ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT

Epivir 150 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150 mg lamivudine.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

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

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. For patients who are unable to swallow tablets, lamivudine is available as an oral solution. Alternatively, the tablets may be crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately (see section 5.2).

Adults and adolescents (over 12 years of age): 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.

Patients changing to the once daily regimen should take 150 mg twice a day and switch to 300 mg once a day the following morning. Where an evening once daily regimen is preferred, 150 mg of Epivir should be taken on the first morning only, followed by 300 mg in the evening. When changing back to a twice daily regimen patients should complete the days treatment and start 150 mg twice a day the following morning.

Children (under 12 years of age):

Since an accurate dosing can not be achieved with this formulation, dosing according to weight bands is recommended for Epivir tablets. This dosing regimen for paediatric patients weighing 14-30 kg is based primarily on pharmacokinetic modelling, with supporting data from clinical studies.

For children weighing at least 30 kg: the adult dosage of 150 mg twice daily should be taken.

For children weighing between 21 kg to 30 kg: the recommended oral dose of Epivir (150 mg) is one-half tablet taken in the morning and one whole tablet taken in the evening.
For children weighing 14 to 21 kg: the recommended oral dose of Epivir (150 mg) is one half of a scored tablet taken twice daily.

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.

Less than three months of age: the limited data available are insufficient to propose specific dosage recommendations (see section 5.2).

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 and adolescents weighing at least 30 kg:

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>First dose</th>
<th>Maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50</td>
<td>150 mg</td>
<td>150 mg twice daily</td>
</tr>
<tr>
<td>30-&lt;50</td>
<td>150 mg</td>
<td>150 mg once daily</td>
</tr>
<tr>
<td>&lt;30</td>
<td>As doses below 150 mg are needed the use of the oral solution is recommended</td>
<td></td>
</tr>
</tbody>
</table>

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.

Dosing recommendations – Children aged at least 3 months and weighing less than 30 kg:

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>First dose</th>
<th>Maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50</td>
<td>4 mg/kg</td>
<td>4 mg/kg twice daily</td>
</tr>
<tr>
<td>30 to &lt;50</td>
<td>4 mg/kg</td>
<td>4 mg/kg once daily</td>
</tr>
<tr>
<td>15 to &lt;30</td>
<td>4 mg/kg</td>
<td>2.6 mg/kg once daily</td>
</tr>
<tr>
<td>5 to &lt;15</td>
<td>4 mg/kg</td>
<td>1.3 mg/kg once daily</td>
</tr>
<tr>
<td>&lt;5</td>
<td>1.3 mg/kg</td>
<td>0.7 mg/kg once daily</td>
</tr>
</tbody>
</table>

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.

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.

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

**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.

**Lactic acidosis:** Lactic acidosis, usually associated with hepatomegaly and hepatic steatosis, has been reported with the use of nucleoside analogues. Early symptoms (symptomatic hyperlactatemia) include benign digestive symptoms (nausea, vomiting and abdominal pain), non-specific malaise, loss of appetite, weight loss, respiratory symptoms (rapid and/or deep breathing) or neurological symptoms (including motor weakness).

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

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

Treatment with nucleoside analogues should be discontinued in the setting of symptomatic hyperlactatemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels.

Caution should be exercised when administering nucleoside analogues to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease and hepatic steatosis (including certain medicinal products and alcohol). Patients co-infected with hepatitis C and treated with alpha interferon and ribavirin may constitute a special risk.

Patients at increased risk should be followed closely.

**Mitochondrial dysfunction:** Nucleoside and nucleotide analogues have been demonstrated in vitro and in vivo to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed in utero and/or post-natally to nucleoside analogues. The main adverse events reported are haematological disorders (anaemia, neutropenia), metabolic disorders (hyperlactatemia, hyperlipasemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether the neurological disorders are transient or permanent is currently unknown. Any child exposed in utero to nucleoside and nucleotide analogues, even HIV-negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

**Lipodystrophy:** Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors (PIs) and lipoatrophy and nucleoside reverse transcriptase inhibitors (NRTIs)
has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).

**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 carinii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

**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).

**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.

Epivir should not be taken with any other medicinal products containing lamivudine or medicinal products containing emtricitabine.

### 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 carinii* 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 $C_{\text{max}}$ (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).

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

### 4.6 Pregnancy and lactation

A large amount of data on pregnant women (more than 1000 exposed outcomes) indicate no malformative toxicity. Epivir can be used during pregnancy if clinically needed.

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).

Following oral administration lamivudine was excreted in breast milk at similar concentrations to those found in serum. Since lamivudine and the virus pass into breast milk, it is recommended that mothers taking Epivir do not breast-feed their infants. It is recommended that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

### 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 ($\geq 1/10$), common ($1/100$ to $<1/10$), uncommon ($1/1000$ to $<1/100$), rare ($1/10000$ to $<1/1000$), very rare ($<1/10000$). 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

**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.

Cases of lactic acidosis, sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis, have been reported with the use of nucleoside analogues (see section 4.4).

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (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 (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).

4.9 Overdose

Administration of lamivudine at very high dose levels in acute animal studies did not result in any organ toxicity. Limited data are available on the consequences of ingestion of acute overdoses in humans. No fatalities occurred, and the patients recovered. No specific signs or symptoms have been identified following such overdose.

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
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. Lamivudine in combination with zidovudine exhibits synergistic anti-HIV activity against clinical isolates in cell culture.

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 experience:

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).

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).

### 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<sub>max</sub>) to maximal serum concentrations (C<sub>max</sub>) is about an hour. Based on data derived from a study in healthy volunteers, at a therapeutic dose of 150mg twice daily, mean (CV) steady-state C<sub>max</sub> and C<sub>min</sub> 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 300mg once daily, the mean (CV) steady-state C<sub>max</sub>, C<sub>min</sub> 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<sub>∞</sub>, C<sub>max</sub>, and t<sub>max</sub>.

Co-administration of lamivudine with food results in a delay of t<sub>max</sub> and a lower C<sub>max</sub> (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 observed half-life of elimination is 5 to 7 hours. 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 cerebrospinal 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.

*Metabolism:* The active moiety, intracellular lamivudine triphosphate, has a prolonged terminal half-life in the cell (16 to 19 hours) compared to the plasma lamivudine half-life (5 to 7 hours). In 60 healthy adult volunteers, Epivir 300 mg once daily has been demonstrated to be pharmacokinetically equivalent at steady-state to Epивir 150 mg twice daily with respect to intracellular triphosphate AUC<sub>24</sub> and C<sub>max</sub>. 

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.

**Pharmacokinetics in children:** In general, lamivudine pharmacokinetics in paediatric patients is similar to adults. However, absolute bioavailability (approximately 55-65%) was reduced in paediatric patients below 12 years of age. In addition, systemic clearance values were greater in younger paediatric patients and decreased with age, approaching adult values around 12 years of age. Due to these differences, the recommended dose for lamivudine in children (aged more than three months and weighing less than 30 kg) is 4 mg/kg twice daily. This dose will achieve an average AUC$_{0-12}$ ranging from approximately 3,800 to 5,300 ng.h/ml. Recent findings indicate that exposure in children < 6 years of age may be reduced by about 30% compared with other age groups. Further data addressing this issue are currently awaited. At present, the available data do not suggest that lamivudine is less efficacious in this age group.

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, the recommended dose for neonates is 4 mg/kg/day. Glomerular filtration estimates suggests that to achieve similar adult and paediatric exposure, the recommended dose for children aged six weeks and older could be 8 mg/kg/day.

**Pharmacokinetics in 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 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.
6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

HDPE bottles: 5 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

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

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER

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

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
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.

Excipients:

Sucrose 20% (3 g/15 ml)
Methyl parahydroxybenzoate
Propyl parahydroxybenzoate

For a 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.

*Adults and adolescents over 12 years of age:* 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).

Patients changing to the once daily regimen should take 150 mg (15 ml) twice a day and switch to 300 mg (30 ml) once a day the following morning. Where an evening once daily regimen is preferred, 150 mg (15 ml) of Epivir should be taken on the first morning only, followed by 300 mg (30 ml) in the evening. When changing back to a twice daily regimen, patients should complete the days treatment and start 150 mg (15 ml) twice a day the following morning.

*Children*

*Three months to 12 years of age:* the recommended dose is 4 mg/kg twice daily up to a maximum of 300 mg daily.

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

Epivir is also available as a tablet formulation.

Epivir may be administered with or without food.
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 and adolescents over 12 years:

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>First dose</th>
<th>Maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50</td>
<td>150 mg (15 ml)</td>
<td>150 mg (15 ml) twice daily</td>
</tr>
<tr>
<td>30 to &lt;50</td>
<td>150 mg (15 ml)</td>
<td>150 mg (15 ml) once daily</td>
</tr>
<tr>
<td>15 to &lt;30</td>
<td>150 mg (15 ml)</td>
<td>100 mg (10 ml) once daily</td>
</tr>
<tr>
<td>5 to &lt;15</td>
<td>150 mg (15 ml)</td>
<td>50 mg (5 ml) once daily</td>
</tr>
<tr>
<td>&lt;5</td>
<td>50 mg (5 ml)</td>
<td>25 mg (2.5 ml) once daily</td>
</tr>
</tbody>
</table>

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.

Dosing recommendations – Children from 3 months to 12 years:

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>First dose</th>
<th>Maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50</td>
<td>4 mg/kg</td>
<td>4 mg/kg twice daily</td>
</tr>
<tr>
<td>30 to &lt;50</td>
<td>4 mg/kg</td>
<td>4 mg/kg once daily</td>
</tr>
<tr>
<td>15 to &lt;30</td>
<td>4 mg/kg</td>
<td>2.6 mg/kg once daily</td>
</tr>
<tr>
<td>5 to &lt;15</td>
<td>4 mg/kg</td>
<td>1.3 mg/kg once daily</td>
</tr>
<tr>
<td>&lt;5</td>
<td>1.3 mg/kg</td>
<td>0.7 mg/kg once daily</td>
</tr>
</tbody>
</table>

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.

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

**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.

**Lactic acidosis:** Lactic acidosis, usually associated with hepatomegaly and hepatic steatosis, has been reported with the use of nucleoside analogues. Early symptoms (symptomatic hyperlactatemia) include benign digestive symptoms (nausea, vomiting and abdominal pain), non-specific malaise, loss of appetite, weight loss, respiratory symptoms (rapid and/or deep breathing) or neurological symptoms (including motor weakness).

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

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

Treatment with nucleoside analogues should be discontinued in the setting of symptomatic hyperlactatemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels.

Caution should be exercised when administering nucleoside analogues to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease and hepatic steatosis (including certain medicinal products and alcohol). Patients co-infected with hepatitis C and treated with alpha interferon and ribavirin may constitute a special risk.

Patients at increased risk should be followed closely.

**Mitochondrial dysfunction:** Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed *in utero* and/or post-natally to nucleoside analogues. The main adverse events reported are haematological disorders (anaemia, neutropenia), metabolic disorders (hyperlactatemia, hyperlipasemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether the neurological disorders are transient or permanent is currently unknown. Any child exposed *in utero* to nucleoside and nucleotide analogues, even HIV-negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

**Lipodystrophy:** Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors (PIs) and lipoatrophy and nucleoside analogue reverse transcriptase inhibitors (NRTIs) has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).

**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 carinii pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

*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).

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).

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.

Epivir should not be taken with any other medicinal products containing lamivudine or medicinal products containing emtricitabine.

### 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 carinii 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\textsubscript{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).

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

### 4.6 Pregnancy and lactation

A large amount of data on pregnant women (more than 1000 exposed outcomes) indicate no malformative toxicity. Epivir can be used during pregnancy if clinically needed.

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).

Following oral administration lamivudine was excreted in breast milk at similar concentrations to those found in serum. Since lamivudine and the virus pass into breast milk, it is recommended that mothers taking Epivir do not breast-feed their infants. It is recommended that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

### 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

**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.

Cases of lactic acidosis, sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis, have been reported with the use of nucleoside analogues (see section 4.4).

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (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 (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).

4.9 Overdose

Administration of lamivudine at very high dose levels in acute animal studies did not result in any organ toxicity. Limited data are available on the consequences of ingestion of acute overdoses in humans. No fatalities occurred, and the patients recovered. No specific signs or symptoms have been identified following such overdose.

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.
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. Lamivudine in combination with zidovudine exhibits synergistic anti-HIV activity against clinical isolates in cell culture.

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 experience:

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).

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).

### 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 ($t_{\text{max}}$) to maximal serum concentrations ($C_{\text{max}}$) is about an hour. Based on data derived from a study in healthy volunteers, at a therapeutic dose of 150mg twice daily, mean (CV) steady-state $C_{\text{max}}$ and $C_{\text{min}}$ 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 300mg once daily, the mean (CV) steady-state $C_{\text{max}}$, $C_{\text{min}}$ 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 $t_{\text{max}}$ and a lower $C_{\text{max}}$ (decreased by 47%). However, the extent (based on the AUC) of lamivudine absorbed is not influenced.

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 observed half-life of elimination is 5 to 7 hours. 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 cerebrospinal 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.

**Metabolism:** The active moiety, intracellular lamivudine triphosphate, has a prolonged terminal half-life in the cell (16 to 19 hours) compared to the plasma lamivudine half-life (5 to 7 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 $\text{AUC}_{24}$ and $C_{\text{max}}$.

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.

Pharmacokinetics in children: In general, lamivudine pharmacokinetics in paediatric patients is similar to adults. However, absolute bioavailability (approximately 55-65%) was reduced in paediatric patients below 12 years of age. In addition, systemic clearance values were greater in younger paediatric patients and decreased with age, approaching adult values around 12 years of age. Due to these differences, the recommended dose for lamivudine in children (aged more than three months and weighing less than 30 kg) is 4 mg/kg twice daily. This dose will achieve an average AUC$_{0-12}$ ranging from approximately 3,800 to 5,300 ng.h/ml. Recent findings indicate that exposure in children < 6 years of age may be reduced by about 30% compared with other age groups. Further data addressing this issue are currently awaited. At present, the available data do not suggest that lamivudine is less efficacious in this age group.

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, the recommended dose for neonates is 4 mg/kg/day. Glomerular filtration estimates suggests that to achieve similar adult and paediatric exposure, the recommended dose for children aged six weeks and older could be 8 mg/kg/day.

Pharmacokinetics in 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose 20 % (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. A 10 ml polypropylene oral dosing syringe and a polyethylene adapter are also included in the pack.
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.

7. MARKETING AUTHORISATION HOLDER

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

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](http://www.ema.europa.eu)
1. **NAME OF THE MEDICINAL PRODUCT**

Epivir 300 mg film-coated tablets

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each film-coated tablet contains 300 mg lamivudine.

For a full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

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. For patients who are unable to swallow tablets, lamivudine is available as an oral solution. Alternatively, the tablets may be crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately (see section 5.2).

**Adults and adolescents over 12 years of age:** 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.

Patients changing to the once daily regimen should take 150 mg twice a day and switch to 300 mg once a day the following morning. Where an evening once daily regimen is preferred, 150 mg of Epivir should be taken on the first morning only, followed by 300 mg in the evening. When changing back to a twice daily regimen patients should complete the days treatment and start 150 mg twice a day the following morning.

**Children:**

**Three months to 12 years of age:** the recommended dose is 4 mg/kg twice daily up to a maximum of 300 mg daily.

**Less than three months of age:** the limited data available are insufficient to propose specific dosage recommendations (see section 5.2)
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 and adolescents over 12 years:

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<td>150 mg</td>
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<tr>
<td>&lt;30</td>
<td>As doses below 150 mg are needed the use of the oral solution is recommended</td>
<td></td>
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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.

Dosing recommendations – Children from 3 months to 12 years:

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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.

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

**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.

**Lactic acidosis:** Lactic acidosis, usually associated with hepatomegaly and hepatic steatosis, has been reported with the use of nucleoside analogues. Early symptoms (symptomatic hyperlactatemia) include benign digestive symptoms (nausea, vomiting and abdominal pain), non-specific malaise, loss of appetite, weight loss, respiratory symptoms (rapid and/or deep breathing) or neurological symptoms (including motor weakness).

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

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

Treatment with nucleoside analogues should be discontinued in the setting of symptomatic hyperlactatemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels.

Caution should be exercised when administering nucleoside analogues to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease and hepatic steatosis (including certain medicinal products and alcohol). Patients co-infected with hepatitis C and treated with alpha interferon and ribavirin may constitute a special risk.

Patients at increased risk should be followed closely.

**Mitochondrial dysfunction:** Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed *in utero* and/or post-natally to nucleoside analogues. The main adverse events reported are haematological disorders (anaemia, neutropenia), metabolic disorders (hyperlactatemia, hyperlipasemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether the neurological disorders are transient or permanent is currently unknown. Any child exposed *in utero* to nucleoside and nucleotide analogues, even HIV-negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

**Lipodystrophy:** Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors (PIs) and lipodystrophy and nucleoside reverse transcriptase inhibitors (NRTIs) has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).

**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 carinii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

**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).

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.

Epivir should not be taken with any other medicinal products containing lamivudine or medicinal products containing emtricitabine.

### 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 carinii* 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 $C_{\text{max}}$ (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).

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

4.6 Pregnancy and lactation

A large amount of data on pregnant women (more than 1000 exposed outcomes) indicate no malformative toxicity. Epivir can be used during pregnancy if clinically needed.

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).

Following oral administration lamivudine was excreted in breast milk at similar concentrations to those found in serum. Since lamivudine and the virus pass into breast milk, it is recommended that mothers taking Epivir do not breast-feed their infants. It is recommended that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

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 ($\geq 1/10$), common ($\geq 1/100$ to $<1/10$), uncommon ($\geq 1/1,000$ to $<1/100$), rare ($\geq 1/10,000$ 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

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.

Cases of lactic acidosis, sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis, have been reported with the use of nucleoside analogues (see section 4.4).

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (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 (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).

4.9 Overdose

Administration of lamivudine at very high dose levels in acute animal studies did not result in any organ toxicity. Limited data are available on the consequences of ingestion of acute overdoses in humans. No fatalities occurred, and the patients recovered. No specific signs or symptoms have been identified following such overdose.

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.

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. Lamivudine in combination with zidovudine exhibits synergistic anti-HIV activity against clinical isolates in cell culture.
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 experience:

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).

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).

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 (tmax) to maximal serum concentrations (Cmax) is about an hour. Based on data derived from a study in healthy volunteers, at a therapeutic dose of 150mg twice daily, mean (CV) steady-state Cmax and Cmin 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 300mg once daily, the mean (CV) steady-state Cmax, Cmin 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∞, Cmax, and tmax.

Co-administration of lamivudine with food results in a delay of tmax and a lower Cmax (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 observed half-life of elimination is 5 to 7 hours. The mean systemic clearance of lamivudine is approximately 0.32 l/h/kg, with predominantly renal clearance (> 70%) via the organic cationic transport system.

Limited data show that lamivudine penetrates the central nervous system and reaches the cerebrospinal 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.

Metabolism: The active moiety, intracellular lamivudine triphosphate, has a prolonged terminal half-life in the cell (16 to 19 hours) compared to the plasma lamivudine half-life (5 to 7 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 AUC24 and Cmax.

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.

**Pharmacokinetics in children:** In general, lamivudine pharmacokinetics in paediatric patients is similar to adults. However, absolute bioavailability (approximately 55-65%) was reduced in paediatric patients below 12 years of age. In addition, systemic clearance values were greater in younger paediatric patients and decreased with age, approaching adult values around 12 years of age. Due to these differences, the recommended dose for lamivudine in children (aged more than three months and weighing less than 30 kg) is 4 mg/kg twice daily. This dose will achieve an average AUC$_{0-12}$ ranging from approximately 3,800 to 5,300 ng h/ml. Recent findings indicate that exposure in children < 6 years of age may be reduced by about 30% compared with other age groups. Further data addressing this issue are currently awaited. At present, the available data do not suggest that lamivudine is less efficacious in this age group.

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, the recommended dose for neonates is 4 mg/kg/day. Glomerular filtration estimates suggests that to achieve similar adult and paediatric exposure, the recommended dose for children aged six weeks and older could be 8 mg/kg/day.

**Pharmacokinetics in 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.

### 6. PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

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

*Tablet film-coat:*
Hypermellose (E464),
Titanium dioxide (E171),
Black iron oxide (E172),
Macrogol, Polysorbate 80

6.2 **Incompatibilities**

Not applicable

6.3 **Shelf life**

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**

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

6.6 **Special precautions for disposal**

No special requirements

7. **MARKETING AUTHORISATION HOLDER**

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

8. **MARKETING AUTHORISATION NUMBER**

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

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

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](http://www.ema.europa.eu)
ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION
A. MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

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

Film-coated tablets:

Glaxo Operations UK Limited
(trading as Glaxo Wellcome Operations)
Priory Street, Ware
Hertfordshire
SG12 0DJ
United Kingdom.

or

GlaxoSmithKline Pharmaceuticals S.A.
ul. Grunwaldzka 189
60-322 Poznan
Poland

Oral solution:

Glaxo Wellcome GmbH & Co. KG
Industriestrasse 32-36
23843 Bad Oldesloe
Germany

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 OF THE MARKETING AUTHORISATION

• CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER

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

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

Not applicable.
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOTTLE CARTON X 60 FILM-COATED TABLETS (150 mg)</td>
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</table>

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
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<tbody>
<tr>
<td>Epivir 150 mg film-coated tablets</td>
</tr>
<tr>
<td>Lamivudine</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each film-coated tablet contains lamivudine 150 mg</td>
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</table>

<table>
<thead>
<tr>
<th>3. LIST OF EXCIPIENTS</th>
</tr>
</thead>
</table>

<table>
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<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 film-coated tablets</td>
</tr>
<tr>
<td>Scored tablets</td>
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</tbody>
</table>

<table>
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<tr>
<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral use</td>
</tr>
<tr>
<td>Read the package leaflet before use.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep out of the reach and sight of children.</td>
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<table>
<thead>
<tr>
<th>7. OTHER SPECIAL WARNING(S), IF NECESSARY</th>
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</thead>
</table>

<table>
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<tr>
<th>8. EXPIRY DATE</th>
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<tr>
<td>EXP {MM/YYYY}</td>
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</table>

<table>
<thead>
<tr>
<th>9. SPECIAL STORAGE CONDITIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not store above 30°C</td>
</tr>
</tbody>
</table>
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 UK Limited
980 Great West Road
Brentford
Middlesex
TW8 9GS
United Kingdom

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
<table>
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<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING</th>
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</thead>
<tbody>
<tr>
<td>BOTTLE LABEL X 60 FILM-COATED TABLETS (150 mg)</td>
</tr>
</tbody>
</table>

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 REACH AND SIGHT OF CHILDREN**

   Keep out of the reach and sight 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 UK Limited
980 Great West Road
Brentford
Middlesex
TW8 9GS
United Kingdom

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
### 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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight 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 UK Limited
980 Great West Road
Brentford
Middlesex
TW8 9GS
United Kingdom

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
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<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>Epivir 150 mg tablets</td>
</tr>
<tr>
<td>lamivudine</td>
</tr>
<tr>
<td><strong>2. NAME OF THE MARKETING AUTHORISATION HOLDER</strong></td>
</tr>
<tr>
<td>ViiV Healthcare UK Limited</td>
</tr>
<tr>
<td><strong>3. EXPIRY DATE</strong></td>
</tr>
<tr>
<td>EXP</td>
</tr>
<tr>
<td><strong>4. BATCH NUMBER</strong></td>
</tr>
<tr>
<td>LOT</td>
</tr>
<tr>
<td><strong>5. OTHER</strong></td>
</tr>
</tbody>
</table>


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

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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight 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 UK Limited
980 Great West Road
Brentford
Middlesex
TW8 9GS
United Kingdom

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
### 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

#### 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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

#### 7. OTHER SPECIAL WARNING(S), IF NECESSARY

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Do not store above 25°C

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Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE
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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight 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 UK Limited |
|     | 980 Great West Road |
|     | Brentford |
|     | Middlesex |
|     | TW8 9GS |
|     | United Kingdom |
| 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 |
## 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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight 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 AUTHORITY | ViiV Healthcare UK Limited |
| | | 980 Great West Road |
| | | Brentford |
| | | Middlesex |
| | | TW8 9GS |
| | | United Kingdom |
| 12. | MARKETING AUTHORIZATION NUMBER(S) | EU/1/96/015/003 |
| 13. | BATCH NUMBER | LOT |
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| 15. | INSTRUCTIONS ON USE | |
| 16. | INFORMATION IN BRAILLE | |
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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight 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
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| 15. INSTRUCTIONS ON USE                                  |

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<td>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</td>
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<td>lamivudine</td>
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<td><strong>2. NAME OF THE MARKETING AUTHORISATION HOLDER</strong></td>
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<td><strong>5. OTHER</strong></td>
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B. PACKAGE LEAFLET
Read all of this leaflet carefully before you start taking this medicine.

- 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 personally. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Epivir is and what it is used for
2. Before you take Epivir
3. How to take Epivir
4. Possible side effects
5. How to store Epivir
6. Further 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. Before you take Epivir

Don’t take Epivir:

- if you’re allergic (hypersensitive) to lamivudine or any of the other ingredients of Epivir (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, don’t stop Epivir without your doctor’s advice, as your hepatitis may come back)
• if you’re seriously **overweight** (especially if you’re a woman)
• if you’re **diabetic** and using insulin
• 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’re 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’re taking Epivir.

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

**Protect other people**

HIV infection is spread by sexual contact with someone who has the infection, or by transfer of infected blood (for example, by sharing injection needles). Epivir will not stop you passing HIV infection on to other people. To protect other people from becoming infected with HIV:

• **Use a condom** when you have oral or penetrative sex.
• **Don’t risk blood transfer** — for example, don’t share needles.

**Other medicines and Epivir**

Tell your doctor or pharmacist if you’re taking any other medicines, or if you’ve 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’re taking Epivir.

**These medicines should not be used with Epivir:**

• 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.
  **Tell your doctor** if you’re 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 become pregnant while you’re taking Epivir, your baby may be given extra check-ups (including blood tests) to make sure it is developing normally.

Children whose mothers took NRTIs (medicines like Epivir) during pregnancy had a reduced risk of being infected with HIV. This benefit is greater than the risk of having side effects.

**Breast-feeding**

**Women who are HIV-positive must not breast-feed**, because HIV infection can be passed on to the baby in breast milk.

If you’re breast-feeding, or thinking about breast-feeding:

  **Talk to your doctor immediately.**
Driving and using machines

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

3. How to take Epivir

Always take Epivir exactly as your doctor has told you to. Check with your doctor or pharmacist if you’re 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 don’t stop taking Epivir without your doctor’s advice.

How much to take

Adults and children who weigh at least 30 kg:

The usual dose of Epivir is 300 mg a day to be taken as:
- one 150 mg tablet twice a day, approximately 12 hours apart

Children weighing 21 – 30 kg
- one half (½) of an Epivir tablet (75 mg) in the morning, and
- one whole Epivir tablet (150 mg) in the evening.

Children weighing 14 – 21 kg
- one half (½) of an Epivir tablet (75 mg) in the morning, and
- one half (½) of an Epivir tablet (75 mg) in the evening.

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 can’t 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 too much Epivir

Accidentally taking too much Epivir is unlikely to cause any serious problems. If you take too much, tell your doctor or your pharmacist, or contact your nearest hospital emergency department for further advice.

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. Don’t take a double dose to make up for a missed dose.

4. Possible side effects

Like all medicines, Epivir can cause side effects, but not everyone gets them.
When you’re 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
- lactic acidosis (see the next section, ‘Other possible side effects of combination therapy for HIV’)
- inflammation of the pancreas (pancreatitis)
- breakdown of muscle tissue
- liver disorders, such as jaundice, enlarged liver or fatty liver, 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:
- 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.

If you get any symptoms of infection while you’re taking Epivir:

Tell your doctor immediately. Don’t take other medicines for the infection without your doctor’s advice.

Your body shape may change

People taking combination therapy for HIV may find that their body shape changes, because of changes in fat distribution:

- Fat may be lost from the legs, arms or face.
- Extra fat may build up around the tummy (abdomen), or on the breasts or internal organs.
- Fatty lumps (sometimes called buffalo hump) may appear on the back of the neck.

It is not yet known what causes these changes, or whether they have any long-term effects on your health. If you notice changes in your body shape:

Tell your doctor.

Lactic acidosis is a rare but serious side effect

Some people taking Epivir, or other medicines like it (NRTIs), develop a condition called lactic acidosis, together with an enlarged liver.

Lactic acidosis is caused by a build-up of lactic acid in the body. It is rare; if it happens, it usually develops after a few months of treatment. It can be life-threatening, causing failure of internal organs.

Lactic acidosis is more likely to develop in people who have liver disease, or in obese (very overweight) people, especially women.

Signs of lactic acidosis include:

- deep, rapid, difficult breathing
- drowsiness
- numbness or weakness in the limbs
- feeling sick (nausea), being sick (vomiting)
- stomach pain.

During your treatment, your doctor will monitor you for signs of lactic acidosis. If you have any of the symptoms listed above, or any other symptoms that worry you:

See your doctor as soon as possible.

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.**

**Other effects may show up in blood tests**

Combination therapy for HIV can also cause:
- increased levels of lactic acid in the blood, which on rare occasions can lead to lactic acidosis
- increased levels of sugar and fats (triglycerides and cholesterol) in the blood
- resistance to insulin (so if you’re diabetic, you may have to change your insulin dose to control your blood sugar).

5. **How to store Epivir**

Keep out of the reach and sight of children.

Do not take Epivir after the expiry date shown on the carton.

Do not store Epivir above 30°C.

If you have any unwanted Epivir tablets, don’t dispose of them in your waste water or your household rubbish. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. **Further 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

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Marketing Authorisation Holder</th>
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<tbody>
<tr>
<td>Glaxo Operations UK Limited</td>
<td>ViiV Healthcare UK Limited</td>
</tr>
<tr>
<td>(trading as Glaxo Wellcome Operations)</td>
<td>980 Great West Road</td>
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For any information about this medicinal product please contact the local representative of the Marketing Authorisation Holder.

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Tel: + 44 (0)800 221441
customercontactuk@gsk.com

Lietuva
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info.lt@gsk.com

This leaflet was approved in
Detailed information on this medicine is available on the European Medicines Agency web site:
Read all of this leaflet carefully before you start taking this medicine.

- 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 symptoms are the same as yours.
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4. Possible side effects
5. How to store Epivir
6. Further 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. Before you take Epivir

Don’t take Epivir:

- if you’re allergic (hypersensitive) to lamivudine or any of the other ingredients in Epivir oral solution (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, don’t stop Epivir without your doctor’s advice, as your hepatitis may come back)
• if you’re seriously overweight (especially if you’re a woman)
• if you’re diabetic and using insulin.
• 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’re 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’re taking Epivir.

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

Protect other people

HIV infection is spread by sexual contact with someone who has the infection, or by transfer of infected blood (for example, by sharing injection needles). Epivir will not stop you passing HIV infection on to other people. To protect other people from becoming infected with HIV:

• Use a condom when you have oral or penetrative sex.
• Don’t risk blood transfer — for example, don’t share needles.

Other medicines and Epivir

Tell your doctor or pharmacist if you’re taking any other medicines, or if you’ve 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’re taking Epivir.

These medicines should not be used with Epivir:

• 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.

  Tell your doctor if you’re 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 and risks to you and your baby of taking Epivir.

Epivir and similar medicines may cause side effects in unborn babies. If you become pregnant while you’re taking Epivir, your baby may be given extra check-ups (including blood tests) to make sure it is developing normally.

Children whose mothers took NRTIs (medicines like Epivir) during pregnancy had a reduced risk of being infected with HIV. This benefit is greater than the risk of having side effects.

Breast-feeding

Women who are HIV-positive must not breast-feed, because HIV infection can be passed on to the baby in breast milk.
If you’re breast-feeding, or thinking about breast-feeding:
  Talk to your doctor immediately.
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).

3. How to take Epivir

Always take Epivir exactly as your doctor has told you to. Check with your doctor or pharmacist if you’re 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 don’t stop taking Epivir without your doctor’s advice.

How much to take

Adults and adolescents over 12 years of age
The usual dose of Epivir is 30 ml a day (300 mg) to be taken as 15 ml (150 mg) twice a day at regular times, leaving approximately 12 hours between each dose.

Children 3 months to 12 years of age
The usual dose of Epivir is 4 mg/kg twice daily up to a maximum of 300 mg daily. Give each dose to your child at regular times, leaving approximately 12 hours between each dose.

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

1. Remove the bottle cap. Keep it safely
2. Hold the bottle firmly. Push the plastic adapter into the neck of the bottle.
3. Insert the syringe firmly into the adapter.
4. Turn the bottle upside down.
5. Pull out syringe plunger until the syringe contains the first part of your full dose.
6. Turn the bottle the correct way up. Remove the syringe from the adapter.
7. 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. Don’t push too hard and squirt the liquid into the back of your throat or you may choke.
8. Repeat steps 3 to 7 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.
9. Take the syringe out of the bottle and wash it thoroughly in clean water. Let it dry completely before you use it again.
10. Close the bottle tightly with the cap, leaving the adaptor in place.

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 too much Epivir
Accidentally taking too much Epivir is unlikely to cause any serious problems. If you take too much, tell your doctor or your pharmacist, or contact your nearest hospital emergency department for further advice.

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. Don’t take a double dose to make up for a missed dose.

4. Possible side effects

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

When you’re 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
• lactic acidosis (see the next section, ‘Other possible side effects of combination therapy for HIV’)
• inflammation of the pancreas (pancreatitis)
• breakdown of muscle tissue
• liver disorders, such as jaundice, enlarged liver or fatty liver, 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:
• 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.
If you get any symptoms of infection while you’re taking Epivir:

**Tell your doctor immediately.** Don’t take other medicines for the infection without your doctor’s advice.

**Your body shape may change**
People taking combination therapy for HIV may find that their body shape changes, because of changes in fat distribution:
• Fat may be lost from the legs, arms or face.
• Extra fat may build up around the tummy (abdomen), or on the breasts or internal organs.
• Fatty lumps (sometimes called buffalo hump) may appear on the back of the neck.
It is not yet known what causes these changes, or whether they have any long-term effects on your health. If you notice changes in your body shape:

**Tell your doctor.**

**Lactic acidosis is a rare but serious side effect**
Some people taking Epivir, or other medicines like it (NRTIs), develop a condition called lactic acidosis, together with an enlarged liver.

Lactic acidosis is caused by a build-up of lactic acid in the body. It is rare; if it happens, it usually develops after a few months of treatment. It can be life-threatening, causing failure of internal organs.

Lactic acidosis is more likely to develop in people who have liver disease, or in obese (very overweight) people, especially women.

**Signs of lactic acidosis include:**
• deep, rapid, difficult breathing
• drowsiness
• numbness or weakness in the limbs
• feeling sick (nausea), being sick (vomiting)
• stomach pain.

During your treatment, your doctor will monitor you for signs of lactic acidosis. If you have any of the symptoms listed above, or any other symptoms that worry you:

**See your doctor as soon as possible.**

**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.**

**Other effects may show up in blood tests**

Combination therapy for HIV can also cause:

• increased levels of lactic acid in the blood, which on rare occasions can lead to lactic acidosis
• increased levels of sugar and fats (triglycerides and cholesterol) in the blood
• resistance to insulin (so if you’re diabetic, you may have to change your insulin dose to control your blood sugar).

5. **How to store Epivir**

Keep out of the reach and sight of children

Do not take Epivir after the expiry date shown on the container.

Discard one month after first opening.

Do not store above 25°C.

If you have any unwanted Epivir, don’t dispose of it in your waste water or your household rubbish. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. **Further 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.

**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**

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<td>ViiV Healthcare UK Limited</td>
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<tr>
<td>Industriestrasse 32-36</td>
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<td>23843 Bad Oldesloe</td>
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For any information about this medicinal product please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was approved in

Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu
Read all of this leaflet carefully before you start taking this medicine.

− 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 personally. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.

− If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Epivir is and what it is used for
2. Before you take Epivir
3. How to take Epivir
4. Possible side effects
5. How to store Epivir
6. Further 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. Before you take Epivir

Don’t take Epivir:

- if you’re allergic (hypersensitive) to lamivudine or any of the other ingredients in Epivir (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, don’t stop Epivir without your doctor’s advice, as your hepatitis may come back)
- if you’re seriously overweight (especially if you’re a woman)
• if you’re diabetic and using insulin
• 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’re 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’re taking Epivir.

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

**Protect other people**

HIV infection is spread by sexual contact with someone who has the infection, or by transfer of infected blood (for example, by sharing injection needles). Epivir will not stop you passing HIV infection on to other people. To protect other people from becoming infected with HIV:

• **Use a condom** when you have oral or penetrative sex.
• **Don’t risk blood transfer** — for example, don’t share needles.

**Other medicines and Epivir**

**Tell your doctor or pharmacist if you’re taking any other medicines, or if you’ve 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’re taking Epivir.

**These medicines should not be used with Epivir:**

• 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.

  **Tell your doctor** if you’re 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 become pregnant while you’re taking Epivir, your baby may be given extra check-ups (including blood tests) to make sure it is developing normally.

Children whose mothers took NRTIs (medicines like Epivir) during pregnancy had a reduced risk of being infected with HIV. This benefit is greater than the risk of having side effects.

**Breast-feeding**

**Women who are HIV-positive must not breast-feed,** because HIV infection can be passed on to the baby in breast milk.

If you’re breast-feeding, or thinking about breast-feeding:

  **Talk to your doctor immediately.**

**Driving and using machines**

Epivir is unlikely to affect your ability to drive or use machines.
3. **How to take Epivir**

**Always take Epivir exactly as your doctor has told you to.** Check with your doctor or pharmacist if you’re 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 don’t stop taking Epivir* without your doctor’s advice.

**How much to take**

The usual dose of Epivir for adults and children who weigh at least 30 kg is:

- one tablet once a day.

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 can’t 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 too much Epivir**

Accidentally taking too much Epivir is unlikely to cause any serious problems. If you take too much, tell your doctor or your pharmacist, or contact your nearest hospital emergency department for further advice.

**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. Don’t take a double dose to make up for a missed dose.

4. **Possible side effects**

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

When you’re 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
• lactic acidosis (see the next section, ‘Other possible side effects of combination therapy for HIV’)
• inflammation of the pancreas (*pancreatitis*)
• breakdown of muscle tissue
• liver disorders, such as jaundice, enlarged liver or fatty liver, 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:
• 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.
If you get any symptoms of infection while you’re taking Epivir:

Tell your doctor immediately. Don’t take other medicines for the infection without your doctor’s advice.

Your body shape may change

People taking combination therapy for HIV may find that their body shape changes, because of changes in fat distribution:
- Fat may be lost from the legs, arms or face.
- Extra fat may build up around the tummy (abdomen), or on the breasts or internal organs.
- Fatty lumps (sometimes called buffalo hump) may appear on the back of the neck.

It is not yet known what causes these changes, or whether they have any long-term effects on your health. If you notice changes in your body shape:

Tell your doctor.

Lactic acidosis is a rare but serious side effect

Some people taking Epivir, or other medicines like it (NRTIs), develop a condition called lactic acidosis, together with an enlarged liver.

Lactic acidosis is caused by a build-up of lactic acid in the body. It is rare; if it happens, it usually develops after a few months of treatment. It can be life-threatening, causing failure of internal organs.

Lactic acidosis is more likely to develop in people who have liver disease, or in obese (very overweight) people, especially women.

**Signs of lactic acidosis include:**
- deep, rapid, difficult breathing
- drowsiness
- numbness or weakness in the limbs
- feeling sick (*nausea*), being sick (*vomiting*)
- stomach pain.

During your treatment, your doctor will monitor you for signs of lactic acidosis. If you have any of the symptoms listed above, or any other symptoms that worry you:

See your doctor as soon as possible.

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.

Other effects may show up in blood tests

Combination therapy for HIV can also cause:
• increased levels of lactic acid in the blood, which on rare occasions can lead to lactic acidosis
• increased levels of sugar and fats (triglycerides and cholesterol) in the blood
• resistance to insulin (so if you’re diabetic, you may have to change your insulin dose to control your blood sugar).

5. How to store Epivir

Keep out of the reach and sight of children.

Do not take Epivir after the expiry date shown on the carton.
Do not store Epivir above 30°C.

If you have any unwanted Epivir tablets, don’t dispose of them in your waste water or your household rubbish. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6 Further 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

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<td>ViiV Healthcare UK Limited</td>
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<td>Middlesex</td>
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<td>United Kingdom</td>
<td>TW8 9GS</td>
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or

<table>
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<tr>
<th>Manufacturer</th>
<th>Marketing Authorisation Holder</th>
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<tr>
<td>GlaxoSmithKline Pharmaceuticals S.A.</td>
<td>United Kingdom</td>
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<tr>
<td>ul. Grunwaldzka 189</td>
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<td>60-322 Poznan</td>
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<td>Poland</td>
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For any information about this medicinal product please contact the local representative of the Marketing Authorisation Holder.

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<tr>
<th>Country</th>
<th>Company</th>
<th>Telephone</th>
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<tbody>
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