Tenofovir Alafenamide HepBest 25mg Film-Coated Tablet 75093454

75093454 Film-Coated Tablet 25 mg HepBest Tenofovir Alafenamide

Tenofovir Alafenamide

HepBest

25 mg

Film-Coated Tablet

Antiviral

℞

1. NAME OF THE MEDICINAL PRODUCT

Tenofovir alafenamide film-coated Tablet 25 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains Tenofovir alafenamide Fumarate equivalent to Tenofovir Alafenamide 25 mg.

Excipient with known effect

Each tablet contains 67.957 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-Coated tablet.

A white to off-white, film-coated, round, biconvex tablet debossed with **M** on one side of the tablet and **TFI** on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tenofovir alafenamide film-coated tablets 25 mg are indicated for the treatment of chronic hepatitis B in adults and adolescents (aged 12 years and older with body weight at least 35 kg) (see section 5.1).

4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the management of chronic hepatitis B.

Posology

Adults and adolescents (aged 12 years and older with body weight at least 35 kg): one tablet once daily.

Treatment discontinuation

Treatment discontinuation may be considered as follows (see section 4.4):

- In HBeAg-positive patients without cirrhosis, treatment should be administered for at least 6-12 months after HBe seroconversion (HBeAg loss and HBV DNA loss with anti-HBe detection) is confirmed or until HBs seroconversion or until there is loss of efficacy (see section 4.4). Regular reassessment is recommended after treatment discontinuation to detect virological relapse.
- In HBeAg-negative patients without cirrhosis, treatment should be administered at least until HBs seroconversion or until there is evidence of loss of efficacy. With prolonged treatment for more than 2 years, regular reassessment is recommended to confirm that continuing the selected therapy remains appropriate for the patient.

Missed dose

If a dose is missed and less than 18 hours have passed from the time it is usually taken, the patient should take Tenofovir alafenamide film-coated tablets 25 mg as soon as possible and then resume their normal dosing schedule. If more than 18 hours have passed from the time it is usually taken, the patient should not take the missed dose and should simply resume the normal dosing schedule.

If the patient vomits within 1 hour of taking Tenofovir alafenamide film-coated tablets 25 mg, the patient should take another film-coated tablet. If the patient vomits more than 1 hour after taking Tenofovir alafenamide film-coated tablets 25 mg, the patient does not need to take another tablet.

Special populations

Elderly

No dose adjustment of Tenofovir alafenamide film-coated 25 mg is required in patients aged 65 years and older (see section 5.2).

Renal impairment

No dose adjustment of Tenofovir alafenamide film-coated tablets 25 mg is required in adults or adolescents (aged at least 12 years and of at least 35 kg body weight) with estimated creatinine clearance (CrCl) ≥ 15 mL/min or in patients with CrCl < 15 mL/min who are receiving haemodialysis.

On days of haemodialysis, Tenofovir alafenamide film-coated tablets 25 mg should be administered after completion of haemodialysis treatment (see section 5.2).

No dosing recommendations can be given for patients with CrCl < 15 mL/min who are not receiving haemodialysis (see section 4.4).

Hepatic impairment

No dose adjustment of Tenofovir alafenamide film-coated tablets 25 mg is required in patients with hepatic impairment (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of Tenofovir alafenamide film-coated tablets 25 mg in children younger than 12 years of age, or weighing < 35 kg, have not yet been established. No data are available.

Method of administration

Oral administration. Tenofovir alafenamide film-coated tablets 25 mg should be taken with food.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

HBV transmission

Patients must be advised that Tenofovir alafenamide film-coated tablets 25 mg does not prevent the risk of transmission of HBV to others through sexual contact or contamination with blood. Appropriate precautions must continue to be used.

Patients with decompensated liver disease

There are no data on the safety and efficacy of Tenofovir alafenamide film-coated tablets 25 mg in HBV infected patients with decompensated liver disease and who have a Child Pugh Turcotte (CPT) score > 9 (i.e. class C). These patients may be at higher risk of experiencing serious hepatic or renal adverse reactions. Therefore, hepatobiliary and renal parameters should be closely monitored in this patient population (see section 5.2).

Exacerbation of hepatitis

Flares on treatment

Spontaneous exacerbations in chronic hepatitis B are relatively common and are characterised by transient increases in serum alanine aminotransferase (ALT). After initiating antiviral therapy, serum ALT may increase in some patients. In patients with compensated liver disease, these increases in serum ALT are generally not accompanied by an increase in serum bilirubin concentrations or hepatic decompensation. Patients with cirrhosis may be at a higher risk for hepatic decompensation following hepatitis exacerbation, and therefore should be monitored closely during therapy.

Flares after treatment discontinuation

Acute exacerbation of hepatitis has been reported in patients who have discontinued treatment for hepatitis B, usually in association with rising HBV DNA levels in plasma. The majority of cases are self-limited but severe exacerbations, including fatal outcomes, may occur after discontinuation of treatment for hepatitis B. Hepatic function should be monitored at repeated intervals with both clinical and laboratory follow-up for at least 6 months after discontinuation of treatment for hepatitis B. If appropriate, resumption of hepatitis B therapy may be warranted.

In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation. Liver flares are especially serious, and sometimes fatal in patients with decompensated liver disease.

Renal impairment

Patients with creatinine clearance < 30 mL/min

The use of Tenofovir alafenamide film-coated tablets 25 mg once daily in patients with CrCl ≥ 15 mL/min but < 30 mL/min and in patients with CrCl < 15 mL/min who are receiving haemodialysis is based on very limited pharmacokinetic data and on modelling and simulation. There are no safety data on the use of Tenofovir alafenamide film-coated tablets 25 mg to treat HBV infected patients with CrCl < 30 mL/min.

The use of Tenofovir alafenamide film-coated tablets 25 mg is not recommended in patients with CrCl < 15 mL/min who are not receiving haemodialysis (see section 4.2).

Nephrotoxicity

A potential risk of nephrotoxicity resulting from chronic exposure to low levels of tenofovir due to dosing with tenofovir alafenamide cannot be excluded (see section 5.3).

Patients coinfected with HBV and hepatitis C or D virus

There are no data on the safety and efficacy of Tenofovir alafenamide film-coated tablets 25 mg in patients co-infected with hepatitis C or D virus. Co-administration guidance for the treatment of hepatitis C should be followed (see section 4.5).

Hepatitis B and HIV coinfection

HIV antibody testing should be offered to all HBV infected patients whose HIV-1 infection status is unknown before initiating therapy with Tenofovir alafenamide film-coated tablets 25 mg. In patients who are co-infected with HBV and HIV, Tenofovir alafenamide film-coated tablets 25 mg should be co-administered with other antiretroviral agents to ensure that the patient receives an appropriate regimen for treatment of HIV (see section 4.5).

Coadministration with other medicinal products

Tenofovir alafenamide film-coated tablets 25 mg should not be co-administered with medicinal products containing tenofovir alafenamide, tenofovir disoproxil or adefovir dipivoxil.

Co-administration of Tenofovir alafenamide film-coated tablets 25 mg with certain anticonvulsants (e.g. carbamazepine, oxcarbazepine, phenobarbital and phenytoin), antimycobacterials (e.g. rifampicin, rifabutin and rifapentine) or St. John's wort, all of which are inducers of P-glycoprotein (P-gp) and may decrease tenofovir alafenamide plasma concentrations, is not recommended.

Co-administration of Tenofovir alafenamide film-coated tablets 25 mg with strong inhibitors of P-gp (e.g. itraconazole and ketoconazole) may increase tenofovir alafenamide plasma concentrations. Co-administration is not recommended.

Lactose intolerance

Tenofovir alafenamide film-coated tablets 25 mg contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Tenofovir alafenamide film-coated tablets 25 mg should not be co-administered with medicinal products containing tenofovir disoproxil, tenofovir alafenamide or adefovir dipivoxil.

Medicinal products that may affect tenofovir alafenamide

Tenofovir alafenamide is transported by P-gp and breast cancer resistance protein (BCRP). Medicinal products that are P-gp inducers (e.g., rifampicin, rifabutin, carbamazepine, phenobarbital or St. John's wort) are expected to decrease plasma concentrations of tenofovir alafenamide, which may lead to loss

of therapeutic effect of Tenofovir alafenamide film-coated tablets 25 mg. Co-administration of such medicinal products with Tenofovir alafenamide film-coated tablets 25 mg is not recommended.

Co-administration of tenofovir alafenamide with medicinal products that inhibit P-gp and BCRP may increase plasma concentrations of tenofovir alafenamide. Co-administration of strong inhibitors of P-gp with tenofovir alafenamide is not recommended.

Tenofovir alafenamide is a substrate of OATP1B1 and OATP1B3 in vitro. The distribution of tenofovir alafenamide in the body may be affected by the activity of OATP1B1 and/or OATP1B3.

Effect of tenofovir alafenamide on other medicinal products

Tenofovir alafenamide is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 *in vitro*. It is not an inhibitor or inducer of CYP3A *in vivo*.

Tenofovir alafenamide is not an inhibitor of human uridine diphosphate glucuronosyltransferase (UGT) 1A1 *in vitro*. It is not known whether tenofovir alafenamide is an inhibitor of other UGT enzymes.

Drug interaction information for Tenofovir alafenamide film-coated tablets 25 mg with potential concomitant medicinal products is summarised in Table 1 below (increase is indicated as "↑", decrease as "↓", no change as "↔"; twice daily as "b.i.d.", single dose as "s.d.", once daily as "q.d."; and intravenously as "IV"). The drug interactions described are based on studies conducted with tenofovir alafenamide, or are potential drug interactions that may occur with Tenofovir alafenamide film-coated tablets 25 mg.

Table 1: Interactions between Tenofovir alafenamide film-coated 25 mg and other medicinal products

Medicinal product by therapeutic areas	Effects on drug levels[a,b] Mean ratio (90% confidence interval) for AUC, C_{max}, C_{min}	Recommendation concerning Coadministration with Tenofovir alafenamide film-coated tablets 25 mg.
ANTICONVULSANTS		
Carbamazepine (300 mg orally, b.i.d.) Tenofovir alafenamide[c] (25 mg orally, s.d.)	*Tenofovir alafenamide* ↓ C_{max} 0.43 (0.36, 0.51) ↓ AUC 0.45 (0.40, 0.51) *Tenofovir* ↓ C_{max} 0.70 (0.65, 0.74) ↔ AUC 0.77 (0.74, 0.81)	Coadministration is not recommended.
Oxcarbazepine Phenobarbital	Interaction not studied. *Expected:* ↓ Tenofovir alafenamide	Co-administration is not recommended.
Phenytoin	Interaction not studied. Expected: ↓ Tenofovir alafenamide	Coadministration is not recommended.
Midazolam[d] (2.5 mg orally, s.d.) Tenofovir alafenamide[c] (25 mg orally, q.d.)	Midazolam ↔ C_{max} 1.02 (0.92, 1.13) ↔ AUC 1.13 (1.04, 1.23)	No dose adjustment of midazolam (administered orally or IV) is required.
Midazolam[d] (1 mg IV, s.d.) Tenofovir alafenamide[c] (25 mg orally, q.d.)	Midazolam ↔ C_{max} 0.99 (0.89, 1.11) ↔ AUC 1.08 (1.04, 1.14)	
Sertraline (50 mg orally, s.d.) Tenofovir alafenamide[c] (10 mg orally, q.d.)	*Tenofovir alafenamide* ↔ C_{max} 1.00 (0.86, 1.16) ↔ AUC 0.96 (0.89, 1.03) Tenofovir ↔ C_{max} 1.10 (1.00, 1.21) ↔ AUC 1.02 (1.00, 1.04) ↔ C_{min} 1.01 (0.99, 1.03)	No dose adjustment of Tenofovir alafenamide film-coated 25 mg or sertraline is required.
Sertraline (50 mg orally, s.d.) Tenofovir alafenamide[c] (10 mg orally, q.d.)	*Sertraline* ↔ C_{max} 1.14 (0.94, 1.38) ↔ AUC 0.93 (0.77, 1.13)	
ANTIFUNGALS		
Itraconazole Ketoconazole	Interaction not studied. *Expected:* ↑ Tenofovir alafenamide	Co-administration is not recommended.
ANTIMYCOBACTERIALS		
Rifampicin Rifapentine	Interaction not studied. *Expected:* ↓ Tenofovir alafenamide	Co-administration is not recommended.
Rifabutin	Interaction not studied. *Expected:* ↓ Tenofovir alafenamide	Co-administration is not recommended.
HCV ANTIVIRAL AGENTS		
Sofosbuvir (400 mg orally, q.d.)	Interaction not studied. *Expected:* ↔ Sofosbuvir ↔ GS331007	No dose adjustment of Tenofovir alafenamide film-coated 25 mg or sofosbuvir is required.
Ledipasvir/sofosbuvir (90 mg/400 mg orally, q.d.) Tenofovir alafenamide[f] (25 mg orally, q.d.)	*Ledipasvir* ↔ C_{max} 1.01 (0.97, 1.05) ↔ AUC 1.02 (0.97, 1.06) ↔ C_{min} 1.02 (0.98, 1.07) *Sofosbuvir* ↔ C_{max} 0.96 (0.89, 1.04) ↔ AUC 1.05 (1.01, 1.09) *GS331007g* ↔ C_{max} 1.08 (1.05, 1.11) ↔ AUC 1.08 (1.06, 1.10) ↔ C_{min} 1.10 (1.07, 1.12) *Tenofovir alafenamide* ↔ C_{max} 1.03 (0.94, 1.14) ↔ AUC 1.32 (1.25, 1.40) *Tenofovir* ↑ C_{max} 1.62 (1.56, 1.68) ↑ AUC 1.75 (1.69, 1.81) ↑ C_{min} 1.85 (1.78, 1.92)	No dose adjustment of Tenofovir alafenamide film-coated 25 mg or ledipasvir/sofosbuvir is required.
Sofosbuvir/velpatasvir (400 mg/100 mg orally, q.d.)	Interaction not studied. *Expected:* ↔ Sofosbuvir ↔ GS331007 ↔ Velpatasvir ↑ Tenofovir alafenamide	No dose adjustment of Tenofovir alafenamide film-coated 25 mg or sofosbuvir/velpatasvir is required.
Sofosbuvir / velpatasvir / voxilaprevir (400 mg / 100 mg/100 mg + 100 mgi orally, q.d.)	Sofosbuvir ↔ C_{max} 0.95 (0.86, 1.05) ↔ AUC 1.01 (0.97, 1.06) GS-331007 () ↔ C_{max} 1.02 (0.98, 1.06) ↔ AUC 1.04 (1.01, 1.06) Velpatasvir ↔ C_{max} 1.05 (0.96, 1.16) ↔ AUC 1.01 (0.94, 1.07) ↔ C_{min} 1.01 (0.95, 1.09) Voxilaprevir ↔ C_{max} 0.96 (0.84, 1.11) ↔ AUC 0.94 (0.84, 1.05) ↔ C_{min} 1.02 (0.92, 1.12)	No dose adjustment of Tenofovir alafenamide film-coated tablets 25 mg or sofosbuvir / velpatasvir / voxilaprevir is required.
HIV ANTIRETROVIRAL AGENTS – PROTEASE INHIBITORS		
Atazanavir/ cobicistat (300 mg/150 mg orally, q.d.) Tenofovir alafenamide[c] (10 mg orally, q.d.)	*Tenofovir alafenamide* ↑ C_{max} 1.80 (1.48, 2.18) ↑ AUC 1.75 (1.55, 1.98) *Tenofovir* ↑ C_{max} 3.16 (3.00, 3.33) ↑ AUC 3.47 (3.29, 3.67) ↑ C_{min} 3.73 (3.54, 3.93) *Atazanavir* ↔ C_{max} 0.98 (0.94, 1.02) ↔ AUC 1.06 (1.01, 1.11) ↔ C_{min} 1.18 (1.06, 1.31) *Cobicistat* ↔ C_{max} 0.96 (0.92, 1.00) ↔ AUC 1.05 (1.00, 1.09) ↑ C_{min} 1.35 (1.21, 1.51)	Coadministration is not recommended.
Atazanavir/ritonavir (300 mg/100 mg orally, q.d.) *Tenofovir alafenamide*[c] (10 mg orally, s.d.)	*Tenofovir alafenamide* ↑ C_{max} 1.77 (1.28, 2.44) ↑ AUC 1.91 (1.55, 2.35) *Tenofovir* ↑ C_{max} 2.12 (1.86, 2.43) ↑ AUC 2.62 (2.14, 3.20) *Atazanavir* ↔ C_{max} 0.98 (0.89, 1.07) ↔ AUC 0.99 (0.96, 1.01) ↔ C_{min} 1.00 (0.96, 1.04)	Coadministration is not recommended.
Darunavir/cobicistat (800 mg/150 mg orally, q.d.) Tenofovir alafenamide[c] (25 mg orally, q.d.)	*Tenofovir alafenamide* ↔ C_{max} 0.93 (0.72, 1.21) ↔ AUC 0.98 (0.80, 1.19) *Tenofovir* ↑ C_{max} 3.16 (3.00, 3.33) ↑ AUC 3.24 (3.02, 3.47) ↑ C_{min} 3.21 (2.90, 3.54) *Darunavir* ↔ C_{max} 1.02 (0.96, 1.09) ↔ AUC 0.99 (0.92, 1.07) ↔ C_{min} 0.97 (0.82, 1.15) *Cobicistat* ↔ C_{max} 1.06 (1.00, 1.12) ↔ AUC 1.09 (1.03, 1.15) ↔ C_{min} 1.11 (0.98, 1.25)	Co-administration is not recommended.
Darunavir/cobicistat (800 mg/150 mg orally, q.d.) Tenofovir alafenamide[c] (25 mg orally, q.d.)	*Tenofovir alafenamide* ↔ C_{max} 0.93 (0.72, 1.21) ↔ AUC 0.98 (0.80, 1.19) *Tenofovir* ↑ C_{max} 3.16 (3.00, 3.33) ↑ AUC 3.24 (3.02, 3.47) ↑ C_{min} 3.21 (2.90, 3.54) *Darunavir* ↔ C_{max} 1.02 (0.96, 1.09) ↔ AUC 0.99 (0.92, 1.07) ↔ C_{min} 0.97 (0.82, 1.15) *Cobicistat* ↔ C_{max} 1.06 (1.00, 1.12) ↔ AUC 1.09 (1.03, 1.15) ↔ C_{min} 1.11 (0.98, 1.25)	Coadministration is not recommended.
Darunavir/ritonavir (800 mg/100 mg orally, q.d.) Tenofovir alafenamide[c] (10 mg orally, s.d.)	*Tenofovir alafenamide* ↑ C_{max} 1.42 (0.96, 2.09) ↔ AUC 1.06 (0.84, 1.35) *Tenofovir* ↑ C_{max} 2.42 (1.98, 2.95) ↑ AUC 2.05 (1.54, 2.72) *Darunavir* ↔ C_{max} 0.99 (0.91, 1.08) ↔ AUC 1.01 (0.96, 1.06) ↔ C_{min} 1.13 (0.95, 1.34)	Co-administration is not recommended.
Lopinavir/ritonavir (800 mg/200 mg orally, q.d.) Tenofovir alafenamide[c] (10 mg orally, s.d.)	*Tenofovir alafenamide* ↑ C_{max} 2.19 (1.72, 2.79) ↑ AUC 1.47 (1.17, 1.85) *Tenofovir* ↑ C_{max} 3.75 (3.19, 4.39) ↑ AUC 4.16 (3.50, 4.96) *Lopinavir* ↔ C_{max} 1.00 (0.95, 1.06) ↔ AUC 1.00 (0.92, 1.09) ↔ C_{min} 0.98 (0.85, 1.12)	Co-administration is not recommended.
Tipranavir/ritonavir	Interaction not studied. Expected: ↓ Tenofovir alafenamide	Co-administration is not recommended.
HIV ANTIRETROVIRAL AGENTS – INTEGRASE INHIBITORS		
Dolutegravir (50 mg orally, q.d.) Tenofovir alafenamide[c] (10 mg orally, s.d.)	*Tenofovir alafenamide* ↑ C_{max} 1.24 (0.88, 1.74) ↑ AUC 1.19 (0.96, 1.48) *Tenofovir* ↔ C_{max} 1.10 (0.96, 1.25) ↑ AUC 1.25 (1.06, 1.47) *Dolutegravir* ↔ C_{max} 1.15 (1.04, 1.27) ↔ AUC 1.02 (0.97, 1.08) ↔ C_{min} 1.05 (0.97, 1.13)	No dose adjustment of Tenofovir alafenamide film-coated 25 mg or dolutegravir is required.
Raltegravir	Interaction not studied. *Expected:* ↔ Tenofovir alafenamide ↔ Raltegravir	No dose adjustment of Tenofovir alafenamide film-coated 25 mg or raltegravir is required.
HIV ANTIRETROVIRAL AGENTS – NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS		
Efavirenz (600 mg orally, q.d.) Tenofovir alafenamide[b] (40 mg orally, q.d.)	*Tenofovir alafenamide* ↓ C_{max} 0.78 (0.58, 1.05) ↔ AUC 0.86 (0.72, 1.02) *Tenofovir* ↓ C_{max} 0.75 (0.67, 0.86) ↔ AUC 0.80 (0.73, 0.87) ↔ C_{min} 0.82 (0.75, 0.89) *Expected:* ↔ Efavirenz	No dose adjustment of Tenofovir alafenamide film-coated 25 mg or efavirenz is required.
Nevirapine	Interaction not studied. *Expected:* ↔ Tenofovir alafenamide ↔ Nevirapine	No dose adjustment of Tenofovir alafenamide film-coated 25 mg or nevirapine is required.
Rilpivirine (25 mg orally, q.d.) Tenofovir alafenamide (25 mg orally, q.d.)	*Tenofovir alafenamide* ↔ C_{max} 1.01 (0.84, 1.22) ↔ AUC 1.01 (0.94, 1.09) *Tenofovir* ↔ C_{max} 1.13 (1.02, 1.23) ↔ AUC 1.11 (1.07, 1.14) ↔ C_{min} 1.18 (1.13, 1.23) *Rilpivirine* ↔ C_{max} 0.93 (0.87, 0.99) ↔ AUC 1.01 (0.96, 1.06) ↔ C_{max} 1.13 (1.04, 1.23)	No dose adjustment of Tenofovir alafenamide film-coated 25 mg or rilpivirine is required.
HIV ANTIRETROVIRAL AGENTS – CCR5 RECEPTOR ANTAGONIST		
Maraviroc	Interaction not studied. Expected: ↔ Tenofovir alafenamide ↔ Maraviroc	No dose adjustment of Tenofovir alafenamide film-coated 25 mg or maraviroc is required.
HERBAL SUPPLEMENTS		
St. John's wort *(Hypericum perforatum)*	Interaction not studied. Expected: ↓ Tenofovir alafenamide	Co-administration is not recommended.
ORAL CONTRACEPTIVES		
Norgestimate (0.180 mg/0.215 mg/ 0.250 mg orally, q.d.) Ethinyl estradiol (0.025 mg orally, q.d.) Tenofovir alafenamide[c] (25 mg orally, q.d.)	*Norgestromin* ↔ C_{max} 1.17 (1.07, 1.26) ↔ AUC 1.12 (1.07, 1.17) ↔ C_{max} 1.16 (1.08, 1.24) *Norgestrel* ↔ C_{max} 1.10 (1.02, 1.18) ↔ AUC 1.09 (1.01, 1.18) ↔ C_{min} 1.11 (1.03, 1.20) *Ethinylestradiol* ↔ C_{max} 1.22 (1.15, 1.29) ↔ AUC 1.11 (1.07, 1.16) ↔ C_{min} 1.02 (0.93, 1.12)	No dose adjustment of Tenofovir alafenamide film-coated 25 mg or norgestimate/ethinyl estradiol is required.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of tenofovir alafenamide in pregnant women. However, a large amount of data on pregnant women (more than 1,000 exposed outcomes) indicate no malformative nor feto/neonatal toxicity associated with the use of tenofovir disoproxil.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

The use of tenofovir alafenamide may be considered during pregnancy, if necessary.

Breast-feeding

It is not known whether tenofovir alafenamide is secreted in human milk. However, in animal studies it has been shown that tenofovir is secreted into milk. There is insufficient information on the effects of tenofovir in newborns/infants.

A risk to the breast-fed newborns/infants cannot be excluded; therefore, tenofovir alafenamide should not be used during breast-feeding.

Fertility

No human data on the effect of tenofovir alafenamide on fertility are available. Animal studies do not indicate harmful effects of tenofovir alafenamide on fertility.

4.6 Effects on ability to drive and use machines

Tenofovir alafenamide film-coated tablets 25 mg has no or negligible influence on the ability to drive and use machines. Patients should be informed that dizziness has been reported during treatment with tenofovir alafenamide.

4.7 Undesirable effects

Summary of the safety profile

Assessment of adverse reactions is based on pooled safety data from 2 controlled Phase 3 studies (GS-US-320-0108 and GS-US-320-0110; "Study 108" and "Study 110", respectively) in which 866 HBV infected viremic patients with elevated serum ALT levels received 25 mg tenofovir alafenamide once daily in a double-blind fashion through Week 96 (median duration of blinded study drug exposure of 104 weeks) and from post-marketing experience. The most frequently reported adverse reactions were headache (12%), nausea (6%), and fatigue (6%). After Week 96, patients either remained on their original blinded treatment or received open-label tenofovir alafenamide.

Changes in lipid laboratory tests were observed in Study 108 and Study 110. No additional adverse reactions to tenofovir alafenamide were identified from Week 96 through Week 144 in the double- blind phase and in the subset of subjects receiving open-label tenofovir alafenamide treatment (see section 5.1).

In an ongoing double-blind, randomized, active-controlled study (GS-US-320-4018; "Study 4018") in virologically suppressed subjects who switched from tenofovir disoproxil to 25 mg tenofovir alafenamide (N=243), changes in lipid laboratory tests were observed. No additional adverse reactions to tenofovir alafenamide were identified through Week 48.

Tabulated summary of adverse reactions

The following adverse drug reactions have been identified with tenofovir alafenamide in patients with chronic hepatitis B (Table 2). The adverse reactions are listed below by body system organ class and frequency based on the Week 96 analysis. Frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10) or uncommon (≥ 1/1,000 to < 1/100).

Table 2: Adverse drug reactions identified with tenofovir alafenamide

System organ class	
Frequency	**Adverse reaction**
Nervous system disorders	
Very common	Headache
Common	Dizziness
Gastrointestinal disorders	
Common	Diarrhoea, vomiting, nausea, abdominal pain, abdominal distension, flatulence
Hepatobiliary disorders	
Common	Increased ALT

System organ class	
Frequency	**Adverse reaction**
Common	
Skin and subcutaneous tissue disorders	
Common	Rash, pruritus
Uncommon	Angioedema , urticaria
Musculoskeletal and connective tissue disorders	
Common	Arthralgia
General disorders and administration site conditions	
Common	Fatigue

[1] Adverse reaction identified through post-marketing surveillance for tenofovir alafenamide-containing products.

Changes in lipid laboratory tests

In a pooled analysis of Studies *108* and *110*, median changes in fasting lipid parameters from baseline to Week 96 were observed in both treatment groups. In the tenofovir alafenamide group, decreases in median fasting total cholesterol and HDL, and increases in median fasting direct LDL and triglycerides were observed, while the tenofovir disoproxil group demonstrated median reductions in all parameters (see Table 6). In patients randomised initially to tenofovir alafenamide and switched to receive open-label tenofovir alafenamide at Week 96, the median (Q1, Q3) changes from double-blind baseline to Week 144 were as follows (mg/dL): total cholesterol was 0 (-16, 18); LDL was 8 (-6, 24); HDL was -5 (-12, 2); triglycerides were 11 (-11, 40); total cholesterol to HDL ratio was 0.3 (0.0, 0.7). In patients randomised initially to tenofovir disoproxil and switched to open-label tenofovir alafenamide at Week 96, the median (Q1, Q3) changes from double-blind baseline to Week 144 were as follows (mg/dL): total cholesterol was 1 (-17, 20); LDL was 9 (-5, 26); HDL was -8 (-15, -1); triglycerides were 14 (-10, 43); total cholesterol to HDL ratio was 0.4 (0.0, 1.0).

In the open-label phase of Studies 108 and 110, where patients switched to open-label tenofovir alafenamide at Week 96, lipid parameters at Week 144 in patients who remained on tenofovir alafenamide were similar to those at Week 96, whereas median increases in fasting total cholesterol, direct LDL, HDL, and triglycerides were observed in patients who switched from tenofovir disoproxil to tenofovir alafenamide at Week 96. In the open label phase, median (Q1, Q3) change from Week 96 to Week 144 in total cholesterol to HDL ratio was 0.0 (-0.2, 0.4) in patients who remained on tenofovir alafenamide and 0.2 (-0.2, 0.6) in patients who switched from tenofovir disoproxil to tenofovir alafenamide at Week 96.

In Study 4018, median changes in fasting lipid parameters from baseline to Week 48 were observed in both treatment groups. In the group that switched from tenofovir disoproxil to tenofovir alafenamide, increases in median fasting total cholesterol, LDL, HDL, and triglycerides were observed, while the group continuing treatment with tenofovir disoproxil demonstrated reductions in median fasting total cholesterol, HDL, and triglycerides, and a minimal median increase in LDL ($p < 0.001$ for the difference between treatment groups in all parameters). Median (Q1, Q3) change from baseline at Week 48 in total cholesterol to HDL ratio was 0.2 (-0.1, 0.5) in the tenofovir alafenamide group and 0.0 (-0.3, 0.3) in the tenofovir disoproxil group ($p < 0.001$ for the difference between treatment groups).

Metabolic parameters

Body weight and levels of blood lipids and glucose may increase during therapy.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

If overdose occurs the patient must be monitored for evidence of toxicity (see section 4.8).

Treatment of overdose with tenofovir alafenamide consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient.

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Vendor Job No.	NA	Affiliate New Code	NA	Product Description	LIT HEPBEST VT (TAF) TAB 25MG PH				
Artwork Proof No.	NA	Aff. Superseded Code	NA						
Pharma Code	NA	Barcode Information	NA	New Material Code	75093454	Actual A/w Size	Flat - 340 x 500 mm		
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Revision History	07.10.2022 - New Component			Date / Remarks		Date / Remarks		
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Tenofovir is efficiently removed by haemodialysis with an extraction coefficient of approximately 54%. It is not known whether tenofovir can be removed by peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiviral for systemic use, nucleoside and nucleotide reverse transcriptase inhibitors; ATC code: J05AF13.

Mechanism of action

Tenofovir alafenamide is a phosphonamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analogue). Tenofovir alafenamide enters primary hepatocytes by passive diffusion and by the hepatic uptake transporters OATP1B1 and OATP1B3. Tenofovir alafenamide is primarily hydrolysed to form tenofovir by carboxylesterase 1 in primary hepatocytes. Intracellular tenofovir is subsequently phosphorylated to the pharmacologically active metabolite tenofovir diphosphate.

Tenofovir diphosphate inhibits HBV replication through incorporation into viral DNA by the HBV reverse transcriptase, which results in DNA chain termination.

Tenofovir has activity that is specific to hepatitis B virus and human immunodeficiency virus (HIV-1 and HIV-2). Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there is no evidence of mitochondrial toxicity in vitro based on several assays including mitochondrial DNA analyses.

Antiviral activity

The antiviral activity of tenofovir alafenamide was assessed in HepG2 cells against a panel of HBV clinical isolates representing genotypes A-H. The EC50 (50% effective concentration) values for tenofovir alafenamide ranged from 34.7 to 134.4 nM, with an overall mean EC50 of 86.6 nM. The CC50 (50% cytotoxicity concentration) in HepG2 cells was > 44,400 nM.

Resistance

In patients receiving tenofovir alafenamide, sequence analysis was performed on paired baseline and on-treatment HBV isolates for patients who either experienced virologic breakthrough (2 consecutive visits with HBV DNA ≥ 69 IU/mL after having been < 69 IU/mL, or 1.0 log10 or greater increase in HBV DNA from nadir) or patients with HBV DNA ≥ 69 IU/mL at Week 48, or Week 96 or at early discontinuation at or after Week 24.

In a pooled analysis of patients receiving tenofovir alafenamide in Study 108 and Study 110 at Week 48 (N = 20) and Week 96 (N = 72), no amino acid substitutions associated with resistance to tenofovir alafenamide were identified in these isolates (genotypic and phenotypic analyses).

In virologically suppressed patients receiving tenofovir alafenamide following switch from tenofovir disoproxil treatment in Study 4018, no patient experienced a virologic blip (one visit with HBV DNA ≥ 69 IU/mL), virologic breakthrough or persistent viremia during treatment. and 0 of 243 (0.0%) patients qualified for resistance analysis through 48 weeks of tenofovir alafenamide treatment.

Cross-resistance

The antiviral activity of tenofovir alafenamide was evaluated against a panel of isolates containing nucleos(t)ide reverse transcriptase inhibitor mutations in HepG2 cells. HBV isolates expressing the rtV173L, rtL180M, and rtM204V/I substitutions associated with resistance to lamivudine remained susceptible to tenofovir alafenamide (< 2-fold change in EC50). HBV isolates expressing the rtL180M, rtM204V plus rtT184G, rtS202G, or rtM250V substitutions associated with resistance to entecavir remained susceptible to tenofovir alafenamide. HBV isolates expressing the rtA181T, rtA181V, or rtT236T single substitutions associated with resistance to adefovir remained susceptible to tenofovir alafenamide; however, the HBV isolate expressing rtA181V plus rtN236T exhibited reduced susceptibility to tenofovir alafenamide (3.7-fold change in EC50). The clinical relevance of these substitutions is not known.

Clinical data

The efficacy and safety of tenofovir alafenamide in patients with chronic hepatitis B are based on 48- and 96-week data from two randomised, double-blind, active-controlled studies, *Study 108* and *Study 110*. The safety of tenofovir alafenamide is also supported by pooled data from patients in Studies 108 and 110 who remained on blinded treatment from Week 96 through Week 144 and additionally from patients in the open-label phase of Studies 108 and 110 from Week 96 through Week 144 (N = 360 remained on tenofovir alafenamide; N = 180 switched from tenofovir disoproxil to tenofovir alafenamide at Week 96).

In *Study 108*, HBeAg-negative treatment-naive and treatment-experienced patients with compensated liver function were randomised in a 2:1 ratio to receive tenofovir alafenamide (25 mg; N = 285) once daily or tenofovir disoproxil (245 mg; N = 140) once daily. The mean age was 46 years, 61% were male, 72% were Asian, 25% were White and 2% (8 subjects) were Black. 24%, 38%, and 31% had HBV genotype B, C, and D, respectively. 21% were treatment-experienced (previous treatment with oral antivirals, including entecavir (N = 41), lamivudine (N = 42), tenofovir disoproxil (N = 21), or other (N = 18)). At baseline, mean plasma HBV DNA was 5.8 log10 IU/mL, mean serum ALT was 94 U/L, and 9% of patients had a history of cirrhosis.

In *Study 110*, HBeAg-positive treatment-naive and treatment-experienced patients with compensated liver function were randomised in a 2:1 ratio to receive tenofovir alafenamide (25 mg; N = 581) once daily or tenofovir disoproxil (245 mg; N = 292) once daily. The mean age was 38 years, 64% were male, 82% were Asian, 17% were White and < 1% (5 subjects) were Black. 17%, 52%, and 23% had HBV genotype B, C, and D, respectively. 26% were treatment-experienced (previous treatment with oral antivirals, including adefovir (N = 42), entecavir (N = 117), lamivudine (N = 84), telbivudine (N = 25), tenofovir disoproxil (N = 70), or other (N = 17)). At baseline, mean plasma HBV DNA was 7.6 log10 IU/mL, mean serum ALT was 120 U/L, and 7% of patients had a history of cirrhosis.

The primary efficacy endpoint in both studies was the proportion of patients with plasma HBV DNA levels below 29 IU/mL at Week 48. Tenofovir alafenamide met the non-inferiority criteria in achieving HBV DNA less than 29 IU/mL when compared to tenofovir disoproxil. Treatment outcomes of *Study 108* and *Study 110 through* Week 48 are presented in Table 3 and Table 4.

Table 3: HBV DNA efficacy parameters at Week 48[a]

	Study 108 (HBeAg-Negative)		*Study 110 (HBeAg-Positive)*	
	TAF (N = 285)	TDF (N = 140)	TAF (N = 581)	TDF (N = 292)
HBV DNA < 29 IU/mL	94%	93%	64%	67%
Treatment difference[b]	1.8% (95% CI = 3.6% to 7.2%)		3.6% (95% CI = 9.8% to 2.6%)	
HBV DNA ≥ 29 IU/mL	2%	3%	31%	30%
Baseline HBV DNA < 7 log_{10} IU/mL ≥ 7 log_{10} IU/mL	9 6 % (221/230) 85% (47/55)	9 2 % (107/116) 96% (23/24)	N/A	N/A
Baseline HBV DNA < 8 log_{10} IU/mL ≥ 8 log_{10} IU/mL	N/A	N/A	8 2 % (254/309) 4 3 % (117/272)	8 2 % (123/150) 5 1 % (72/142)
Nucleoside naive[c] Nucleoside experienced	94% (212/225) 93% (56/60)	93% (102/110) 93% (28/30)	68% (302/444) 50% (69/137)	70% (156/223) 57% (39/69)
No Virologic data at Week 48	4%	4%	5%	3%
Discontinued study drug due to lack of efficacy	0	0	<1%	0
Discontinued study drug due to AE or death	1%	1%	1%	1%
Discontinued study drug due to other reasons[d]	2%	3%	3%	2%
Missing data during window but on study drug	<1%	1%	<1%	0

N/A = not applicable
TDF = tenofovir disoproxil fumarate
a. Missing = failure analysis.
b. Adjusted by baseline plasma HBV DNA categories and oral antiviral treatment status strata.
c. Treatment naive subjects received < 12 weeks of oral antiviral treatment with any nucleoside or nucleotide analog including tenofovir disoproxil fumarate or tenofovir alafenamide.
d. Includes patients who discontinued for reason other than an AE, death or lack or loss of efficacy, e.g. withdrew consent, loss to followup, etc.

Table 4: Additional efficacy parameters at Week 48[a]

	Study 108 (HBeAg-Negative)		*Study 110* (HBeAg-Positive)	
	TAF (N = 285)	TDF (N = 140)	TAF (N = 581)	TDF (N = 292)
ALT Normalized ALT (Central lab)[b]	83%	75%	72%	67%
Normalized ALT (AASLD)[c]	50%	32%	45%	36%
Serology HBeAg loss / seroconversion[d]	N/A	N/A	14% / 10%	12% / 8%
HBsAg loss / seroconversion	0 / 0	0 / 0	1% / 1%	< 1% / 0

N/A = not applicable
TDF = tenofovir disoproxil
TAF = tenofovir alafenamide
a Missing = failure analysis.
b The population used for analysis of ALT normalisation included only patients with ALT above upper limit of normal (ULN) of the central laboratory range at baseline. Central laboratory ULN for ALT are as follows: ≤ 43 U/L for males aged 18 to < 69 years and ≤ 35 U/L for males ≥ 69 years; ≤ 34 U/L for females 18 to < 69 years and ≤ 32 U/L for females ≥ 69 years.
c The population used for analysis of ALT normalisation included only patients with ALT above ULN of the 2016 American Association of the Study of Liver Diseases (AASLD) criteria (> 30 U/L males and > 19 U/L females) at baseline.
d The population used for serology analysis included only patients with antigen (HBeAg) positive and antibody (HBeAb) negative or missing at baseline.

Experience beyond 48 weeks in Study 108 and Study 110
At Week 96, viral suppression as well as biochemical and serological responses were maintained with continued tenofovir alafenamide treatment (see Table 5).

Table 5: HBV DNA and additional efficacy parameters at Week 96[a]

	Study 108 (HBeAg-Negative)		*Study 110* (HBeAg-Positive)	
	TAF (N = 285)	TDF (N = 140)	TAF (N = 581)	TDF (N = 292)
HBV DNA < 29 IU/mL	90%	91%	73%	75%
Baseline HBV DNA < 7 log_{10} IU/mL ≥ 7 log_{10} IU/mL	90% (203/225) 90% (54/60)	92% (101/110) 87% (26/30)	75% (331/444) 67% (92/137)	75% (168/223) 72% (50/69)
ALT Normalised ALT (Central lab)[c] Normalised ALT (AASLD)[d]	81% 50%	71% 40%	75% 52%	68% 42%
Serology HBeAg loss / seroconversion[e]	N/A	N/A	22% / 18%	18% / 12%
HBsAg loss / seroconversion	< 1% / < 1%	0 / 0	1% / 1%	1% / 0

N/A = not applicable
TDF = tenofovir disoproxil
TAF = tenofovir alafenamide
a Missing = failure analysis
b Treatment-naive subjects received < 12 weeks of oral antiviral treatment with any nucleoside or nucleotide analogue including tenofovir disoproxil or tenofovir alafenamide.
c The population used for analysis of ALT normalisation included only patients with ALT above ULN of the central laboratory range at baseline. Central laboratory ULN for ALT are as follows: ≤ 43 U/L for males aged 18 to < 69 years and ≤ 35 U/L for males ≥ 69 years; ≤ 34 U/L for females 18 to < 69 years and ≤ 32 U/L for females ≥ 69 years.
d The population used for analysis of ALT normalisation included only patients with ALT above ULN of the 2016 AASLD criteria (> 30 U/L males and > 19 U/L females) at baseline.
e The population used for serology analysis included only patients with antigen (HBeAg) positive and antibody (HBeAb) negative or missing at baseline.

Changes in measures of bone mineral density in Study 108 and Study 110
In both studies tenofovir alafenamide was associated with smaller mean percentage decreases in bone mineral density (BMD; as measured by hip and lumbar spine dual energy X ray absorptiometry [DXA]
analysis) compared to tenofovir disoproxil after 96 weeks of treatment.
In patients who remained on blinded treatment beyond Week 96, mean percentage change in BMD in each group at Week 144 was similar to that at Week 96. In the open-label phase of both studies, mean percentage change in BMD from Week 96 to Week 144 in patients who remained on tenofovir alafenamide was +0.4% at the lumbar spine and -0.3% at the total hip, compared to +2.0% at the lumbar spine and +0.9% at the total hip in those who switched from tenofovir disoproxil to tenofovir alafenamide at Week 96.
Changes in renal function in Study 108 and Study 110
In both studies tenofovir alafenamide was associated with smaller changes in renal safety parameters (smaller median reductions in estimated CrCl by Cockcroft-Gault and smaller median percentage increases in urine retinol binding protein to creatinine ratio and urine beta-2-microglobulin to creatinine ratio) compared to tenofovir disoproxil after 96 weeks of treatment (see also section 4.4).
In patients who remained on blinded treatment beyond Week 96 in Studies 108 and 110, changes from baseline in renal laboratory parameter values in each group at Week 144 were similar to those at Week 96. In the open-label phase of Studies 108 and 110, the mean (SD) change in serum creatinine from Week 96 to Week 144 was +0.002 (0.0924) mg/dL in those who remained on tenofovir alafenamide, compared to -0.018 (0.0691) mg/dL in those who switched from tenofovir disoproxil to tenofovir alafenamide at Week 96. In the open-label phase, the median change in eGFR from Week 96 to Week 144 was -1.2 mL/min in patients who remained on tenofovir alafenamide, compared to +4.2 mL/min in patients who switched from tenofovir disoproxil to tenofovir alafenamide at Week 96.
Changes in lipid laboratory tests in Study 108 and Study 110
For patients who switched to open label tenofovir alafenamide at Week 96, changes from double-blind baseline for patients randomised initially to tenofovir alafenamide and tenofovir disoproxil at Week 96 and Week 144 in total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, and total cholesterol to HDL ratio are presented in Table 6.

Table 6: Median changes from double-blind baseline in lipid laboratory tests at Weeks 96 and 144 for patients who switched to open - label tenofovir alafenamide at Week 96

	TAF-TAF (N = 360)		
	Double blind baseline	Week 96	Week 144
	Median (Q1, Q3) (mg/dL)	Median change (Q1, Q3) (mg/dL)	Median change (Q1, Q3) (mg/dL)
Total Cholesterol (fasted)	185 (166, 210)	0 (-18, 17)	0 (-16, 18)
HDL-Cholesterol (fasted)	59 (49, 72)	-5 (-12, 1) [a]	-5 (-12,2) [b]
LDL-Cholesterol (fasted)	113 (95, 137)	6 (-8, 21) [a]	8 (-6, 24) [b]
Triglycerides (fasted)	87 (67, 122)	8 (-12, 28) [a]	11 (-11, 40) [b]
Total Cholesterol to HDL ratio	3.1 (2.6, 3.9)	0.2 (0.0, 0.6) a	0.3 (0.0, 0.7) b
Total Cholesterol (fasted)	189 (163, 215)	-23 (-40, -1) a	1 (-17, 20)
HDL-Cholesterol (fasted)	61 (49, 72)	-12 (-19, -3) a	-8 (-15, -1) b
LDL-Cholesterol (fasted)	120 (95, 140)	-7 (-25, 8) a	9 (-5, 26) b
Triglycerides (fasted)	89 (69, 114)	-11 (-31, 11) a	14 (-10, 43) b
Total Cholesterol to HDL ratio	3.1 (2.5, 3.7)	0.2 (-0.1, 0.7) a	0.4 (0.0, 1.0) b

TAF = tenofovir alafenamide
TDF = tenofovir disoproxil
a P-value was calculated for change from double blind baseline at Week 96, from Wilcoxon Signed Rank test and was statistically significant (p < 0.001).
b P-value was calculated for change from double blind baseline at Week 144, from Wilcoxon Signed Rank test and was statistically significant (p < 0.001).

Virologically suppressed adult patients in Study 4018
The efficacy and safety of tenofovir alafenamide in virologically suppressed adults with chronic hepatitis B is based on 48-week data from an ongoing randomized, double-blind, active-controlled study, *Study 4018*.
In *Study 4018* virologically suppressed adults with chronic hepatitis B (N = 488) were enrolled who had been previously maintained on 245 mg tenofovir disoproxil once daily for at least 12 months, with HBV DNA < lower limit of quantification (LLOQ) by local laboratory assessment for at least 12 weeks prior to screening and HBV DNA < 20 IU/mL at screening. Patients were stratified by HBsAg status (HBeAg-positive or HBeAg-negative) and age (≥ 50 or < 50 years) and randomized in a 1:1 ratio to switch to 25 mg tenofovir alafenamide (N = 243) or remain on 245 mg tenofovir disoproxil once daily (N = 245). Mean age was 51 years (22% were ≥ 60 years), 71% were male, 82% were Asian, 14% were White, and 68% were HBeAg-negative. At baseline, median duration of prior tenofovir disoproxil treatment was 220 and 224 weeks in the tenofovir alafenamide and tenofovir disoproxil groups, respectively. Previous treatment with antivirals also included interferon (N = 63), lamivudine (N = 191), adefovir dipivoxil (N = 185), entecavir (N = 99), telbivudine (N = 48), or other (N = 23). At baseline, mean serum ALT was 27 U/L, median eGFR by Cockcroft-Gault was 90.5 mL/min; 16% of patients had a history of cirrhosis.
The primary efficacy endpoint was the proportion of patients with plasma HBV DNA levels ≥ 20 IU/mL at Week 48 (as determined by the modified US FDA Snapshot algorithm). Additional efficacy endpoints included the proportion of patients with HBV DNA levels < 20 IU/mL, ALT normal and ALT normalization, HBsAg loss and seroconversion, and HBeAg loss and seroconversion. Tenofovir alafenamide was non-inferior in the proportion of subjects with HBV DNA ≥ 20 IU/mL at Week 48 when compared to tenofovir disoproxil as assessed by the modified US FDA Snapshot algorithm. Treatment outcomes (HBV DNA < 20 IU/mL by missing = failure) at Week 48 between treatment groups were similar across subgroups by age, sex, race, baseline HBeAg status, and ALT.
Treatment outcomes of Study 4018 at Week 48 are presented in Table 7 and Table 8.

Table 7: HBV DNA efficacy parameters at Week 48 a,b

	TAF (N = 243)	TDF (N = 245)
HBV DNA ≥ 20 IU/mL [b,c]	1 (0.4%)	1 (0.4%)
Treatment Difference [d]	0.0% (95% CI = -1.9% to 2.0%)	
HBV DNA < 20 IU/mL	234 (96.3%)	236 (96.3%)
Treatment Difference [d]	0.0% (95% CI = -3.7% to 3.7%)	
No Virologic Data at Week 48	8 (3.3%)	8 (3.3%)
Discontinued Study Drug Due to AE or Death and Last Available HBV DNA < 20 IU/mL	2 (0.8%)	0
Discontinued Study Drug Due to Other Reasons[e] and Last Available HBV DNA < 20 IU/mL	6 (2.5%)	8 (3.3%)
Missing Data During Window but on Study Drug	0	0

TDF = tenofovir disoproxil
TAF = tenofovir alafenamide
a Week 48 window was between Day 295 and 378 (inclusive).
b As determined by the modified US FDA-defined snapshot algorithm.
c No patient discontinued treatment due to lack of efficacy.
d Adjusted by baseline age groups (< 50, ≥ 50 years) and baseline HBeAg status strata.
e Includes patients who discontinued for reasons other than an AE, death or lack of efficacy, e.g., withdrew consent, loss to follow-up, etc.

Table 8: Additional efficacy parameters at Week 48 a

	TAF (N = 243)	TDF (N = 245)
ALT		
Normal ALT (Central Lab)	89%	85%
Normal ALT (AASLD)	79%	75%
Normalized ALT (Central Lab) [b,c]	50%	37%
Normalized ALT (AASLD)[d,e]	50%	26%
Serology		
HBeAg Loss / Seroconversion[f]	8% / 3%	6% / 0
HBsAg Loss / Seroconversion	0 / 0	2% / 0

TDF = tenofovir disoproxil
TAF = tenofovir alafenamide
a Missing = failure analysis
b The population used for analysis of ALT normalization included only patients with ALT above upper limit of normal (ULN) of the central laboratory range (> 43 U/L males 18 to < 69 years and > 35 U/L males ≥ 69 years; > 34 U/L females 18 to < 69 years and > 32 U/L females ≥ 69 years) at baseline.
c Proportion of patients at Week 48: TAF, 16/32; TDF, 7/19.
d The population used for analysis of ALT normalization included only patients with ALT above ULN of the 2018 American Association of the Study of Liver Diseases (AASLD) criteria (35 U/L males and 25 U/L females) at baseline.
e Proportion of patients at Week 48: TAF, 26/52; TDF, 14/53.
f The population used for serology analysis included only patients with antigen (HBeAg) positive and anti-body (HBeAb) negative or missing at baseline.

Changes in bone mineral density in Study 4018
The median change from baseline to Week 48 in eGFR by Cockcroft-Gault method was +0.9 mL per
minute in the tenofovir alafenamide group and −2.7 mL per minute in those receiving tenofovir disoproxil. At Week 48, there was a median increase from baseline in serum creatinine among patients randomized to continue treatment with tenofovir disoproxil (0.02 mg/dL) compared with no median change from baseline among those who were switched to tenofovir alafenamide (0.00 mg/dL). Further, median percentage decreases from baseline were observed in the tenofovir alafenamide group at Week 48 in urine retinol binding protein to creatinine ratio and urine beta-2-microglobulin to creatinine ratio, compared with median percentage increases from baseline for both of these renal parameters in the tenofovir disoproxil group.
Changes in lipid laboratory tests in Study 4018
Changes from baseline to Week 48 in total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, and total cholesterol to HDL ratio among subjects treated with tenofovir alafenamide and tenofovir disoproxil are presented in Table 9.

Table 9: Median changes in lipid laboratory tests at Week 48

	TAF (N = 243)		TDF (N = 245)	
	Baseline (Q1, Q3) (mg/dL)	Week 48 Median change[a] (Q1, Q3) (mg/dL)	Baseline (Q1, Q3) (mg/dL)	Week 48 Median change[a] (Q1, Q3) (mg/dL)
Total Cholesterol (fasted)	166 (147, 189)	19 (6, 33)	169 (147, 188)	−4 (−16, 8)
HDL-Cholesterol (fasted)	48 (41, 56)	3 (−1, 8)	48 (40, 57)	−1 (−5, 2)
LDL-Cholesterol (fasted)	1 0 2 (87,123)	16 (5, 27)	103 (87, 122)	1 (−8, 12)
Triglycerides (fasted)	90 (66, 128)	16 (−3, 44)	89 (68, 126)	−2 (−22, 18)
Total Cholesterol to HDL ratio	3.4 (2.9, 4.2)	0.2 (−0.1, 0.5)	3.4 (2.9, 4.2)	0.0 (−0.3, 0.3)

TAF = tenofovir alafenamide

P-value was calculated for the difference between the TAF and TDF groups, from Wilcoxon Rank Sum test and was statistically significant (p < 0.001) for median changes (Q1, Q3) from baseline in total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides and total cholesterol to HDL ratio.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of tenofovir alafenamide under fasted conditions in adult patients with chronic hepatitis B, peak plasma concentrations of tenofovir alafenamide were observed approximately 0.48 hours post-dose. Based on Phase 3 population pharmacokinetic analysis in subjects with chronic hepatitis B, mean steady state AUC0-24 for tenofovir alafenamide (N = 698) and tenofovir (N = 856) were 0.22 μg•h/mL and 0.32 μg•h/mL, respectively. Steady state Cmax for tenofovir alafenamide and tenofovir were 0.18 and 0.02 μg/mL, respectively. Relative to fasting conditions, the administration of a single dose of tenofovir alafenamide with a high fat meal resulted in a 65% increase in tenofovir alafenamide exposure.

Distribution

The binding of tenofovir alafenamide to human plasma proteins in samples collected during clinical studies was approximately 80%. The binding of tenofovir to human plasma proteins is less than 0.7% and is independent of concentration over the range of 0.01-25 μg/mL

Biotransformation

Metabolism is a major elimination pathway for tenofovir alafenamide in humans, accounting for > 80% of an oral dose. In vitro studies have shown that tenofovir alafenamide is metabolised to tenofovir (major metabolite) by carboxylesterase-1 in hepatocytes; and by cathepsin A in peripheral blood mononuclear cells (PBMCs) and macrophages. *In vivo*, tenofovir alafenamide is hydrolysed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite, tenofovir diphosphate.

In vitro, tenofovir alafenamide is not metabolised by CYP1A2, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. Tenofovir alafenamide is minimally metabolised by CYP3A4.

Elimination

Renal excretion of intact tenofovir alafenamide is a minor pathway with < 1% of the dose eliminated in urine. Tenofovir alafenamide is mainly eliminated following metabolism to tenofovir. Tenofovir alafenamide and tenofovir have a median plasma half-life of 0.51 and 32.37 hours, respectively.

Tenofovir is renally eliminated from the body by the kidneys by both glomerular filtration and active tubular secretion.

Linearity/non-linearity

Tenofovir alafenamide exposures are dose proportional over the dose range of 8 to 125 mg.

Pharmacokinetics in special populations

Age, gender and ethnicity

No clinically relevant differences in pharmacokinetics according to age or ethnicity have been identified. Differences in pharmacokinetics according to gender were not considered to be clinically relevant.

Hepatic impairment

In patients with severe hepatic impairment, total plasma concentrations of tenofovir alafenamide and tenofovir are lower than those seen in subjects with normal hepatic function. When corrected for protein binding, unbound (free) plasma concentrations of tenofovir alafenamide in severe hepatic impairment and normal hepatic function are similar.

Renal impairment

No clinically relevant differences in tenofovir alafenamide or tenofovir pharmacokinetics were observed between healthy subjects and patients with severe renal impairment (estimated CrCl > 15 but < 30 mL/min) in studies of tenofovir alafenamide.

Paediatric population

The pharmacokinetics of tenofovir alafenamide and tenofovir were evaluated in HIV-1 infected, treatment-naive adolescents who received tenofovir alafenamide (10 mg) given with elvitegravir, cobicistat and emtricitabine as a fixed-dose combination tablet (E/C/F/TAF). No clinically relevant differences in tenofovir alafenamide or tenofovir pharmacokinetics were observed between adolescent and adult HIV-1 infected subjects.

5.3 Preclinical safety data

Non-clinical studies in rats and dogs revealed bone and kidney as the primary target organs of toxicity. Bone toxicity was observed as reduced BMD in rats and dogs at tenofovir exposures at least four times greater than those expected after administration of tenofovir alafenamide. A minimal infiltration of histiocytes was present in the eye in dogs at tenofovir alafenamide and tenofovir exposures of approximately 4 and 17 times greater, respectively, than those expected after administration of tenofovir alafenamide.

Tenofovir alafenamide was not mutagenic or clastogenic in conventional genotoxic assays.

Because there is a lower tenofovir exposure in rats and mice after tenofovir alafenamide administration compared to tenofovir disoproxil, carcinogenicity studies and a rat peri-postnatal study were conducted only with tenofovir disoproxil. No special hazard for humans was revealed in conventional studies of carcinogenic potential with tenofovir disoproxil (as fumarate) and toxicity to reproduction and development with tenofovir disoproxil (as fumarate) or tenofovir alafenamide.

Reproductive toxicity studies in rats and rabbits showed no effects on mating, fertility, pregnancy or foetal parameters. However, tenofovir disoproxil reduced the viability index and weight of pups in a peri-postnatal toxicity study at maternally toxic doses. A long-term oral carcinogenicity study in mice showed a low incidence of duodenal tumours, considered likely related to high local concentrations in the gastrointestinal tract at the high dose of 600 mg/kg/day. The mechanism of tumour formation in mice and potential relevance for humans is uncertain.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose monohydrate
Microcrystalline cellulose Croscarmellose sodium
Magnesium stearate

Film-coating
Polyvinyl alcohol
Titanium dioxide
Polyethylene Glycol
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at temperatures not exceeding 30°C. Store in the original container.

6.5 Nature and contents of container

HDPE bottle of 30's.
40 mL- capacity blue opaque HDPE bottle with blue opaque polypropylene screw cap containing 30 film-coated tablet.

6.6 Special precautions for disposal

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Viatris Pharmaceuticals, Inc.
22nd floor, Units C&D, Menarco Tower
32nd St. Bonifacio Global City, Taguig City, Metro Manila

8. MANUFACTURER

Mylan Laboratories Limited
Plot No. 11, 12 & 13, Indore SEZ, Pharma Zone, Phase-II
Sector III, Pithampur - 454775, Dist.- Dhar (MP) India.

9. DATE OF REVISION OF THE TEXT

September 2022

Caution: Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Registration Number: DR-XY48330

Date of First Authorization: 01 September 2022

Product is manufactured under license from Gilead Sciences Inc.

Reference:
Vemlidy (Tenofovir Alafenamide 25 mg Tablets); FEB 2020; Gilead Sciences Ireland UC; Accessed from;

https://www.ema.europa.eu/en/documents/product-information/vemlidy-epar-product-information_en.pdf ; Accessed on April 13th 2020.

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Date/Time of Creation	07/10/22 11:30 mm	Track-Wise PR No.	NA	Date of Final	dd / mm / yy
Vendor Job No.	NA	Affiliate New Code	NA	Client Market	Philippines
Artwork Proof No.	NA	Aff. Superseded Code	NA	Product Description	LIT HEPBEST VT (TAF) TAB 25MG PH
Pharma Code	NA	Barcode Information	NA	New Material Code	75093454
Product Render ID No.	NA	MA Number	....	ITF Barcode	
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	After Consumption of Existing (superseded) stock
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Printed Colors CMYK / PMS Coated / PMS Color Bridge Coated	BLACK 100%	NA	NA	NA	NA
Non Printed Colors	Die Line				
Equivalent with CMYK (Pantones Ref. Code)	NA				
Material of Construction	40gsm ITC Tribeni Paper				
Design & Style	Supply in Folded form as proposed size (with tape)				

LABEL CONTROL / BUSINESS DEVELOPMENT / REGULATORY / MARKETING

Sign Offs	Prepared By	Checked By	Approved By		
	Amol Gangawane-M265088 (Packaging Technical Services) Digitally signed by Amol Gangawane-M265088 Date: 2022.11.09 16:42:33 +05'30' Digital Signature	Vipin Kumar Singh-M511975 (Packaging Technical Services) Digitally signed by Vipin Kumar Singh-M511975 Date: 2022.11.09 16:15:42 +05'30' Digital Signature	Digital Signature	Digital Signature	

Revision History	07.10.2022 - New Component	Date / Remarks	Date / Remarks	Date / Remarks	Date / Remarks
	Date / Remarks	Date / Remarks	Date / Remarks	Date / Remarks	Date / Remarks
	Date / Remarks	Date / Remarks	Date / Remarks	Date / Remarks	Date / Remarks