ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS
1. **NAME OF THE MEDICINAL PRODUCT**

EPIVIR®

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

EPIVIR® contains 10 mg/ml lamivudine in a solution containing 20% (w/v) sucrose, 6% (v/v) ethanol, and preservatives (methyl parahydroxybenzoate and propyl parahydroxybenzoate).

3. **PHARMACEUTICAL FORM**

Oral solution.

4. **CLINICAL PARTICULARS**

4.1. **THERAPEUTIC INDICATIONS**

EPIVIR® is indicated in combination with other antiretroviral agents for the treatment of HIV infected adults and children >12 years of age, with progressive immunodeficiency (CD4+ count ≤ 500 cells/mm³).

EPIVIR® is not recommended for use as monotherapy. Only the combination with zidovudine has been extensively studied in terms of safety and efficacy. Combination studies with other antiretrovirals are in progress.

Lamivudine in combination with zidovudine reduces HIV-1 viral load and increases CD4+ count. A meta-analysis of clinical events in the phase II comparative studies indicates that lamivudine in combination with zidovudine slows the progression of the disease. A study to confirm the effects on AIDS progression and survival is ongoing.

4.2. **POSOLOGY AND METHOD OF ADMINISTRATION**

Adults and children over the age of 12 years:

The recommended dose of EPIVIR® is 150 mg (15 ml) twice daily.

EPIVIR® is also available as a tablet formulation.

EPIVIR® should usually be taken without food. Ingestion with food reduces the Cmax considerably but does not alter the area under the curve (AUC) (see 5.2. PHARMACOKINETIC PROPERTIES). Therefore ingestion with food might be considered when required due to clinical reasons.
The therapy should be initiated by a physician experienced in the management of HIV infection.

Renal Impairment:

Lamivudine levels are increased in patients with moderate - severe renal impairment due to decreased clearance. The dose should therefore be adjusted (see table).

Dosing Recommendations

<table>
<thead>
<tr>
<th>Renal Function (Clcr, ml/min)</th>
<th>First Dose</th>
<th>Maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clcr≥50</td>
<td>150 mg (15 ml)</td>
<td>150 mg (15 ml) daily Twice daily</td>
</tr>
<tr>
<td>50&gt;Clcr≥30</td>
<td>150 mg (15 ml)</td>
<td>150 mg (15 ml) daily Once daily</td>
</tr>
<tr>
<td>30&gt;Clcr≥15</td>
<td>150 mg (15 ml)</td>
<td>100 mg (10 ml) daily Once daily</td>
</tr>
<tr>
<td>15&gt;Clcr≥5</td>
<td>150 mg (15 ml)</td>
<td>50 mg (5 ml) Once daily</td>
</tr>
<tr>
<td>5&gt;Clcr</td>
<td>50 mg (5 ml)</td>
<td>25 mg (2.5 ml) Once daily</td>
</tr>
</tbody>
</table>

Hepatic Impairment:

The influence of hepatic impairment on lamivudine levels is under investigation. Lamivudine clearance is largely renal. Based on preliminary safety data no dosage adjustment is necessary.

4.3. CONTRA-INDICATIONS

The use of EPIVIR® is contra-indicated in patients with known hypersensitivity to lamivudine or to any ingredient of the preparation.

4.4. SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

SPECIAL WARNINGS:

EPIVIR® is not recommended for use as monotherapy.

Cases of pancreatitis have occurred rarely. However it is not clear whether these cases were due to drug 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.

There are insufficient data on the use of EPIVIR® in children under the age of 12 years.
Administration of EPIVIR® is not recommended during the first 3 months of pregnancy (See 4.6. PREGNANCY AND LACTATION).

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.

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 conduct or blood contamination. Appropriate precautions should continue to be employed.

**SPECIAL PRECAUTIONS FOR USE:**

In patients with moderate - severe renal impairment, the terminal plasma half-life of lamivudine is increased due to decreased clearance. The dose should be adjusted. (See dosage in renal impairment, in section 4.2. POSOLOGY AND METHOD OF ADMINISTRATION).

EPIVIR® should be used with caution in patients with advanced cirrhotic liver disease due to chronic Hepatitis B infection, as there is a small risk of rebound hepatitis if treatment is discontinued.

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

Patients should be advised that this medicine contains alcohol.

**4.5. INTERACTION WITH OTHER MEDICAMENTS AND OTHER FORMS OF INTERACTION**

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

A modest increase in Cmax (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 5.2. PHARMACOKINETIC PROPERTIES section).
The possibility of interactions with other drugs 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 drugs (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 and zalcitabine) like zidovudine, are not eliminated by this mechanism and are unlikely to interact with lamivudine.

Administration of prophylactic doses of co-trimoxazole results in a 40% increase in lamivudine exposure, because of the trimethoprim component; the sulphamethoxazole component did not interact. However, unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary (see section 4.2. POSOLOGY AND METHOD OF ADMINISTRATION). When concomitant administration is warranted, patients should be monitored clinically. Co-administration of EPIVIR® with high doses of co-trimoxazole for the treatment of Pneumocystis carinii pneumonia (PCP) and toxoplasmosis should be avoided. Lamivudine has no effect on the pharmacokinetics of co-trimoxazole.

Lamivudine metabolism does not involve CYP3A, making interactions with drugs metabolised by this system (e.g. protease inhibitors) unlikely.

Co-administration of EPIVIR® with intravenous ganciclovir or foscarnet is not recommended until further information is available.

4.6. PREGNANCY AND LACTATION

PREGNANCY:

The safety of lamivudine in human pregnancy has not been established. Reproductive studies in animals have not shown evidence of teratogenicity, and showed no effect on male or female fertility. Lamivudine induces early embryolethality when administered to pregnant rabbits at exposure levels comparable to those achieved in man. Lamivudine crosses the placenta in animals but there is no information on placental transfer in humans.

Although animal reproductive studies are not always predictive of the human response, administration during the first three months of pregnancy is not recommended (see 4.4. SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE).
LACTATION:

A study in lactating rats showed that, following oral administration, lamivudine was concentrated four fold and excreted in the milk. It is not known if lamivudine is excreted in human breast milk. Since the drug may pass into breast milk, it is recommended that mothers taking EPIVIR® do not breast feed their infants. Some health experts recommend 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

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

4.8. UNDESIRABLE EFFECTS

Adverse events have been reported during therapy for HIV disease with EPIVIR® alone and in combination with zidovudine. With many it is unclear whether they are drug related or are as a result of the underlying disease process.

Adverse events which have been commonly reported are headache, malaise, fatigue, nausea, diarrhoea, vomiting, abdominal pain or cramps, insomnia, cough, nasal symptoms and musculoskeletal pain.

Cases of pancreatitis and peripheral neuropathy (or paraesthesia) have been recorded, although no relationship to the dose of EPIVIR® has been noted.

Neutropenia and anaemia (both occasionally severe) have occurred in combination with zidovudine. Thrombocytopenia, transient rises in liver enzymes (AST, ALT) and rises in serum amylase have been reported.

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: J05A B10.

Lamivudine is a nucleoside analogue. Lamivudine is metabolised intracellularly to lamivudine 5′-triphosphate, its main mode of action is as a chain terminator of HIV 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.

The relationships between in vitro susceptibility of HIV to lamivudine and the clinical response to therapy remain under investigation. In vitro sensitivity testing has not been standardised and results may vary according to methodological factors.

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

Lamivudine has been shown to be highly synergistic with zidovudine, inhibiting the replication of HIV in cell culture.

In vitro studies indicate that zidovudine-resistant virus isolates can become zidovudine sensitive when they simultaneously acquire resistance to lamivudine. Furthermore, in vivo, there is evidence showing that lamivudine plus zidovudine delays the emergence of zidovudine-resistant isolates in individuals with no prior antiretroviral therapy.

In vitro, lamivudine demonstrates low cytotoxicity to peripheral blood lymphocytes, to established lymphocyte and monocyte-macrophage cell lines and to a variety of bone marrow progenitor cells in vitro. Lamivudine therefore has, in vitro, a high therapeutic index.
5.2. PHARMACOKINETIC PROPERTIES

Absorption

Lamivudine is well absorbed from the gut, 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. At therapeutic dose levels i.e. 4 mg/kg/day (as two 12-hourly doses), C\text{max} is in the order of 1.5-1.9 µg/ml.

Co-administration of lamivudine with food results in a delay of t\text{max} and a lower C\text{max} (decreased by 47%). However, lamivudine bioavailability (based on the AUC) 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 1.3L/kg. The observed half-life of elimination is 5 to 7 hours. The mean systemic clearance of lamivudine is approximately 0.32L/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 \textit{in vitro} studies).

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

Metabolism

Lamivudine is predominantly cleared by renal excretion of unchanged drug. The likelihood of metabolic drug interactions with lamivudine is low due to the small extent of hepatic metabolism (5-10%) and low plasma protein binding.
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 (section 4.2. POSOLOGY AND METHOD OF ADMINISTRATION).

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 section 4.5. INTERACTION WITH OTHER MEDICAMENTS AND OTHER FORMS OF INTERACTION, and dosage adjustments in renal impairment in section 4.2. POSOLOGY AND METHOD OF ADMINISTRATION). Administration of co-trimoxazole with EPIVIR® in patients with renal impairment should be carefully assessed.

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 30-40 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.

Long term carcinogenicity studies in animals are ongoing.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Sucrose PhEur (20% w/v)
Ethanol BP (6% v/v)
Methyl parahydroxybenzoate PhEur (E218)
Propyl parahydroxybenzoate PhEur (E216)
Citric Acid Anhydrous PhEur
Propylene glycol PhEur
Disodium Edetate PhEur
Artificial Strawberry Flavour
Artificial Banana Flavour
Water purified PhEur

6.2. INCOMPATIBILITIES

None reported
6.3. **SHELF-LIFE**

2 years

6.4. **SPECIAL PRECAUTIONS FOR STORAGE**

Store between 2 and 25°C.

6.5. **NATURE AND CONTENT OF CONTAINER**

Cartons containing 240 ml lamivudine 10 mg/ml in a white high density polyethylene (HDPE) bottle, with a child resistant closure.

6.6. **INSTRUCTIONS FOR USE/HANDLING**

Discard one month after first opening.

7. **MARKETING AUTHORISATION HOLDER**

Glaxo Group Ltd
Greenford Road
Greenford
Middlesex UB6 0NN
UK

8. **MARKETING AUTHORISATION NUMBER**

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

10. **DATE OF (PARTIAL) REVISION OF THE TEXT**
1. NAME OF THE MEDICINAL PRODUCT
EPIVIR®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
EPIVIR® contains 150 mg lamivudine.

3. PHARMACEUTICAL FORM
Coated tablets. The tablets are white film coated, diamond shaped tablets engraved “GX CJ7” on one face.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS
EPIVIR® is indicated in combination with other antiretroviral agents for the treatment of HIV infected adults and children >12 years of age, with progressive immunodeficiency (CD4+ count ≤ 500 cells/mm³).

EPIVIR® is not recommended for use as monotherapy. Only the combination with zidovudine has been extensively studied in terms of safety and efficacy. Combination studies with other antiretrovirals are in progress.

Lamivudine in combination with zidovudine reduces HIV-1 viral load and increases CD4+ count. A meta-analysis of clinical events in the phase II comparative studies indicates that lamivudine in combination with zidovudine slows the progression of the disease. A study to confirm the effects on AIDS progression and survival is ongoing.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION
Adults and children over the age of 12 years:
The recommended dose of EPIVIR® is 150 mg (one tablet) twice daily.

EPIVIR® is also available as an oral solution for those patients for whom the tablets are inappropriate.

EPIVIR® should usually be taken without food. Ingestion with food reduces the Cmax considerably but does not alter the area under the curve (AUC) (see 5.2. PHARMACOKINETIC PROPERTIES). Therefore ingestion with food might be considered when required due to clinical reasons.
The therapy should be initiated by a physician experienced in the management of HIV infection.

Renal Impairment:

Lamivudine levels are increased in patients with moderate - severe renal impairment due to decreased clearance. The dose should therefore be adjusted, using the oral solution presentation of EPIVIR® for patients whose creatinine clearance falls below 30 ml/min (see table).

Dosing Recommendations

<table>
<thead>
<tr>
<th>Renal Function (Clcr, ml/min)</th>
<th>First Dose</th>
<th>Maintenance Dose</th>
</tr>
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<tbody>
<tr>
<td>Clcr≥50</td>
<td>150 mg</td>
<td>150 mg Twice daily</td>
</tr>
<tr>
<td>50&gt;Clcr≥30</td>
<td>150 mg</td>
<td>150 mg Once daily</td>
</tr>
<tr>
<td>Clcr&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>

Hepatic Impairment:

The influence of hepatic impairment on lamivudine levels is under investigation. Lamivudine clearance is largely renal. Based on preliminary safety data no dosage adjustment is necessary.

4.3. CONTRA-INDICATIONS

The use of EPIVIR® is contra-indicated in patients with known hypersensitivity to lamivudine or to any ingredient of the preparation.

4.4. SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

SPECIAL WARNINGS:

EPIVIR® is not recommended for use as monotherapy.
Cases of pancreatitis have occurred rarely. However it is not clear whether these cases were due to drug 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.

There are insufficient data on the use of EPIVIR® in children under the age of 12 years.

Administration of EPIVIR® is not recommended during the first 3 months of pregnancy (see 4.6. PREGNANCY AND LACTATION).

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.

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 conduct or blood contamination. Appropriate precautions should continue to be employed.

**SPECIAL PRECAUTIONS FOR USE:**

In patients with moderate - severe renal impairment, the terminal plasma half-life of lamivudine is increased due to decreased clearance. The dose should be adjusted. (See dosage in renal impairment, in section 4.2. POSOLOGY AND METHOD OF ADMINISTRATION).

EPIVIR® should be used with caution in patients with advanced cirrhotic liver disease due to chronic Hepatitis B infection, as there is a small risk of rebound hepatitis if treatment is discontinued.

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

A modest increase in Cmax (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 5.2. PHARMACOKINETIC PROPERTIES section).
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Lamivudine metabolism does not involve CYP3A, making interactions with drugs metabolised by this system (e.g. protease inhibitors) unlikely.

Co-administration of EPIVIR® with intravenous ganciclovir or foscarnet is not recommended until further information is available.

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PREGNANCY:

The safety of lamivudine in human pregnancy has not been established. Reproductive studies in animals have not shown evidence of teratogenicity, and showed no effect on male or female fertility. Lamivudine induces early embryolethality when administered to pregnant rabbits at exposure levels comparable to those achieved in man. Lamivudine crosses the placenta in animals but there is no information on placental transfer in humans.

Although animal reproductive studies are not always predictive of the human response, administration during the first 3 months of pregnancy is not recommended (see 4.4. SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE).

LACTATION:

A study in lactating rats showed that, following oral administration, lamivudine was concentrated four fold and excreted in the milk. It is not known if lamivudine is excreted in human breast milk. Since the drug may pass into breast milk, it is recommended that mothers taking EPIVIR® do not breast feed their infants. Some health experts recommend 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

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

4.8. UNDESIRABLE EFFECTS

Adverse events have been reported during therapy for HIV disease with EPIVIR® alone and in combination with zidovudine. With many it is unclear whether they are drug related or are as a result of the underlying disease process.

Adverse events which have been commonly reported are headache, malaise, fatigue, nausea, diarrhoea, vomiting, abdominal pain or cramps, insomnia, cough, nasal symptoms and musculoskeletal pain.

Cases of pancreatitis and peripheral neuropathy (or paraesthesia) have been recorded, although no relationship to the dose of EPIVIR® has been noted.

Neutropenia and anaemia (both occasionally severe) have occurred in combination with zidovudine. Thrombocytopenia, transient rises in liver enzymes (AST, ALT) and rises in serum amylase have been reported.

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: J05A B10.

Lamivudine is a nucleoside analogue. Lamivudine is metabolised intracellularly to lamivudine 5’-triphosphate, its main mode of action is as a chain terminator of HIV 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.

The relationships between in vitro susceptibility of HIV to lamivudine and the clinical response to therapy remain under investigation. In vitro sensitivity testing has not been standardised and results may vary according to methodological factors.

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

Lamivudine has been shown to be highly synergistic with zidovudine, inhibiting the replication of HIV in cell culture.

In vitro studies indicate that zidovudine-resistant virus isolates can become zidovudine sensitive when they simultaneously acquire resistance to lamivudine. Furthermore, in vivo, there is evidence showing that lamivudine plus zidovudine delays the emergence of zidovudine-resistant isolates in individuals with no prior antiretroviral therapy.

In vitro, lamivudine demonstrates low cytotoxicity to peripheral blood lymphocytes, to established lymphocyte and monocyte-macrophage cell lines and to a variety of bone marrow progenitor cells in vitro. Lamivudine therefore has, in vitro, a high therapeutic index.

5.2. PHARMACOKINETIC PROPERTIES

Absorption

Lamivudine is well absorbed from the gut, and the bioavailability of oral lamivudine in adults is normally between 80 and 85%. Following oral administration, the mean time (t_{max}) to maximal serum concentrations (C_{max}) is about an hour. At therapeutic dose levels ie. 4 mg/kg/day (as two 12-hourly doses), C_{max} is in the order of 1.5-1.9 µg/ml.

Co-administration of lamivudine with food results in a delay of t_{max} and a lower C_{max} (decreased by 47%). However, lamivudine bioavailability (based on the AUC) 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 \textit{in vitro} studies).

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

**Metabolism**

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

**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. POSOLOGY AND METHOD OF ADMINISTRATION).

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 section 4.5. INTERACTION WITH OTHER MEDICAMENTS AND OTHER FORMS OF INTERACTION, and dosage adjustments in renal impairment in section 4.2. POSOLOGY AND METHOD OF ADMINISTRATION). Administration of co-trimoxazole with EPIVIR® in patients with renal impairment should be carefully assessed.
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 30-40 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.

Long term carcinogenicity studies in animals are ongoing.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Tablet Core
Cellulose, microcrystalline PhEur (E460)
Sodium starch glycollate BP
Magnesium stearate PhEur (E572)

Tablet film coat
Methylhydroxypropyl cellulose PhEur (E464)
Titanium Dioxide PhEur (E171)
Macrogol PhEur
Polysorbate 80 PhEur (E433)
Purified water PhEur

6.2. INCOMPATIBILITIES

None reported

6.3. SHELF-LIFE

2 years
6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store between 2 and 30°C.

6.5. NATURE AND CONTENT OF CONTAINER

Cartons containing 60 coated tablets in a white high density polyethylene (HDPE) bottle, with a child-resistant closure.

6.6. INSTRUCTIONS FOR USE/HANDLING

None required.

7. MARKETING AUTHORISATION HOLDER

Glaxo Group Ltd
Greenford Road
Greenford
Middlesex UB6 0NN
UK

8. MARKETING AUTHORITY NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION

10. DATE OF (PARTIAL) REVISION OF THE TEXT
ANNEX II
MANUFACTURING AUTHORISATIONS AND CONDITIONS
OF THE MARKETING AUTHORISATION
A. - HOLDER(S) OF THE MANUFACTURING AUTHORISATION(S)

Manufacturer of the active substance:

Glaxo Operations (UK) Ltd
Cobden Street, Montrose, Angus DD10 8EA, UK

Manufacturer of the finished medicinal product, EPIVIR® coated tablets, and responsible for batch release in the European Economic Area:

Glaxo Operations (UK) Ltd
Priory Street, Ware, Hertfordshire SG12 0DJ, UK


Manufacturer of the finished medicinal product, EPIVIR® oral solution, and responsible for batch release in the European Economic Area:

Glaxo Pharmaceuticals (UK) Ltd
Speke Boulevard, Speke, Liverpool L24 9JD, UK


B. - CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to non-renewable restricted medical prescription.

C. - SPECIFIC OBLIGATIONS OF THE MARKETING AUTHORISATION HOLDER

The Applicant, after having been consulted (letter dated 17 April 1996) agreed to fulfil the commitment to submit to the EMEA, within the specific time-frame, the results of the additional studies set out below:

1. EPIVIR® coated tablets

1.1 Annual re-assessment:

The results of the following information shall form the basis of an annual re-assessment of the benefit/risk profile of the medicinal product.

a. Clinical aspects:

• The preliminary report and the final report of trial NUCB3007, by 30 June 1997 and by 30 September 1997, respectively.
Data from the following list of ongoing collaborative combination studies with EPIVIR\textsuperscript{®}, once the final reports are available (target dates can only be provided for GlaxoWellcome sponsored studies):

<table>
<thead>
<tr>
<th>Study</th>
<th>Sponsor</th>
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<tbody>
<tr>
<td>RITONAVIR :</td>
<td>NUCB 2019 Glaxo Wellcome/Abbott (June 1998)</td>
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<td>INDINAVIR :</td>
<td>AVANTI II Glaxo Wellcome (June 1998)</td>
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<td>NELFINAVIR (Viracept):</td>
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<td>SAQUINAVIR :</td>
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<td>D4T :</td>
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<td>ACTG 306 ACTG</td>
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<td>DDC :</td>
<td>QUATTRO STUDY UK-MRC</td>
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<tr>
<td>LOVIRIDE :</td>
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</tr>
<tr>
<td></td>
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</tr>
</tbody>
</table>

1.2 Other obligations:

a. Chemical, pharmaceutical and biological aspects:

- Completion of the purity testing by routine control of heavy metals and sulphated ashes or justification if the test is not performed routinely, by 15 June 1996.
- Batch results on UV absorbance at 440 nm, by 15 June 1996.
- Additional data on the characterisation of the reference substance used in the analytical validations, by 15 June 1996.
- A test method and an end-of-life specification for microbial purity, by 15 June 1996.
- An identification test for colorant E171 (titanium dioxide) and justification if the test is not performed routinely, by 15 June 1996.
- Dissolution data, using 0.1M HCl and, if necessary new specifications, by 15 June 1996.
- Complete description of the container designed for storage of the active ingredient, by 15 June 1996.

b. Toxicological and pharmacological aspects:

- Results of a triple dose micronucleus test on lamivudine, to investigate potential in-vivo mutagenic effects on repeat dosing, by 15 June 1996.
c. Clinical aspects:
- The final study report of trial NUCB1003 (patients with impaired renal function), by 31 October 1996.
- The final analysis of the population pharmacokinetics of trials NUCA3001 and NUCA3002 (including the investigation of interactions between zidovudine and lamivudine and a document summarising the pharmacokinetics), by 31 October 1996.
- The initial results relating to dose optimisation (pharmacokinetic/pharmacodynamic studies with zidovudine), by 31 December 1996.

2. EPIVIR® oral solution

2.1. Annual re-assessment:
The results of the following information shall form the basis of an annual re-assessment of the benefit/risk profile of the medicinal product.

a. Chemical, pharmaceutical and biological aspects:
- Submission of a variation of the formulation in order to reduce the amount of ethanol to the minimum necessary, to optimise the pH of the solution and to eliminate the disodium edetate, if its use is not clearly justified, by 31 July 1997.

b. Clinical aspects:
- The preliminary report and the final report of trial NUCB3007, by 30 June 1997 and by 30 September 1997, respectively.
- Data from the following list of ongoing collaborative combination studies with EPIVIR®, once the final reports are available (target dates can only be provided for GlaxoWellcome sponsored studies):

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<td>MERCK 042  Merck</td>
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</table>
NELFINAVIR (Viracept): AVANTI III Glaxo Wellcome (June 1998)
AGOURON 509 Agouron
SAQUINAVIR : NV 15114 Roche
DDI : ICC 002 Inter Company Collaboration
NUCA 2005 Glaxo Wellcome (Dec. 1996)
D4T : ANRS 057 ANRS
DDC : QUATTRO STUDY UK-MRC
LOVIRIDE : AVANTI I Glaxo Wellcome (June 1998)
NUCB 3007 Glaxo Wellcome (Sept. 1997)

2.2 Other obligations:

a. Chemical, pharmaceutical and biological aspects:
   - A proposal for a suitable measuring device, by 30 November 1996.
   - Completion of the purity testing by routine control of heavy metals and sulphated ashes or justification if the test is not performed routinely, by 15 June 1996.
   - Batch results on UV absorbance at 440 nm, by 15 June 1996.
   - Additional data on the characterisation of the reference substance used in the analytical validations, by 15 June 1996.
   - Additional documentation on routine identification of the flavours used, by 15 June 1996.
   - Complete description of the container designed for storage of the active ingredient, by 15 June 1996.
   - Additional data on the compatibility of the primary pack with the solution at the shelf-life, by 15 June 1996.
   - Additional data on the characterisation of the degradation product, by 15 June 1996.

b. Toxicological and pharmacological aspects:
   - Results of a triple dose micronucleus test on lamivudine, to investigate potential in-vivo mutagenic effects on repeat dosing, by 15 June 1996.
c. Clinical aspects:

- The final study report of trial NUCB1003 (patients with impaired renal function), by 31 October 1996.

- The final analysis of the population pharmacokinetics of trials NUCA3001 and NUCA3002 (including the investigation of interactions between zidovudine and lamivudine and a document summarising the pharmacokinetics), by 31 October 1996.

- The initial results relating to dose optimisation (pharmacokinetic/pharmacodynamic studies with zidovudine), by 31 December 1996.
A- LABELLING
Text Brief for EPIVIR® (Lamivudine) Oral Solution Pack

Description: Standard tamper evident cartons containing 240 ml EPIVIR® Oral Solution (10 mg/ml) in a white HDPE bottle and a user package leaflet.

Outer packaging:

EPIVIR® Oral Solution
Lamivudine

Bottle contents:
240 ml lamivudine (10 mg/ml)

Read enclosed leaflet before use

Use only as directed by your doctor
For oral administration

Keep all medicines out of the reach of children.

This product also contains
sugar (sucrose), alcohol (6% ethanol), preservatives: methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216)

Store between 2 and 25° C
Discard one month after first opening

MA number......

Glaxo Group Ltd
Greenford
Middlesex    UB6 0NN
UK

Medicinal product subject to medical prescription.

Batch number and expiry date
Immediate packaging:

**EPIVIR® Oral Solution**  
Lamivudine

Contents  
240 ml Lamivudine (10 mg/ml)

*Also contains*  
sugar (sucrose), alcohol (6% ethanol) and preservatives: methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216)

Use only as directed by your doctor  
For oral administration

Keep all medicines out of the reach of children.

Store between 2 and 25° C  
Discard one month after first opening

MA number.....

Glaxo Group Ltd  
Greenford  
Middlesex UB6 0NN  
UK

Medicinal product subject to medical prescription.

Batch number and expiry date
Text Brief for EPIVIR® (Lamivudine) Tablets Carton Pack

Description: Standard tamper evident cartons containing 60 EPIVIR® Tablets in a white HDPE bottle and a user package leaflet.

Outer packaging:

EPIVIR® Tablets
Lamivudine

Each coated tablet contains
lamivudine 150 mg

60 tablets

Read enclosed leaflet before use

Use only as directed by your doctor
For oral administration

Keep all medicines out of the reach of children.

Store between 2 and 30° C

MA number......

Glaxo Group Ltd
Greenford
Middlesex UB6 0NN
UK

Medicinal product subject to medical prescription.

Batch number and expiry date
Immediate packaging:

EPIVIR® Tablets
Lamivudine

Each coated tablet contains
lamivudine 150 mg

60 tablets

Use only as directed by your doctor
For oral administration

Keep all medicines out of the reach of children.

Store between 2 and 30° C

MA number.....

Glaxo Group Ltd
Greenford
Middlesex UB6 0NN
UK

Medicinal product subject to medical prescription.

Batch number and expiry date
B- USER PACKAGE LEAFLET
This leaflet only talks about EPIVIR® Oral Solution. Please read it carefully before you start to take your medicine. It tells you the main points about your medicine.

For more information or advice, ask your doctor or pharmacist.

1- NAME OF THE MEDICINAL PRODUCT

EPIVIR® (lamivudine) Oral Solution.

2- FULL STATEMENT OF THE ACTIVE SUBSTANCE AND EXCIPIENTS

Active ingredient: lamivudine.
Other ingredients: sugar (20% sucrose), alcohol (6% ethanol), methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), citric acid anhydrous, propylene glycol, disodium edetate, water, artificial strawberry and banana flavourings.

3- PHARMACEUTICAL FORM AND CONTENTS

EPIVIR® Oral Solution is supplied in cartons containing a white polyethylene bottle, with a child resistant cap.
The bottle contains 240 ml (10 mg/ml) of lamivudine solution for oral use only.

4- PHARMACO-THERAPEUTIC GROUP.

EPIVIR® belongs to a group of medicines called antivirals, used in the treatment of Human Immunodeficiency Virus (HIV) infection.

5- NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURER.

Manufacturer: Glaxo Pharmaceuticals UK Ltd, Speke Boulevard, Speke, Liverpool L24 9JD, UK.

Marketing authorisation holder: Glaxo Group Ltd, Greenford Road, Greenford, Middlesex UB6 0NN, UK.

6- THERAPEUTIC INDICATIONS
EPIVIR® is used in combination with other antiretroviral agents for the treatment of HIV infection.

EPIVIR® has been studied only in combination with zidovudine. Complete information on clinical effects is not yet available, but a further study is in progress.

7- INFORMATION NECESSARY BEFORE TAKING THE PRODUCT

Contra-indications

This drug must not be used in case of allergy to EPIVIR®, lamivudine or any of the other ingredients found in EPIVIR® Oral Solution.

Special precautions for use

Discuss the use of EPIVIR® with your doctor if you have a kidney disease or if you have or ever had liver disease. Particularly if you have a chronic liver disease due to hepatitis B infection, you should not stop your treatment without instructions from your doctor, as there is a small risk of rebound of the hepatitis.

It is important that your doctor knows about all your symptoms, even if you think they are not related to HIV infection. Your doctor may then be obliged to adapt the dose of your medicine.

Pregnancy and lactation

If you are pregnant, or likely to become pregnant soon, or if you are breast feeding, please inform your doctor before taking any drugs, including EPIVIR®. EPIVIR® should not be taken during the first three months of pregnancy. Some health experts recommend that HIV infected women do not breast feed their infants under any circumstances in order to avoid transmission of HIV.

Driving and using machines

EPIVIR® is unlikely to affect your ability to drive or operate machinery. However, such effects cannot be completely ruled out, and HIV disease can seriously affect these abilities.

Interactions

It is important that your doctor knows about all your medicines so that you get the best possible treatment. Tell your doctor about all your medicines, including vitamin supplements, herbal remedies or homeopathic remedies including those you have bought yourself. EPIVIR® should not be given with ganciclovir or foscarnet injections.

Special warnings

At present, there are insufficient data to recommend the use of EPIVIR® in children under 12 years of age.

EPIVIR® should not be taken during the first 3 months of pregnancy.
Remember that treatment with EPIVIR® does not reduce the risk of passing the infection on to others, and you will still be able to pass HIV by sexual contact or by blood transfer and you should use appropriate precautions.

While taking EPIVIR® or any other therapy for HIV disease, you may continue to develop other infections and other complications of HIV infection, and therefore you should keep in regular contact with the doctor who is treating your condition.

Because your medicine helps to control your condition but does not cure it, you will need to take it every day. Do not stop taking your medicine without first talking to your doctor.

This medicine contains a small quantity of alcohol.

If you are a diabetic, please note that each dose (150 mg=15 ml) contains 3 g sugar.

Due to this sugar content, EPIVIR® users should brush and clean their teeth regularly to reduce the risk of tooth decay.

**8- DOSAGE AND INSTRUCTIONS FOR PROPER USE**

Take your medicine as your doctor has advised you. The label on it will usually tell you the amount to take, and how frequently. If it does not, or you are not sure, ask your doctor or pharmacist.

As a general guide, take 15 ml (150 mg) twice a day, preferably not with a meal.

If you have a kidney problem, your dose may be altered. Please follow the instructions of your doctor.

**Action to be taken in case of overdose**

Accidentally taking too much of your medicine is unlikely to cause any serious problems. However, you should tell your doctor or your pharmacist, or contact your nearest hospital emergency department for further advice.

**Action to be taken in case of missed dose**

If you forget to take your medicine, take it as soon as you remember. Then continue as before.

**9- UNDESIRABLE EFFECTS**

As with other drugs, some people may have some undesirable effects which are due to EPIVIR®. Undesirable effects have been reported during treatment of HIV disease with EPIVIR® alone and in combination with zidovudine. In many cases it is unclear whether these are related to EPIVIR® or your disease.

Some people can be allergic to medicines.
If you have any of the following symptoms soon after taking EPIVIR® STOP taking the medicine and tell your doctor immediately:

Very severe stomach cramps with nausea and vomiting, which may be due to a condition called pancreatitis.
Sudden wheeziness and chest pain or tightness.
Swelling of eyelids, face or lips.
Skin rash or ‘hives’ anywhere on the body.

Consult your doctor at your next visit if any of the following undesirable events occur:

Headaches, nausea, vomiting, diarrhoea, rash, fatigue or a general feeling of being unwell.
Numbness, tingling sensation or sensation of weakness in your limbs.

Other undesirable effects are:
Insomnia, cough, nasal symptoms, muscle and joint pain, a decrease in certain types of blood counts (including red blood cells, white blood cells and platelets) and an increase in certain liver enzymes.

Always tell your doctor or pharmacist about any undesirable effect, even those not mentioned in this leaflet.
If you feel ill in any other way that you do not understand, tell your doctor or pharmacist.

10- STORAGE PRECAUTIONS

Do not take the medicine after the expiry date shown on the bottle and the carton.

Storing your medicine

As with all medicines, keep EPIVIR® out of the reach of children.

Store EPIVIR® Oral Solution between 2 and 25°C.
Discard one month after first opening.
11- DATE OF LEAFLET REVISION

Remember

This medicine is for you. Never give it to someone else. It may harm them even if their symptoms are the same as yours.

This leaflet does not tell you everything about your medicine. If you have any questions or are not sure about anything, then ask your doctor or pharmacist. You may need to read this leaflet again. Please do not throw it away until you have finished your medicine.

For any information about this product, please contact the local representative of the Marketing Authorisation Holder:

<table>
<thead>
<tr>
<th>Country</th>
<th>Address</th>
<th>Telephone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgique/ België</td>
<td>Boulevard du triomphe 172 Triomflaan 1160 Bruxelles/Brussel</td>
<td>02/676.57.11</td>
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<tr>
<td>Danmark</td>
<td>Nykær 68 DK2605 Brøndby</td>
<td>36 75 90 00</td>
</tr>
<tr>
<td>Deutschland</td>
<td>Industriestraße 32 - 36 23843 Bad Oldesloe</td>
<td>040 415 230</td>
</tr>
<tr>
<td>Eire</td>
<td>PO Box No. 700 Grange Road Rathfarnham Dublin 16</td>
<td>(01) 298 4733</td>
</tr>
<tr>
<td>Ελλάς</td>
<td>Λεωφ. Κηρυσίας 266 152 32 Χαλανδρί</td>
<td>6882100-200-300</td>
</tr>
<tr>
<td>España</td>
<td>Parque Tecnológico de Madrid c/ Dr. Severo Ochoa 2 28760 Tres Cantos Madrid</td>
<td>91 80 70 30 1</td>
</tr>
<tr>
<td>France</td>
<td>43 rue Vineuse 75764 Paris Cedex 16</td>
<td>(1) 47 55 33 00</td>
</tr>
<tr>
<td>Italia</td>
<td>Via Alessandro Fleming, 2 37100 Verona</td>
<td>045 9218111</td>
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<td>Country</td>
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<tr>
<td>Luxembourg</td>
<td>Boulevard du triomphe 172&lt;br&gt;1160 Bruxelles&lt;br&gt;Belgique</td>
<td>+32 2 676 57 11</td>
</tr>
<tr>
<td>Nederland</td>
<td>Huis ter Heideweg 62&lt;br&gt;3705 LZ Zeist</td>
<td>030 - 6938100</td>
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<tr>
<td>Österreich</td>
<td>Albert Schweitzer -Gaße 6&lt;br&gt;A-1140 Wien</td>
<td>0222 97075-0</td>
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<tr>
<td>Portugal</td>
<td>R. Dr. Antônio Loureiro Borges, Nº3&lt;br&gt;Arquiparque - Miraflores&lt;br&gt;1495 Algés</td>
<td>01 4129500</td>
</tr>
<tr>
<td>Sverige</td>
<td>Box 263&lt;br&gt;S-431 23 Mölndal</td>
<td>031 670900</td>
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<tr>
<td>Suomi/Finland</td>
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<td>0181 990 9000</td>
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</table>
This leaflet only talks about EPIVIR® Tablets. Please read it carefully before you start to take your medicine. It tells you the main points about your medicine.

For more information or advice, ask your doctor or pharmacist.

1- NAME OF THE MEDICINAL PRODUCT

EPIVIR® (lamivudine) Tablets.

2- FULL STATEMENT OF THE ACTIVE SUBSTANCE AND EXCIPIENTS

Active ingredient: lamivudine.
Other ingredients: cellulose, microcrystalline (E460), sodium starch glycollate, magnesium stearate (E572), methylhydroxypropyl cellulose (E464), titanium dioxide (E171), macrogol, polysorbate 80 (E433).

3- PHARMACEUTICAL FORM AND CONTENTS

EPIVIR® Tablets are supplied in cartons containing 60 coated tablets in a white polyethylene bottle, with a child resistant cap.
The tablets are white film coated, diamond shaped tablets engraved ‘GXCJ7’ on one face.
Each EPIVIR® tablet contains 150 mg lamivudine.

4- PHARMACO-THERAPEUTIC GROUP

EPIVIR® belongs to a group of medicines called antivirals, used in the treatment of Human Immunodeficiency Virus (HIV) infection.
5- NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURER.

Manufacturer: Glaxo Operations UK Ltd, Priory Street, Ware, Herts SG12 ODJ, UK.

Marketing authorisation holder: Glaxo Group Ltd, Greenford Road, Greenford, Middlesex UB6 0NN, UK.

6- THERAPEUTIC INDICATIONS

EPIVIR® is used in combination with other antiretroviral agents for the treatment of HIV infection.

EPIVIR® has been studied only in combination with zidovudine. Complete information on clinical effects is not yet available, but a further study is in progress.

7- INFORMATION NECESSARY BEFORE TAKING THE PRODUCT

Contra-indications

This drug must not be used in case of allergy to EPIVIR®, lamivudine or any of the other ingredients found in EPIVIR® Tablets.

Special precautions for use

Discuss the use of EPIVIR® with your doctor if you have a kidney disease or if you have or ever had liver disease. Particularly if you have a chronic liver disease due to hepatitis B infection, you should not stop your treatment without instructions from your doctor, as there is a small risk of rebound of the hepatitis.

It is important that your doctor knows about all your symptoms even if you think they are not related to HIV infection. Your doctor may then be obliged to adapt the dose of your medicine.

Pregnancy and lactation

If you are pregnant, or likely to become pregnant soon, or if you are breast feeding, please inform your doctor before taking any drugs, including EPIVIR®. EPIVIR® should not be taken during the first 3 months of pregnancy. Some health experts recommend that HIV infected women do not breast feed their infants under any circumstances in order to avoid transmission of HIV.
Driving and using machines

EPIVIR® is unlikely to affect your ability to drive or operate machinery. However, such effects cannot be completely ruled out, and HIV disease can seriously affect these abilities.

Interactions

It is important that your doctor knows about all your medicines so that you get the best possible treatment. Tell your doctor about all your medicines, including vitamin supplements, herbal remedies or homeopathic remedies including those you have bought yourself. EPIVIR® should not be given with ganciclovir or foscarnet injections.

Special warnings

At present there are insufficient data to recommend the use of EPIVIR® in children under 12 years of age.

EPIVIR® should not be taken during the first 3 months of pregnancy.

Remember that treatment with EPIVIR® does not reduce the risk of passing the infection on to others, and you will still be able to pass HIV by sexual contact or by blood transfer and you should use appropriate precautions.

While taking EPIVIR® or any other therapy for HIV disease, you may continue to develop other infections and other complications of HIV infection, and therefore you should keep in regular contact with the doctor who is treating your condition.

Because your medicine helps to control your condition but does not cure it, you will need to take it every day. Do not stop taking your medicine without first talking to your doctor.

8- DOSAGE AND INSTRUCTIONS FOR PROPER USE

Take your medicine as your doctor has advised you. The label on it will usually tell you the amount to take, and how frequently. If it does not, or you are not sure, ask your doctor or pharmacist.

As a general guide, swallow one tablet (150 mg) twice a day, preferably not with a meal.

An oral solution (10 mg/ml) is also available for patients unable to take tablets.

If you have a kidney problem, your dose may be altered. Please follow the instructions of your doctor.
**Action to be taken in case of overdose**

Accidentally taking too much of your medicine is unlikely to cause any serious problems. However, you should tell your doctor or your pharmacist, or contact your nearest hospital emergency department for further advice.

**Action to be taken in case of missed dose**

If you forget to take your medicine, take it as soon as you remember. Then continue as before.

**9- UNDESIRABLE EFFECTS**

As with other drugs, some people may have some undesirable effects which are due to EPIVIR®. Undesirable effects have been reported during treatment of HIV disease with EPIVIR® alone and in combination with zidovudine. In many cases it is unclear whether these are related to EPIVIR® or your disease.

Some people can be allergic to medicines.

If you have any of the following symptoms soon after taking EPIVIR® STOP taking the medicine and tell your doctor immediately:

- Very severe stomach cramps with nausea and vomiting, which may be due to a condition called pancreatitis.
- Sudden wheeziness and chest pain or tightening.
- Swelling of eyelids, face or lips.
- Skin rash or ‘hives’ anywhere on the body.

Consult your doctor at your next visit if any of the following undesirable events occur:

- Headaches, nausea, vomiting, diarrhoea, rash, fatigue or a general feeling of being unwell.

Numbness, tingling sensation or sensation of weakness in your limbs.

Other undesirable effects are:

- Insomnia, cough, nasal symptoms, muscle and joint pain, a decrease in certain types of blood counts (including red blood cells, white blood cells and platelets) and an increase in certain liver enzymes.

Always tell your doctor or pharmacist about any undesirable effect, even those not mentioned in this leaflet.

If you feel ill in any other way that you do not understand, tell your doctor or pharmacist.
10- STORAGE PRECAUTIONS

Do not take the medicine after the expiry date shown on the carton and tablet pack.

Storing your medicine

As with all medicines, keep EPIVIR® out of the reach of children.

Store EPIVIR® Tablets between 2 and 30 degrees C.

11- DATE OF LEAFLET REVISION

Remember

This medicine is for you. Never give it to someone else. It may harm them even if their symptoms are the same as yours.

This leaflet does not tell you everything about your medicine. If you have any questions or are not sure about anything, then ask your doctor or pharmacist. You may need to read this leaflet again. Please do not throw it away until you have finished your medicine.

For any information about this product, please contact the local representative of the Marketing Authorisation Holder:

Belgique/ België Boulevard du triomphe 172 Triomflaan 1160 Bruxelles/Brussel 02/676.57.11

Danmark Nykær 68 DK2605 Brøndby 36 75 90 00

Deutschland Industriestraße 32 - 36 23843 Bad Oldesloe 040 415 230

Eire PO Box No. 700 Grange Road Rathfarnham Dublin 16 (01) 298 4733

Ελλάς Λεωφ. Κηφισιας 266 152 32 Χαλανδρι 6882100-200-300
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<td>España</td>
<td>Parque Tecnológico de Madrid c/ Dr. Severo Ochoa 2 28760 Tres Cantos Madrid</td>
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<td>43 rue Vineuse 75764 Paris Cedex 16</td>
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<td>Luxembourg</td>
<td>Boulevard du triomphe 172 1160 Bruxelles Belgique</td>
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