white blood cell count (*neutropenia*)
- an increase in the level of liver enzymes.

Rare side effects

These may affect **up to 1 in 1000** people:

- serious allergic reaction causing swelling of the face, tongue or throat which may cause difficulty in swallowing or breathing
- inflammation of the pancreas (*pancreatitis*)

- breakdown of muscle tissue
- inflammation (*hepatitis*).

A rare side effect that may show up in blood tests is:
- increase in an enzyme called amylase.

Very rare side effects
These may affect **up to 1 in 10,000** people:
- Lactic acidosis (excess lactic acid in the blood)
- tingling or numbness of the arms, legs, hands or feet.

A very rare side effect that may show up in blood tests is:
- a failure of the bone marrow to produce new red blood cells *(pure red cell aplasia)*.

If you get side effects

Tell your doctor or pharmacist if any of the side effects gets severe or troublesome, or if you notice any side effects not listed in this leaflet.

Other possible side effects of combination therapy for HIV
Combination therapy such as Epivir may cause other conditions to develop during HIV treatment.

Old infections may flare up
People with advanced HIV infection (AIDS) have weak immune systems and are more likely to develop serious infections (opportunistic infections). When these people start treatment, they may find that old, hidden infections flare up, causing signs and symptoms of inflammation. These symptoms are probably caused by the body's immune system becoming stronger, so that the body starts to fight these infections.

In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.

If you get any symptoms of infection while you are taking Epivir:

Tell your doctor immediately. Do not take other medicines for the infection without your doctor's advice.

You may have problems with your bones
Some people taking combination therapy for HIV develop a condition called osteonecrosis. With this condition, parts of the bone tissue die because of reduced blood supply to the bone. People may be more likely to get this condition:
- if they have been taking combination therapy for a long time
- if they are also taking anti-inflammatory medicines called corticosteroids
- if they drink alcohol
- if their immune systems are very weak
- if they are overweight.

Signs of osteonecrosis include:
- stiffness in the joints
- aches and pains (especially in the hip, knee or shoulder)
- difficulty moving.

If you notice any of these symptoms:

Tell your doctor.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Epivir

Keep this medicine out of the sight and reach of children

Do not use this medicine after the expiry date which is stated on the container.

Discard one month after first opening.

Do not store above 25ºC.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away the medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Epivir contains
The active substance is lamivudine.
The oral solution also contains the following other ingredients: sugar (sucrose 3 g/15 ml), methyl parahydroxybenzoate, propyl parahydroxybenzoate, anhydrous citric acid, sodium citrate, propylene glycol, water, artificial strawberry and banana flavourings.

This medicine contains 300 mg propylene glycol in each 15ml.

What Epivir looks like and the contents of the pack
Epivir oral solution is supplied in a white polyethylene bottle containing 240 ml of solution. An oral dosing syringe and a plastic adapter for the bottle is included in the pack.

Marketing Authorisation Holder and Manufacturer

Manufacturer	**Marketing Authorisation Holder**
ViiV Healthcare Trading Services UK Limited 12 Riverwalk, Citywest Business Campus Dublin 24, Ireland	ViiV Healthcare BV Van Asch van Wijckstraat 55H 3811 LP Amersfoort Netherlands

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Package leaflet: Information for the user

Epivir 300 mg film-coated tablets
lamivudine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any of the side effects talk to your doctor. This includes any side effects not listed in this leaflet. See section 4.

In this leaflet:

1. What Epivir is and what it is used for
2. What you need to know before you take Epivir
3. How to take Epivir
4. Possible side effects
5. How to store Epivir
6. Contents of the pack and other information

1. What Epivir is and what it is used for

Epivir is used to treat HIV (human immunodeficiency virus) infection in adults and children.

The active ingredient in Epivir is lamivudine. Epivir is a type of medicine known as an anti-retroviral. It belongs to a group of medicines called *nucleoside analogue reverse transcriptase inhibitors* (*NRTIs*).

Epivir does not completely cure HIV infection; it reduces the amount of virus in your body, and keeps it at a low level. It also increases the CD4 cell count in your blood. CD4 cells are a type of white blood cells that are important in helping your body to fight infection.

Not everyone responds to treatment with Epivir in the same way. Your doctor will monitor the effectiveness of your treatment.

2. What you need to know before you take Epivir

Do not take Epivir:

- if you are **allergic** to lamivudine or any of the other ingredients in this medicine (*listed in Section 6*).

  Check with your doctor if you think this applies to you.

Take special care with Epivir

Some people taking Epivir or other combination treatments for HIV are more at risk of serious side effects. You need to be aware of the extra risks:

- if you have ever had **liver disease,** including hepatitis B or C (if you have hepatitis B infection, do not stop Epivir without your doctor's advice, as your hepatitis may come back)
- if you are seriously **overweight** (especially if you are a woman)
- **if you have a kidney problem**, your dose may be altered.
  Talk to your doctor if any of these apply to you. You may need extra check-ups, including blood tests, while you are taking your medicine. **See Section 4 for more information**.

Look out for important symptoms

Some people taking medicines for HIV infection develop other conditions, which can be serious. You need to know about important signs and symptoms to look out for while you are taking Epivir.

Read the information 'Other possible side effects of combination therapy for HIV' in Section 4 of this leaflet.

Other medicines and Epivir

Tell your doctor or pharmacist if you are taking any other medicines, or if you have taken any recently, including herbal medicines or other medicines you bought without a prescription.

Remember to tell your doctor or pharmacist if you begin taking a new medicine while you are taking Epivir.

These medicines should not be used with Epivir:

- medicines (usually liquids) containing sorbitol and other sugar alcohols (such as xylitol, mannitol, lactitol or maltitol), if taken regularly
- other medicines containing lamivudine, (used to treat **HIV infection** or **hepatitis B infection)**
- emtricitabine (used to treat **HIV infection**)
- high doses of **co-trimoxazole**, an antibiotic.
- cladribine (used to treat hairy cell leukaemia).

Tell your doctor if you are being treated with any of these.

Pregnancy

If you are pregnant, if you become pregnant, or are planning to become pregnant, talk to your doctor about the risks and benefits to you and your baby of taking Epivir.

Epivir and similar medicines may cause side effects in unborn babies. If you have taken Epivir during your pregnancy, your doctor may request regular blood tests and other diagnostic tests to monitor the development of your child. In children whose mothers took NRTIs during pregnancy, the benefit from the protection against HIV outweighed the risk of side effects.

Breast-feeding

Breast-feeding is **not recommended** in women living with HIV because HIV infection can be passed on to the baby in breast milk.

A small amount of the ingredients in Epivir can also pass into your breast milk.

If you are breast-feeding, or thinking about breast-feeding, you should **discuss it with your doctor as soon as possible**.

Driving and using machines

Epivir is unlikely to affect your ability to drive or use machines.

Epivir contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

3. How to take Epivir

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Swallow the tablet with some water. Epivir can be taken with or without food.

If you cannot swallow the tablet whole, you may crush and combine it with a small amount of food or drink, and take all the dose immediately.

Stay in regular contact with your doctor

Epivir helps to control your condition. You need to keep taking it every day to stop your illness getting worse. You may still develop other infections and illnesses linked to HIV infection.

Keep in touch with your doctor, and do not stop taking Epivir without your doctor's advice.

How much to take

Adults, adolescents and children who weigh at least 25 kg:

The usual dose is one 300 mg tablet once a day.

A 150 mg strength Epivir tablet is also available for the treatment of children from 3 months of age who weigh less than 25 kg:

An oral solution is also available for the treatment of children over 3 months of age, or for people who need a lower dose than usual, or who cannot take tablets.

If you have a kidney problem, your dose may be altered.
Talk to your doctor if this applies to you.

If you take more Epivir than you should

If you take too much Epivir, tell your doctor or your pharmacist, or contact your nearest hospital emergency department for further advice. If possible, show them the Epivir pack.

If you forget to take Epivir

If you forget to take a dose, take it as soon as you remember. Then continue your treatment as before. Do not take a double dose to make up for a forgotten dose.

4. Possible side effects

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Like all medicines, this medicine can cause side effects, but not everyone gets them.

When you are being treated for HIV, it can be hard to tell whether a symptom is a side effect of Epivir or other medicines you are taking, or an effect of the HIV disease itself. **So it is very important to talk to your doctor about any changes in your health**.

As well as the side effects listed below for Epivir, other conditions can develop during combination therapy for HIV.

It is important to read the information later in this section under 'Other possible side effects of combination therapy for HIV'.

Common side effects
These may affect **up to 1 in 10** people:

- headache
- feeling sick (*nausea*)
- being sick (*vomiting*)
- diarrhoea
- stomach pains
- tiredness, lack of energy
- fever (high temperature)
- general feeling of being unwell
- muscle pain and discomfort
- joint pain
- difficulty in sleeping (*insomnia*)
- cough
- irritated or runny nose
- rash
- hair loss (*alopecia*).

Uncommon side effects
These may affect **up to 1 in 100** people:

Uncommon side effects that may show up in blood tests are:
- a decrease in the number of cells involved in blood clotting (*thrombocytopenia*)
- a low red blood cell count (*anaemia*) or low white blood cell count (*neutropenia*)
- an increase in the level of liver enzymes.

Rare side effects
These may affect **up to 1 in 1000** people:
- serious allergic reaction causing swelling of the face, tongue or throat which may cause difficulty in swallowing or breathing
- inflammation of the pancreas *(pancreatitis)*
- breakdown of muscle tissue
- inflammation (*hepatitis*).

A rare side effect that may show up in blood tests is:
- increase in an enzyme called amylase.

Very rare side effects
These may affect **up to 1 in 10,000** people:
- Lactic acidosis (excess lactic acid in the blood)
- tingling or numbness of the arms, legs, hands or feet.

A very rare side effect that may show up in blood tests is:
- a failure of the bone marrow to produce new red blood cells *(pure red cell aplasia)*.

If you get side effects

Tell your doctor or pharmacist if any of the side effects gets severe or troublesome, or if you notice any side effects not listed in this leaflet.

Other possible side effects of combination therapy for HIV

Combination therapy including Epivir may cause other conditions to develop during HIV treatment.

Old infections may flare up

People with advanced HIV infection (AIDS) have weak immune systems, and are more likely to develop serious infections (opportunistic infections). When these people start treatment, they may find that old, hidden infections flare up, causing signs and symptoms of inflammation. These symptoms are

probably caused by the body's immune system becoming stronger, so that the body starts to fight these infections.

In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.

If you get any symptoms of infection while you are taking Epivir:

Tell your doctor immediately. Do not take other medicines for the infection without your doctor's advice.

You may have problems with your bones

Some people taking combination therapy for HIV develop a condition called *osteonecrosis*. With this condition, parts of the bone tissue die because of reduced blood supply to the bone. People may be more likely to get this condition:

- if they have been taking combination therapy for a long time
- if they are also taking anti-inflammatory medicines called corticosteroids
- if they drink alcohol
- if their immune systems are very weak
- if they are overweight.

Signs of osteonecrosis include:

- stiffness in the joints
- aches and pains (especially in the hip, knee or shoulder)
- difficulty moving.

If you notice any of these symptoms:

Tell your doctor.

Reporting of side effects

- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Epivir

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton.
Do not store Epivir above 30ºC.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away the medicines you no longer use. These measures will help to protect the environment.

6 Contents of the pack and other information

What Epivir contains

The active substance is lamivudine.
The tablets also contain the following other ingredients:
Tablet core: microcrystalline cellulose, sodium starch glycollate (gluten free), magnesium stearate
Film-coat: hypromellose, titanium dioxide, black iron oxide (E172), macrogol, polysorbate 80

What Epivir looks like and the contents of the pack
Epivir 300 mg film-coated tablets are supplied in white polyethylene bottles or blister packs containing 30 tablets. They are grey, diamond shaped film-coated tablets, marked with the code ‘GXEJ7’ on one side.

Marketing Authorisation Holder and Manufacturer

Manufacturer	**Marketing Authorisation Holder**
Delpharm Poznań Spółka Akcyjna ul. Grunwaldzka 189 60-322 Poznan Poland	ViiV Healthcare BV Van Asch van Wijckstraat 55H 3811 LP Amersfoort Netherlands

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