# *3TC*
## Lamivudine

**QUALITATIVE AND QUANTITATIVE COMPOSITION**
*3TC* film coated tablets contain 150 mg of lamivudine. 150 mg tablets are white, diamond shaped, scored and engraved with the code “GX CJ7” on both faces.

**CLINICAL INFORMATION**
**Indications**
*3TC*, in combination with other antiretroviral agents, is indicated for the treatment of HIV infected adults and children.

**Dosage and Administration**
Film coated tablets.

*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. 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 (1 x 150 mg tablet) twice daily or 300 mg (2 x 150 mg tablet) once daily (*see Warnings and Precautions*).

**Children aged ≥ three months and weighing less than 25 kg**
- **Children weighing 14 to <20 kg:**

The recommended oral dose of *3TC* is either one-half (75 mg) 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 (75 mg) tablet taken in the morning and one whole tablet taken in the evening.

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

**Children less than three months**
The limited data available are insufficient to propose specific dosage recommendations (*see 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. The same percentage reduction in dose applies for paediatric patients with renal impairment.

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

**Dosing Recommendations - Adult, adolescents and children weighing at least 25 kg**

| Creatinine Clearance (mL/min) | First Dose | Maintenance Dose |
|---|---|---|
| 30 to less than 50 | 150 mg | 150 mg once daily |
| 15 to less than 30 | 150 mg | 100 mg once daily |
| 5 to less than 15 | 150 mg | 50 mg once daily |
| less than 5 | 50 mg | 25 mg once daily |

**Dosing Recommendations - Children aged more than 3 months and weighing less than 25 kg**

| Creatinine Clearance (mL/min) | First Dose | Maintenance Dose |
|---|---|---|
| 30 to less than 50 | 4 mg/kg | 4 mg/kg once daily |
| 15 to less than 30 | 4 mg/kg | 2.6 mg/kg once daily |
| 5 to less than 15 | 4 mg/kg | 1.3 mg/kg once daily |
| less than 5 | 1.3 mg/kg | 0.7 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 (*see 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 lifestyle 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 antiretroviral 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 Grave's disease, polymyositis and Guillain-Barré 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 co-infection, periodic monitoring of both liver function tests and markers of HBV replication should be considered.

**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 $IC_{50}$ values of 17 and 33 µM, 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:* Co-administration 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 ($AUC_{\infty}$) 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 co-administration 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**
**Fertility**
No text.

**Pregnancy**
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%. Available human data from the Antiretroviral Pregnancy Registry does not show a significantly higher risk of major birth defects for lamivudine compared to the background rate. 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 Non-Clinical Information*) 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.

**Lactation**
Health experts recommend that where possible women infected with HIV do not breastfeed 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 breastfeeding 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 antiretroviral 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**
**Symptoms and signs**
No specific signs or symptoms have been identified following acute overdose with lamivudine, apart from those listed as undesirable effects.

**Treatment**
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 A F05.

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 intracellular 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 vitro* were seen with lamivudine and other antiretrovirals (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 antiretroviral 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.

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 $AUC_{\infty}$, $C_{max}$, and $t_{max}$. Administration of tablets is bioequivalent to oral solution with respect to $AUC_{\infty}$ and $C_{max}$ in adults. Absorption differences have been observed between adult and paediatric populations (*see Special Patient Populations/Children*).

**Distribution**
From i.v. studies, the mean volume of distribution is 1.3 L/kg.

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 plasma lamivudine half-life after oral dosing is (18 to 19 h) and the active moiety, intracellular lamivudine triphosphate, has a prolonged terminal half-life in the cell (16 to 19 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 $AUC_{\infty}$ and $C_{max}$ than oral solution given concomitantly with other antiretroviral oral solutions. 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 $AUC_{0\text{-}24}$ 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 (*see 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. 1,206 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 (<200 c/mL, <400 c/mL, <1,000 c/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 randomisation 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 >1,000 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.

**Non-Clinical Information**

**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 INFORMATION**

**List of Excipients**

Tablet core: microcrystalline cellulose, sodium starch glycollate Type A, magnesium stearate.
White tablet film coat: opadry white YS-1-7706-G (hypromellose, titanium dioxide, macrogol 400, polysorbate 80) and purified water.

**Shelf Life**

The expiry date is indicated on the packaging.

**Storage**

Store below 30°C.

**Nature and Contents of Container**

A white high-density polyethylene (HDPE) bottle, with a child-resistant/tamper evident closure.

**Incompatibilities**

None reported.

**Use and Handling**

There are no special requirements for use or handling for this formulation.

**HARUS DENGAN RESEP DOKTER**

*3TC* Tablet 150 mg, Box, bottle @ 60 film coated tablets Reg. No. DKI1833900417A1

Manufactured by:
Delpharm Poznań Spółka Akcyjna
Poznań, Poland

Imported by:
PT Glaxo Wellcome Indonesia
Jakarta, Indonesia

Version number: GDS26/IPI14 – *Manufacturer name change (Project PINE)*
Date of issue: 27 May 2022

**INFORMASI UNTUK PASIEN**

# *3TC* Tablet Salut Selaput
## Lamivudine 150 mg

**Baca keseluruhan brosur ini secara teliti sebelum Anda mulai menggunakan obat ini karena mengandung informasi penting untuk Anda.**

- Simpan brosur ini. Anda mungkin perlu membacanya kembali.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan pada dokter, perawat atau apoteker.
- Obat ini hanya diresepkan untuk Anda. Jangan diberikan kepada orang lain. Hal tersebut dapat membahayakan mereka, meskipun gejala penyakit mereka sama dengan gejala Anda.
- Jika Anda merasakan efek samping, konsultasikan dengan dokter, perawat atau apoteker. Hal ini termasuk kemungkinan efek samping lain yang tidak tertulis dalam brosur ini. *Lihat Bagian 4.*

**Apa Saja yang Ada dalam Brosur Ini:**



### 1. Apa itu *3TC* dan digunakan untuk apa

***3TC* digunakan untuk mengobati infeksi HIV (*Human Immunodeficiency Virus)* pada pasien dewasa dan anak.**

*3TC* mengandung zat aktif lamivudine, yang mana masuk ke dalam kelompok obat antiretrovirus dan bekerja sebagai *nucleoside analogue reverse transcriptase inhibitors (NRTIs).*

*3TC* tidak sepenuhnya menyembuhkan infeksi HIV; *3TC* mengurangi jumlah virus dalam tubuh Anda, dan menjaganya pada tingkat yang rendah. *3TC* juga meningkatkan jumlah sel CD4 dalam darah Anda. Sel CD4 adalah jenis sel darah putih yang penting dalam membantu tubuh Anda melawan infeksi.

Tidak semua orang memberikan respon dengan cara yang sama terhadap pengobatan dengan *3TC*. Dokter Anda akan memantau efektivitas pengobatan Anda.

### 2. Apa yang perlu Anda ketahui sebelum menggunakan *3TC*

**Jangan gunakan *3TC***:

- Jika Anda **alergi** terhadap lamivudine atau salah satu bahan obat ini (*Lihat Bagian 6*).

**Konsultasikan dengan dokter Anda** jika ini berlaku untuk Anda.

**Perhatian khusus dan pencegahan**

Beberapa orang yang menggunakan *3TC* atau kombinasi pengobatan lainnya untuk HIV lebih berisiko terhadap efek samping yang serius. Anda perlu mewaspadai risiko tambahan:

- Jika Anda pernah menderita **penyakit hati**, termasuk hepatitis B (jika Anda memiliki infeksi hepatitis B, jangan menghentikan penggunaan *3TC* tanpa saran dari dokter Anda, karena hepatitis Anda dapat kambuh).
- **Jika Anda atau anak Anda memiliki masalah ginjal**, dosis Anda dapat diubah.

**Konsultasikan dengan dokter Anda jika hal tersebut berlaku untuk Anda**. Anda mungkin memerlukan pemeriksaan tambahan, termasuk tes darah, saat Anda menggunakan obat. **Lihat Bagian 4 untuk informasi lebih lanjut.**

**Waspadai gejala penting**

Beberapa orang yang menggunakan obat untuk infeksi HIV mengalami kondisi lain yang bisa menjadi serius. Anda harus mengetahui tanda dan gejala yang penting untuk diwaspadai saat Anda mengunakan *3TC*.

**Baca informasi "Kemungkinan efek samping lain dari terapi kombinasi untuk HIV" pada Bagian 4 dalam leaflet ini.**

**Lindungi orang lain**
Infeksi HIV disebarkan melalui hubungan seksual dengan seseorang yang terinfeksi, atau melalui perpindahan darah yang terinfeksi (misalnya, dengan berbagi jarum suntik). Anda masih bisa menularkan HIV saat menggunakan obat ini, meskipun risikonya akan berkurang dengan terapi antiretrovirus yang efektif.

Diskusikan dengan dokter Anda mengenai pencegahan yang dibutuhkan untuk menghindari penularan kepada orang lain.

**Obat lain dan *3TC***
**Beritahu dokter atau apoteker Anda jika Anda menggunakan obat lain** atau jika Anda telah menggunakannya baru-baru ini, termasuk obat-obatan herbal atau obat lain yang Anda beli tanpa resep.

Ingatlah untuk memberitahu dokter dan apoteker Anda jika Anda mulai menggunakan obat baru bersamaan saat Anda menggunakan *3TC*.

**Obat-obatan yang tidak boleh digunakan bersamaan dengan *3TC***
- Obat (biasanya berbentuk cairan) yang mengandung sorbitol dan bentuk alkohol dari gula lainnya (seperti xylitol, mannitol, lactitol atau maltitol), jika digunakan secara teratur.
- Obat lain yang mengandung lamivudine (digunakan untuk mengobati **infeksi HIV** atau **infeksi hepatitis B**).
- Emtricitabine (digunakan untuk mengobati **infeksi HIV**).
- **Cotrimoxazole** dosis tinggi, merupakan sebuah antibiotik.

**Beritahu dokter Anda** jika Anda sedang dirawat menggunakan salah satu obat di atas.

**Kehamilan**
Jika Anda sedang hamil, curiga mungkin hamil atau berencana untuk hamil, konsultasikan dengan dokter Anda mengenai risiko dan manfaat bagi Anda dan bayi Anda jika Anda menggunakan *3TC*.

*3TC* dan obat-obatan serupa dapat mengakibatkan efek samping pada bayi yang belum lahir. Jika Anda telah menggunakan *3TC* selama kehamilan Anda, dokter Anda mungkin meminta tes darah rutin dan tes diagnostik lainnya untuk memantau perkembangan anak Anda. Pada anak yang ibunya menggunakan *NRTIs* selama kehamilan, manfaat dari pelindungan terhadap HIV lebih besar daripada risiko efek sampingnya.

**Menyusui**
**Wanita yang positif HIV tidak boleh menyusui**, karena infeksi HIV dapat ditularkan kepada bayi melalui ASI.

Sejumlah kecil bahan dalam *3TC* juga dapat masuk ke dalam ASI Anda. Jika Anda menyusui atau berpikir untuk menyusui: **Bicaralah segera dengan dokter Anda**.

**Mengemudi dan menggunakan mesin**
*3TC* cenderung tidak mempengaruhi kemampuan Anda untuk mengemudi atau menggunakan mesin.

## 3. Cara menggunakan *3TC*

**Selalu gunakan obat ini sesuai saran dokter atau apoteker kepada Anda**. Konsultasikan dengan dokter atau apoteker jika Anda tidak yakin.

Telan tablet menggunakan air. *3TC* dapat diminum bersama dengan makanan atau dalam keadaan perut kosong.

Jika Anda tidak dapat menelan tablet secara utuh, Anda boleh menghancurkan tablet dan menggabungkannya dengan sedikit makanan atau minuman, dan segera minum semua dosis tersebut.

**Tetap lakukan komunikasi secara teratur dengan dokter Anda**
*3TC* membantu mengontrol kondisi Anda. Anda harus terus menggunakannya setiap hari untuk mencegah penyakit Anda memburuk. Anda mungkin masih mengalami infeksi dan penyakit lain yang terkait dengan infeksi HIV.

**Tetap lakukan komunikasi dengan dokter Anda dan jangan menghentikan penggunaan *3TC*** tanpa saran dari dokter Anda.

**Dosis yang dianjurkan**
**Dewasa, remaja dan anak-anak dengan berat badan minimal 25 kg:**
**Dosis *3TC* yang direkomendasikan adalah 300 mg sehari.** Ini dapat diberikan dengan cara meminum 1 tablet 150 mg sebanyak dua kali sehari (dengan jarak 12 jam setelah dosis pertama), atau dua tablet 150 mg sekali sehari sesuai dengan yang disarankan oleh dokter Anda.

**Anak-anak dengan umur ≥ tiga bulan dan berat badan kurang dari 25 kg:**
- **Anak dengan berat badan 14 hingga <20 kg**

**Dosis *3TC* yang direkomendasikan adalah 150 mg sehari.** Ini dapat diberikan dengan cara meminum tablet 75 mg (setengah tablet 150 mg) sebanyak dua kali sehari (dengan jarak 12 jam setelah dosis pertama), atau 150 mg (satu tablet 150 mg) sekali sehari sesuai dengan yang disarankan oleh dokter Anda.

- **Anak dengan berat badan ≥20 kg hingga <25 kg**

**Dosis *3TC* yang direkomendasikan adalah 225 mg sehari.** Ini dapat diberikan dengan cara meminum tablet 75 mg (setengah tablet 150 mg) di pagi hari dan 150 mg (satu tablet 150 mg utuh) di malam hari sesuai dengan yang disarankan oleh dokter Anda.

**Anak-anak dengan berat badan minimal 25 kg**
Gunakan dosis dewasa 150 mg dua kali sehari atau 300 mg satu kali sehari.

**Anak dengan umur di bawah tiga bulan**
Data yang tersedia terbatas sehingga tidak dapat digunakan untuk merekomendasikan dosis tertentu pada kelompok pasien dengan umur di bawah tiga bulan.

**Lansia**
Tidak ada data khusus yang tersedia. Namun, perawatan khusus disarankan pada kelompok usia ini karena perubahan yang terjadi terkait usia, seperti penurunan fungsi ginjal dan perubahan parameter hematologis.

**Gangguan ginjal**
Diperlukan penurunan dosis pada pasien dengan gangguan ginjal. Jika Anda atau anak Anda memiliki masalah ginjal, konsultasikan terlebih dahulu dengan dokter Anda.

**Gangguan hati**
Tidak diperlukan penyesuaian dosis pada pasien dengan gangguan hati sedang atau berat kecuali jika disertai dengan gangguan ginjal.

**Apabila Anda menggunakan *3TC* lebih dari yang seharusnya**

Menggunakan *3TC* terlalu banyak tanpa disengaja cenderung tidak akan menyebabkan masalah serius. Jika Anda menggunakan *3TC* terlalu banyak, konsultasikan dengan dokter atau apoteker Anda, atau hubungi bagian gawat darurat rumah sakit terdekat untuk informasi dan saran lebih lanjut.

**Apabila Anda lupa menggunakan *3TC***
Jika Anda lupa menggunakan *3TC*, gunakan segera setelah Anda ingat. Kemudian lanjutkan pengobatan Anda seperti semula. Jangan menggunakan dosis ganda untuk mengganti dosis yang terlupakan.

## 4. Efek samping yang mungkin terjadi

Selama pengobatan HIV, Anda mungkin mengalami peningkatan berat badan dan kadar lipid dan glukosa darah. Hal ini sebagian terkait dengan pemulihan kesehatan dan gaya hidup, dan dalam kasus lipid darah terkadang berkaitan dengan obat-obatan HIV itu sendiri. Dokter Anda akan melakukan tes untuk mengetahui perubahan ini.

Seperti semua obat lainnya, obat ini dapat menimbulkan efek samping, tapi tidak semua orang mungkin akan mengalaminya.

Ketika Anda dirawat karena HIV, sulit untuk menentukan apakah suatu gejala yang muncul adalah efek samping dari penggunaan *3TC* atau efek dari penyakit HIV itu sendiri. **Oleh karena itu, sangat penting untuk mengonsultasikan kepada dokter Anda mengenai perubahan apapun yang terjadi pada kondisi kesehatan Anda.**

**Selain efek samping yang tercantum di bawah ini untuk *3TC***, kondisi lainnya dapat timbul selama terapi kombinasi untuk HIV.

Penting untuk membaca informasi selanjutnya pada bagian "Kemungkinan efek samping lain dari terapi kombinasi untuk HIV".

Berikut efek samping yang mungkin terjadi dengan obat ini:
**Umum** (terjadi hingga **1 dari 10 orang**)
- Sakit kepala.
- Mual.
- Muntah.
- Diare.
- Sakit perut bagian atas.
- Kelelahan, kekurangan energi.
- Demam (suhu tinggi).
- Perasaan tidak sehat secara keseluruhan.
- Nyeri otot dan ketidaknyamanan.
- Nyeri sendi.
- Ruam.
- Rambut rontok (*alopecia*).
- Hiperlaktatemia.

**Tidak umum** (terjadi hingga **1 dari 100 orang**)
Efek samping tidak umum yang dapat terlihat dalam tes darah adalah:
- Penurunan jumlah sel yang terlibat dalam pembekuan darah (trombositopenia).
- Jumlah sel darah merah rendah (anemia) atau jumlah sel darah putih rendah (neutropenia).
- Peningkatan kadar enzim hati (AST, ALT).

**Jarang** (terjadi hingga **1 dari 1.000 orang**)
- Radang pankreas (pankreatitis).
- Kerusakan jaringan otot.
- Asidosis laktat (kelebihan asam laktat dalam darah).

Efek samping jarang yang dapat terlihat dalam tes darah adalah:
- Peningkatan enzim amilase.

**Sangat jarang** (terjadi hingga **1 dari 10.000 orang**)

- Kesemutan atau mati rasa pada lengan, tungkai, tangan atau kaki.

Efek samping sangat jarang yang dapat terlihat dalam tes darah adalah:
- Kegagalan sumsum tulang dalam memproduksi sel darah merah baru (aplasia sel darah merah murni).

**Kemungkinan efek samping lain dari terapi kombinasi untuk HIV**
Terapi kombinasi termasuk *3TC* dapat menyebabkan terjadinya kondisi lain selama pengobatan HIV.

**Infeksi lama mungkin akan kembali**
Orang dengan infeksi HIV lanjutan (AIDS) memiliki sistem imun yang lemah dan cenderung mengalami infeksi serius (infeksi oportunistik). Ketika kelompok orang-orang ini memulai pengobatan, mereka mungkin mengalami infeksi lama yang tersembunyi itu muncul kembali, menyebabkan tanda dan gejala peradangan. Gejala-gejala ini mungkin disebabkan oleh sistem imun tubuh yang semakin kuat, sehingga tubuh mulai melawan infeksi tersebut.

Selain infeksi oportunistik, gangguan autoimun (sebuah kondisi yang terjadi ketika sistem imun menyerang jaringan tubuh yang sehat) juga dapat terjadi setelah Anda mulai minum obat untuk pengobatan infeksi HIV Anda. Gangguan autoimun dapat terjadi beberapa bulan setelah dimulainya pengobatan. Jika Anda memperhatikan adanya gejala infeksi atau gejala lain seperti kelemahan otot, kelemahan dimulai dari tangan dan kaki dan bergerak ke atas menuju batang tubuh, jantung berdebar, tremor atau hiperaktif, harap segera beritahu dokter Anda untuk mencari pengobatan yang diperlukan.

Jika Anda mengalami gejala infeksi saat Anda menggunakan *3TC*:
**Segera beritahu dokter Anda**. Jangan menggunakan obat lain untuk infeksi tanpa saran dari dokter Anda.

**Beritahu dokter Anda** jika Anda memperhatikan adanya salah satu dari gejala tersebut di atas.

**Pelaporan efek samping**
Jika Anda merasakan efek samping, harap konsultasikan ke dokter, apoteker, atau perawat. Termasuk kemungkinan efek samping lain yang tidak tertulis dalam informasi ini.

## 5. Bagaimana cara penyimpanan *3TC*

Jauhkan *3TC* dari pandangan dan jangkauan anak-anak.

Jangan simpan *3TC* di atas suhu 30°C.

Jangan menggunakan obat setelah tanggal kedaluwarsa yang tertulis pada kemasan. Tanggal kedaluwarsa merujuk pada hari terakhir bulan tersebut.

Jangan membuang obat apapun di air limbah atau limbah rumah tangga. Tanyakan pada apoteker bagaimana membuang obat yang tidak digunakan lagi. Tindakan ini akan membantu melindungi lingkungan.

## 6. Isi dari kemasan dan informasi lain

**Penampakan *3TC* dan isi kemasan**
Tablet salut selaput *3TC* 150 mg tersedia dalam botol polietilen putih berisi 60 tablet. Tablet ini berwarna putih, berbentuk seperti berlian, tablet salut selaput cetak yang ditandai dengan kode 'GXCJ7' di kedua sisi.

**Kandungan pada *3TC***
- Bahan aktif lamivudine.
- *3TC* tablet salut selaput juga mengandung bahan lainnya.
  Inti tablet: microcrystalline cellulose, sodium starch glycollate Type A, magnesium stearate.
  Salut selaput: opadry white YS-1-7706-G (hypromellose, titanium dioxide, macrogol 400, polysorbate 80) dan *purified water.*
- *3TC* mengandung kurang dari 1 mmol natrium (23 mg) per dosis, sehingga pada dasarnya *3TC* 'bebas natrium'.

**HARUS DENGAN RESEP DOKTER**

Dus, botol @ 60 tablet salut selaput  Reg. No. DKI1833900417A1

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