3TC TABLETS
3TC ORAL SOLUTION
Lamivudine (HIV)

QUALITATIVE AND QUANTITATIVE COMPOSITION

3TC TABLETS:

Each film-coated tablet contain 150 mg of lamivudine.

Sugar-free.

3TC ORAL SOLUTION:

Each 1 ml contains 10 mg lamivudine.

Preservatives: methyl hydroxybenzoate 0,15 % m/v, propyl hydroxybenzoate 0,018 % m/v.

Contains sugar (sucrose 20 % m/v).

PHARMACEUTICAL FORM

3TC TABLETS:

White film-coated, diamond shaped scored tablets engraved ‘GX CJ7’ on both faces.

3TC ORAL SOLUTION:

A clear, colourless to pale yellow solution with the odour of fruit.

CLINICAL PARTICULARS

Indications

3TC, in combination with other anti-retroviral agents, is indicated for the treatment of HIV infected adults and children.

Dosage and Administration

3TC therapy should be initiated by a physician experienced in the management of HIV infection.

3TC can be taken with or without food.

To ensure administration of the entire dose, the tablet(s) should ideally be swallowed without crushing. For patients who are unable to swallow tablets, lamivudine is available as an oral solution. Alternatively, the tablets may be crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately (*see Pharmacokinetics*).

- **Adults, adolescents and children weighing at least 25 kg**

The recommended dose of *3TC* is 300 mg daily. This may be administered as 150 mg (15 ml oral solution, 1 x 150 mg tablet) twice daily or 300 mg (30 ml oral solution, 2 x 150 mg tablet) once daily *(see Warnings and Precautions)*.

- **Children aged more than three months and weighing less than 25 kg**

Oral solution

The recommended dose is 0.5 mL/kg (5 mg/kg) twice daily or 1 mL/kg (10 mg/kg) once daily *(see Warnings and Precautions)*.

150 mg scored tablets

Children weighing 14 to < 20 kg:-

The recommended oral dose of 3TC is either one half tablet taken twice daily or one whole tablet taken once daily.

For children weighing ≥ 20 kg to < 25 kg:-

The recommended oral dose of 3TC is either one-half tablet taken in the morning and one whole tablet taken in the evening, or one and a half tablets taken once daily.

Children weighing at least 25 kg:
The adult dosage of 150 mg twice daily or 300 mg once daily should be taken.

Patients changing between lamivudine oral solution and lamivudine tablets should follow the dosing recommendations that are specific for the formulation (*see Pharmacokinetics*).

- **Children less than three months**

The limited data available are insufficient to propose specific dosage recommendations (s*ee Pharmacokinetics*).

- **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.

- **Renal impairment**

Lamivudine plasma concentrations (AUC) are increased in patients with moderate to severe renal impairment due to decreased clearance (*see Pharmacokinetics*). The dosage should therefore be reduced for patients with a creatinine clearance of less than 50 ml/min as shown in the table below.

When doses below 150 mg are required *3TC* oral solution is recommended.

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

Creatinine clearance (ml/min)	First Dose	Maintenance Dose
30 to less than 50	150 mg (15 ml)	150 mg (15 ml) once daily
15 to less than 30	150 mg (15 ml)	100 mg (10 ml) once daily
5 to less than 15	150 mg (15 ml)	50 mg (5 ml) once daily
less than 5	50 mg (5 ml)	25 mg (2.5 ml) once daily

There are no data available on the use of lamivudine in children with renal impairment.

A reduction in the dose and/or increase in the dosing interval should be considered in children aged at least three months and weighing less than 25 kg.

The same percentage reduction in the adult dose is recommended for paediatric patients with renal impairment.

Dosing Recommendations - Children aged more than three months and weighing less than 25 kg

Creatinine clearance (ml/min)	First Dose	Maintenance Dose
30 to less than 50	5 mg/kg	5 mg/kg once daily
15 to less than 30	5 mg/kg	3.25 mg/kg once daily
5 to less than 15	5 mg/kg	1.63 mg/kg once daily
less than 5	1.63 mg/kg	0.88 mg/kg once daily

- **Hepatic impairment**

No dose adjustment is necessary in patients with moderate or severe hepatic impairment unless accompanied by renal impairment (*see Pharmacokinetics*).

Contraindications

The use of *3TC* is contraindicated in patients with known hypersensitivity to lamivudine or to any ingredient of the preparation.

Warnings and Precautions

3TC is not recommended for use as monotherapy.

Patients should be advised that current antiretroviral therapy, including *3TC*, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Patients receiving *3TC* or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore they should remain under close clinical observation by physicians experienced in the treatment of patients with associated HIV diseases.

Renal impairment

Lamivudine plasma concentrations (AUC) are increased in patients with moderate to severe renal impairment due to decreased clearance. The dose should therefore be adjusted (s*ee Dosage and Administration*).

Pancreatitis

Pancreatitis has been observed in some patients receiving *3TC*. However, it is unclear whether this was due to treatment with the medicinal product or to the underlying HIV disease. Pancreatitis must be considered whenever a patient develops abdominal pain,

nausea, vomiting or elevated biochemical markers. Discontinue use of *3TC* until diagnosis of pancreatitis is excluded.

Lactic acidosis/severe hepatomegaly with steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues either alone or in combination, including *3TC*. A majority of these cases have been in women.

Clinical features which may be indicative of the development of lactic acidosis include generalised weakness, anorexia, and sudden unexplained weight loss, gastrointestinal symptoms and respiratory symptoms (dyspnoea and tachypnoea).

Caution should be exercised when administering *3TC* particularly to those with known risk factors for liver disease. Treatment with *3TC* should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis with or without hepatitis (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Serum lipids and blood glucose

Serum lipid and blood glucose levels may increase during antiretroviral therapy Disease control and life style changes may also be contributing factors. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

Immune Reconstitution Syndrome

In HIV-infected patients with severe immune deficiency at the time of initiation of anti-retroviral therapy (ART), an inflammatory reaction to asymptomatic or residual opportunistic infections 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 ART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and *Pneumocystis jiroveci* pneumonia (often referred to as PCP). Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary. Autoimmune disorders (such as Graves' disease, polymyositis and Guillain-Barre syndrome) have also been reported to occur in the setting of immune reconstitution, however the time to onset is more variable, and can occur many months after initiation of treatment and sometimes can be an atypical presentation.

Patients co-infected with Hepatitis B virus

Clinical trial and marketed use of *3TC*, have shown that some patients with chronic hepatitis B virus (HBV) disease may experience clinical or laboratory evidence of recurrent hepatitis upon discontinuation of *3TC*, which may have more severe consequences in patients with decompensated liver disease. If *3TC* is discontinued in a patient with HIV and HBV coinfection, periodic monitoring of both liver function tests and markers of HBV replication should be considered.

Oral solution:

Diabetic patients should be advised that an adult dose contains 3 g of sucrose.

Special patient population

Children

Children who at any time received *3TC* oral solution concomitantly with other antiretroviral oral solutions in clinical trials experienced lower rates of virological suppression, had lower plasma lamivudine exposure and developed viral resistance more frequently than children receiving tablets (*see Clinical Studies and Pharmacokinetics*).

An all tablet regimen should be used when possible. *3TC* oral solution given concomitantly with sorbitol-containing medicines should be used only when an all-tablet regimen cannot be used and the benefits of treatment outweigh possible risks including lower virological suppression. Consider more frequent monitoring of HIV-1 viral load when *3TC* is used with chronically-administered, sorbitol-containing medicines *(see Interactions).*

Interactions

The likelihood of interactions is low due to limited metabolism and plasma protein binding and almost complete renal elimination of unchanged lamivudine.

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

Active substances shown to be predominately excreted either via the active organic anionic pathway, or by glomerular filtration are unlikely to yield clinically significant interactions with lamivudine.

Effect of lamivudine on the pharmacokinetics of other agents

In vitro, lamivudine demonstrates no or weak inhibition of the drug transporters organic anion transporter 1B1 (OATP1B1), OATP1B3, breast cancer resistance protein (BCRP) or P-glycoprotein (Pgp), multidrug and toxin extrusion protein 1 (MATE1), MATE2-K or organic cation transporter 3 (OCT3). *3TC* is therefore not expected to affect the plasma concentrations of drugs that are substrates of these drug transporters.

Lamivudine is an inhibitor of OCT1 and OCT2 In vitro with IC50 values of 17 and 33 uM, respectively, however lamivudine has low potential to affect the plasma concentrations of OCT1 and OCT2 substrates at therapeutic drug exposures (up to 300 mg).

Effect of other agents on the pharmacokinetics of lamivudine

Lamivudine is a substrate of MATE1, MATE2-K and OCT2 *in vitro*. Trimethoprim (an inhibitor of these drug transporters) has been shown to increase lamivudine plasma concentrations, however this interaction is not considered clinically significant as no dose adjustment of *3TC* is needed.

Lamivudine is a substrate of the hepatic uptake transporter OCT1. As hepatic elimination plays a minor role in the clearance of lamivudine, drug interactions due to inhibition of OCT1 are unlikely to be of clinical significance.

Lamivudine is a substrate of Pgp and BCRP, however due to its high bioavailability it is unlikely that these transporters play a significant role in the absorption of lamivudine. Therefore co-administration of drugs that are inhibitors of these efflux transporters is unlikely to affect the disposition and elimination of lamivudine.

Interactions relevant to lamivudine

Sorbitol: Coadministration of sorbitol solution (3.2 g, 10.2 g, 13.4 g) with a single 300 mg dose of lamivudine oral solution resulted in dose-dependent decreases of 14%, 32%, and 36% in lamivudine exposure (AUC_{∞}) and 28%, 52%, and 55% in the C_{max} of lamivudine in adults. When possible, avoid use of *3TC* with sorbitol-containing medicines or consider more frequent monitoring of HIV-1 viral load when chronic coadministration cannot be avoided *(see Warnings and Precautions).*

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

Trimethoprim/sulphamethoxazole: Administration of trimethoprim/sulphamethoxazole 160 mg/800 mg (co-trimoxazole) causes a 40% increase in lamivudine exposure because of the trimethoprim component. However, unless the patient has renal impairment, no dosage adjustment of *3TC* is necessary (*see Dosage and Administration*). Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulphamethoxazole. The effect of co-administration of *3TC* with higher doses of co-trimoxazole for the treatment of *Pneumocystis jiroveci* pneumonia and toxoplasmosis has not been studied.

Emtricitabine: 3TC may inhibit the intracellular phosphorylation of emtricitabine when the two medicinal products are used concurrently. Additionally, the mechanism of viral resistance for both *3TC* and emtricitabine is mediated via mutation of the same viral reverse transcriptase gene (M184V) and therefore the therapeutic efficacy of these drugs in combination therapy may be limited. *3TC* is not recommended for use in combination with emtricitabine or emtricitabine-containing fixed dose combinations.

Pregnancy and Lactation

Lamivudine has been evaluated in the Antiretroviral Pregnancy Registry in over 11,000 women during pregnancy and postpartum. Available human data from the Antiretroviral Pregnancy Registry do not show an increased risk of major birth defects for lamivudine compared to the background rate (*see Clinical Studies*). However, there are no adequate and well-controlled trials in pregnant women and the safe use of lamivudine in human pregnancy has not been established.

Studies in humans have confirmed that lamivudine crosses the placenta. Use in pregnancy should be considered only if the benefit outweighs the risk. Although the results of animal studies (*see Pre-clinical Safety Data*) are not always predictive of human response, the findings in the rabbit suggest a potential risk of early embryonic loss.

There have been reports of mild, transient elevations in serum lactate levels, which may be due to mitochondrial dysfunction, in neonates and infants exposed *in utero* or peri-partum to nucleoside reverse transcriptase inhibitors (NRTIs). The clinical relevance of transient elevations in serum lactate is unknown. There have also been very rare reports of developmental delay, seizures and other neurological disease. However, a causal relationship between these events and NRTI exposure *in utero* or peri-partum has not been established. These findings do not affect current recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Health experts recommend that where possible women infected with HIV do not breast feed their infants in order to avoid the transmission of HIV. In settings where formula feeding is not feasible, local official lactation and treatment guidelines should be followed when considering breast feeding during antiretroviral therapy.

In a study following repeat oral dose of either 150 mg lamivudine twice daily (given in combination with 300 mg zidovudine twice daily) or 300 mg lamivudine twice daily, lamivudine was excreted in human breast milk (0.5 to 8.2 micrograms/ml) at similar concentrations to those found in serum. In other studies following repeat oral dose of 150 mg lamivudine twice daily (given either in combination with 300 mg zidovudine or as Combivir or Trizivir) the breast milk:maternal plasma ratio ranged between 0.6 and 3.3. Lamivudine median infant serum concentrations ranged between 18 and 28 ng/mL and were not detectable in one of the studies (assay sensitivity 7 ng/mL). Intracellular lamivudine triphosphate (active metabolite of lamivudine) levels in the breastfed infants were not measured therefore the clinical relevance of the serum concentrations of the parent compound measured is unknown.

Effects on Ability to Drive and Use Machines

There have been no studies to investigate the effect of *3TC* on driving performance or the ability to operate machinery. Further, a detrimental effect on such activities cannot be predicted from the pharmacology of lamivudine. Nevertheless, the clinical status of the patient and the adverse event profile of *3TC* should be borne in mind when considering the patient's ability to drive or operate machinery.

Adverse Reactions

The following events have been reported during therapy for HIV disease with *3TC* alone and in combination with other anti-retroviral agents. With many it is unclear whether they are related to the medicinal products or are as a result of the underlying disease process.

The following convention has been utilised for the classification of undesirable effects: very common (>1/10), common (>1/100, <1/10), uncommon (>1/1,000, <1/100), rare (>1/10,000, <1/1,000) very rare (<1/10,000).

Blood and lymphatic systems disorders

Uncommon: Neutropenia, anaemia, thrombocytopenia.

Very rare: Pure red cell aplasia

Metabolism and nutrition disorders

Common: Hyperlactataemia.

Rare: Lactic acidosis (*see Warnings and Precautions*)

Nervous system disorders

Common: Headache.

Very rare: Paraesthesia. Peripheral neuropathy has been reported although a causal relationship to treatment is uncertain.

Gastrointestinal disorders

Common: Nausea, vomiting, upper abdominal pain, diarrhoea.

Rare: Pancreatitis, although a causal relationship to treatment is uncertain. Rises in serum amylase.

Hepatobiliary disorders

Uncommon: Transient rises in liver enzymes (AST, ALT).

Skin and subcutaneous tissue disorders

Common: Rash, alopecia.

Musculoskeletal and connective tissue disorders

Common: Arthralgia, muscle disorders.

Rare: Rhabdomyolysis.

General disorders and administration site conditions

Common: Fatigue, malaise, fever.

Paediatric population

The safety database to support lamivudine once daily dosing in paediatric patients comes from the ARROW Trial (COL105677) in which 669 HIV-1 infected paediatric subjects received abacavir and lamivudine either once or twice daily (*see Clinical Studies*). No additional safety issues have been identified in paediatric subjects receiving either once or twice daily dosing compared to adults.

Overdose

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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Pharmacotherapeutic group - nucleoside analogue; ATC Code: J05 AF05.

Lamivudine is a potent, selective inhibitor of HIV-1 and HIV-2 replication *in vitro*. It is also active against zidovudine-resistant clinical isolates of HIV. Lamivudine is metabolised intracellularly to the 5'-triphosphate, the active moiety, which has an intra-cellular half-life of 16 to 19 h. Lamivudine 5'-triphosphate is a weak inhibitor of the RNA and DNA dependant activities of HIV reverse transcriptase, its main mode of action is as a chain terminator of HIV reverse transcription. No antagonistic effects *in vitr*o were seen with lamivudine and other anti retrovirals (tested agents: abacavir, didanosine, nevirapine, zalcitabine, and zidovudine).

Lamivudine does not interfere with cellular deoxynucleotide metabolism and has little effect on mammalian cell and mitochondrial DNA content.

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

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.

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 less than 4-fold decrease in susceptibility to didanosine and zalcitabine; the clinical significance of these findings is unknown. *In vitro* susceptibility testing has not been standardised and results may vary according to methodological factors.

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

Reduced *in vitro* sensitivity to lamivudine has been reported for HIV isolates from patients who have received *3TC* therapy.

Evidence from clinical studies show that lamivudine plus zidovudine delays the emergence of zidovudine-resistant isolates in individuals with no prior anti-retroviral therapy.

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

Clinical trial evidence from paediatric patients receiving *3TC* with other antiretroviral drugs (abacavir, nevirapine/efavirenz or zidovudine) has shown that the resistance profile observed in paediatric patients is similar to that observed in adults, in terms of the genotypic substitutions detected and their relative frequency.

Children receiving *3TC* oral solution concomitantly with other antiretroviral oral solutions in clinical trials developed viral resistance more frequently than children receiving tablets (*see Clinical Studies and Pharmacokinetics*).

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 the clinical response to therapy remain under investigation.

Post-exposure prophylaxis (PEP):

Internationally recognised guidelines (Centre for Disease Control and Prevention - June 1998), recommend that in the event of accidental exposure to HIV infected blood e.g. from a needlestick injury, a combination of zidovudine and lamivudine should be administered promptly (within 1 to 2 h). In cases of higher risk of infection, a protease inhibitor should be included in the regimen. It is recommended that antiretroviral prophylaxis be continued for four weeks. No controlled clinical studies have been carried out in post-exposure prophylaxis and supporting data is limited. Seroconversion may still occur despite prompt treatment with antiretroviral agents.

Pharmacokinetics

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. At therapeutic dose levels i.e. 4 mg/kg/day (as two 12-hourly doses), C_{max} is in the order of 1 to 1.9 micrograms/ml.

Co-administration of lamivudine with food resulted in a delay of t_{max} and a lower C_{max} (decreased by up to 47%). However, the extent (based on the AUC) of lamivudine absorbed was not influenced. No dose adjustment is needed when co-administered with 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 the physicochemical and pharmacokinetic characteristics of the active ingredient and the *in vitro* dissolution behaviour of lamivudine tablets in water, assuming that the patient crushes and transfers 100% of the tablet and ingests immediately.

Tablets:

Administration of two 150 mg tablets is bioequivalent to administration of one 300 mg tablet with respect to AUC_{∞}, C_{max}, and t_{max}. Administration of tablets is bioequivalent to oral solution with respect to AUC_{∞} and C_{max} in adults. Absorption differences have been observed between adult and pediatric populations (see special patient populations/children).

Distribution

From i.v. studies, the mean volume of distribution is 1.3 l/kg and the mean terminal half-life of elimination is 5 to 7 h.

Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays low plasma protein binding to albumin.

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

Metabolism and Elimination

Lamivudine mean systemic clearance is approximately 0.32 l/h/kg, with predominantly renal clearance (greater than 70%) via the organic cationic transport system, and little (less than 10%) hepatic metabolism.

The active moiety, intracellular lamivudine triphosphate, has a prolonged terminal half-life in the cell (16 to 19 h) compared to the plasma lamivudine half-life (5 to 7 h). 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 $C_{max.}$

The likelihood of adverse interactions between lamivudine and other medicinal products is low due to limited metabolism and plasma protein binding and almost complete renal elimination of unchanged lamivudine.

Special Patient Populations

- **Children**

The absolute bioavailability of lamivudine (approximately 58 to 66%) was lower and more variable in paediatric patients under 12 years of age. In children, administration of tablets given concomitantly with other antiretroviral tablets delivered higher plasma lamivudine AUC_{∞} and C_{max} than oral solution given concomitantly with other antiretroviral oral solutions. Children receiving *3TC* oral solution according to the recommended dosage regimen achieve plasma lamivudine exposure within the range of values observed in adults. Children receiving *3TC* 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 Dosage and Administration*). 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, the recommended dose for neonates is 2 mg/kg twice a day. However, there is no data available in neonates older than one week old.

Elderly

No pharmacokinetic data are available in patients over 65 years of age.

Renal impairment

Lamivudine plasma concentrations (AUC) are increased in patients with renal dysfunction due to decreased clearance. The dosage should therefore be reduced for patients with a creatinine clearance of less than 50 ml/min (s*ee Dosage and Administration*).

Hepatic impairment

Data obtained in patients with moderate to severe hepatic impairment show that lamivudine pharmacokinetics are not significantly affected by hepatic dysfunction.

Pregnancy

The pharmacokinetics of lamivudine are similar to that of non-pregnant adults. In humans, consistent with passive transmission of lamivudine across the placenta, lamivudine concentrations in infant serum at birth were similar to those in maternal and cord serum at delivery.

Clinical Studies

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. 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	

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

At the time of randomization to once daily vs twice daily dosing (Week 0), those patients who had received tablet formulations had a higher rate of viral load suppression than those who had received any solution formulations at any time. These differences were observed in each different age group studied. This difference in suppression rates between tablets and solutions remained through Week 96 with once daily dosing.

Proportions of Subjects in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW with Plasma HIV-1 RNA <80 copies/mL: Subgroup Analysis by Formulation

	Twice Daily Plasma HIV-1 RNA <80 c/mL: n/N (%)	Once Daily Plasma HIV-1 RNA <80 c/mL: n/N (%)
Week 0 (after 36 weeks on Treatment)		
Any solution regimen at any time	14/26 (54)	15/30 (50)
All tablet based regimen throughout	236/305 (77)	222/305 (73)
Week 96		
Any solution regimen at any time	13/26 (50)	17/30 (57)
All tablet based regimen throughout	221/300 (74)	213/301 (71)

Genotypic resistance analyses were conducted on samples with plasma HIV-1 RNA >1000 copies/ml. More cases of resistance were detected among patients who had received *3TC* solution, in combination with other antiretroviral solutions, compared with those who received similar doses tablet formulation. This is consistent with the lower rates of antiviral suppression observed in these patients.

The Antiretroviral Pregnancy Registry has received reports of over 11,000 exposures to lamivudine during pregnancy resulting in live birth. These consist of over 4,200 exposures during the first trimester, over 6, 900 exposures during the second/third trimester and included 135 and 198 birth defects respectively. The prevalence (95% CI) of defects in the first trimester was 3.2% (2.6, 3.7%) and in the second/third trimester, 2.8% (2.4, 3.2%). Among pregnant women in the reference population, the background rate of birth defects is 2.7%. The Antiretroviral Pregnancy Registry does not show an increased risk of major birth defects for lamivudine compared to the background rate.

Pre-clinical Safety Data

- **Carcinogenesis, mutagenesis**

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 to 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 *3TC* should not represent a genotoxic hazard to patients undergoing treatment.

The results of long term oral carcinogenicity studies with lamivudine in rats and mice did not show any carcinogenic potential.

- **Reproductive toxicology**

Reproductive studies in animals have not shown evidence of teratogenicity, and showed no effect on male or female fertility. Lamivudine produced small increases in early embryonic loss when administered to pregnant rabbits, at exposure levels comparable to

those achieved in man. However, there was no evidence of embryonic loss in rats at exposure levels of approximately 35 times the clinical exposure (based on C_{max}).

- **Animal toxicology**

Administration of lamivudine in animal toxicity studies at very high doses was not associated with any major organ toxicity. Reductions of erythrocyte and neutrophil counts were identified as the effects most likely to be of clinical relevance.

PHARMACEUTICAL PARTICULARS

List of Excipients

3TC TABLETS:

Tablet core: microcrystalline cellulose, sodium starch glycollate Type A, magnesium stearate.

White tablet film coat: hydroxypropylmethyl cellulose, titanium dioxide, black iron oxide (E172) (300mg tablet only), macrogol, polysorbate 80.

Red tablet film coat: opadry red: Hydroxypropylmethyl cellulose, titanium dioxide, polyethylene glycol, allura red, sunset yellow

3TC ORAL SOLUTION:

Sucrose (20% w/v)
Methyl hydroxybenzoate
Propyl hydroxybenzoate
Citric acid anhydrous
Propylene glycol
Sodium citrate
Artificial strawberry flavour
Artificial banana flavour
Water (purified).

Incompatibilities

None reported.

Shelf Life

The expiry date is indicated on the packaging.

Special Precautions for Storage

Keep out of reach of children.

Do not store *3TC* oral solution above 25°C. Discard *3TC* oral solution one month after first opening.

Do not store *3TC* tablets above 30°C.

Nature and Contents of Container

3TC TABLETS:

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

3TC ORAL SOLUTION:

Cartons containing a white high density polyethylene (HDPE) bottle, with a child resistant cap and dosing device.

The bottle contains 240 ml (10 mg/ml) of lamivudine solution for oral use only.

Instructions for Use/Handling

Where supplied, the oral dosing syringe should be used for accurate measurement of the prescribed dose of *3TC* oral solution.

1. Remove the bottle cap.
2. Push the plastic adapter into the neck of the bottle, while holding the bottle firmly.
3. Insert the syringe firmly into the adapter.
4. Invert bottle.
5. Pull out syringe plunger until the correct amount is withdrawn.
6. Turn the bottle the correct way up and remove the syringe from the adapter.
7. Replace and tighten the bottle cap.
8 Administer the dose into the mouth by placing the tip of the syringe against the inside of the cheek. Slowly depress the plunger, allowing time to swallow. Forceful squirting to the back of the throat may cause choking.

9. After use the syringe must not be left in the bottle and should be washed thoroughly in clean water.

Name and address of the holder of the certificate of registration

GlaxoSmithKline South Africa (Pty) Ltd

57 Sloane Street

Bryanston, 2021

South Africa

Manufacturer

3TC TABLETS:

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

3TC ORAL SOLUTION:

GlaxoSmithKline Inc., 7333 Mississauga Road North, Mississauga, Ontario L5N 6L4, Canada

Registration details

Botswana:

3TC TABLETS - Reg No BOT9800150 S2

3TC ORAL SOLUTION - Reg No BOT9800149 S2

Malawi:

3TC TABLETS - Reg No PMPB/PL270/32 POM

3TC ORAL SOLUTION - Reg No PMPB/PL270/31 POM

Namibia:

3TC TABLETS - Reg No 04/20.2.8/0937 NS2

3TC ORAL SOLUTION - Reg No 04/20.2.8/0938 NS2

Zambia:

3TC TABLETS - Reg No 179/007 POM

3TC ORAL SOLUTION - Reg No 179/006 POM

Zimbabwe:

3TC TABLETS - Reg No 97/7.13/3278 PP

3TC ORAL SOLUTION - Reg No 97/7.13/3279 PP

Version number: GDS24/IPI12

Date of issue: 14 May 2018