ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Lamivudine ViiV 150 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150 mg lamivudine.
For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Red, diamond shaped scored tablets and engraved with “A11” on both faces.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

The therapy should be initiated by a physician experienced in the management of HIV infection.
Lamivudine 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, adolescents and children (weighing at least 25 kg): The recommended dose of lamivudine is 300 mg daily. This may be administered as either 150 mg twice daily or 300 mg once daily (see section 4.4).

Children (weighing less than 25 kg):
Dosing according to weight bands is recommended for Lamivudine ViiV tablets.

For children weighing≥ 20 kg to <25 kg The recommended dose is 225 mg daily. This may be administered as either 75 mg (one half of a 150 mg tablet) taken in the morning and 150 mg (one whole 150 mg tablet) taken in the evening, or 225 mg (0ne and a half 150 mg tablets taken once daily. of Lamivudine ViiV 150 mg tablets is one-half tablet taken in the morning and one whole tablet taken in the evening.

For children weighing 14 to < 20 kg: the recommended dose is 150 mg daily. This may be administered as 75 mg (one- half of a 150 mg tablet) taken twice daily, or 150 mg (one whole 150 mg tablet) taken once daily.

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

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

Special populations:

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

Renal impairment:- Lamivudine concentrations are increased in patients with moderate - severe renal impairment due to decreased clearance. The dose should therefore be adjusted, for patients whose creatinine clearance falls below 30 ml/min (see tables).

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

Creatinine clearance (ml/min)	**First dose**	**Maintenance dose**
≥50	300 mg or 150 mg	300 mg once daily 150 mg Twice daily
30-<50	150 mg	150 mg Once daily
<30	this form is not suitable for patients with clearance creatinine <30 ml/min	
15 to <30	150 mg	100 mg once daily
5 to <15	150 mg	50 mg once daily
<5	50 mg	25 mg once daily

There are no data available on the use of lamivudine in children with renal impairment. Based on the assumption that creatinine clearance and lamivudine clearance are correlated similarly in children as in adults it is recommended that the dosage in children with renal impairment be reduced according to their creatinine clearance by the same proportion as in adults.

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

Creatinine clearance (ml/min)	**First dose**	**Maintenance dose**
≥50	8 mg/kg or 4 mg/kg	8 mg/kg once daily 4 mg/kg twice daily
30 to<50	4 mg/kg	4 mg/kg once daily
15 to <30	4 mg/kg	2.6 mg/kg once daily
5 to <15	4 mg/kg	1.3 mg/kg once daily
<5	1.3 mg/kg	0.7 mg/kg once daily

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

4.3 Contraindications

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

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.

Lamivudine is not recommended for use as monotherapy.

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

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

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

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

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

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

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

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

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

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

Patients at increased risk should be followed closely .

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

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

Immune Reactivation Syndrome: In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterium infections, and *Pneumocystis carinii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. 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.

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

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

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.

Lamivudine ViiV should not be taken with any other medicinal products containing lamivudine or medicinal products containing emtricitabine (see section 4.5).

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

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

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

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

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

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

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

In vitro lamivudine inhibits the intracellular phosphorylation of cladribine leading to a potential risk of cladribine loss of efficacy in case of combination in the clinical setting. Some clinical findings also support a possible interaction between lamivudine and cladribine. Therefore, the concomitant use of lamivudine with cladribine is not recommended (see section 4.4).

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

4.6 Fertility, Pregnancy and lactation

Pregnancy

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

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

More than 1000 outcomes from first trimester and more than 1000 outcomes from second and third trimester exposure in pregnant women indicate no malformative and foeto/neonatal effect. Epivir can

be used during pregnancy if clinically needed. The malformative risk is unlikely in humans based on those data

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

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

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The following adverse reactions have been reported during therapy for HIV disease with Lamivudine ViiV tablets. With many it is unclear whether they are related to Lamivudine ViiV tablets, other medications taken concurrently or are as a result of the underlying disease process.

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 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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

Nervous system disorders
Common: Headache, insomnia
Very rare: Cases of peripheral neuropathy (or paraesthesia) 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.

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 reconstitution; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

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

Paediatric population

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

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 F05.

Mechanism of action

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

Resistance

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

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

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

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

Clinical efficacy and safety

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

Evidence from clinical studies shows that lamivudine plus zidovudine delays the emergence of zidovudine resistant isolates in individuals with no prior antiretroviral therapy.

Lamivudine has been widely used as a component of antiretroviral combination therapy with other antiretroviral agents of the same class (NRTIs) or different classes (PIs, non-nucleoside reverse transcriptase inhibitors).

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

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

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

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

Paediatric population:

A randomised comparison of a regimen including once daily vs twice daily dosing of abacavir and lamivudine was undertaken within a randomised, multicentre, controlled study of HIV-infected, paediatric patients. 1206 paediatric patients aged 3 months to 17 years enrolled in the ARROW Trial (COL105677) and were dosed according to the weight - band dosing recommendations in the World Health Organisation treatment guidelines (Antiretroviral therapy of HIV infection in infants and children, 2006). After 36 weeks on a regimen including twice daily abacavir and lamivudine, 669 eligible subjects were randomised to either continue twice daily dosing or switch to once daily abacavir and lamivudine for at least 96 weeks. Of note, from this study clinical data were not available for children under one year old. The results are summarised in the table below:

Virological Response Based on Plasma HIV-1 RNA less than 80 copies/ml at Week 48 and Week 96 in the Once Daily versus Twice Daily abacavir + lamivudine randomisation of ARROW (Observed Analysis)

	Twice Daily N (%)	**Once Daily N (%)**
Week 0 (After ≥36 Weeks on Treatment)		
Plasma HIV-1 RNA <80 c/mL	250/331 (76)	237/335 (71)
Risk difference (once daily-twice daily)	-4.8% (95% CI -11.5% to +1.9%), p=0.16	
Week 48		
Plasma HIV-1 RNA <80 c/mL	242/331 (73)	236/330 (72)
Risk difference (once daily-twice daily)	-1.6% (95% CI -8.4% to +5.2%), p=0.65	
Week 96		
Plasma HIV-1 RNA <80 c/mL	234/326 (72)	230/331 (69)
Risk difference (once daily-twice daily)	-2.3% (95% CI -9.3% to +4.7%), p=0.52	

In a pharmacokinetic study (PENTA 15), four virologically controlled subjects less than 12 months of age switched from abacavir plus lamivudine oral solution twice daily to a once daily regimen. Three subjects had undetectable viral load and one had plasmatic HIV-RNA of 900 copies/ml at Week 48. No safety concerns were observed in these subjects.

The abacavir + lamivudine once daily dosing group was demonstrated to be non-inferior to the twice daily group according to the pre-specified non-inferiority margin of -12%, for the primary endpoint of <80 c/mL at Week 48 as well as at Week 96 (secondary endpoint) and all other thresholds tested (<200c/mL, <400c/mL, <1000c/mL), which all fell well within this non-inferiority margin. Subgroup analyses testing for heterogeneity of once vs twice daily demonstrated no significant effect of sex, age, or viral load at randomisation. Conclusions supported non-inferiority regardless of analysis method.

5.2 Pharmacokinetic properties

Absorption

Lamivudine is well absorbed from the gastrointestinal tract, and the bioavailability of oral lamivudine in adults is normally between 80 and 85%. Following oral administration, the mean time (t_{max}) to maximal serum concentrations (C_{max}) is about an hour. Based on data derived from a study in healthy volunteers, at a therapeutic dose of 150mg twice daily, mean (CV) steady-state C_{max} and C_{min} of lamivudine in plasma are 1.2 µg/ml (24%) and 0.09 µg/ml (27%), respectively. The mean (CV) AUC over a dosing interval of 12 hours is 4.7 µg.h/ml (18%). At a therapeutic dose of 300mg once daily, the mean (CV) steady-state C_{max}, C_{min} and 24h AUC are 2.0 µg/ml (26%), 0.04 µg/ml (34%) and 8.9 µg.h/ml (21%), respectively.

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

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

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

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

Distribution

From intravenous studies, the mean volume of distribution is 1.3 l/kg. The observed half-life of elimination is 5 to 7 hours. The mean systemic clearance of lamivudine is approximately 0.32 l/h/kg, with predominantly renal clearance (> 70%) via the organic cationic transport system.

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

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

Biotransformation

The active moiety, intracellular lamivudine triphosphate, has a prolonged terminal half-life in the cell (16 to 19 hours) compared to the plasma lamivudine half-life (5 to 7 hours). In 60 healthy adult volunteers, lamivudine 300 mg once daily has been demonstrated to be pharmacokinetically

equivalent at steady-state to lamivudine 150 mg twice daily with respect to intracellular triphosphate AUC_{24} and C_{max}.

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

Elimination

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

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

Special populations

The absolute bioavailability of lamivudine (approximately 58-66%) was reduced in paediatric patients below 12 years of age. In children, administration of tablets delivered higher plasma lamivudine AUC_{∞} and C_{max} than oral solution. Children receiving lamivudine oral solution according to the recommended dosage regimen achieve plasma lamivudine exposure within the range of values observed in adults. Children receiving lamivudine oral tablets according to the recommended dosage regimen achieve higher plasma lamivudine exposure than children receiving oral solution because higher mg/kg doses are administered with the tablet formulation and the tablet formulation has higher bioavailability (see section 4.2). Paediatric pharmacokinetic studies with both oral solution and tablet formulations have demonstrated that once daily dosing provides equivalent AUC_{0-24} to twice daily dosing of the same total daily dose.

There are limited pharmacokinetic data for patients less than three months of age. In neonates one week of age, lamivudine oral clearance was reduced when compared to paediatric patients and is likely to be due to immature renal function and variable absorption. Therefore to achieve similar adult and paediatric exposure, an appropriate dose for neonates is 4 mg/kg/day. Glomerular filtration estimates suggests that to achieve similar adult and paediatric exposure, an appropriate dose for children aged six weeks and older could be 8 mg/kg/day.

Pharmacokinetic data were derived from 3 pharmacokinetic studies (PENTA 13, PENTA 15 and ARROW PK substudy) enrolling children under 12 years of age. The data are displayed in the table below:

Summary of Stead-State Plasma Lamivudine AUC (0-24) (µg.h/mL) and Statistical Comparisons for Once and Twice-Daily Oral Administration Across Studies

Study	Age Group	Lamivudine 8mg/kg Once-Daily Dosing Geometric Mean (95% Cl)	Lamivudine 4 mg/kg Twice-Daily Dosing Geometric Mean (95% Cl)	Once-Versus Twice-Daily Comparison GLS Mean Ratio (90% Cl)
ARROW PK Substudy Part 1	3 to 12 years (N=35)	13.0 (11.4,14.9)	12.0 (10.7, 13.4)	1.09 (0.979, 1.20)
PENTA 13	2 to 12 years (N=19)	9.80 (8.64, 11.1)	8.88 (7.67, 10.3)	1.12 (1.03, 1.21)
PENTA 15	3 to 36 months (N=17)	8.66 (7.46, 10.1)	9.48 (7.89, 11.40)	0.91 (0.79, 1.06)

In PENTA 15 study, the geometric mean plasma lamivudine AUC(0-24) (95% CI) of the four subjects under 12 months of age who switch from a twice daily to a once daily regimen (see section 5.1) are 10.31 (6.26, 17.0) µg.h/mL in the once-daily dosing and 9.24 (4.66, 18.3) µg.h/mL) in the twice-daily dosing.

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

5.3 Preclinical safety data

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

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core:
Microcrystalline cellulose (E460),

Sodium starch glycollate
Magnesium stearate

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

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

HDPE bottles : 2 years

6.4 Special precautions for storage

Do not store above 30°C

6.5 Nature and content of container

Lamivudine ViiV tablets are available in child resistant HDPE bottles containing 60 tablets.

6.6 Special precautions for disposal

No special requirements for disposal

Any unused 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 manufacturers responsible for batch release

Film-coated tablets:

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

or

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 SUPPLY 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

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

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

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

1. NAME OF THE MEDICINAL PRODUCT

Lamivudine ViiV 150 mg film-coated tablets
Lamivudine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains
lamivudine 150 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

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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 X 60 FILM-COATED TABLETS (150 mg)

1. NAME OF THE MEDICINAL PRODUCT

Lamivudine ViiV 150 mg film-coated tablets
Lamivudine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains
lamivudine 150 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

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Lamivudine ViiV 150 mg film-coated tablets

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 is and what it is used for

Lamivudine ViiV 150 mg film-coated tablets are supplied in white polyethylene bottles containing 60 tablets. They are red, diamond shaped film-coated tablets, marked with the code 'A11' on one side.

Lamivudine 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 is used in antiretroviral combination therapy for the treatment of HIV infection in adults and children. Lamivudine 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. Response to treatment with lamivudine varies between patients. Your doctor will be monitoring the effectiveness of your treatment.

2. What you need to know before you take lamivudine

Do not take lamivudine:

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

If you are not sure please ask your doctor.

Take special care with lamivudine

Discuss the use of lamivudine with your doctor if you have kidney disease. The standard recommended dose of lamivudine may have to be reduced.

The class of medicines to which lamivudine 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, 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 ViiV tablets contain a colouring called sunset yellow (E110), which may cause allergic reactions in some people.

You will need to take lamivudine every day. This medicine helps to control your condition, 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 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, or lamivudine may affect their action. Lamivudine should not be given with:

- other medicinal products containing lamivudine (used to treat HIV infection or hepatitis B infection)

- emtrictabine (used to treat HIV)

high doses of co-trimoxazole.

- cladribine (used to treat hairy cell leukaemia)

Pregnancy
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 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 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

Always take this medicine exactly as your doctor or pharmacist has told you. You should check with your doctor or pharmacist if you are not sure. Swallow lamivudine tablets with water or another drink. The tablets 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.

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

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

For children weighing at least 20 kg and less than 25 kg: the recommended oral dose of Lamivudine ViiV 150 mg tablets is 225 mg a day**.** This can be given as 75 mg (half a 150 mg tablet) in the morning and 150 mg (one whole 150 mg tablet) in the evening, or 225 mg (one and a half 150 mg tablets) once a day as advised by your doctor
Children weighing at least 14 kg and less than 20 kg: the recommended oral dose of Lamivudine ViiV 150 mg tablets is 150 mg a day. This can be given as 75 mg (half a 150 mg tablet) twice a day (leaving approximately 12 hours between each dose), or 150 mg (one 150 mg tablet) once a day as advised by your doctor.

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

If you take more lamivudine than you should
Accidentally taking too much lamivudine 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
If you forget to take a dose of lamivudine, 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, 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.

The most commonly reported (greater than 1 in every 100 patients treated) side effects are nausea, vomiting, stomach pain, diarrhoea, headache, joint pain, muscle disorders, cough, nasal symptoms (irritation, runny nose), fever, tiredness, general feeling of being unwell, skin rash, hair loss and difficulty in sleeping.

The following side effects are uncommon (between 1 in 1,000 and 1 in 100 patients treated); anaemia (low red blood cell count), neutropenia (low white blood cell count), and reductions in platelets (blood cells important for blood clotting). If the number of red blood cells is reduced you may have symptoms of tiredness or breathlessness. A reduction in your white blood cell count can make you more prone to infection. If you have a low platelet count you may notice that you bruise more easily. Increases in some liver enzymes have also been noted in blood samples from patients being treated with lamivudine.

There are rare reports (between 1 in 10,000 to 1 in 1,000 patients treated) of serious allergic reaction causing swelling of the face, tongue or throat which may cause difficulty in swallowing or breathing. Inflammation of the liver (hepatitis), inflammation of the pancreas (pancreatitis), breakdown of muscle tissue.

There are very rare reports (less than 1 in 10,000 patients treated) of numbness, tingling sensation or sensation of weakness in the limbs, and severe anaemia and neutropenia.

Cases of a condition called lactic acidosis, which is a build up of lactic acid in the body, that can cause dehydration and coma have been reported on rare occasions in patients taking NRTIs (see Take special care with lamivudine).

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.

Always tell your doctor or pharmacist about any side effects that occur while taking lamivudine, even those not mentioned in this leaflet.

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

Keep this medicine out of the sight and reach of children

Do not store above 30°C.

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 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 ViiV 150 contains

The active substance in Lamivudine ViiV tablets is called lamivudine. Each film-coated tablet contains 150 mg of lamivudine. The tablets also contain the following other ingredients:

Tablet core: microcrystalline cellulose, sodium starch glycollate (gluten free), magnesium stearate
Film-coat: hypromellose, titanium dioxide, allura red, sunset yellow, polyethylene glycol

What Lamivudine ViiV 150 looks like and contents of the pack

Lamivudine film coated tablets are provided in polyethylene bottles containing 60 tablets. They are red, diamond shaped scored tablets engraved with "A11" 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

This leaflet was last revised in {MMYYYY}