3TC-HBV
Lamivudine (Hepatitis B)

QUALITATIVE AND QUANTITATIVE COMPOSITION
Film coated tablet: lamivudine 100 mg. The tablets are butterscotch coloured, film coated, capsule-shaped biconvex and engraved “GX CG5” on one tablet face.

CLINICAL INFORMATION
Indications
3TC-HBV is indicated for the treatment of patients with chronic hepatitis B and evidence of hepatitis B virus (HBV) replication.

Dosage and Administration
Pharmaceutical Form
Film coated tablets.

The recommended dosage for adults is 100 mg once daily. The dose in children has not yet been established. Treatment discontinuation may be considered when HBe and HBs antigen seroconversion occurs. There is insufficient data to confirm that seroconversion will be sustained once treatment with *3TC-HBV* is stopped.

Patient compliance should be monitored while on therapy. If *3TC-HBV* is discontinued, patients should be observed carefully as there may be a small risk of exacerbation of hepatitis in some patients.

3TC-HBV should be initiated and monitored by a physician experienced in the management of chronic hepatitis B infection.

Contraindications
3TC-HBV is contraindicated in patients with known hypersensitivity to *3TC-HBV* or to any ingredient of the preparations.

Warnings and Precautions
Initiation of lamivudine treatment should only be considered when the use of an alternative antiviral agent with a higher genetic barrier to resistance is not available or appropriate.

During initiation and maintenance of treatment patients should be monitored regularly by a physician experienced in the management of chronic hepatitis B.

If *3TC-HBV* is discontinued or there is a loss of efficacy, some patients may experience clinical or laboratory evidence of recurrent hepatitis. Exacerbation of hepatitis has primarily been detected by serum ALT elevations, in addition to the re-emergence of HBV DNA. See Table 2 in *Pharmacological Properties* (*Clinical Studies*) for more information regarding frequency of post treatment ALT elevations. Most events appear to have been self-limited. Fatalities are very rare and the causal relationship to discontinuation of *3TC-HBV* treatment is unknown.

If *3TC-HBV* is discontinued, patients should be periodically monitored both clinically and by assessment of serum liver function tests (ALT and bilirubin levels), for at least four months for evidence of recurrent hepatitis; patients should then be followed as clinically indicated. For patients who develop evidence of recurrent hepatitis post-treatment, there are insufficient data on the benefits of re-initiation of *3TC-HBV* treatment.

In patients with moderate to severe renal impairment serum lamivudine concentrations (AUC) are increased due to decreased renal clearance, therefore the dose should be reduced for patients with a creatinine clearance of less than 50 mL/minute. *3TC-HBV* is not suitable for patients who require doses below 100 mg (*see Dosage and Administration*).

Transplantation recipients and patients with advanced liver disease are at greater risk from active viral replication. Due to marginal liver function in these patients, hepatitis reactivation at discontinuation of *3TC-HBV* or loss of efficacy during treatment may induce severe and even fatal decompensation. It is

recommended that these patients are monitored for parameters associated with hepatitis B, for liver and renal function, and for antiviral response during treatment. If treatment is discontinued for any reason, it is recommended that these patients are monitored for at least 6 months post cessation of treatment. Patients experiencing signs of hepatic insufficiency during or post-treatment should be monitored frequently, as appropriate.

There are limited data on the use of *3TC-HBV* in patients receiving concurrent immunosuppressive regimes, including cancer chemotherapy.

In HBeAg positive or negative patients, the development of YMDD (tyrosine-methionine-aspartate-aspartate) mutant HBV may result in a diminished therapeutic response to lamivudine, indicated by a rise in HBV DNA and ALT from previous on-treatment levels. In order to reduce the risk of resistance in patients receiving lamivudine monotherapy, a switch to or addition of an alternative agent without cross-resistance to lamivudine should be considered if serum HBV DNA remains detectable at or beyond 24 weeks of treatment (*see Clinical studies*).

For the treatment of patients who are co-infected with HIV and are currently receiving or are planning to receive an antiretroviral treatment regimen including lamivudine, the dose of lamivudine usually prescribed for HIV infection should be maintained.

There is limited information available on maternal-foetal transmission of hepatitis B virus in pregnant women receiving treatment with *3TC-HBV*. The standard recommended procedures for hepatitis B virus immunisation in infants should be followed.

Patients should be advised that therapy with *3TC-HBV* has not been proven to reduce the risk of transmission of hepatitis B virus to others and therefore, appropriate precautions should still be taken.

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

3TC-HBV is predominantly eliminated by active organic cationic secretion. The possibility of interactions with other drugs 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 drugs (e.g. ranitidine, cimetidine) are eliminated only in part by this mechanism and were shown not to interact with *3TC-HBV*.

Drugs shown to be predominately excreted either via the active organic anionic pathway, or by glomerular filtration are unlikely to yield clinically significant interactions with *3TC-HBV*.

Interactions relevant to lamivudine
Trimethoprim/sulphamethoxazole: Administration of trimethoprim/sulphamethoxazole 160 mg/800 mg increased *3TC-HBV* exposure by about 40%. *3TC-HBV* had no effect on the pharmacokinetics of trimethoprim or sulphamethoxazole. However, unless the patient has renal impairment, no dosage adjustment of *3TC-HBV* is necessary.

Zidovudine: A modest increase in C_{max} (28%) was observed for zidovudine when administered with *3TC-HBV*, however overall exposure (AUC) was not significantly altered. Zidovudine had no effect on the pharmacokinetics of *3TC-HBV (see Pharmacokinetics*).

Emtricitabine: 3TC-HBV may inhibit the intracellular phosphorylation of emtricitabine when the two medicinal products are used concurrently. *3TC-HBV* is not recommended for use in combination with emtricitabine.

Sorbitol: Co-administration of sorbitol solution (3.2 g, 10.2 g, 13.4 g) with a single 300 mg dose (Adult HIV daily 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 lamivudine with sorbitol-containing medicines or consider more frequent monitoring of HBV viral load when chronic co-administration cannot be avoided.

Alpha-interferon: 3TC-HBV has no pharmacokinetic interaction with alpha-interferon when the two drugs are concurrently administered. There were no observed clinically significant adverse interactions in

patients taking *3TC-HBV* concurrently with commonly used immunosuppressant drugs (e.g. cyclosporin A). However, formal interaction studies have not been performed.

Pregnancy and Lactation
Fertility
Reproductive studies in animals have shown no effect on male or female fertility.

Pregnancy
The Antiretroviral Pregnancy Registry has received reports of over 11,000 exposures to lamivudine during pregnancy resulting in live birth, less than 1% of which were in patients with HBV. These consist of over 4,500 exposures during the first trimester, over 7,200 exposures during the second/third trimester and included 143 and 207 major birth defects respectively. The prevalence (95% CI) of defects in the first trimester was 3.1% (2.6, 3.7%) and in the second/third trimester, 2.9% (2.5, 3.3%). 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 *3TC-HBV* 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, there was no evidence of teratogenicity in animals but, findings in rabbits suggest a potential risk of early embryonic loss that was not observed in the rat. For patients who are being treated with *3TC-HBV* and subsequently become pregnant consideration should be given to the possibility of a recurrence of hepatitis on discontinuation of *3TC-HBV* (*see Warnings and Precautions*).

Lactation
Following repeat oral administration of either 150 mg 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 administration of 150 mg lamivudine twice daily 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). The clinical relevance of this finding is unknown.

Data from animal studies in which neonatal rats received *3TC-HBV* at much higher concentrations via maternal milk suggest that the concentrations of lamivudine in human breast milk are unlikely to produce toxicity in breast fed infants.

3TC-HBV should only be used in a nursing mother if the expected benefit justifies the potential risk to the infant. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from *3TC-HBV* therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Effects on Ability to Drive and Use Machines
There have been no studies to investigate the effect of *3TC-HBV* on driving performance or the ability to operate machinery. Further, a detrimental effect on such activities would not be predicted from the pharmacology of the drug.

Adverse Reactions
Clinical trial data
In clinical studies of patients with chronic hepatitis B, *3TC-HBV* was well tolerated. The incidence of adverse events and laboratory abnormalities (with the exception of elevations of ALT and CPK, see below) were similar between placebo and *3TC-HBV* treated patients (*see Table 1*). The most common adverse events reported were malaise and fatigue, respiratory tract infections, headache, abdominal discomfort and pain, nausea, vomiting and diarrhoea.

Table 1.

Adverse event	**Clinical trial data: Integrated phase III data**	
	Placebo (n= 200)	***3TC-HBV* 100 mg (n= 416)**

Malaise & Fatigue	28%	26%
Respiratory tract infection	17%	19%
Headache	21%	22%
Abdominal discomfort & pain	17%	15%
Nausea & vomiting	17%	16%
Diarrhoea	12%	14%
ALT elevations during treatment†	13%	13%
ALT elevations post treatment††	8%	19%
Elevated CPK†	5%	9%

† Percentage of patients experiencing a grade III or IV laboratory abnormality during treatment.
†† Percentage of patients experiencing a grade III or IV elevation in ALT post-treatment.

Adverse reactions are listed below by system organ class and frequency. Frequency categories are only assigned to those adverse reactions considered to be at least possibly causally related to *3TC-HBV*. 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) and very rare (<1/10,000).

The frequency categories assigned to the adverse reactions below are estimates: for most events, suitable data for calculating incidence are not available. Very common and common adverse drug reaction frequency categories were determined from clinical trial data and the background incidence in placebo groups was not taken into account.

Adverse drug reactions identified through post-marketing surveillance were categorised as rare or very rare.

- **Hepatobiliary disorders**

Very common: Elevations of ALT
Elevations in ALT were more common post-treatment in patients treated with *3TC-HBV* than placebo. In controlled trials in patients with compensated liver disease, however, there was no appreciable difference post treatment in clinically severe ALT elevations associated with bilirubin elevations and/or signs of hepatic insufficiency, between *3TC-HBV* and placebo treated patients. The relationship of these recurrent hepatitis events to *3TC-HBV* treatment or to the previous underlying disease is uncertain (*see Warnings and Precautions*).

- **Skin and subcutaneous tissue disorder**

Common: Rash

- **Musculoskeletal and connective tissue disorders**

Common: Elevations of CPK

Post marketing data
In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of *3TC-HBV*.

- **Blood and lymphatic system disorders**

Very rare: Thrombocytopenia

- **Musculoskeletal and connective tissue disorders**

Common: Muscle disorders, including myalgia and cramps
Very rare: Rhabdomyolysis

In patients with HIV infection, cases of pancreatitis and peripheral neuropathy (or paraesthesia) have been reported, although no relationship to treatment with lamivudine (*3TC*) has been clearly established. In patients with chronic hepatitis B there was no observed difference in incidence of these events between placebo and *3TC-HBV* treated patients.

Cases of lactic acidosis, usually associated with severe hepatomegaly and hepatic steatosis, have been reported with the use of combination nucleoside analogue therapy in patients with HIV. There have been occasional reports of these adverse events in hepatitis B patients with decompensated liver disease, however there is no evidence that these events were related to treatment with *3TC-HBV*.

Overdose

Symptoms and signs

No specific signs or symptoms have been identified following acute overdose with lamivudine, apart from those listed as adverse reactions.

Treatment

If overdose 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 overdose, although this has not been studied.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Pharmacotherapeutic group − nucleoside analogue; ATC Code: J05A F05.

3TC-HBV is an antiviral agent which is highly active against hepatitis B virus in all cell lines tested and in experimentally infected animals.

Lamivudine is metabolised by both infected and uninfected cells to the triphosphate (TP) derivative which is the active form of the parent compound. The intracellular half-life of the triphosphate in hepatocytes is 17 to 19 h *in vitro*. Lamivudine-TP acts a substrate for the HBV viral polymerase. The formation of further viral DNA is blocked by incorporation of lamivudine-TP into the chain and subsequent chain termination.

Lamivudine-TP does not interfere with normal cellular deoxynucleotide metabolism. It is also only a weak inhibitor of mammalian DNA polymerases alpha and beta. Furthermore, lamivudine-TP has little effect on mammalian cell DNA content.

In assays relating to potential drug effects on mitochondrial structure and DNA content and function, lamivudine lacked appreciable toxic effects. It has a very low potential to decrease mitochondrial DNA content, is not permanently incorporated into mitochondrial DNA, and does not act as an inhibitor of mitochondrial DNA polymerase γ.

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. 100 mg once daily, C_{max} is in the order of 1.1 to 1.5 micrograms/mL and trough levels were 0.015 to 0.020 micrograms/mL.

Co-administration of *3TC-HBV* 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, therefore *3TC-HBV* can be administered with or without food.

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 hours after oral administration was approximately 0.12.

Metabolism

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

- **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) when given in combination with sulphamethoxazole, has been shown to increase lamivudine plasma concentrations (s*ee Interactions*).

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 an *in vitro* 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.

- **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). Lamivudine 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 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 which is three times higher than the recommended maximum dose for HBV).

Elimination

The mean systemic clearance of lamivudine is approximately 0.3 L/h/kg. The observed half-life of elimination is 18 to 19 hours. The majority of lamivudine is excreted unchanged in the urine via glomerular filtration and active secretion (organic cationic transport system).

Renal clearance accounts for about 70% of lamivudine elimination.

Special patient populations

- **Elderly**

In elderly patients the pharmacokinetic profile of lamivudine suggests that normal ageing with accompanying renal decline has no clinically significant effect on lamivudine exposure, except in patients with creatinine clearance of less than 50 mL/min *(see Dosage and Administration).*

- **Renal impairment**

Studies in patients with renal impairment show lamivudine elimination is affected by renal dysfunction. Dose reduction in patients with a creatinine clearance of less than 50 mL/min is necessary *(see Dosage and Administration)*.

- **Hepatic impairment**

A study in hepatically impaired patients (non-HIV and non-HBV infected) showed *3TC-HBV* is well tolerated in this patient group with no changes in laboratory parameters or the adverse event profile of *3TC-HBV*. The pharmacokinetics of lamivudine are unaffected by hepatic impairment.

Limited data in patients undergoing liver transplantation show that impairment of hepatic function does not impact significantly on the pharmacokinetics of lamivudine unless accompanied by renal dysfunction.

- **Pregnancy**

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

Lamivudine concentrations in infant serum at birth were similar to those in maternal and cord serum at delivery.

Clinical Studies

3TC-HBV has potent anti-viral activity *in vivo*, rapidly suppressing HBV replication following initiation of treatment resulting in continued HBV suppression, normalisation of serum aminotransferase, significant reductions in liver necro-inflammatory activity, reduced progression of fibrosis and increased HBeAg seroconversion. *3TC-HBV* has been administered to chronic hepatitis B patients for up to four years in clinical studies. Similar results have been seen in patients regardless of ethnic origin.

In controlled studies in over 800 HBeAg positive patients, treatment with *3TC-HBV* for one year significantly suppressed HBV DNA replication (34 to 57% of patients), normalised ALT levels (40 to 72% of patients), induced HBeAg seroconversion (HBeAg and HBV DNA loss with HBeAb detection, 16 to 18% of patients), improved histology (38 to 52% of patients), and reduced progression of fibrosis (3 to 17% of patients) and progression to cirrhosis (1.8% of patients).

The HBeAg seroconversion was maintained in 81% (34/42) of patients off drug followed for approximately two years. In addition, HBsAg seroconversion was achieved in 21% (9/42) patients.

In HBeAg positive patients who had not experienced HBeAg seroconversion in one-year controlled studies and were subsequently treated with 2 years of *3TC-HBV*, 77/128 (60%) had improvement in liver inflammation and 26/51 (51%) had improvement in bridging fibrosis.

In an additional study, after four years of *3TC-HBV* therapy HBeAg seroconversion (HBeAg loss and HBeAb detection) was seen in 47% (27/58) patients (59% [24/41] of patients with abnormal baseline ALT).

In patients who have not HBeAg seroconverted during treatment, discontinuation of *3TC-HBV* results in a return of HBV replication with both HBV DNA and serum aminotransferases returning towards pre-treatment levels within 2 to 6 months.

In patients followed for up to 16 weeks after discontinuation of treatment, post-treatment ALT elevations were observed more frequently in patients who had received *3TC-HBV* than in patients who had received placebo. A comparison of ALT elevations between weeks 52 and 68 in patients who discontinued *3TC-HBV* at week 52 and patients in the same studies who received placebo throughout the treatment course is shown in Table 2.

Table 2: Post-treatment ALT Elevations in 2 Placebo-Controlled Studies in Adults With No-Active-Treatment Follow-up.

Abnormal Value	Patients with ALT Elevation/ Patients with Observations[#]	
	3TC-HBV	**Placebo**
ALT ≥2 x baseline value	37/137 (27%)	22/116 (19%)
ALT ≥3 x baseline value[†]	29/137 (21%)	9/116 (8%)
ALT ≥2 x baseline value and absolute ALT >500 IU/L	21/137 (15%)	8/116 (7%)
ALT ≥2 x baseline value; and bilirubin >2 x ULN and ≥2 x baseline value	1/137 (0.7%)	1/116 (0.9%)

[#] Each patient may be represented in one or more category.
[†] Comparable to a Grade 3 toxicity in accordance with modified WHO criteria.
ULN = Upper Limit of Normal.

In a placebo-controlled study of 286 hepatitis B patients aged 2 to 17 years, patients treated with *3TC-HBV* for one year had a significantly better complete virological response (loss of HBeAg and HBV DNA) compared with patients receiving placebo (23% [44/191] vs 13% [12/95]). Normalisation of serum ALT was more frequent in patients treated with *3TC-HBV* compared with placebo (55% [100/183] vs 13% [11/88]). In a stratified follow-on study for six months, complete virological response was maintained in 83% [33/40] of patients who had responded after one year of treatment with *3TC-HBV* and then stopped therapy. *3TC-HBV* treated patients who did not respond after one-year continued treatment for a further 6 months resulting in an additional 10% (12/123) of patients achieving virological response and a cumulative complete virological response of 28% (45/163) over 18 months.

HBV viral sub-populations with reduced susceptibility to *3TC-HBV in vitro* have been identified. These HBV variants (YMDD variant HBV) are also found in hepatitis B patients who experience a return of detectable serum HBV DNA levels whilst on *3TC-HBV* treatment. The incidence of YMDD variant HBV (*see Warnings and Precautions*), as detected by polymerase chain reaction, increases with duration of treatment; 20% after one year, 53% after three years, 70% after four years and may be higher in immunocompromised patients.

Despite the emergence of YMDD variant HBV, patients treated for one year had significantly lower serum HBV DNA and ALT levels and improved liver histology compared to patients on placebo. After 2 years of

3TC-HBV treatment, the majority of patients with YMDD variant HBV maintained serum HBV DNA and ALT levels lower than their pre-treatment values and a proportion experienced HBeAg seroconversion. The adverse event profile is similar for patients with or without YMDD variant HBV.

Given the risk of YMDD mutant HBV, maintenance of lamivudine monotherapy is not appropriate in patients with detectable serum HBV DNA at or beyond 24 weeks of treatment (*see Warnings and Precautions*).

In patients with HBeAg negative chronic hepatitis B, the efficacy of *3TC-HBV* was similar to those infected with wild type HBV (e.g. 71% of patients with HBV DNA suppression, 67% with ALT normalisation and 38% with Knodell HAI-score improvement at one year on treatment). If therapy with *3TC-HBV* is stopped after one year of treatment, the majority of patients with HBeAg negative chronic hepatitis B have a return of viral replication. Limited data indicate that extended *3TC-HBV* treatment (two years) maintains HBV DNA suppression and ALT normalisation in this patient population. The incidence of serious adverse events at anytime during and post-treatment was low and similar in patients with HBeAg negative chronic hepatitis B with or without YMDD variant HBV.

In non-controlled studies in liver transplant patients in which *3TC-HBV* was administered prior to and during transplantation, effective HBV DNA suppression and ALT normalisation was demonstrated. When *3TC-HBV* therapy was continued post-transplantation, there was reduced graft re-infection by HBV, increased HBsAg loss, and a one-year survival rate of 76 to 100%. These studies were not placebo-controlled as this was regarded inappropriate in patients with decompensated liver disease.

As anticipated due to the concomitant immunosuppression, the rate of emergence of YMDD variant HBV after 52 weeks treatment was higher (36% to 64%) in liver transplant patients compared with immunocompetent chronic hepatitis B patients (14% to 32%). Studies provide evidence however that the emergence of YMDD variant is not consistently associated with hepatic disease progression and that the majority of patients may continue to benefit from continued *3TC-HBV* therapy.

Studies of monotherapy with *3TC-HBV* compared to alpha-interferon alone or in combination for treatment of chronic hepatitis B patients showed no significant difference in histologic response or HBeAg seroconversion rates between the treatment groups. The safety profile of *3TC-HBV* was superior to the alpha-interferon containing treatment regimens.

There is no clinical data on the efficacy of *3TC-HBV* in patients co-infected with Delta hepatitis.

Non-Clinical Information
Administration of *3TC-HBV* 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 reduction in liver weights. Reduction of erythrocytes and neutrophil counts were identified as the effects most likely to be of clinical relevance. These events were seen infrequently in clinical studies.

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 60 to 70 times higher than the anticipated clinical plasma levels. As the *in vitro* mutagenic activity of *3TC-HBV* could not be confirmed by *in vivo* tests, it is concluded that *3TC-HBV* should not represent a genotoxic hazard to patients undergoing treatment.

The results of long term carcinogenicity studies with *3TC-HBV* in rats and mice did not show any carcinogenic potential.

Reproductive studies in animals have not shown evidence of teratogenicity and showed no effect on male or female fertility in rats. 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 60 times the clinical exposure (based on C_{max}).

PHARMACEUTICAL INFORMATION
List of Excipients
Tablet core:
Microcrystalline cellulose

Sodium starch glycollate
Magnesium stearate

Tablet film coat:
Hypromellose
Titanium dioxide
Macrogol 400
Polysorbate 80
Synthetic yellow and red iron oxides

Shelf Life
The expiry date is indicated on the packaging.

Storage
The storage conditions are detailed on the packaging.

Nature and Contents of Container
Lamivudine tablets are supplied in double foil blisters, laminated with polyvinyl chloride.

Incompatibilities
None reported.

Use and Handling
There are no special requirements for use or handling of this product.

Package Quantities and Reg. No.
3TC-HBV 100 mg, 2 blisters @ 14 film coated tablets Reg.No. DKI1733900317A1

HARUS DENGAN RESEP DOKTER

Manufactured by
Delpharm Poznań Spółka Akcyjna
Poznań, Poland

Imported by
PT Glaxo Wellcome Indonesia
Jakarta, Indonesia

Version number: GDS18/IPI10 - *Manufacturer name change (Project PINE) and new GSK logo*
Date of issue: 30 Oct 2020

INFORMASI UNTUK PASIEN

3TC-HBV Tablet Salut Selaput
Lamivudine 100 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-HBV dan digunakan untuk apa

3TC-HBV digunakan untuk mengobati infeksi hepatitis B kronis dengan bukti replikasi virus hepatitis B (HBV).

2. Apa yang perlu Anda ketahui sebelum menggunakan 3TC-HBV

Jangan gunakan 3TC-HBV:

- 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-HBV atau pengobatan serupa lainnya lebih berisiko terhadap efek samping yang serius. Anda perlu mewaspadai risiko tambahan:

- Jika Anda pernah menderita **penyakit hati**, seperti hepatitis C.

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.

Jangan menghentikan penggunaan 3TC-HBV tanpa saran dari dokter Anda, dikarenakan adanya risiko memburuknya kondisi hepatitis Anda. Ketika Anda menghentikan penggunaan 3TC-HBV, dokter Anda akan memantau setidaknya selama 4 bulan untuk memeriksa jika terdapat masalah. Hal ini berarti Anda akan diminta untuk mengambil sampel darah untuk memeriksa adanya peningkatan enzim hati yang dapat mengindikasikan kerusakan hati. **Lihat Bagian 3** untuk informasi lebih lanjut mengenai cara menggunakan 3TC-HBV.

Lindungi orang lain

Infeksi hepatitis B disebarkan melalui hubungan seksual dengan seseorang yang terinfeksi, atau melalui perpindahan darah yang terinfeksi (misalnya, dengan berbagi jarum suntik). 3TC-HBV tidak akan memberhentikan Anda menularkan infeksi hepatitis B pada orang lain. Untuk melindungi orang lain dari terinfeksi hepatitis B:

- **Gunakan kondom** saat Anda melakukan seks oral atau penetrasi
- **Jangan mengambil risiko perpindahan darah** – contohnya, jangan berbagi jarum suntik.

Obat lain dan 3TC-HBV
Beritahu dokter atau apoteker Anda jika Anda sedang menggunakan, telah menggunakannya baru-baru ini atau mungkin akan menggunakan obat lain, 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-HBV.

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

Obat-obatan yang memiliki interaksi dengan 3TC-HBV:
- Trimethoprim/sulphamethoxazole
- Zidovudine.

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-HBV selama masa kehamilan. Jangan menghentikan pengobatan 3TC-HBV tanpa saran dari dokter Anda.

Menyusui
3TC-HBV dapat masuk ke dalam ASI. Jika Anda sedang menyusui atau berpikir untuk menyusui, **konsultasikan dengan dokter Anda** sebelum Anda menggunakan 3TC-HBV.

Mengemudi dan menggunakan mesin
3TC-HBV dapat menyebabkan Anda merasa lelah yang dapat mempengaruhi kemampuan Anda untuk mengemudi atau mengoperasikan mesin. Jangan mengemudi atau mengoperasikan mesin kecuali Anda yakin bahwa Anda tidak terpengaruh.

3. Cara menggunakan 3TC-HBV

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

Tetap lakukan komunikasi secara teratur dengan dokter Anda
3TC-HBV membantu mengontrol infeksi hepatitis B Anda. Anda harus terus menggunakannya setiap hari untuk mengontrol infeksi dan mencegah penyakit Anda memburuk.

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

Dosis yang dianjurkan
Dosis umum 3TC-HBV adalah satu tablet (100 mg lamivudine) **sekali sehari**.

Dokter Anda mungkin meresepkan dosis yang lebih rendah jika Anda memiliki masalah pada ginjal.

Konsultasikan dengan dokter Anda jika hal tersebut berlaku untuk Anda.

Jika Anda termasuk dalam pasien koinfeksi dengan HIV dan sedang menerima atau berencana menerima rejimen pengobatan antiretroviral termasuk lamivudine, dosis lamivudine yang telah diresepkan untuk

infeksi HIV harus dipertahankan. Jika Anda berencana untuk mengubah pengobatan infeksi HIV Anda, diskusikan dengan dokter Anda terlebih dahulu.

Telan tablet secara utuh menggunakan air. 3TC-HBV dapat diminum bersama dengan makanan atau dalam keadaan perut kosong.

Apabila Anda menggunakan 3TC-HBV lebih dari yang seharusnya
Menggunakan 3TC-HBV terlalu banyak tanpa disengaja cenderung tidak akan menyebabkan masalah serius. Jika Anda menggunakan 3TC-HBV 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-HBV
Jika Anda lupa menggunakan 3TC-HBV, gunakan segera setelah Anda ingat. Kemudian lanjutkan pengobatan Anda seperti semula. Jangan menggunakan dosis ganda untuk mengganti dosis yang terlupakan.

Jangan hentikan penggunaan 3TC-HBV
Anda tidak boleh berhenti menggunakan 3TC-HBV tanpa berkonsultasi dengan dokter Anda dikarenakan adanya risiko memburuknya kondisi hepatitis Anda (*Lihat Bagian 2*). Ketika Anda menghentikan penggunaan 3TC-HBV, dokter Anda akan memantau setidaknya selama 4 bulan untuk memeriksa jika terdapat masalah. Hal ini berarti Anda akan diminta untuk mengambil sampel darah untuk memeriksa adanya peningkatan enzim hati yang dapat mengindikasikan kerusakan hati.

4. Efek samping yang mungkin terjadi

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

Efek samping yang sering dilaporkan dalam uji klinis 3TC-HBV adalah kelelahan, infeksi saluran pernapasan, ketidaknyamanan pada tenggorokan, sakit kepala, nyeri dan ketidaknyamanan pada perut, mual, muntah dan diare, peningkatan enzim hati dan enzim yang diproduksi di otot (lihat di bawah).

Berikut efek samping yang mungkin terjadi dengan obat ini:
Sangat umum (terjadi hingga lebih dari **1 dari 10 orang**)
- Peningkatan kadar enzim hati ALT.

Umum (terjadi hingga **1 dari 10 orang**)
- Ruam
- Gangguan otot, termasuk myalgia dan kram
- Peningkatan kadar enzim yang diproduksi di otot (kreatin fosfokinase) yang mungkin menandakan jaringan tubuh rusak.

Sangat jarang (terjadi pada hingga **1 dari 10.000 orang**)
- Penurunan jumlah sel yang terlibat dalam pembekuan darah (trombositopenia)
- Kerusakan jaringan otot (*rhabdomyolisis*).

Kadang-kadang ada laporan tentang efek samping asidosis laktik pada pasien hepatitis B dengan penyakit hati dekompensasi, namun tidak ada bukti bahwa kejadian ini terkait dengan pengobatan dengan 3TC-HBV.

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

5. Bagaimana cara penyimpanan 3TC-HBV

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

Jangan menggunakan obat setelah tanggal kedaluwarsa yang tertulis pada kemasan karton dan blister.

Tanggal kedaluwarsa merujuk pada tanggal terakhir bulan tersebut.

Simpan 3TC-HBV sesuai dengan cara penyimpanan yang dapat dilihat pada kemasan.

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

Kandungan pada 3TC-HBV

- Bahan aktif lamivudine. Setiap tablet salut selaput mengandung lamivudine 100 mg
- 3TC-HBV tablet salut selaput juga mengandung bahan lainnya: *microcrystalline cellulose, sodium starch glycollate, magnesium stearate, hypromellose, titanium dioxide, macrogol 400, polysorbate 80, synthetic yellow* dan *red iron oxide*.

Penampakan 3TC-HBV dan isi kemasan

Tablet salut selaput 3TC-HBV 100 mg tersedia dalam blister *foil temper evident* berisi 28 tablet. Tablet ini berwarna *butterscotch* (krem kecoklatan), berbentuk seperti kapsul, bikonveks dan ditandai dengan kode 'GX CG5' pada salah satu sisinya.

HARUS DENGAN RESEP DOKTER

Dus, 2 blister @ 14 tablet salut selaput Reg. No. DKI1733900317A1

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