ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Lamivudine/zidovudine ViiV film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150 mg lamivudine and 300 mg zidovudine.

For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Red, capsule-shaped film-coated scored tablets engraved with “A22” on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Lamivudine/zidovudine is indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection (see section 4.2).

4.2 Posology and method of administration

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

Lamivudine/zidovudine ViiV tablets 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, 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 weighing at least 30 kg: the recommended dose of lamivudine/zidovudine is one tablet twice daily.

Children weighing between 21 kg and 30 kg: the recommended oral dose of Lamivudine/zidovudine ViiV tablets is one-half tablet taken in the morning and one whole tablet taken in the evening.

Children weighing from 14 kg to 21 kg: the recommended oral dose of Lamivudine/zidovudine ViiV tablets is one-half tablet taken twice daily.
The dosing regimen for paediatric patients weighing 14-30 kg is based primarily on pharmacokinetic modelling and supported by data from clinical studies using the individual components lamivudine and zidovudine. A pharmacokinetic overexposure of zidovudine can occur, therefore close safety monitoring is warranted in these patients. If gastrointestinal intolerance occurs in patients weighing 21 to 30 kg, an alternative dosing schedule with one-half tablet taken thrice daily can be applied in attempt to improve tolerability.

Lamivudine/zidovudine ViiV tablets should not be used for children weighing less than 14 kg, since doses can not be appropriately adjusted for the weight of the child. In these patients, lamivudine and zidovudine should be taken as separate formulations according to the prescribed dosing recommendations for these products.

For situations where discontinuation of therapy with one of the active substances of Lamivudine/zidovudine ViiV tablets, or dose reduction is necessary separate preparations of lamivudine and zidovudine are available in tablets/capsules.

*Renal impairment***:** Lamivudine and zidovudine concentrations are increased in patients with renal impairment due to decreased clearance. Therefore as dosage adjustment of these may be necessary it is recommended that separate preparations of lamivudine and zidovudine be administered to patients with reduced renal function (creatinine clearance ≤ 50 ml/min). Physicians should refer to the individual prescribing information for these medicinal products.

Hepatic impairment: Limited data in patients with cirrhosis suggest that accumulation of zidovudine may occur in patients with hepatic impairment because of decreased glucuronidation. Data obtained in patients with moderate to severe hepatic impairment show that lamivudine pharmacokinetics are not significantly affected by hepatic dysfunction. However, as dosage adjustments for zidovudine may be necessary, it is recommended that separate preparations of lamivudine and zidovudine be administered to patients with severe hepatic impairment. Physicians should refer to the individual prescribing information for these medicinal products.

Dosage adjustments in patients with haematological adverse reactions: Dosage adjustment of zidovudine may be necessary if the haemoglobin level falls below 9 g/dl or 5.59 mmol/l or the neutrophil count falls below 1.0 x 10^9/l (see sections 4.3 and 4.4). As dosage adjustment of Lamivudine/zidovudine ViiV tablets is not possible, separate preparations of zidovudine and lamivudine should be used. Physicians should refer to the individual prescribing information for these medicinal products.

Dosage in the elderly: No specific data are available, however special care is advised in this age group due to age associated changes such as the decrease in renal function and alteration of haematological parameters.

4.3 Contraindications

Hypersensitivity to lamivudine, zidovudine or to any of the excipients listed in section 6.1.

Zidovudine is contraindicated in patients with abnormally low neutrophil counts (< 0.75 x 10^9/l), or abnormally low haemoglobin levels (< 7.5 g/dl or 4.65 mmol/l). Lamivudine/zidovudine is therefore contra-indicated in these patients (see section 4.4).

4.4 Special warnings and precautions for use

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

The special warnings and precautions relevant to both lamivudine and zidovudine are included in this section. There are no additional precautions and warnings relevant to the combination lamivudine/zidovudine.

It is recommended that separate preparations of lamivudine and zidovudine should be administered in cases where dosage adjustment is necessary (see section 4.2). In these cases the physician should refer to the individual prescribing information for these medicinal products.

Patients should be cautioned about the concomitant use of self-administered medications. The concomitant use of stavudine with zidovudine should be avoided (see section 4.5).

Opportunistic infections: Patients receiving lamivudine/zidovudine or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection. Therefore

patients should remain under close clinical observation by physicians experienced in the treatment of HIV infection.

Haematological adverse reactions: Anaemia, neutropenia and leucopenia (usually secondary to neutropenia) can be expected to occur in patients receiving zidovudine. These occurred more frequently at higher zidovudine dosages (1200-1500 mg/day) and in patients with poor bone marrow reserve prior to treatment, particularly with advanced HIV disease. Haematological parameters should therefore be carefully monitored (see section 4.3) in patients receiving lamivudine/zidovudine. These haematological effects are not usually observed before four to six weeks therapy. For patients with advanced symptomatic HIV disease, it is generally recommended that blood tests are performed at least every two weeks for the first three months of therapy and at least monthly thereafter.

In patients with early HIV disease haematological adverse reactions are infrequent. Depending on the overall condition of the patient, blood tests may be performed less often, for example every one to three months. Additionally dosage adjustment of zidovudine may be required if severe anaemia or myelosuppression occurs during treatment with lamivudine/zidovudine, or in patients with pre-existing bone marrow compromise e.g. haemoglobin <9 g/dl (5.59 mmol/l) or neutrophil count <1.0 x 10^9/l (see section 4.2). As dosage adjustment of Lamivudine/zidovudine ViiV tablets is not possible separate preparations of zidovudine and lamivudine should be used. Physicians should refer to the individual prescribing information for these medicinal products.

Use in pregnancy: As the active substances of Lamivudine/zidovudine ViiV tablets may inhibit cellular DNA replication, any use, especially during the first trimester of pregnancy, presents a potential risk to the foetus. (see section 4.6).

Pancreatitis: Cases of pancreatitis have occurred rarely in patients treated with lamivudine and zidovudine. However it is not clear whether these cases were due to the antiretroviral treatment or to the underlying HIV disease. Treatment with lamivudine/zidovudine 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 if there is 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. Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and can occur many months after initiation of treatment.

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

The safety and efficacy of zidovudine has not been established in patients with significant underlying liver disorders.

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 lamivudine/zidovudine is discontinued in patients co-infected with hepatitis B virus, periodic monitoring of both 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.

Patients co-infected with hepatitis C virus: The concomitant use of ribavirin with zidovudine is not recommended due to an increased risk of anaemia (see section 4.5).

Osteonecrosis: Although the etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to

combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Excipients: Lamivudine/zidovudine ViiV tablets contain the azo colouring agent sunset yellow (E110), which may cause allergic reactions.

Lamivudine/zidovudine ViiV should not be taken with any other medicinal products containing lamivudine or medicinal products containing emtricitabine.

The combination of lamivudine with cladribine is not recommended (see section 4.5)

4.5 Interaction with other medicinal products and other forms of interaction

Lamivudine/zidovudine ViiV contains lamivudine and zidovudine, therefore any interactions identified for these individually are relevant to Lamivudine/zidovudine ViiV. Clinical studies have shown that there are no clinically significant interactions between lamivudine and zidovudine.

Zidovudine is primarily metabolised by UGT enzymes; co-administration of inducers or inhibitors of UGT enzymes could alter zidovudine exposure. Lamivudine is cleared renally. Active renal secretion of lamivudine in the urine is mediated through organic cation transporters (OCTs); co-administration of lamivudine with OCT inhibitors or nephrotoxic drugs may increase lamivudine exposure.

Lamivudine and zidovudine are not significantly metabolised by cytochrome P_{450} enzymes (such as CYP 3A4, CYP 2C9 or CYP 2D6) nor do they inhibit or induce this enzyme system. Therefore, there is little potential for interactions with antiretroviral protease inhibitors, non-nucleosides and other medicinal products metabolised by major P_{450} enzymes.

Interaction studies have only been performed in adults. The list below should not be considered exhaustive but is representative of the classes studied.

Drugs by Therapeutic Area	**Interaction Geometric mean change (%) (Possible mechanism)**	**Recommendation concerning co-administration**
ANTIRETROVIRAL MEDICINAL PRODUCTS		
Didanosine/Lamivudine	Interaction not studied.	No dosage adjustment necessary.
Didanosine /Zidovudine	Interaction not studied.	
Stavudine/Lamivudine	Interaction not studied.	Combination not recommended.
Stavudine/Zidovudine	In vitro antagonism of anti-HIV activity between stavudine and zidovudine could result in decreased efficacy of both drugs.	
ANTI-INFECTIVE PRODUCTS		
Atovaquone/Lamivudine	Interaction not studied.	As only limited data available the clinical significance is unknown.
Atovaquone/Zidovudine (750 mg twice daily with food/200 mg thrice daily)	Zidovudine AUC ↑33% Atovaquone AUC ↔	
Clarithromycin/Lamivudine	Interaction not studied.	Separate administration of Lamivudine/zidovudine ViiV and clarithromycin by at least 2 hours
Clarithromycin/Zidovudine (500 mg twice daily/100 mg every 4 hours)	Zidovudine AUC ↓12%	

Trimethoprim/sulfamethoxazole (Co-trimoxazole)/Lamivudine (160mg/800mg once daily for 5 days/300mg single dose)	Lamivudine: AUC ↑40% Trimethoprim: AUC ↔ Sulfamethoxazole: AUC ↔ (organic cation transporter inhibition)	No Lamivudine/zidovudine ViiV dosage adjustment necessary, unless patient has renal impairment (See Section 4.2). When concomitant administration with co-trimoxazole is warranted, patients should be monitored clinically. High doses of trimethoprim/ sulfamethoxazole for the treatment of *Pneumocystis jirovecii* pneumonia (PCP) and toxoplasmosis have not been studied and should be avoided.
Trimethoprim/sulfamethoxazole (Co-trimoxazole)/Zidovudine	Interaction not studied.	
ANTIFUNGALS		
Fluconazole/Lamivudine	Interaction not studied.	As only limited data are available the clinical significance is not known. Monitor for signs of zidovudine toxicity (see section 4.8).
Fluconazole/Zidovudine (400 mg once daily/200 mg thrice daily)	Zidovudine AUC ↑74% (UGT inhibition)	
ANTIMYCOBACTERIALS		
Rifampicin/Lamivudine	Interaction not studied.	Insufficient data to recommend dosage adjustment.
Rifampicin/Zidovudine (600mg once daily/200 mg thrice daily)	Zidovudine AUC ↓48% (UGT induction)	
ANTICONVULSANTS		
Phenobarbital/Lamivudine	Interaction not studied.	Insufficient data to recommend dosage adjustment.
Phenobarbital/Zidovudine	Interaction not studied. Potential to slightly decrease zidovudine plasma concentrations through UGT induction.	
Phenytoin/Lamivudine	Interaction not studied.	Monitor phenytoin concentrations.
Phenytoin/Zidovudine	Phenytoin AUC ↑↓	
Valproic acid/Lamivudine	Interaction not studied.	As only limited data are available the clinical significance is not known. Monitor for signs of zidovudine toxicity (see section 4.8).
Valproic acid/Zidovudine (250 mg or 500 mg thrice daily/100 mg thrice daily)	Zidovudine AUC ↑80% (UGT inhibition)	
ANTIHISTAMINES (HISTAMINE H1 RECEPTOR ANTAGONISTS)		
Ranitidine/Lamivudine	Interaction not studied. Clinically significant interaction unlikely. Ranitidine eliminated only in part by renal organic cation transport system.	No dosage adjustment necessary.
Ranitidine/Zidovudine	Interaction not studied	

Cimetidine/Lamivudine	Interaction not studied. Clinically significant interaction unlikely. Cimetidine eliminated only in part by renal organic cation transport system.	No dosage adjustment necessary.
Cimetidine/Zidovudine	Interaction not studied.	
CYTOTOXICS		
Cladribine/Lamivudine	Interaction not studied *In vitro* lamivudine inhibits the intracellular phosphorylation of cladribine leading to a potential risk of cladribine loss of efficacy in case of combination in the clinical setting. Some clinical findings also support a possible interaction between lamivudine and cladribine	Therefore, the concomitant use of lamivudine with cladribine is not recommended (see section 4.4).
OPIOIDS		
Methadone/Lamivudine	Interaction not studied.	As only limited data are available the clinical significance is not known. Monitor for signs of zidovudine toxicity (see section 4.8). Methadone dosage adjustment unlikely in majority of patients; occasionally methadone re-titration may be required.
Methadone/Zidovudine (30 to 90 mg once daily/200 mg every 4 hours)	Zidovudine AUC ↑43% Methadone AUC ↔	
URICOSURIC		
Probenecid/Lamivudine	Interaction not studied.	As only limited data are available the clinical significance is not known. Monitor for signs of zidovudine toxicity (see section 4.8).
Probenecid/Zidovudine (500 mg four times daily/2mg/kg thrice daily)	Zidovudine AUC ↑106% (UGT inhibition)	

Abbreviations: ↑ = Increase; ↓=decrease; ↔= no significant change; AUC=area under the concentration versus time curve; Cmax=maximum observed concentration; CL/F=apparent oral clearance

Exacerbation of anaemia due to ribavirin has been reported when zidovudine is part of the regimen used to treat HIV although the exact mechanism remains to be elucidated. The concomitant use of ribavirin with zidovudine is not recommended due to an increased risk of anaemia (see section 4.4). Consideration should be given to replacing zidovudine in a combination ART regimen if this is already established. This would be particularly important in patients with a known history of zidovudine induced anaemia.

Concomitant treatment, especially acute therapy, with potentially nephrotoxic or myelosuppressive medicinal products (e.g. systemic pentamidine, dapsone, pyrimethamine, co-trimoxazole, amphotericin, flucytosine, ganciclovir, interferon, vincristine, vinblastine and doxorubicin) may also increase the risk of adverse reactions to zidovudine. If concomitant therapy with Lamivudine/zidovudine ViiV and any of these medicinal products is necessary then extra care should be taken in monitoring renal function and haematological parameters and, if required, the dosage of one or more agents should be reduced.

Limited data from clinical trials do not indicate a significantly increased risk of adverse reactions to zidovudine with cotrimoxazole (see interaction information above relating to lamivudine and co-trimoxazole), aerosolised pentamidine, pyrimethamine and acyclovir at doses used in prophylaxis.

4.6 Fertility, Pregnancy and lactation

Pregnancy

As a general rule, when deciding to use antiretroviral agents for the treatment of HIV infection in pregnant women and consequently for reducing the risk of HIV vertical transmission to the newborn, the animal data as well as the clinical experience in pregnant women should be taken into account. In the present case, the use in pregnant women of zidovudine with subsequent treatment of the newborn infants, has been shown to reduce the rate of materna l-foetal transmission of HIV. A large amount of data on pregnant women taking lamivudine or zidovudine indicate no malformative toxicity (more than 3000 outcomes from first trimester exposure each, of which over 2000 outcomes involved exposure to both lamivudine and zidovudine). The malformative risk is unlikely in humans based on the mentioned large amount of data.

The active ingredients of lamivudine/zidovudine ViiV may inhibit cellular DNA replication and zidovudine has been shown to be transplacental carcinogen in one animal study (see section 5.3). The clinical relevance of these findings is unknown

For patients co-infected with hepatitis who are being treated with lamivudine containing medicinal products such as Lamivudine/zidovudine ViiV 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 HIV-negative infants exposed in utero and/or post-natally to nucleoside analogues (see section 4.4).

Breastfeeding

Both lamivudine and zidovudine are excreted in breast milk at similar concentrations to those found in serum.

Based on more than 200 mother/child pairs treated for HIV, serum concentrations of lamivudine in breastfed infants of mothers treated for HIV are very low (< 4% of maternal serum concentrations) and progressively decrease to undetectable levels when breastfed infants reach 24 weeks of age. There are no data available on the safety of lamivudine when administered to babies less than three months old.

After administration of a single dose of 200 mg zidovudine to HIV-infected women, the mean concentration of zidovudine was similar in human milk and serum.

It is recommended that mothers infected by HIV do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

Fertility

Neither zidovudine nor lamivudine have shown evidence of impairment of fertility in studies in male and female rats. There are no data on their affect on human female fertility. In men zidovudine has not been shown to affect sperm count, morphology or motility.

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

Adverse reactions have been reported during therapy for HIV disease with lamivudine and zidovudine separately or in combination. For many of these events, it is unclear whether they are related to lamivudine, zidovudine, the wide range of medicinal products used in the management of HIV disease, or as a result of the underlying disease process.

As Lamivudine/zidovudine ViiV tablets contain lamivudine and zidovudine, the type and severity of adverse reactions associated with each of the compounds may be expected. There is no evidence of added toxicity following concurrent administration of the two compounds.

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. Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

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

Lamivudine:

The adverse events 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, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000), 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: Cases of peripheral neuropathy (or paraesthesiae) have been reported

Respiratory, thoracic and mediastinal disorders
Common: Cough, nasal symptoms

Gastrointestinal disorders
Common: Nausea, vomiting, abdominal pain or cramps, diarrhoea
Rare : Cases of pancreatitis have been reported. Rises in serum amylase.

Hepatobiliary disorders

Uncommon: Transient rises 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.

Zidovudine:

The adverse event profile appears similar for adults and adolescents. The most serious adverse reactions include anaemia (which may require transfusions), neutropenia and leucopenia. These occurred more frequently at higher dosages (1200-1500 mg/day) and in patients with advanced HIV disease (especially when there is poor bone marrow reserve prior to treatment), and particularly in patients with CD4 cell counts less than 100/mm^3. Dosage reduction or cessation of therapy may become necessary (see section 4.4).

The incidence of neutropenia was also increased in those patients whose neutrophil counts, haemoglobin levels and serum vitamin B_{12} levels were low at the start of zidovudine therapy.

The adverse events 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, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000), very rare (<1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Blood and lymphatic system disorders
Common : Anaemia, neutropenia and leucopenia,
Uncommon: Thrombocyopenia and pancytopenia (with marrow hypoplasia)
Rare : Pure red cell aplasia
Very rare : Aplastic anaemia

Metabolism and nutrition disorders
Rare : Lactic acidosis in the absence of hypoxaemia, anorexia

Psychiatric disorders
Rare: Anxiety and depression

Nervous system disorders
Very common : Headache
Common : Dizziness
Rare : Insomnia, paraesthesiae, somnolence, loss of mental acuity, convulsions,

Cardiac disorders
*Rare :*Cardiomyopathy

Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnoea
Rare : Cough

Gastrointestinal disorders
Very common : Nausea
Common : Vomiting, abdominal pain and diarrhoea
Uncommon : Flatulence
Rare : Oral mucosa pigmentation, taste perversion and dyspepsia. Pancreatitis

Hepatobiliary disorders
Common : Raised blood levels of liver enzymes and bilirubin
Rare : Liver disorders such as severe hepatomegaly with steatosis

Skin and subcutaneous tissue disorders
Uncommon : Rash and pruritus
Rare : Nail and skin pigmentation, urticaria and sweating

Musculoskeletal and connective tissue disorders
Common : Myalgia
Uncommon : Myopathy

Renal and urinary disorders
Rare: Urinary frequency

Reproductive system and breast disorders
Rare : Gynaecomastia

General disorders and administration site conditions
Common : Malaise
Uncommon : Fever, generalised pain and asthenia
*Rare :*Chills, chest pain and influenza-like syndrome

The available data from both placebo-controlled and open-label studies indicate that the incidence of nausea and other frequently reported clinical adverse events consistently decreases over time during the first few weeks of therapy with zidovudine.

4.9 Overdose

There is limited experience of overdosage with lamivudine/zidovudine. No specific symptoms or signs have been identified following acute overdose with zidovudine or lamivudine apart from those listed as undesirable effects. No fatalities occurred, and all patients recovered.

If overdosage occurs the patient should be monitored for evidence of toxicity (see section 4.8), and standard supportive treatment applied as necessary. Since lamivudine is dialysable, continuous haemodialysis could be used in the treatment of overdosage, although this has not been studied. Haemodialysis and peritoneal dialysis appear to have a limited effect on elimination of zidovudine, but enhance the elimination of the glucuronide metabolite. For more details physicians should refer to the individual prescribing information for lamivudine and zidovudine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for treatment of HIV infections, combinations, ATC Code: J05AR01

Lamivudine and zidovudine are nucleoside analogues which have activity against HIV. Additionally, lamivudine has activity against hepatitis B virus (HBV). Both medicinal products are metabolised intracellularly to their active moieties, lamivudine 5'- triphosphate (TP) and zidovudine 5'-

triphosphate respectively. Their main modes of action are as chain terminators of viral reverse transcription. Lamivudine-TP and zidovudine-TP have selective inhibitory activity against HIV-1 and HIV-2 replication *in vitro*; lamivudine is also active against zidovudine-resistant clinical isolates of HIV. No antagonistic effects in vitro were seen with lamivudine and other antiretrovirals (tested agents: abacavir, didanosine and nevirapine). No antagonistic effects in vitro were seen with zidovudine and other antiretrovirals (tested agents: abacavir, didanosine and interferon-alpha).

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*. Resistance to thymidine analogues (of which zidovudine is one) is well characterised and is conferred by the stepwise accumulation of up to six specific mutations in the HIV reverse transcriptase at codons 41, 67, 70, 210, 215 and 219. Viruses acquire phenotypic resistance to thymidine analogues through the combination of mutations at codons 41 and 215 or by the accumulation of at least four of the six mutations. These thymidine analogue mutations alone do not cause high-level cross-resistance to any of the other nucleosides, allowing for the subsequent use of any of the other approved reverse transcriptase inhibitors.

Two patterns of multi-drug resistance mutations, the first characterised by mutations in the HIV reverse transcriptase at codons 62, 75, 77, 116 and 151 and the second involving a T69S mutation plus a 6-base pair insert at the same position, result in phenotypic resistance to AZT as well as to the other approved NRTIs. Either of these two patterns of multinucleoside resistance mutations severely limits future therapeutic options.

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.

Lamivudine and zidovudine have been widely used as components 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.

Evidence from clinical studies shows that lamivudine plus zidovudine delays the emergence of zidovudine resistant isolates in individuals with no prior antiretroviral therapy. Subjects receiving lamivudine and zidovudine with or without additional concomitant antiretroviral therapies and who already present with the M184V mutant virus also experience a delay in the onset of mutations that confer resistance to zidovudine and stavudine (Thymidine Analogue Mutations; TAMs).

The relationship between *in vitro* susceptibility of HIV to lamivudine and zidovudine and clinical response to lamivudine/zidovudine 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.

5.2 Pharmacokinetic properties

Absorption

Lamivudine and zidovudine are well absorbed from the gastrointestinal tract. The bioavailability of oral lamivudine in adults is normally between 80 – 85% and for zidovudine 60 – 70%.

A bioequivalence study compared Lamivudine/zidovudine ViiV tablets with lamivudine 150 mg and zidovudine 300 mg tablets taken together. The effect of food on the rate and extent of absorption was also studied. Lamivudine/zidovudine ViiV tablets were shown to be bioequivalent to lamivudine 150 mg and zidovudine 300 mg given as separate tablets, when administered to fasting subjects.

Following single dose lamivudine/zidovudine administration in healthy volunteers, mean (CV) lamivudine and zidovudine C_{max} values were 1.6 µg/ml (32 %) and 2.0 µg/ml (40 %), respectively and the corresponding values for AUC were 6.1 µg.h/ml (20 %) and 2.4 µg.h/ml (29 %) respectively. The median (range) lamivudine and zidovudine t_{max} values were 0.75 (0.50 - 2.00) hours and 0.50 (0.25 - 2.00) hours respectively. The extent of lamivudine and zidovudine absorption (AUC_{∞}) and estimates of half-life following administration of lamivudine/zidovudine with food were similar when compared to fasting subjects, although the rates of absorption (C_{max}, t_{max}) were slowed. Based on these data lamivudine/zidovudine may be administered with or without food.

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

Distribution

Intravenous studies with lamivudine and zidovudine showed that the mean apparent volume of distribution is 1.3 and 1.6 l/kg respectively. Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays limited binding to the major plasma protein albumin (< 36% serum albumin *in vitro*). Zidovudine plasma protein binding is 34% to 38%. Interactions involving binding site displacement are not anticipated with lamivudine/zidovudine.

Data show that lamivudine and zidovudine penetrate the central nervous system (CNS) and reach the cerebrospinal fluid (CSF). The mean ratios of CSF/serum lamivudine and zidovudine concentrations

2 - 4 hours after oral administration were approximately 0.12 and 0.5 respectively. The true extent of CNS penetration of lamivudine and its relationship with any clinical efficacy is unknown.

Biotransformation

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

The 5'-glucuronide of zidovudine is the major metabolite in both plasma and urine, accounting for approximately 50 – 80% of the administered dose eliminated by renal excretion. 3'-amino-3'-deoxythymidine (AMT) has been identified as a metabolite of zidovudine following intravenous dosing.

Elimination: The observed lamivudine 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. Studies in patients with renal impairment show lamivudine elimination is affected by renal dysfunction. Dose reduction is required for patients with creatinine clearance ≤ 50 ml/min (see section 4.2).

From studies with intravenous zidovudine, the mean terminal plasma half-life was 1.1 hours and the mean systemic clearance was 1.6 l/h/kg. Renal clearance of zidovudine is estimated to be 0.34 l/h/kg, indicating glomerular filtration and active tubular secretion by the kidneys. Zidovudine concentrations are increased in patients with advanced renal failure.

Pharmacokinetics in children

In children over the age of 5-6 months, the pharmacokinetic profile of zidovudine is similar to that in adults. Zidovudine is well absorbed from the gut and at all dose levels studied in adults and children, the bioavailability was between 60-74% with a mean of 65%. Css_{max} levels were 4.45 μM (1.19 μg/ml) following a dose of 120 mg zidovudine (in solution)/m^2 body surface area and 7.7 μM (2.06 μg/ml) at 180 mg/m^2 body surface area. Dosages of 180 mg/m^2 four times daily in children produced similar systemic exposure (24 hour AUC 40.0 hr μM or 10.7 hr μg/ml) as doses of 200 mg six times daily in adults (40.7 hr μM or 10.9 hr μg/ml).

In six HIV-infected children from 2 to 13 years of age, zidovudine plasma pharmacokinetics were evaluated while subjects were receiving 120 mg/m^2 zidovudine three times daily and again after switching to 180 mg/m^2 twice daily. Systemic exposures (daily AUC and C_{max}) in plasma from the twice daily regimen appeared equivalent to those from the same total daily dose given in three divided doses [Bergshoeff, 2004].

In general, lamivudine pharmacokinetics in paediatric patients are 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.

Pharmacokinetics in pregnancy

The pharmacokinetics of lamivudine and zidovudine were similar to that of non-pregnant women.

5.3 Preclinical safety data

The clinically relevant effects of lamivudine and zidovudine in combination are anaemia, neutropenia and leucopenia.

Mutagenicity and carcinogenicity

Neither lamivudine nor zidovudine are mutagenic in bacterial tests, but consistent with other nucleoside analogues, inhibit cellular DNA replication in *in vitro* mammalian tests such as the mouse lymphoma assay.

Lamivudine has not shown any genotoxic activity in *in vivo* studies at doses that gave plasma concentrations up to 40-50 times higher than clinical plasma levels. Zidovudine showed clastogenic effects in an oral repeated dose micronucleus test in mice. Peripheral blood lymphocytes from AIDS patients receiving zidovudine treatment have also been observed to contain higher numbers of chromosome breakages.

A pilot study has demonstrated that zidovudine is incorporated into leukocyte nuclear DNA of adults, including pregnant women, taking zidovudine as treatment for HIV-1 infection, or for the prevention of mother to child viral transmission. Zidovudine was also incorporated into DNA from cord blood leukocytes of infants from zidovudine-treated mothers. 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 carcinogenic potential of a combination of lamivudine and zidovudine has not been tested

In long-term oral carcinogenicity studies in rats and mice, lamivudine did not show any carcinogenic potential.

In oral carcinogenicity studies with zidovudine in mice and rats, late appearing vaginal epithelial tumours were observed. A subsequent intravaginal carcinogenicity study confirmed the hypothesis that the vaginal tumours were the result of long term local exposure of the rodent vaginal epithelium to high concentrations of unmetabolised zidovudine in urine. There were no other zidovudine-related tumours observed in either sex of either species.

In addition, two transplacental carcinogenicity studies have been conducted in mice. In one study, by the US National Cancer Institute, zidovudine was administered at maximum tolerated doses to pregnant mice from day 12 to 18 of gestation. One year post-natally, there was an increase in the incidence of tumours in the lung, liver and female reproductive tract of offspring exposed to the highest dose level (420 mg/kg term body weight).

In a second study, mice were administered zidovudine at doses up to 40 mg/kg for 24 months, with exposure beginning prenatally on gestation day 10. Treatment related findings were limited to late-occurring vaginal epithelial tumours, which were seen with a similar incidence and time of onset as in the standard oral carcinogenicity study. The second study thus provided no evidence that zidovudine acts as a transplacental carcinogen.

While the clinical relevance of these findings is unknown, these data suggest that a carcinogenic risk to humans is outweighed by the potential clinical benefit.

In reproductive toxicity studies lamivudine has demonstrated evidence of causing an increase in early embryonic deaths in the rabbit at relatively low systemic exposures, comparable to those achieved in man, but not in the rat even at very high systemic exposure. Zidovudine had a similar effect in both species, but only at very high systemic exposures. Lamivudine was not teratogenic in animal studies.

At maternally toxic doses, zidovudine given to rats during organogenesis resulted in an increased incidence of malformations, but no evidence of foetal abnormalities was observed at lower doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Microcrystalline cellulose (E460),
sodium starch glycollate,
colloidal silicon dioxide,
magnesium stearate

Tablet film coat:
Hypromellose (E464),
titanium dioxide (E171),
Allura red (E129)
Sunset yellow (E110)
Polyethylene glycol 400

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

2 years

6.4 Special precautions for storage

Do not store above 30°C

6.5 Nature and content of container

Tamper-evident cartons containing white high density polyethylene (HDPE) bottles with a child-resistant closure. Each pack contains 60 film-coated tablets.

6.6 Special precautions for disposal

No special requirements for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Not applicable

8. MARKETING AUTHORISATION NUMBER

Not applicable

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Not applicable

10. DATE OF REVISION OF THE TEXT

Not applicable

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE SCIENTIFIC OPINION

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

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

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

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

or

Pharmacare (Trading as Aspen Pharmacare Ltd), 7 Fairclough Road, Korsten, 6020, Port Elizabeth, South Africa

or

Aurobindo Pharma Ltd., Unit-III -, Survey No 313, Bachupally Village, Qutbullapur Mandal, Ranga Reddy District, Andhra Pradesh, Hyderabad, India

B. CONDITIONS OR RESTRICTIONS REGARDING SUPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE SCIENTIFIC OPINION

- Periodic Safety Update Reports

The Scientific Opinion holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD) list provided for under article 107c(7) of Directive 2001/83/EC and published on the European Medicines web portal.

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

- Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed the RMP presented in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP.

An updated RMP should be submitted:

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

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND ON THE IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Lamivudine/zidovudine ViiV film-coated tablets
Lamivudine/zidovudine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains
lamivudine 150 mg
zidovudine 300 mg

3. LIST OF EXCIPIENTS

Contains sunset yellow (E110). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

60 film-coated tablets
Scored tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use

Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

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

Not applicable

12. MARKETING AUTHORISATION NUMBER(S)

Not applicable

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 AND THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Lamivudine/zidovudine ViiV film-coated tablets
Lamivudine/zidovudine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains
lamivudine 150 mg
zidovudine 300 mg

3. LIST OF EXCIPIENTS

Contains sunset yellow (E110). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

60 film-coated tablets
Scored tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

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

Not applicable

12. MARKETING AUTHORISATION NUMBER(S)

Not applicable

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

B. PACKAGE LEAFLET

Package Leaflet: Information for the user

Lamivudine/zidovudine ViiV film-coated tablets
Lamivudine/zidovudine

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

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

What is in this leaflet:

1. What lamivudine/zidovudine is and what it is used for

Lamivudine/zidovudine belongs to a group of antiviral medicines, also known as antiretrovirals, called nucleoside analogue reverse transcriptase inhibitors (NRTIs). These are used to treat Human Immunodeficiency Virus (HIV) infection.

Lamivudine/zidovudine is used in antiretroviral combination therapy for the treatment of HIV infection in patients weighing more than 14 kg. Lamivudine/zidovudine reduces the amount of HIV virus in your body, and keeps it at a low level. It also increases CD4 cell counts. CD4 cells are a type of white blood cell, that play an important role in maintaining a healthy immune system to help fight infection. Lamivudine/zidovudine has been shown to significantly reduce the risk of disease progression. Response to treatment with lamivudine/zidovudine varies between patients. Your doctor will be monitoring the effectiveness of your treatment.

2. What you need to know before you take lamivudine/zidovudine

Do not take Lamivudine/zidovudine
- If you are allergic to lamivudine or zidovudine or any of the other ingredients of this medicine (*listed in Section 6)*
- If you have very low red blood cell count (severe anaemia) or very low white blood cell count (neutropenia).

If you are not sure please ask your doctor.

Take special care with Lamivudine/zidovudine

Discuss the use of lamivudine/zidovudine with your doctor if you have kidney or liver disease to ensure the doses of the active substances in lamivudine/zidovudine are suitable for you.

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 decide to prescribe lamivudine or zidovudine as separate medicines instead of Lamivudine/zidovudine ViiV tablets.

Anaemia (low red blood cell count) and neutropenia/leucopenia (low white blood cell count) may occur within 4-6 weeks due to treatment with zidovudine, one of the active substances in Lamivudine/zidovudine ViiV tablets. If severe, your physician may stop treatment with Lamivudine/zidovudine ViiV tablets. This has occurred more commonly in patients with advanced HIV disease and with higher doses of zidovudine than the dose in lamivudine/zidovudine. Regular blood tests will be arranged to check whether there is a problem. This adverse reaction is infrequent in patients with early HIV disease and blood tests may be performed less frequently.

If you take ribavirin and zidovudine together it may cause or worsen anaemia. Please contact your doctor if you notice symptoms of anaemia (such as tiredness and shortness of breath). Your doctor will advise you whether you should stop taking Lamivudine/zidovudine ViiVtablets.

The class of medicines to which lamivudine/zidovudine belongs (NRTIs) can cause a condition called lactic acidosis, together with an enlarged liver. Lactic acidosis, if it occurs, usually develops after a few months of treatment. Deep, rapid breathing, drowsiness, and non specific symptoms such as nausea, vomiting and stomach pain, might indicate the development of lactic acidosis. This rare, but serious side effect occurs more often in women, particularly if very overweight. If you have liver disease you may also be more at risk of getting this condition. While you are being treated with lamivudine/zidovudine, your doctor will monitor you closely for any signs that you may be developing lactic acidosis.

Redistribution, accumulation or loss of body fat may occur in patients receiving combination antiretroviral therapy. Contact your doctor if you notice changes in body fat.

In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please inform your doctor immediately.

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

Please speak with your doctor if you have a history of liver disease. Patients with chronic hepatitis B or C and treated with antiretroviral agents are at increased risk of severe and potentially fatal liver adverse events and may require blood tests for monitoring of liver function.

If you have a chronic hepatitis B infection, you should not stop your treatment without instructions from your doctor, as you may have a recurrence of your hepatitis. This recurrence may be more severe if you have serious liver disease.

Lamivudine/zidovudine ViiV tablets contain a colouring called sunset yellow (E110), which may cause allergic reactions in some people.

You will need to take lamivudine/zidovudine every day. This medicine helps to control your condition and delay disease progression, but it is not a cure for HIV infection. You may continue to develop other infections and other illnesses associated with HIV disease. You should keep in regular contact with your doctor. Do not stop taking your medicine without first talking to your doctor.

Treatment with lamivudine/zidovudine has not been shown to reduce the risk of passing HIV infection on to others by sexual contact or by blood transfer. You can still pass on HIV when taking this medicine although the risk is lowered by effective antiretroviral therapy.
Discuss with your doctor the precautions needed to avoid infecting other people.

Bone problems*:* Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your doctor.

Taking other medicines
It is important that you tell your doctor about all the medicines you are taking including those you have bought yourself. These may affect the action of lamivudine/zidovudine, or lamivudine/zidovudine may affect their action. Lamivudine/zidovudine should not be taken with other medicinal products containing lamivudine (used to treat HIV infection or hepatitis B infection), emtricitabine (used to treat HIV), high doses of co-trimoxazole or cladribine used to treat hairy cell leukaemia. This is because lamivudine, one of the active substances in lamivudine/zidovudine may interact with these. Lamivudine/zidovudine should also not be taken with stavudine, as zidovudine the other active substance in lamivudine/zidovudine may reduce the action of this medicinal product.

Zidovudine may also interact with the following medicines and may make any side effects worse: Phenytoin, probenecid, rifampicin, atovaquone, valproic acid, methadone, dapsone, pentamidine, pyrimethamine, co-trimoxazole, fluconazole, amphotericin, flucytosine, ganciclovir, interferon, clarithromycin, vincristine, vinblastine and doxorubicin.

Pregnancy and breast-feeding

If you become pregnant, or are planning to become pregnant, you must contact your doctor to discuss the potential adverse effects and the benefits and risks of your antiretroviral therapy to you and your child.

If you have taken lamivudine/zidovudine during your pregnancy, your doctor may request regular visits to monitor the development of your child. Such visits may include blood tests and other diagnostic tests.

In children whose mothers took nucleoside and nucleotide analogues during pregnancy, the benefit from the reduced chance of being infected with HIV is greater than the risk of suffering from 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.

A small amount of the ingredients in lamivudine and zidovudine ViiV can also pass into your breast milk.

If you are breast-feeding, or thinking about breast-feeding:
Talk to your doctor immediately

3. How to take lamivudine/zidovudine

Always take this medicine exactly as your doctor or pharmacist has told you to. You should check with your doctor or pharmacist if you are not sure. Swallow lamivudine/zidovudine tablets with water or another drink. They can be taken with or without food.

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

The usual dose of lamivudine/zidovudine for adults and adolescents weighing at least 30 kg is one tablet twice a day.

For children weighing between 21 kg and 30 kg the recommended oral dose of Lamivudine/zidovudine ViiV tablets is one-half tablet taken in the morning and one whole tablet taken in the evening.

For children weighing 14 kg to 21 kg the recommended oral dose of Lamivudine/zidovudine ViiV tablets is one-half tablet taken twice daily.

Each dose of Lamivudine/zidovudine ViiV tablets should be taken approximately 12 hours apart.

For children weighing less than 14 kg, lamivudine and zidovudine should be taken as separate formulations according to the prescribed dosing for these products.

If your doctor wishes to reduce your dose of lamivudine/zidovudine, for example if you have kidney problems, then your medicine may be changed to lamivudine and zidovudine taken as separate medicines, which are available as tablets or liquid.

If you take more lamivudine/zidovudine than you should
Accidentally taking too much lamivudine/zidovudine 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.

If you forget to take lamivudine/zidovudine
If you forget to take a dose of lamivudine/zidovudine, take it as soon as you remember and then continue as before. Do not take a double dose to make up for a forgotten dose.

4. POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects although not everybody gets them. When treating HIV infection, it is not always possible to tell whether some of the undesirable effects that occur are caused by lamivudine/zidovudine, by other medicines you are taking at the same time or by the HIV disease. For this reason it is very important that you inform your doctor about any changes in your health. Do not be alarmed by this list of possible side effects, you may not experience them.

Combination antiretroviral therapy may cause changes in body shape due to changes in fat distribution. These may include loss of fat from legs, arms and face, increased fat in the abdomen (belly), and other internal organs, breast enlargement and fatty lumps on the back of the neck (‘buffalo hump’). The cause and long-term health effects of these conditions are not known at this time.

Combination antiretroviral therapy may also cause raised lactic acid and sugar in the blood, hyperlipaemia (increased fats in the blood) and resistance to insulin.

The most commonly reported (greater than 1 in every 100 patients treated) side effects that may occur are headache, nausea, vomiting, stomach pain, diarrhoea, fever, rash (red, raised or itchy), increase in

certain liver enzymes, joint pain, muscle pain and other muscle disorders, dizziness, cough, nasal symptoms, tiredness, difficulty sleeping, hair loss, anaemia (low red blood cell count) and neutropenia (low white blood cell count). If the number of red blood cells is reduced you may have symptoms of tiredness or breathlessness and a reduction in your white blood cell count can make you more prone to infection.

Uncommon (between 1 in 1000 and 1 in 100 patients treated) side effects that may occur are flatulence, breathlessness, general aches and pains and reduction in platelets (blood cells important for blood clotting). If you have a low platelet count you may notice that you bruise more easily

There are rare reports (between 1 in 10 000 and 1 in 1000 patients treated) of serious allergic reaction causing swelling of the face, tongue or throat which may cause difficulty in swallowing or breathing. Patchy colour changes inside the mouth, heartburn, chest pain (possibly indicating a heart muscle disease called cardiomyopathy), breakdown of muscle tissue, liver disorders such as enlarged liver, fatty liver, inflammation of the liver (hepatitis), inflammation of the pancreas, nail and skin colour changes, sweating, flu-like feeling, drowsiness, passing urine more frequently, breast enlargement in male patients, chest pain, chills, loss of appetite, taste changes, tingling in the limbs, seizures, inability to concentrate, depression and feeling anxious, increase of lactic acid in the body known as lactic acidosis (see Take special care with Lamivudine/zidovudine).

While many of the side effects that have been reported occur with both lamivudine and zidovudine when given as separate medicines, some are more likely to occur with one of the medicines only. Your doctor may decide that you need to stop taking lamivudine/zidovudine and take lamivudine and zidovudine separately. This will allow your doctor to vary the dose or stop one of the active substances if it is considered that this will help manage any side effects.

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.

5. How to store lamivudine/zidovudine

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

Do not use this medicine after the expiry date which is stated on the container. The expiry date refers to the last day of that month.

Do not store above 30°C.

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

6 Contents of the pack and other information

What Lamivudine/zidovudine ViiV film-coated tablets contains

Lamivudine/zidovudine ViiV tablets is a medicine that contains a combination of two active substances, lamivudine and zidovudine, that are also available as separate medicines. Each film-coated tablet contains 150 mg lamivudine and 300 mg zidovudine.

The film-coated tablets also contain the following ingredients:
Tablet core: microcrystalline cellulose, sodium starch glycollate (gluten free), magnesium stearate, colloidal silicon dioxide
Tablet film-coat: hypromellose, titanium dioxide, allura red, sunset yellow, polyethylene glycol.

What Lamivudine/zidovudine ViiV film-coated tablets looks like and contents of the pack

Lamivudine/zidovudine film-coated tablets are provided in polyethylene bottles containing 60 tablets. They are red, capsule-shaped scored tablets engraved with “A22” on both sides.

Manufacturer	**Marketing Authorisation Holder**
Glaxo Operations UK Limited (trading as Glaxo Wellcome Operations) Priory Street Ware Herts SG12 0DJ United Kingdom or Pharmacare (Trading as Aspen Pharmacare Ltd) 7 Fairclough Road Korsten, 6020 Port Elizabeth South Africa or Aurobindo Pharma Ltd. Unit-III -, Survey No 313, Bachupally Village, Qutbullapur Mandal Ranga Reddy District Andhra Pradesh. Hyderabad India	Not applicable

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