SUMMARY OF PRODUCTS CHARACTERISTICS

1. Name of the medicinal product

INN Name **:** Tenofovir Disoproxil Fumarate and Lamivudine Tablets300mg/300mg

Propriority Name : Tenofovir Disoproxil Fumarate and Lamivudine Tablets300mg/300mg

Strength **:** 300 mg/300mg

Pharmaceutical form: film coated Tablet

2. Qualitative and quantitative composition

Each film coated tablet contains 300mg of Tenofovir disoproxil fumarate equivalent to 245 mg Tenofovir disoproxil and 300mg Lamivudine USP.

For Excipients kindly refer to 6.1 list of excipients

3. Pharmaceutical form

Dosage form: Tablet

Description: Light blue to blue, capsule shaped, biconvex film coated tablets, debossed with '129' on one side and 'H' on other side

4. Clinical particulars

4.1 Therapeutic indications

Tenofovir Disoproxil Fumarate is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. The following points should be considered when initiating therapy with Tenofovir Disoproxil Fumarate for the treatment of HIV-1 infection: Tenofovir Disoproxil Fumarate should not be used in combination with Truvada® or Atripla. 1.2 Chronic Hepatitis B Tenofovir Disoproxil Fumarate is indicated for the treatment of chronic hepatitis B in adults.The following points should be considered when initiating therapy with Tenofovir DisoproxilFumarate

Tenofovir Disoproxil Fumarate is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. The following points should be considered when initiating therapy with Tenofovir Disoproxil Fumarate for the treatment of HIV-1 infection: Tenofovir Disoproxil Fumarate should not be used in combination with Truvada® or Atripla. 1.2 Chronic Hepatitis B Tenofovir Disoproxil Fumarate is indicated for the treatment of chronic hepatitis B in adults.The following points should be considered when initiating therapy with Tenofovir Disoproxil Fumarate

Lamivudine

Lamivudine-HBV is indicated for the treatment of chronic hepatitis B associated with evidence of hepatitis B viral replication and active liver inflammation. This indication is based on 1-year histologic and serologic responses in adult patients with compensated chronic hepatitis B, and more limited information from a study in pediatric patients ages 2 to 17 years.

4.2 Posology and method of administration

Dosage and Administration

Lamivudine

Adults and Adolescents > 16 years of age

The recommended oral dose of Lamivudine in HIV-1-infected adults and adolescents > 16 years of age is 300 mg daily, administered as either 150 mg twice daily or 300 mg once daily, in combination with other antiretroviral agents. If Lamivudine is administered to a patient infected with HIV-1 and HBV, the dosage indicated for HIV-1 therapy should be used as part of an appropriate combination regimen.

Pediatric Patients

The recommended oral dose of Lamivudine Oral Solution in HIV-1-infected pediatric patients 3 months to 16 years of age is 4 mg/kg twice daily (up to. a maximum of 150 mg twice a day), administered in combination with other antiretroviral agents.

Lamivudine is also available as a scored tablet for HIV-1-infected pediatric patients who weigh ≥ 14 kg for whom a solid dosage form is appropriate. Before prescribing Lamivudine Tablets, children should be assessed for the ability to swallow tablets. If a child is unable to reliably swallow Lamivudine Tablets, the oral solution formulation should be prescribed. The recommended oral dosage of Lamivudine Tablets for HIV-1 -infected pediatric patients is presented in Table.

Table: Dosing Recommendations for Lamivudine Tablets in Pediatric Patients

Weight (kg)	Dosage Regimen Using Scored 150 mg Tablet		Total Daily Dose
	AM Dose	PM Dose	
14 to 21	½ tablet (75 mg)	½ tablet (75 mg)	150 mg

>21 to <30	½ tablet (75 mg)	1 tablet (150 mg)	225 mg
≥ 30	1 tablet (150 mg)	1 tablet '(T50mB)	300 mg

Patients with Renal Impairment

Dosing of Lamivudine is adjusted in accordance with renal function. Dosage adjustments are listed in Table.

Table: Adjustment of Dosage of Lamivudine in Adults and Adolescents (> 30 kg) in Accordance With Creatinine Clearance

Creatinine Clearance (mL/min)	**Recommended Dosage of Lamivudine**
≥ 50	150 mg twice daily or 300mg once daily
30-49	150 mg once daily
15-29	150 mg first dose, then 100 mg once daily
5-14	150 mg first dose, then 50 mg once daily
< 5	50 mg first dose, then 25 mg once daily

No additional dosing of Lamivudine is required after routine (4-hour) hemodialysis or peritoneal dialysis. Although there are insufficient data to recommend a specific dose adjustment of Lamivudine in pediatric patients with renal impairment, a reduction in the dose and/or an increase in the dosing interval should be considered.

Tenofovir disoproxil fumarate

Recommended Dose

For the treatment of HIV-1 or chronic hepatitis B: The dose of Tenofovir disoproxil Fumarate is 300 mg once daily taken orally, without regard to food. In the treatment of chronic hepatitis B, the optimal duration of treatment is unknown.

Dose Adjustment for Renal Impairment

Significantly increased drug exposures occurred when Tenofovir Disoproxil Fumarate was administered to subjects with moderate to severe renal impairment. Therefore, the dosing interval of Tenofovir disoproxil Fumarate should be adjusted in patients with baseline creatinine clearance < 50 mL/min using the recommendations in Table 1. These dosing interval recommendations are based on modeling of single-dose pharmacokinetic data in non-HIV and

non-HBV infected subjects with varying degrees of renal impairment, including end-stage renal disease requiring hemodialysis. The safety and effectiveness of these dosing interval adjustment recommendations have not been clinically evaluated in patients with moderate or severe renal impairment, therefore clinical response to treatment and renal function should be closely monitored in these patients.No dose adjustment is necessary for patients with mild renal impairment (creatinine clearance 50–80 mL/min). Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients with mild renal impairment.

Table: Dosage Adjustment for Patients with Altered Creatinine Clearance

	Creatinine Clearance (mL/min)[a]			**Hemodialysis Patients**
	≥ 50	30–49	10–29	
Recommended 300 mg Dosing Interval	Every 24 hours	Every 48 hours	Every 72 to 96 hours	Every 7 days orafter a total Of approximately 12 hours of dialysis[b]
a. Calculated using ideal (lean) body weight. b. Generally once weekly assuming three hemodialysis sessions a week of approximately 4 hours duration. Tenofovir disoproxil Fumarate should be administered following completion of dialysis.				

The pharmacokinetics of tenofovir have not been evaluated in non-hemodialysis patients with creatinine clearance < 10 mL/min; therefore, no dosing recommendation is available for these patients

4.3 Contraindications

Tenofovir disoproxil fumarate and Lamivudine tablets are contraindicated in patients with previously demonstrated hypersensitivity (e.g., anaphylaxis) to any of the components of the products.

4.4 Special warnings and precautions for use

Precautions

Tenofovir disoproxil fumarate

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination with other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with tenofovir disoproxil fumarate should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Patients Coinfected with HIV-1 and HBV

It is recommended that all patients with HIV-1 be tested for the presence of chronic Hepatitis B virus (HBV) before initiating antiretroviral therapy. Tenofovir disoproxil fumarate is not approved for the treatment of chronic HBV infection and the safety and efficacy of tenofovir disoproxil fumarate have not been established in patients coinfected with HBV and HIV-1. Severe acute exacerbations of Hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued tenofovir disoproxil fumarate. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are co infected with HIV-1 and HBV and discontinue tenofovir disoproxil fumarate. If appropriate, initiation of anti-Hepatitis B therapy may be warranted.

New Onset or Worsening Renal Impairment

Tenofovir is principally eliminated by the kidney. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir disoproxil fumarate

It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with tenofovir disoproxil fumarate. Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients at risk for renal impairment.

Dosing interval adjustment of tenofovir disoproxil fumarate and close monitoring of renal function are recommended in all patients with creatinine clearance <50 mL/min No safety or efficacy data are available in patients with renal impairment who received tenofovir disoproxil fumarate using these dosing guidelines, so the potential benefit of tenofovir disoproxil fumarate therapy should be assessed against the potential risk of renal toxicity.

Tenofovir disoproxil fumarate should be avoided with concurrent or recent use of a nephrotoxic agent.

Co administration with Related Products

Tenofovir disoproxil fumarate should not be used in combination with the fixed-dose combination products Emtricitabine and Tenofovir Disoproxil Fumarate or Efavirenz, Emtricitabine, and Tenofovir Disoproxil Fumarate since tenofovir disoproxil fumarate is a component of these products.

Decreases in Bone Mineral Density

Bone mineral density monitoring should be considered for HIV-1 infected patients who have a history of pathologic bone fracture or are at risk for osteopenia. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained.

In Study 903 through 144 weeks, decreases from baseline in bone mineral density (BMD) were seen at the lumbar spine and hip in both arms of the study. At Week 144, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in patients receiving tenofovir disoproxil fumarate + Lamivudine + efavirenz (-2.2% ± 3.9) compared with patients receiving stavudine + Lamivudine + efavirenz (-1.0% ± 4.6). Changes in BMD at the hip were similar between the two treatment groups (-2.8% ± 3.5 in the tenofovir disoproxil fumarate group vs. -2.4% ± 4.5 in the stavudine group). In both groups, the majority of the reduction in BMD occurred in the first 24 to 48 weeks of the study and this reduction was sustained through Week 144. Twenty-eight percent of tenofovir disoproxil fumarate-treated patients vs. 21% of the stavudine-treated patients lost at least 5% of BMD at the spine or 7% of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4 patients in the tenofovir disoproxil fumarate group and 6 patients in the stavudine group. In

addition, there were significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide, and urinary N-telopeptide) in the tenofovir disoproxil fumarate group relative to the stavudine group, suggesting increased bone turnover. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in the tenofovir disoproxil fumarate group. Except for bone specific alkaline phosphatase, these changes resulted in values that remained within the normal range. The effects of tenofovir disoproxil fumarate-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown.Cases of osteomalacia (associated with proximal renal tubulopathy) have been reported in association with the use of tenofovir disoproxil fumarate

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including tenofovir disoproxil fumarate. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections [such as Mycobacterium avium infection, cytomegalovirus, Pneumocystis jirovecii pneumonia (PCP), or tuberculosis], which may necessitate further evaluation and treatment.

Lamivudine

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including Lamivudine and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering Lamivudine to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with Lamivudine should be

suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations.

Patients With HIV-1 and Hepatitis B Virus Co-infection

Post treatment Exacerbations of Hepatitis: In clinical trials in non-HIV-1-infected patients treated with Lamivudine for chronic hepatitis B, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of Lamivudine. These exacerbations have been detected primarily by serum ALT elevations in addition to re-emergence of HBV DNA. Although most events appear to have been self-limited, fatalities have been reported in some cases. Similar events have been reported from post marketing experience after changes from Lamivudine-containing HIV-1 treatment regimens to non-Lamivudine-containing regimens in patients infected with both HIV-1 and HBV. The causal relationship to discontinuation of Lamivudine treatment is unknown. Patients should be closely monitored with both clinical and laboratory follows up for at least several months after stopping treatment. There is insufficient evidence to determine whether re-initiation of Lamivudine alters the course of posttreatment exacerbations of hepatitis.

Important Differences Among Lamivudine-Containing Products: Lamivudine Tablets contain a higher dose of the same active ingredient than Lamivudine Tablets. Lamivudine was developed for patients with chronic hepatitis B. The formulation and dosage of Lamivudine in Lamivudine are not appropriate for patients co-infected with HIV-1 and HBV. Safety and efficacy of Lamivudine have not been established for treatment of chronic hepatitis B in patients co-infected with HIV-1 and HBV. If treatment with Lamivudine is prescribed for chronic hepatitis B for a patient with unrecognized or untreated HIV-1 infection, rapid emergence of HIV-1 resistance is likely to result because of the subtherapeutic dose and the inappropriateness of monotherapy HIV-1 treatment. If a decision is made to administer Lamivudine to patients co-infected with HIV-1 and HBV, Lamivudine tablets,Lamivudine/zidovudine Tablets, abacavir sulfate and Lamivudine Tablets, or abacavir sulfate, Lamivudine, and zidovudine Tablets should be used as part of an appropriate combination regimen.

Emergence of Lamivudine-Resistant HBV: In non-HIV-l-infected patients treated

with Lamivudine for chronic hepatitis B, emergence of Lamivudine-resistant HBV has been detected and has been associated with diminished treatment response. Emergence of hepatitis B

virus variants associated with resistance to Lamivudine has also been reported in HIV-1-infected patients who have received Lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus

Use With Other Lamivudine- and Emtricitabine-Containing Products

Lamivudine should not be administered concomitantly with other Lamivudine-containing products including Lamivudine Tablets, Lamivudine/zidovudine Tablets, abacavir sulfate and Lamivudine Tablets, or abacavir sulfate, Lamivudine, and zidovudine or emtricitabine-containing products, including efavirenz, emtricitabine, and tenofovir, emtricitabine or emtricitabine and tenofovir.

Use with Interferon- and Ribavirin-Based Regimens

In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as Lamivudine. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV-l/HCV virologic suppression) was seen when ribavirin was coadministered with Lamivudine in HIV-l/HCV co-infected patients, hepatic decompensation (some fatal) has occurred in HIV-l/HCV co-infected patients receiving combination antiretroviral therapy for HIV -1 and interferon alfa with or without ribavirin. Patients receiving interferon alfa with or without ribavirin and Lamivudine should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. Discontinuation of Lamivudine should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Childs Pugh >6). See the complete prescribing information for interferon and ribavirin.

Pancreatitis

In pediatric patients with a history of prior antiretroviral nucleoside exposure, a history of pancreatitis, or other significant risk factors for the development of pancreatitis, Lamivudine should be used with caution. Treatment with Lamivudine should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretrovira1 therapy, including Lamivudine. During the initial phase of combination

antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as Mycobacterium avium infection, cytomegalovirus, Pneumocystis jirovecii pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established

4.5 Interaction with other medicinal products and other forms of interaction

Tenofovir disoproxil fumarate

This section describes clinically relevant drug interactions with Tenofovir disoproxil fumarate. Drug interactions studies are described elsewhere in the labeling

Didanosine

Coadministration of Tenofovir disoproxil fumarate and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse reactions. Didanosine should be discontinued in patients who develop didanosine-associated adverse reactions**.**

When administered with Tenofovir disoproxil fumarate, Cmax and AUC of didanosine (administered as either the buffered or enteric-coated formulation increased significantly). The mechanism of this interaction is unknown. Higher didanosine concentrations could potentiate didanosine-associated adverse reactions, including pancreatitis and neuropathy. Suppression of CD4+ cell counts has been observed in patients receiving Tenofovir disoproxil fumarate (tenofovir DF) with didanosine 400 mg daily.

In adults weighing >60 kg, the didanosine dose should be reduced to 250 mg when it is coadministered with Tenofovir disoproxil fumarate. Data are not available to recommend a dose adjustment of didanosine for patients weighing <60 kg. When coadministered, Tenofovir disoproxil fumarate and didanosine EC may be taken under fasted conditions or with a light meal

(<400 kcal, 20% fat). Coadministration of didanosine buffered tablet formulation with Tenofovir disoproxil fumarate should be under fasted conditions.

Atazanavir

Atazanavir has been shown to increase Tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving atazanavir and Tenofovir disoproxil fumarate should be monitored for Tenofovir disoproxil fumarate-associated adverse reactions. Tenofovir disoproxil fumarate should be discontinued in patients who develop Tenofovir disoproxil fumarate-associated adverse reactions.

Tenofovir disoproxil fumarate decreases the AUC and Cmin of atazanavir. When coadministered with Tenofovir disoproxil fumarate, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg. Atazanavir without ritonavir should not be coadministered with Tenofovir disoproxil fumarate.

Lopinavir/Ritonavir

Lopinavir/ritonavir has been shown to increase Tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving lopinavir/ritonavir and Tenofovir disoproxil fumarate should be monitored for Tenofovir disoproxil fumarate-associated adverse reactions. Tenofovir disoproxil fumarate should be discontinued in patients who develop Tenofovir disoproxil fumarate-associated adverse reactions.

Drugs Affecting Renal Function

Since Tenofovir is primarily eliminated by the kidneys, coadministration of Tenofovir disoproxil fumarate with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of Tenofovir and/or increase the concentrations of other renally eliminated drugs. Some examples include, but are not limited to adefovir dipivoxil, cidofovir, acyclovir, valacyclovir, ganciclovir, and valganciclovir. Drugs that decrease renal function may also increase serum concentrations of Tenofovir.

Lamivudine

Lamivudine is predominantly eliminated in the urine 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). No data are available regarding interactions with other drugs that have renal clearance mechanisms similar to that of lamivudine.

Interferon- and Ribavirin-Based Regimens
Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when ribavirin was coadministered with Lamivudine in HIV-l/HCV co-infected patients, hepatic decompensation (some fatal) has occurred in HIV–l/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin Zalcitabine
Lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another. Therefore, use of Lamivudine in combination with zalcitabine is not recommended.

Trimethoprim/Sulfamethoxazole (TMP/SMX)
No change in dose of either drug is recommended. There is no information regarding the effect on Lamivudine pharmacokinetics of higher doses of TMP/SMX such as those used to treat PCP.

Drugs with No Observed Interactions with Lamivudine
A drug interaction study showed no clinically significant interaction between Lamivudine and zidovudine.

4.6 Fertility, pregnancy and lactation

Tenofovir disoproxil fumarate

Pregnancy

Pregnancy Category B:

Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to Tenofovir. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always

predictive of human response, tenofovir disoproxil fumarate should be used during pregnancy only if clearly needed

Nursing Mothers

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV-1. Studies in rats have demonstrated that tenofovir is secreted in milk. It is not known whether tenofovir is excreted in human milk. Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving tenofovir disoproxil fumarate.

Pediatric Use

Safety and effectiveness in patients less than 18 years of age have not been established.

Geriatric Use

Clinical studies of tenofovir disoproxil fumarate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for the elderly patient should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy

Patients with Impaired Renal Function

It is recommended that the dosing interval for Tenofovir disoproxil fumarate be modified in patients with creatinine clearance <50 mL/min or in patients with ESRD who require dialysis

Lamivudine

Pregnancy

Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled studies of Lamivudine in pregnant women. Animal reproduction studies in rats and rabbits revealed no evidence of teratogenicity. Increased early embryolethality occurred in rabbits at exposure levels similar to those in humans. Lamivudine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lamivudine pharmacokinetics were studied in pregnant women during 2 clinical studies conducted in South Africa. The study assessed pharmacokinetics in: 16 women at 36 weeks

gestation using 150 mg Lamivudine twice daily with zidovudine, 10 women at 38 weeks gestation using 150 mg Lamivudine twice daily with zidovudine, and 10 women at 38 weeks gestation using Lamivudine 300 mg twice daily without other antiretrovirals. These studies were not designed or powered to provide efficacy information. Lamivudine pharmacokinetics in the pregnant women were similar to those seen in non-pregnant adults and in postpartum women. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples. In a subset of subjects, lamivudine amniotic fluid specimens were collected following natural rupture of membranes. Amniotic fluid concentrations of Lamivudine were typically 2 times greater than maternal serum levels and ranged from 1.2 to 2.5 mcg/mL (150 mg twice daily) and 2.1 to 5.2 mcg/mL (300 mg twice daily). It is not known whether risks of adverse events associated with Lamivudine are altered in pregnant women compared with other HIV-1-infected patients.

Animal reproduction studies performed at oral doses up to 130 and 60 times the adult dose in rats and rabbits, respectively, revealed no evidence of teratogenicity due to Lamivudine. Increased early embryolethality occurred in rabbits at exposure levels similar to those in humans. However, there was no indication of this effect in rats at exposure levels up to 35 times those in humans. Based on animal studies, Lamivudine crosses the placenta and is transferred to the fetus.

Nursing Mothers

Te Centers for Disease Control and Prevention recommend that HIV-1-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-l infection. Because of the potential for serious adverse reactions in nursing infants and HIV-l transmission, mothers should be instructed not to breastfeed if they are receiving Lamivudine. is excreted into human milk. Samples of breast milk obtained from20 mothers receiving Lamivudine monotherapy (300 mg twice daily) or combination therapy (150 mg Lamivudine twice daily and 300 mg zidovudine twice daily) had measurable concentrations of Lamivudine.

Pediatric Use

The safety and effectiveness of twice-daily Lamivudine in combination with other antiretroviral agents have been established in pediatric patients 3 months of age and older

Geriatric Use

Clinical studies of Lamivudine did not include sufficient numbers of subjects aged 65 and over

to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. In particular, because Lamivudine is substantially excreted by the kidney and elderly patients are more likely to have decreased renal function, renal function should be monitored and dosage adjustments should be made accordingly.

Patients with Impaired Renal Function

Reduction of the dosage of Lamivudine is recommended for patients with impaired renal function

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, patients should be informed that dizziness has been reported during treatment with Tenofovir disoproxil fumarate.

4.8 Undesirable effects

Clinical studies: The most common side effects of Tenofovir disoproxil fumarate and Lamivudine are: diarrhea, nausea, vomiting, and dizziness. Less common side effects include flatulence (intestinal gas).

Marketing experience: Other side effects reported since Tenofovir Disoproxil fumarate and Lamivudine has been marketed include: allergic reaction, low blood phosphate, shortness of breath, increased liver enzymes, increased amylase, inflammation the liver, stomach pain, inflammation of the pancreas, rash, muscle problems and weakness.

Some patients treated with Tenofovir disoproxil fumarate and Lamivudine had kidney problems. If you have had kidney problems in the past or need to take another drug that can cause kidney problems, your healthcare provider may need to perform additional blood tests.

Laboratory tests show changes in the bones of patients treated with Tenofovir disoproxil fumarate and Lamivudine. It is not known whether long-term use of Tenofovir Disoproxil Fumarate and Lamivudine will cause damage to your bones. If you have had bone problems in the past, your healthcare provider may need to perform additional tests or may suggest additional medication.

Some patients taking antiviral drugs like Tenofovir Disoproxil Fumarate and Lamivudine have developed a condition called lactic acidosis (a buildup in the blood of lactic acid, the same substance that causes your muscles to burn during heavy exercise). Symptoms of lactic acidosis include nausea, vomiting, unusual or unexpected stomach discomfort, and weakness. If you notice these symptoms or if your medical condition changes suddenly, call your healthcare provider right away. Changes in body fat have been seen in some patients taking anti-HIV-1 medicine. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the main part of your body (trunk). Loss of fat from the legs, arms and face may also happen. The cause and long term health effects of these conditions are not known at this time. If you have Hepatitis B virus (HBV) infection, you may have a "flare-up" of Hepatitis B, in which the disease suddenly returns in a worse way than before if you stop taking Tenofovir Disoproxil Fumarate and Lamivudine. Tenofovir Disoproxil Fumarate and Lamivudine is not approved for the treatment of Hepatitis B Virus infection.

There have been other side effects in patients taking Tenofovir disoproxil fumarate and Lamivudine. However, these side effects may have been due to other medicines that patients were taking or to the illness itself. Some of these side effects can be serious.
This list of side effects is not complete. If you have questions about side effects, ask your healthcare provider. You should report any new or continuing symptoms to your healthcare provider right away. Your healthcare provider may be able to help you manage these side effects.
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4.9 Overdose

Tenofovir disoproxil fumarate

Limited clinical experience at doses higher than the therapeutic dose of tenofovir disoproxil fumarate 300 mg is available. In Study 901, 600 mg tenofovir disoproxil fumarate was administered to 8 patients orally for 28 days. No severe adverse reactions were reported. The effects of higher doses are not known.

If overdose occurs the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary.

Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of tenofovir disoproxil fumarate, a four-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

Lamivudine

There is no known antidote for Lamivudine. One case of an adult ingesting 6 g of Lamivudine was reported; there were no clinical signs or symptoms noted and hematologic tests remained normal. Two cases of pediatric overdose were reported in ACTG300. One case involved a single dose of 7 mg/kg of Lamivudine; the second case involved use of 5 mg/kg of Lamivudine twice daily for 30 days. There were no clinical signs or symptoms noted in either case. Because a negligible amount of Lamivudine was removed via (4-hour) hemodialysis, continuous ambulatory-peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a Lamivudine overdose event. If overdose occurs, the patient should be monitored, and standard supportive treatment applied as required.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Tenofovir: Tenofovir disoproxil fumarate is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir disoproxil fumarate requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase by competing with the natural substrate deoxyadenosine 5’-triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases alpha and beta, and mitochondrial DNA polymerase gamma.

Lamivudine: Lamivudine is a synthetic nucleoside analogue. Intracellularly, lamivudine is phosphorylated to its active 5'-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is inhibition of reverse transcriptase (RT) via DNA chain termination after incorporation of thenucleotide analogue. 3TC-TP is a weak inhibitor of mammalian DNA polymerases alpha and beta, and mitochondrial DNA polymerase- gamma

5.2 Pharmacokinetic properties

Absorption

Following oral administration of tenofovir disoproxil fumarate to HIV infected patients, tenofovir disoproxil fumarate is rapidly absorbed and converted to tenofovir. Administration of multiple doses of tenofovir disoproxil fumarate with a meal to HIV infected patients resulted in mean (%CV) tenofovir C_{max}, $AUC_{0-\infty}$, and C_{min} values of 326 (36.6%) ng/ml, 3,324 (41.2%) ng·h/ml and 64.4 (39.4%) ng/ml, respectively. Maximum tenofovir concentrations are observed in serum within one hour of dosing in the fasted state and within two hours when taken with food. The oral bioavailability of tenofovir from tenofovir disoproxil fumarate in fasted patients was approximately 25%. Administration of tenofovir disoproxil fumarate with a high fat meal enhanced the oral bioavailability, with an increase in tenofovir AUC by approximately 40% and C_{max} by approximately 14%. Following the first dose of tenofovir disoproxil fumarate in fed patients, the median C_{max} in serum ranged from 213 to 375 ng/ml. However, administration of tenofovir disoproxil fumarate with a light meal did not have a significant effect on the pharmacokinetics of tenofovir.

Distribution

Following intravenous administration the steady-state volume of distribution of tenofovir was estimated to be approximately 800 ml/kg. After oral administration of tenofovir disoproxil fumarate, tenofovir is distributed to most tissues with the highest concentrations occurring in the kidney, liver and the intestinal contents (preclinical studies). In vitro protein binding of tenofovir to plasma or serum protein was less than 0.7 and 7.2%, respectively, over the tenofovir concentration range 0.01 to 25 µg/ml.

Biotransformation

In vitro studies have determined that neither tenofovir disoproxil fumarate nor tenofovir are substrates for the CYP450 enzymes. Moreover, at concentrations substantially higher (approximately 300-fold) than those observed in vivo, tenofovir did not inhibit in vitro drug metabolism mediated by any of the major human CYP450 isoforms involved in drug biotransformation (CYP3A4, CYP2D6, CYP2C9, CYP2E1, or CYP1A1/2). Tenofovir disoproxil fumarate at a concentration of 100 µmol/l had no effect on any of the CYP450 isoforms, except CYP1A1/2, where a small (6%) but statistically significant reduction in metabolism of CYP1A1/2 substrate was observed. Based on these data, it is unlikely that clinically significant interactions involving tenofovir disoproxil fumarate and medicinal products metabolised by CYP450 would occur.

Elimination

Tenofovir is primarily excreted by the kidney by both filtration and an active tubular transport system with approximately 70 80% of the dose excreted unchanged in urine following intravenous administration. Total clearance has been estimated to be approximately 230 ml/h/kg (approximately 300 ml/min). Renal clearance has been estimated to be approximately 160 ml/h/kg (approximately 210 ml/min), which is in excess of the glomerular filtration rate. This indicates that active tubular secretion is an important part of the elimination of tenofovir.
Following oral administration the terminal half-life of tenofovir is approximately 12 to 18 hours.
Studies have established the pathway of active tubular secretion of tenofovir to be influx into proximal tubule cell by the human organic anion transporters (hOAT) 1 and 3 and efflux into the urine by the multidrug resistant protein 4 (MRP 4).
Linearity/non-linearity
The pharmacokinetics of tenofovir were independent of tenofovir disoproxil fumarate dose over the dose range 75 to 600 mg and were not affected by repeated dosing at any dose level.
Age and gender
Limited data on the pharmacokinetics of tenofovir in women indicate no major gender effect.
Pharmacokinetic studies have not been performed in children and adolescents (under 18) or in the elderly (over 65).
Pharmacokinetics have not been specifically studied in different ethnic groups.
Renal impairment
Pharmacokinetic parameters of tenofovir were determined following administration of a single dose of tenofovir disoproxil 245 mg to 40 non‑HIV, non‑HBV infected patients with varying degrees of renal impairment defined according to baseline creatinine clearance (CrCl) (normal renal function when CrCl> 80 ml/min; mild with CrCl = 50‑79 ml/min; moderate with CrCl = 30‑49 ml/min and severe with CrCl = 10‑29 ml/min). Compared with patients with normal renal function, the mean (%CV) tenofovir exposure increased from 2,185 (12%) ng·h/ml in subjects with CrCl> 80 ml/min to respectively 3,064 (30%) ng·h/ml, 6,009 (42%) ng·h/ml and 15,985 (45%) ng·h/ml in patients with mild, moderate and severe renal impairment. The dosing recommendations in patients with renal impairment, with increased dosing interval, are expected to result in higher peak plasma concentrations and lower C_{min} levels in patients with renal impairment compared with patients with normal renal function. The clinical implications of this are unknown.

In patients with end-stage renal disease (ESRD) (CrCl < 10 ml/min) requiring haemodialysis, between dialysis tenofovir concentrations substantially increased over 48 hours achieving a mean C_{max} of 1,032 ng/ml and a mean AUC_{0-48h} of 42,857 ng·h/ml.

It is recommended that the dosing interval for tenofovir disoproxil 245 mg (as fumarate) is modified in patients with creatinine clearance < 50 ml/min or in patients who already have ESRD and require dialysis.

The pharmacokinetics of tenofovir in non-haemodialysis patients with creatinine clearance < 10 ml/min and in patients with ESRD managed by peritoneal or other forms of dialysis have not been studied.

Hepatic impairment

A single 245 mg dose of tenofovir disoproxil was administered to non-HIV, non-HBV infected patients with varying degrees of hepatic impairment defined according to Child-Pugh-Turcotte (CPT) classification. Tenofovir pharmacokinetics were not substantially altered in subjects with hepatic impairment suggesting that no dose adjustment is required in these subjects. The mean (%CV) tenofovir C_{max} and AUC_0 values were 223 (34.8%) ng/ml and 2,050 (50.8%) ng·h/ml, respectively, in normal subjects compared with 289 (46.0%) ng/ml and 2,310 (43.5%) ng·h/ml in subjects with moderate hepatic impairment, and 305 (24.8%) ng/ml and 2,740 (44.0%) ng·h/ml in subjects with severe hepatic impairment.

Intracellular pharmacokinetics

In non-proliferating human peripheral blood mononuclear cells (PBMCs) the half-life of tenofovir diphosphate was found to be approximately 50 hours, whereas the half-life in phytohaemagglutinin-stimulated PBMCs was found to be approximately 10 hours.

Lamivudine:

Pharmacotherapeutic group: nucleoside analogue, ATC Code: J05AF05.

Lamivudine is a nucleoside analogue which has activity against human immunodeficiency virus (HIV) and hepatitis B virus (HBV). It is metabolised intracellularly to the active moiety, lamivudine 5'-triphosphate. Its main mode of action is as a chain terminator of viral reverse transcription. The triphosphate has selective inhibitory activity against HIV-1 and HIV-2 replication in vitro, it is also active against zidovudine-resistant clinical isolates of HIV. Lamivudine in combination with zidovudine exhibits synergistic anti-HIV activity against clinical isolates in cell culture.

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

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

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

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

Clinical experience:

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

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

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

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

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

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

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

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

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

The 150 mg tablet is bioequivalent and dose proportional to the 300 mg tablet with respect to AUC_{∞}, C_{max}, and t_{max}.

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

Administration of crushed tablets with a small amount of semi-solid food or liquid would not be expected to have an impact on the pharmaceutical quality, and would therefore not be expected

to alter the clinical effect. This conclusion is based on the physiochemical and pharmacokinetic data assuming that the patient crushes and transfers 100% of the tablet and ingests immediately.

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

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

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

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

Metabolism: The active moiety, intracellular lamivudine triphosphate, has a prolonged terminal half-life in the cell (16 to 19 hours) compared to the plasma lamivudine half-life (5 to 7 hours). In 60 healthy adult volunteers, Lamivudine 300 mg once daily has been demonstrated to be pharmacokinetically equivalent at steady-state to Lamivudine 150 mg twice daily with respect to intracellular triphosphate AUC_{24} and C_{max}.

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

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

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

Pharmacokinetics in children: In general, lamivudine pharmacokinetics in paediatric patients is similar to adults. However, absolute bioavailability (approximately 55-65%) was reduced in paediatric patients below 12 years of age. In addition, systemic clearance values were greater in younger paediatric patients and decreased with age, approaching adult values around 12 years of age. Due to these differences, the recommended dose for lamivudine in children (aged more than three months and weighing less than 30 kg) is 4 mg/kg twice daily. This dose will achieve an average AUC_{0-12} ranging from approximately 3,800 to 5,300 ng.h/ml. Recent findings indicate that exposure in children < 6 years of age may be reduced by about 30% compared with other age groups. Further data addressing this issue are currently awaited. At present, the available data do not suggest that lamivudine is less efficacious in this age group.
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 4 mg/kg/day. Glomerular filtration estimates suggests that to achieve similar adult and paediatric exposure, the recommended dose for children aged six weeks and older could be 8 mg/kg/day.

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

5.3 Preclinical safety data

Tenefovir disproxil fumarate

Preclinical studies conducted in rats, dogs and monkeys revealed target organ effects in gastrointestinal tract, kidney, bone and a decrease in serum phosphate concentration. Bone toxicity was diagnosed as osteomalacia (monkeys) and reduced bone mineral density (rats and dogs). Findings in the rat and monkey studies indicated that there was a substance-related decrease in intestinal absorption of phosphate with potential secondary reduction in bone mineral density. However, no conclusion could be drawn on the mechanism(s) underlying these toxicities.
Reproductive studies were conducted in rats and rabbits. There were no effects on mating or fertility parameters or on any pregnancy or foetal parameter. There were no gross foetal alterations of soft or skeletal tissues. Tenofovir disoproxil fumarate reduced the viability index and weight of pups in peri-

post natal toxicity studies.Genotoxicity studies have shown that tenofovir disoproxil fumarate was negative in the *in vivo* mouse bone marrow micronucleus assay but was positive for inducing forward mutations in the *in vitro* L5178Y mouse lymphoma cell assay in the presence or absence of S9 metabolic activation. Tenofovir disoproxil fumarate was positive in the Ames test (strain TA 1535) in two out of three studies, once in the presence of S9 mix (6.2- to 6.8-fold increase) and once without S9 mix. Tenofovir disoproxil fumarate was also weakly positive in an in vivo / in vitro unscheduled DNA synthesis test in primary rat hepatocytes.Tenofovir disoproxil fumarate did not show any carcinogenic potential in a long-term oral carcinogenicity study in rats. A long-term oral carcinogenicity study in mice showed a low incidence of duodenal tumours, considered likely related to high local concentrations of tenofovir disoproxil fumarate in the gastrointestinal tract at a dose of 600 mg/kg/day. While the mechanism of tumour formation is uncertain, the findings are unlikely to be of relevance to humans.

Lamivudine

Administration of Lamivudine in animal toxicity studies at high doses was not associated with any major organ toxicity. At the highest dosage levels, minor effects on indicators of liver and kidney function were seen together with occasional reductions in liver weight. The clinically relevant effects noted were a reduction in red blood cell count and neutropenia. Lamivudine was not mutagenic in bacterial tests but, like many nucleoside analogues, showed activity in an *in vitro* cytogenetic assay and the mouse lymphoma assay. Lamivudine was not genotoxic *in vivo* at doses that gave plasma concentrations around 40-50 times higher than the anticipated clinical plasma levels. As the in vitro mutagenic activity of Lamivudine could not be confirmed in *in vivo* tests, it is concluded that Lamivudine should not represent a genotoxic hazard to patients undergoing treatment.

A transplacental genotoxicity study conducted in monkeys compared zidovudine alone with the combination of zidovudine and Lamivudine at human-equivalent exposures. The study demonstrated that foetuses exposed *in utero* to the combination sustained a higher level of nucleoside analogue-DNA incorporation into multiple foetal organs, and showed evidence of more telomere shortening than in those exposed to zidovudine alone. The clinical significance of these findings is unknown. The results of long-term carcinogenicity studies in rats and mice did not show any carcinogenic potential relevant for humans.

6. Pharmaceutical particulars

6.1 List of excipients

Lactose monohydrate Pharmatose 200M)# Corn starch, (Extra white Maize Starch) Croscarmellose sodium, (Primellose) Povidone, (Kollidon 30) Isopropyl Alcohol, Microcrystalline cellulose, (Cyclocel PH 101) Crospovidone, (Kollidon CL) Colloidal silicon dioxide, (Aerosil 200 Magnesium stearate, (LIGAMED MF-2-V) FD&C Blue #2/lndigo carmine AL 30%- 36% Opadry Light blue (Y-30-10671-A)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store below 30°C and protect from moisture.

6.5 Nature and contents of container

HDPE container pack of 30's count

6.6 Special precautions for disposal and other handling

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

7. Marketing Authorisation Holder and Manufacturing Site Addresses

Marketing authorization Holder:

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8. Marketing authorization number
06413/08330/NMR/2020

9. Date of first registration/renewal of the registration
Jul 26, 2021

10. Date of revision of the text