HepBest

Tenofovir Alafenamide Tablets 25 mg

1. Name of the medicinal product

Tenofovir Alafenamide Tablets 25 mg

2. Qualitative and quantitative composition

Each 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 tablets 25 mg is 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 HBeAgpositive patients without cirrhosis, treatment should be administered for at least 612 months after HBe seroconversion (HBeAg loss and HBV DNA loss with antiHBe 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 HBeAgnegative 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 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 tablets 25 mg, the patient should take another tablet. If the patient vomits more than 1 hour after taking Tenofovir Alafenamide tablets 25 mg, the patient does not need to take another tablet.

Special populations

Elderly

No dose adjustment of Tenofovir Alafenamide tablets 25 mg is required in patients aged 65 years and older (see section 5.2).

Renal impairment

No dose adjustment of Tenofovir Alafenamide 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) $\geq$ 15 mL/min or in patients with CrCl < 15 mL/min who are receiving haemodialysis.

On days of haemodialysis, Tenofovir Alafenamide 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 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 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 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

HBV transmission

Patients must be advised that Tenofovir Alafenamide 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 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 selflimited 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 followup 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 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 tablets 25 mg to treat HBV infected patients with CrCl < 30 mL/min.

The use of Tenofovir Alafenamide 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 tablets 25 mg in patients coinfected with hepatitis C or D virus. Coadministration 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 HIV1 infection status is unknown before initiating therapy with Tenofovir Alafenamide tablets 25 mg. In patients who are coinfected with HBV and HIV, Tenofovir Alafenamide tablets 25 mg should be coadministered 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 tablets 25 mg should not be coadministered with products containing tenofovir alafenamide, tenofovir disoproxil fumarate or adefovir dipivoxil.

Coadministration of Tenofovir Alafenamide 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 Pglycoprotein (Pgp) and may decrease tenofovir alafenamide plasma concentrations, is not recommended.

Coadministration of Tenofovir Alafenamide tablets 25 mg with strong inhibitors of Pgp (e.g. itraconazole and ketoconazole) may increase tenofovir alafenamide plasma concentrations. Coadministration is not recommended.

Lactose intolerance

Tenofovir Alafenamide tablets 25 mg contains lactose monohydrate. Consequently, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucosegalactose 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 tablets 25 mg should not be coadministered with medicinal products containing tenofovir disoproxil fumarate, tenofovir alafenamide or adefovir dipivoxil.

Medicinal products that may affect tenofovir alafenamide

Tenofovir alafenamide is transported by Pgp and breast cancer resistance protein (BCRP). Medicinal products that are Pgp 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 tablets 25 mg. Coadministration of such medicinal products with Tenofovir Alafenamide tablets 25 mg is not recommended.

Coadministration of Tenofovir Alafenamide tablets 25 mg with medicinal products that inhibit Pgp and/or BCRP may increase plasma concentration of tenofovir alafenamide. Coadministration of strong inhibitors of Pgp with Tenofovir Alafenamide tablets 25 mg 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 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 tablets 25 mg with potential concomitant medicinal products is summarized in Table 1 below (increase is indicated as "1'", decrease as "-J,", no change as "B"; 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 tablets 25 mg.

Table 1: Interactions between Tenofovir Alafenamide tablets 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 tablets 25 mg**
ANTICONVULSANTS		
Carbamazepine (300 mg orally, b.i.d.) Tenofovir alafenamide[c] (25 mg orally, s.d.)	Tenofovir alafenamide -J, C_{max} 0.43 (0.36, 0.51) -J, AUC 0.45 (0.40, 0.51) Tenofovir -J, C_{max} 0.70 (0.65, 0.74) B AUC 0.77 (0.74, 0.81)	Coadministration is not recommended.
Oxcarbazepine Phenobarbital	Interaction not studied. Expected: -J, Tenofovir alafenamide	Coadministration is not recommended.
Phenytoin	Interaction not studied. Expected: -J, Tenofovir alafenamide	Coadministration is not recommended.
Midazolam[d] (2.5 mg orally, s.d.) Tenofovir alafenamide[c] (25 mg orally, q.d.)	Midazolam B C_{max} 1.02 (0.92, 1.13) B 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 B C_{max} 0.99 (0.89, 1.11) B AUC 1.08 (1.04, 1.14)	

ANTIDEPRESSANTS		
Sertraline (50 mg orally, s.d.) Tenofovir alafenamide[e] (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 tablets 25 mg or sertraline is required.
Sertraline (50 mg orally, s.d.) Tenofovir alafenamide[e] (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	Coadministration is not recommended.
ANTIMYCOBACTERIALS		
Rifampicin Rifapentine	Interaction not studied. Expected: ↓, Tenofovir alafenamide	Coadministration is not recommended.
Rifabutin	Interaction not studied. Expected: ↓, Tenofovir alafenamide	Coadministration is not recommended.
HCV ANTIVIRAL AGENTS		
Sofosbuvir (400 mg orally, q.d.)	Interaction not studied. Expected: ↔ Sofosbuvir ↔ GS331007	No dose adjustment of Tenofovir Alafenamide tablets 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) GS331007[g] ↔ 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 tablets 25 mg or ledipasvir/sofosbuvir is required.

Sofosbuvir/velpatasvir (400 mg/100 mg orally, q.d.)	Interaction not studied. Expected: ↓ Sofosbuvir ↓ GS-331007 ↓ Velpatasvir ↑ Tenofovir alafenamide	No dose adjustment of Tenofovir Alafenamide tablets 25 mg or sofosbuvir/velpatasvir 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)	Coadministration is not recommended.

Darunavir/cobicistat (800 mg/150 mg orally, q.d.) Tenofovir alafenamidec (25 mg orally, q.d.)	Tenofovir alafenamide ↔ C_{max} 0.93 (0.72, 1.21) ↔ AUC 0.98 (0.80, 1.19) Tenofovir 1' C_{max} 3.16 (3.00, 3.33) 1' AUC 3.24 (3.02, 3.47) 1' 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 1' C_{max} 1.42 (0.96, 2.09) ↔ AUC 1.06 (0.84, 1.35) Tenofovir 1' C_{max} 2.42 (1.98, 2.95) 1' 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)	Coadministration is not recommended.
Lopinavir/ritonavir (800 mg/200 mg orally, q.d.) Tenofovir alafenamide[c] (10 mg orally, s.d.)	Tenofovir alafenamide 1' C_{max} 2.19 (1.72, 2.79) 1' AUC 1.47 (1.17, 1.85) Tenofovir 1' C_{max} 3.75 (3.19, 4.39) 1' 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)	Coadministration is not recommended.
Tipranavir/ritonavir	Interaction not studied. Expected: -J, Tenofovir alafenamide	Coadministration is not recommended.
HIV ANTIRETROVIRAL AGENTS – INTEGRASE INHIBITORS		
Dolutegravir (50 mg orally, q.d.) Tenofovir alafenamide[c] (10 mg orally, s.d.)	Tenofovir alafenamide 1' C_{max} 1.24 (0.88, 1.74) 1' AUC 1.19 (0.96, 1.48) Tenofovir ↔ C_{max} 1.10 (0.96, 1.25) 1' AUC 1.25 (1.06, 1.47) Dolutegravir ↔ C_{max} 1.15 (1.04, 1.27)	No dose adjustment of Tenofovir Alafenamide tablets 25 mg or dolutegravir is required.

	↑ AUC 1.02 (0.97, 1.08) ↑ C_{min} 1.05 (0.97, 1.13)	
Raltegravir	Interaction not studied. Expected: ↑ Tenofovir alafenamide ↑ Raltegravir	No dose adjustment of Tenofovir Alafenamide tablets 25 mg or raltegravir is required.
HIV ANTIRETROVIRAL AGENTS – NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS		
Efavirenz (600 mg orally, q.d.) Tenofovir alafenamide[h] (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 tablets 25 mg or efavirenz is required.
Nevirapine	Interaction not studied. Expected: ↑ Tenofovir alafenamide ↑ Nevirapine	No dose adjustment of Tenofovir Alafenamide tablets 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_{min} 1.13 (1.04, 1.23)	No dose adjustment of Tenofovir Alafenamide tablets 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 tablets 25 mg or maraviroc is required.
HERBAL SUPPLEMENTS		
St. John's wort (*Hypericum perforatum*)	Interaction not studied. Expected: ↓, Tenofovir alafenamide	Coadministration 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]	Norgestromin ↑ C_{max} 1.17 (1.07, 1.26) ↑ AUC 1.12 (1.07, 1.17) ↑ C_{min} 1.16 (1.08, 1.24) Norgestrel ↑ C_{max} 1.10 (1.02, 1.18)	No dose adjustment of Tenofovir Alafenamide tablets 25 mg or norgestimate/ethinyl estradiol is required.

(25 mg orally, q.d.)	↔ AUC 1.09 (1.01, 1.18) ↔ C_{min} 1.11 (1.03, 1.20) Ethinyl estradiol ↔ C_{max} 1.22 (1.15, 1.29) ↔ AUC 1.11 (1.07, 1.16) ↔ C_{min} 1.02 (0.93, 1.12)	

a. All interaction studies are conducted in healthy volunteers
b. All No Effect Boundaries are 70% 143%
c. Study conducted with emtricitabine/tenofovir alafenamide fixed dose combination tablet
d. A sensitive CYP3A4 substrate
e. Study conducted with elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fixed dose combination tablet
f. Study conducted with emtricitabine/rilpivirine/tenofovir alafenamide fixed dose combination tablet
g. The predominant circulating nucleoside metabolite of sofosbuvir
h. Study conducted with tenofovir alafenamide 40 mg and emtricitabine 200 mg

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 1000 exposed outcomes) indicates no malformative nor feto/neonatal toxicity associated with the use of tenofovir disoproxil fumarate.

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

The use of Tenofovir Alafenamide tablets 25 mg may be considered during pregnancy, if necessary.

Breastfeeding

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 breastfed child cannot be excluded; therefore, Tenofovir Alafenamide tablets 25 mg should not be used during breastfeeding.

Fertility

No human data on the effect of Tenofovir Alafenamide tablets 25 mg on fertility are available. Animal studies do not indicate harmful effects of tenofovir alafenamide on fertility.

4.7 Effects on ability to drive and use machines

Tenofovir Alafenamide 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 tablets 25 mg.

4.8 Undesirable effects

Summary of the safety profile

Assessment of adverse reactions is based on safety data from the analysis performed through to the Week 72 analysis (median duration of exposure of 88 weeks), from 2 Phase 3 studies in which 866 HBV infected patients received tenofovir alafenamide 25 mg once daily. The most frequently reported adverse reactions were headache (11%), nausea (6%), and fatigue (6%).

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. Frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) or very rare (< 1/10,000).

Table 2: Adverse drug reactions identified with tenofovir alafenamide

System organ class	
Frequency	**Adverse reaction**
Gastrointestinal disorders	
Common	Diarrhoea, vomiting, nausea, abdominal pain, abdominal distension, flatulence
General disorders and administration site conditions	
Common	Fatigue
Nervous system disorders	
Very common	Headache
Common	Dizziness
Skin and subcutaneous tissue disorders	
Common	Rash, pruritus
Hepatobiliary disorders	
Common	Increased ALT
Musculoskeletal and connective tissue disorders	
Common	Arthralgia

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:

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard

Ireland
HPRA Pharmacovigilance
Earlsfort Terrace
IRL Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
email:medsafety@hpra.ie

Malta
ADR Reporting
Website: www.medicinesauthority.gov.mt/adrportal

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 tablets 25 mg consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient. 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.

Namibia Pharmacological Classification : 20.2.8 - Antiviral agents

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 hydrolyzed 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 (HIV1 and HIV2). Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase y 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 AH. The EC_{50} (50% effective concentration) values for tenofovir alafenamide ranged from 34.7 to 134.4 nM, with an overall mean EC_{50} of 86.6 nM. The CC_{50} (50% cytotoxicity concentration) in HepG2 cells was > 44400 nM.

Resistance

In a pooled analysis of patients receiving Tenofovir Alafenamide tablets 25 mg, 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 log_{10} or greater increase in HBV DNA from nadir) through Week 48, or had HBV DNA ≥ 69 IU/mL at early discontinuation at or after Week 24. No amino acid substitutions associated with resistance to Tenofovir Alafenamide tablets 25 mg were identified in 20 paired isolates.

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 (< 2fold change in EC_{50}). 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 rtN236T 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 EC_{50}). The clinical relevance of these substitutions is not known.

Clinical data

The efficacy and safety of Tenofovir Alafenamide tablets 25 mg in patients with chronic hepatitis B are based on 48 week data from two randomized, double blind, active controlled studies, GSUS3200108 ("Study 108") and GSUS3200110 ("Study 110").

In Study 108, HBeAg negative treatment naïve and treatment experienced patients with compensated liver function were randomized in a 2:1 ratio to receive Tenofovir Alafenamide tablets 25 mg (25 mg; N =

285) once daily or tenofovir disoproxil fumarate (300 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 fumarate (N = 21), or other (N = 18)). At baseline, mean plasma HBV DNA was 5.8 $\log_{10}$ IU/mL, mean serum ALT was 94 U/L, and 9% of patients had a history of cirrhosis.

In Study 110, HBeAg positive treatment naïve and treatment experienced patients with compensated liver function were randomized in a 2:1 ratio to receive Tenofovir Alafenamide tablets 25 mg (25 mg; N = 581) once daily or tenofovir disoproxil fumarate (300 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 fumarate (N = 70), or other (n = 17)). At baseline, mean plasma HBV DNA was 7.6 $\log_{10}$ IU/mL, mean serum ALT was 120 U/L, and 7% of patients had a history of cirrhosis.

The primary efficacy endpoint in both trials was the proportion of patients with plasma HBV DNA levels below 29 IU/mL.

Tenofovir Alafenamide tablets 25 mg met the noninferiority criteria in achieving HBV DNA less than 29 IU/mL when compared to tenofovir disoproxil fumarate.

Treatment outcomes of Study 108 and Study 110 through Week 48 are presented in Table 3 and Table 4. Additional outcomes through Week 72 are presented in Table 5.

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

	Study 108 (HBeAg-Negative)		**Study 110 (HBeAg-Positive)**	
	Tenofovir Alafenamide tablets 25 mg (N = 285)	TDF (N = 140)	Tenofovir Alafenamide tablets 25 mg (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	 96% (221/230) 85% (47/55)	 92% (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	82% (254/309) 43% (117/272)	82% (123/150) 51% (72/142)
Nucleoside naïve[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 naïve 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)	
	Tenofovir Alafenamide tablets 25 mg (N = 285)	TDF (N = 140)	Tenofovir Alafenamide tablets 25 mg (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 fumarate
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 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 normalization included only patients with ALT above ULN of the American Association of the Study of Liver Diseases (AASLD) criteria at baseline. AASLD ULN for ALT criteria are as follows: ≥ 30 U/L for males and ≥ 19 U/L for females.
d. The population used for serology analysis included only patients with antigen positive and antibody negative or missing at baseline

Experience beyond 48 weeks in Study 108 and Study 110

At Week 72, viral suppression as well as biochemical and serological responses were maintained with continued tenofovir alafenamide treatment (see Table 5). Serological data were not collected at the Week 72 timepoint.

Table 5: HBV DNA and additional effficacy parameters at Week 72[a]

	Study 108 (HBeAg-Negative)		Study 110 (HBeAg-Positive)	
	Tenofovir Alafenamide tablets 25 mg (N = 285)	TDF (N = 140)	Tenofovir Alafenamide tablets 25 mg (N = 581)	TDF (N = 292)
HBV DNA < 29 IU/mL	93%	92%	72%	72%
Baseline HBV DNA < 7 $\log_{10}$ IU/mL ≥ 7 $\log_{10}$ IU/mL	93% (215/230) 89% (49/55)	91% (106/116) 96% (23/24)	N/A	N/A
Baseline HBV DNA < 8 $\log_{10}$ IU/mL ≥ 8 $\log_{10}$ IU/mL	N/A	N/A	86% (265/309) 56% (151/272)	83% (124/150) 61% (86/142)
Nucleoside naïve[b] Nucleoside experienced	93% (210/225) 90% (54/60)	93% (102/110) 90% (27/30)	75% (332/444) 61% (84/137)	73% (163/223) 68% (47/69)
ALT Normalized ALT (Central lab)[c] Normalized ALT (AASLD)[d]	83% 50%	77% 40%	73% 49%	65% 39%

N/A = not applicable
TDF = tenofovir disoproxil fumarate
a. Missing = failure analysis
b. Treatment naïve subjects received < 12 weeks of oral antiviral treatment with any nucleoside or nucleotide analogue including tenofovir disoproxil fumarate or tenofovir alafenamide.
c. The population used for analysis of ALT normalization 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.
d. The population used for analysis of ALT normalization included only patients with ALT above ULN of the American Association of the Study of Liver Diseases (AASLD) criteria (> 30 U/L males and > 19 U/L females) at baseline.

Changes in measures of bone mineral density

In both studies tenofovir alafenamide was associated with smaller 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 fumarate after 72 weeks of treatment.

Changes in measures of renal function

In both studies tenofovir alafenamide was associated with smaller changes in renal safety parameters (smaller reductions in estimated CrCl by CockcroftGault and smaller percentage increases in urine protein to creatinine ratio and urine albumin to creatinine ratio) compared to tenofovir disoproxil fumarate after 72 weeks of treatment (see also section 4.4).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Tenofovir Alafenamide tablets 25 mg in one or more subsets of the paediatric population in the treatment of chronic hepatitis B (see sections 4.2 and 5.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Following oral administration of Tenofovir Alafenamide tablets 25 mg under fasted conditions in adult patients with chronic hepatitis B, peak plasma concentrations of tenofovir alafenamide were observed approximately 0.48 hours postdose. Based on Phase 3 population pharmacokinetic analysis in subjects with CHB, mean steady state AUC_{0-24} for tenofovir alafenamide (N = 698) and tenofovir (N = 856) were 0.22 µg•hr/mL and 0.32 µg•hr/mL, respectively. Steady state C_{max} for tenofovir alafenamide and tenofovir were 0.18 and 0.02 µg•hr/mL, respectively. Relative to fasting conditions, the administration of a single dose of Tenofovir Alafenamide tablets 25 mg 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 trials 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 metabolized to tenofovir (major metabolite) by carboxylesterase1 in hepatocytes; and by cathepsin A in 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 metabolized by CYP1A2, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. Tenofovir alafenamide is minimally metabolized 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/nonlinearity

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 HIV1infected, treatment naïve adolescents who received tenofovir alafenamide (10 mg) given with elvitegravir, cobicistat and emtricitabine as a fixed dose combination tablet (E/C/F/TAF; Genvoya). No clinically

relevant differences in tenofovir alafenamide or tenofovir pharmacokinetics were observed between adolescent and adult HIV1infected subjects.

5.3 Preclinical safety data

Nonclinical 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 fumarate, carcinogenicity studies and a rat peripostnatal study were conducted only with tenofovir disoproxil fumarate. No special hazard for humans was revealed in conventional studies of carcinogenic potential with tenofovir disoproxil (as fumarate) and 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 fumarate reduced the viability index and weight of pups in a peripostnatal toxicity study at maternally toxic doses. A longterm 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

Core tablet

Lactose Monohydrate, Microcrystalline Cellulose, Croscarmellose Sodium, Magnesium Stearate

Film coat

Polyvinyl Alcohol, Polyethylene Glycol, Titanium Dioxide & Talc.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30°C.Store in original container.

6.5 Nature and contents of container

HDPE bottle of 30’s, 90’s & 180’s*

* Not all packs may be marketed.

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 AUTHORIZATION HOLDER

Mylan Laboratories Limited, India

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

References
Summary of Product Characteristics (SmPC) - Vemlidy 25 mg film coated tablets [EMC] {Gilead Sciences Ltd, UK}

Zambia Regn No.:
Zimbabwe Regn No.:
Botswana Regn No.:
Namibia Regn No.:
Namibia Scheduling Status: NS2

Product is manufactured under license from Gilead Sciences Inc.

POM	Schedule 2	PP	List - 1

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