Vemlidy®

(tenofovir alafenamide fumarate)
Film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Vemlidy®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains tenofovir alafenamide fumarate equivalent to 25 mg of tenofovir alafenamide.

Excipient with known effect

Each tablet contains 95 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Yellow, round, film-coated tablets, 8 mm in diameter, debossed with “GSI” on one side of the tablet and “25” on the other side of the tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vemlidy is indicated for the treatment of chronic hepatitis B (CHB) 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 CHB.

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 this medicinal product 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 the treatment, the patient should take another tablet. If the patient vomits more than 1 hour after taking the treatment, the patient does not need to take another tablet.

Special populations

Elderly
No dose adjustment of this medicinal product is required in patients aged 65 years and older (see section 5.2).

Renal impairment
No dose adjustment of this medicinal product 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, this medicinal product 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 this medicinal product is required in patients with hepatic impairment (see sections 4.4 and 5.2).

Paediatric population
The safety and efficacy of Vemlidy in children younger than 12 years of age, and weighing < 35 kg, have not yet been established. No data are available.

Method of administration

Oral use. Vemlidy film-coated tablets should be taken with food (see section 5.2). There is no information available regarding the crushing/splitting of the product. It is recommended that the film-coated tablet is not chewed, split or crushed.

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

Hepatitis B Virus (HBV) transmission

Patients must be advised that this medicinal product 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 limited data on the safety and efficacy of tenofovir alafenamide 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 CHB 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 CHB, 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 CHB. 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 CHB. If appropriate, resumption of CHB 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 once daily in patients with CrCl ≥ 15 mL/min and < 30 mL/min is based on Week 96 data on the efficacy and safety of switching from another antiviral regimen to tenofovir alafenamide in an open-label clinical study of virologically suppressed chronic HBV infected patients (see sections 4.8 and 5.1). There are very limited data on the safety and efficacy of tenofovir alafenamide in HBV infected patients with CrCl < 15 mL/min on chronic haemodialysis (see sections 4.8, 5.1 and 5.2).

The use of this medicinal product is not recommended in patients with CrCl < 15 mL/min who are not receiving haemodialysis (see section 4.2).

Nephrotoxicity

Post-marketing cases of renal impairment, including acute renal failure and proximal renal tubulopathy have been reported with tenofovir alafenamide-containing products. 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).

It is recommended that renal function is assessed in all patients prior to, or when initiating, therapy with this treatment and that it is also monitored during therapy in all patients as clinically appropriate. In patients who develop clinically significant decreases in renal function, or evidence of proximal renal tubulopathy, discontinuation of this medicinal product should be considered.

Patients co-infected with HBV and hepatitis C or D virus

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

HBV and Human Immunodeficiency Virus (HIV) co-infection

HIV antibody testing should be offered to all HBV infected patients whose HIV-1 infection status is unknown before initiating therapy with this medicinal product. In patients who are co-infected with HBV and HIV, Vemlidy should be co-administered with other antiretroviral medicinal products to ensure that the patient receives an appropriate regimen for treatment of HIV (see section 4.5).

Co-administration with other medicinal products

This medicinal product should not be co-administered with medicinal products containing tenofovir alafenamide, tenofovir disoproxil or adefovir dipivoxil.

Co-administration of this treatment 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 this treatment with strong inhibitors of P-gp (e.g. itraconazole and ketoconazole) may increase tenofovir alafenamide plasma concentrations. Co-administration is not recommended.

Excipients with known effect

This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

This medicinal product 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 Vemlidy. Co-administration of such medicinal products with tenofovir alafenamide 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 Vemlidy 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."). The drug interactions described are based on studies conducted with tenofovir alafenamide, or are potential drug interactions that may occur with Vemlidy.

Table 1: Interactions between Vemlidy 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 co-administration with Vemlidy**
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)	Co-administration is not recommended.
Oxcarbazepine Phenobarbital	Interaction not studied. *Expected:* ↓ Tenofovir alafenamide	Co-administration is not recommended.
Phenytoin	Interaction not studied. *Expected:* ↓ Tenofovir alafenamide	Co-administration 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 intravenously) is required.
Midazolam[d] (1 mg intravenously, 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)	
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 Vemlidy 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		

Medicinal product by therapeutic areas	**Effects on drug levels.[a,b] Mean ratio (90% confidence interval) for AUC, C_{max}, C_{min}**	**Recommendation concerning co-administration with Vemlidy**
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 ↔ GS-331007	No dose adjustment of Vemlidy 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) *GS-331007[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 Vemlidy 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 Vemlidy or sofosbuvir/velpatasvir is required.

Medicinal product by therapeutic areas	**Effects on drug levels.[a,b] Mean ratio (90% confidence interval) for AUC, C_{max}, C_{min}**	**Recommendation concerning co-administration with Vemlidy**
Sofosbuvir/velpatasvir/ voxilaprevir (400 mg/100 mg/ 100 mg + 100 mg[i] orally, q.d.) Tenofovir alafenamide[f] (25 mg orally, q.d.)	*Sofosbuvir* ↔ C_{max} 0.95 (0.86, 1.05) ↔ AUC 1.01 (0.97, 1.06) *GS-331007[g]* ↔ 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) *Tenofovir alafenamide* ↑ C_{max} 1.32 (1.17, 1.48) ↑ AUC 1.52 (1.43, 1.61)	No dose adjustment of Vemlidy 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)	Co-administration 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)	Co-administration is not recommended.

Medicinal product by therapeutic areas	**Effects on drug levels.[a,b] Mean ratio (90% confidence interval) for AUC, C_{max}, C_{min}**	**Recommendation concerning co-administration with Vemlidy**
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/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 Vemlidy or dolutegravir is required.

Medicinal product by therapeutic areas	**Effects on drug levels.[a,b] Mean ratio (90% confidence interval) for AUC, C_{max}, C_{min}**	**Recommendation concerning co-administration with Vemlidy**
Raltegravir	Interaction not studied. *Expected:* ↔ Tenofovir alafenamide ↔ Raltegravir	No dose adjustment of Vemlidy 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 Vemlidy or efavirenz is required.
Nevirapine	Interaction not studied. *Expected:* ↔ Tenofovir alafenamide ↔ Nevirapine	No dose adjustment of Vemlidy 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 Vemlidy or rilpivirine is required.
HIV ANTIRETROVIRAL AGENTS – CCR5 RECEPTOR ANTAGONIST		
Maraviroc	Interaction not studied. *Expected:* ↔ Tenofovir alafenamide ↔ Maraviroc	No dose adjustment of Vemlidy 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.) Ethinylestradiol (0.025 mg orally, q.d.) Tenofovir alafenamide[c] (25 mg orally, q.d.)	*Norelgestromin* ↔ 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) ↔ 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 Vemlidy or norgestimate/ethinyl estradiol is required.

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
i. Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

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.

4.7 Effects on ability to drive and use machines

Vemlidy may have minor influence on the ability to drive and use machines. Patients should be informed that dizziness has been reported during treatment with tenofovir alafenamide.

4.8 Undesirable effects

Summary of the safety profile

Assessment of adverse reactions is based on clinical study data and postmarketing data. In pooled safety data from 2 controlled Phase 3 studies (GS-US-320-0108 and GS-US-320-0110; "*Study 108*" and "*Study 110*", respectively), the most frequently reported adverse reactions at Week 96 analysis were headache (12%), nausea (6%), and fatigue (6%). After Week 96, patients either remained on their original blinded treatment up to Week 144 or received open-label tenofovir alafenamide.

The safety profile of tenofovir alafenamide was similar in virologically suppressed patients switching from tenofovir disoproxil to tenofovir alafenamide in *Study 108*, *Study 110* and a controlled Phase 3 study GS-US-320-4018 *(Study 4018).* Changes in lipid laboratory tests were observed in these studies following a switch from tenofovir disoproxil (see section 5.1).

Tabulated summary of adverse reactions

The following adverse reactions have been identified with tenofovir alafenamide in patients with CHB (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 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
Skin and subcutaneous tissue disorders	
Common	Rash, pruritus
Uncommon	Angioedema[1], urticaria[1]
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**.**

In the open-label Phase 2 study (GS-US-320-4035; "*Study 4035*") to evaluate the efficacy and safety of switching from another antiviral regimen to tenofovir alafenamide in virologically suppressed chronic HBV infected patients, small median increases in fasting total cholesterol, direct LDL, HDL, and triglycerides from baseline to Week 96 were observed in subjects with moderate or severe renal impairment (Part A Cohort 1) and subjects with moderate or severe hepatic impairment (Part B), consistent with changes observed in *Studies 108 and 110*. Small median decreases in total cholesterol, LDL and triglycerides were observed in subjects with ESRD on hemodialysis in Part A Cohort 2, while small median increases were observed in HDL from baseline to Week 96. Median (Q1, Q3) change from baseline at Week 96 in total cholesterol to HDL ratio was 0.1 (-0.4, 0.4) in the moderate or severe renal impairment group, and -0.4 (-0.8,-0.1) in subjects with ESRD on hemodialysis and 0.1 (-0.2, 0.4) in subjects with moderate or severe hepatic impairment.

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

Other special populations

In *Study 4035* in virologically suppressed patients with moderate to severe renal impairment (eGFR by Cockcroft-Gault method 15 to 59 mL/min; Part A, Cohort 1, N = 78), end stage renal disease (ESRD) (eGFR < 15 mL/min) on haemodialysis (Part A, Cohort 2, N = 15), and/or moderate to severe hepatic impairment (Child-Pugh Class B or C at screening or by history; Part B, N = 31) who switched from another antiviral regimen to tenofovir alafenamide, no additional adverse reactions to tenofovir alafenamide were identified through Week 96.

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.

You can report any side effects to the Ministry of Health by clicking on the link "Report side effects due to medical treatment" that is located on the Ministry of Health homepage (www.health.gov.il)

which redirects to the online form for reporting side effects or by clicking on the link: https://sideeffects.health.gov.il.

You can also report any side effects directly to the registration holder via email: DrugSafety.Israel@gilead.com .

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.

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 HBV and HIV (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 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 > 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 $\log_{10}$ 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*, through 96 weeks of tenofovir alafenamide treatment one patient in the TAF-TAF group experienced a virologic blip (one visit with HBV DNA ≥ 69 IU/mL) and one patient in the TDF-TAF group experienced a virologic breakthrough. No HBV amino acid substitutions associated with resistance to TAF or TDF were detected through 96 weeks of 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 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 in patients with CHB 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-naïve 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 $\log_{10}$ 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 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 $\log_{10}$ IU/mL, mean serum ALT was 120 U/L, and 7% of patients had a history of cirrhosis.

The primary efficacy endpoint in both 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			N/A	N/A
< 7 $\log_{10}$ IU/mL	96% (221/230)	92% (107/116)		
≥ 7 $\log_{10}$ IU/mL	85% (47/55)	96% (23/24)		
Baseline HBV DNA	N/A	N/A		
< 8 $\log_{10}$ IU/mL			82% (254/309)	82% (123/150)
≥ 8 $\log_{10}$ IU/mL			43% (117/272)	51% (72/142)
Nucleoside naïve[c]	94% (212/225)	93% (102/110)	68% (302/444)	70% (156/223)
Nucleoside experienced	93% (56/60)	93% (28/30)	50% (69/137)	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
TAF = tenofovir alafenamide
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 analogue including tenofovir disoproxil or tenofovir alafenamide.
d. Includes patients who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy, e.g. withdrew consent, loss to follow-up, 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 Normalised ALT (Central lab)[b]	83%	75%	72%	67%
Normalised 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			N/A	N/A
< 7 $\log_{10}$ IU/mL	90% (207/230)	91% (105/116)		
≥ 7 $\log_{10}$ IU/mL	91% (50/55)	92% (22/24)		
Baseline HBV DNA	N/A	N/A		
< 8 $\log_{10}$ IU/mL			84% (260/309)	81% (121/150)
≥ 8 $\log_{10}$ IU/mL			60% (163/272)	68% (97/142)
Nucleoside naïve[b]	90% (203/225)	92% (101/110)	75% (331/444)	75% (168/223)
Nucleoside experienced	90% (54/60)	87% (26/30)	67% (92/137)	72% (50/69)
ALT				
Normalised ALT (Central lab)[c]	81%	71%	75%	68%
Normalised ALT (AASLD)[d]	50%	40%	52%	42%
Serology	N/A	N/A	22% / 18%	18% / 12%
HBeAg loss / seroconversion[e]				
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-naïve 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 measures of 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
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. 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, high density lipid (HDL)-cholesterol, low density lipid (LDL)-cholesterol, triglycerides, and total cholesterol to HDL ratio are presented in Table 6. At Week 96, the end of the double-blind phase, decreases in median fasting total cholesterol and HDL, and increases in median fasting direct LDL and triglycerides were observed in the tenofovir alafenamide group, while the tenofovir disoproxil group demonstrated median reductions in all parameters.

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.

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]
	TDF-TAF (N=180)		
	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)	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 a randomized, double-blind, active-controlled study, *Study 4018* (N=243 on tenofovir alafenamide; N=245 on tenofovir disoproxil), including data from patients who participated in the open-label phase of *Study 4018* from Week 48 through Week 96 (N=235

remained on tenofovir alafenamide [TAF-TAF]; N=237 switched from tenofovir disoproxil to tenofovir alafenamide at Week 48 [TDF-TAF]).

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 HBeAg 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 and Week 96 are presented in Table 7 and Table 8.

Table 7: HBV DNA efficacy parameters at Week 48[a,b] and Week 96[b,c]

	TAF (N=243)	**TDF (N=245)**	**TAF-TAF (N=243)**	**TDF-TAF (N=245)**
	Week 48		**Week 96**	
HBV DNA ≥ 20 IU/mL[b,d]	1 (0.4%)	1 (0.4%)	1 (0.4%)	1 (0.4%)
Treatment Difference[e]	0.0% (95% CI = -1.9% to 2.0%)		0.0% (95% CI = -1.9% to 1.9%)	
HBV DNA < 20 IU/mL	234 (96.3%)	236 (96.3%)	230 (94.7%)	230 (93.9%)
Treatment Difference[e]	0.0% (95% CI = -3.7% to 3.7%)		0.9% (95% CI = -3.5% to 5.2%)	
No Virologic Data	8 (3.3%)	8 (3.3%)	12 (4.9%)	14 (5.7%)
Discontinued Study Drug Due to AE or Death and Last Available HBV DNA < 20 IU/mL	2 (0.8%)	0	3 (1.2%)	1 (0.4%)
Discontinued Study Drug Due to Other Reasons[f] and Last Available HBV DNA < 20 IU/mL	6 (2.5%)	8 (3.3%)	7 (2.9%)	11 (4.5%)
Missing Data During Window but on Study Drug	0	0	2 (0.8%)	2 (0.8%)

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. Open-label phase, Week 96 window is between Day 589 and 840 (inclusive).
d. No patient discontinued treatment due to lack of efficacy.
e. Adjusted by baseline age groups (< 50, ≥ 50 years) and baseline HBeAg status strata.

f. 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 and Week 96[a]

	TAF (N=243)	TDF (N=245)	TAF-TAF (N=243)	TDF-TAF (N=245)
	Week 48		Week 96	
ALT				
Normal ALT (Central Lab)	89%	85%	88%	91%
Normal ALT (AASLD)	79%	75%	81%	87%
Normalized ALT (Central Lab)[b,c,d]	50%	37%	56%	79%
Normalized ALT (AASLD)[e,f,g]	50%	26%	56%	74%
Serology				
HBeAg Loss / Seroconversion[h]	8% / 3%	6% / 0	18% / 5%	9% / 3%
HBsAg Loss / Seroconversion	0 / 0	2% / 0	2% / 1%	2% / < 1%

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. Proportion of patients at Week 96: TAF, 18/32; TDF, 15/19.
e. 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.
f. Proportion of patients at Week 48: TAF, 26/52; TDF, 14/53.
g. Proportion of patients at Week 96: TAF, 29/52; TDF, 39/53
h. 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 mean percentage change in BMD from baseline to Week 48 as assessed by DXA was +1.7% with tenofovir alafenamide compared to −0.1% with tenofovir disoproxil at the lumbar spine and +0.7% compared to −0.5% at the total hip. BMD declines of greater than 3% at the lumbar spine were experienced by 4% of tenofovir alafenamide patients and 17% of tenofovir disoproxil patients at Week 48. BMD declines of greater than 3% at the total hip were experienced by 2% of tenofovir alafenamide patients and 12% of tenofovir disoproxil patients at Week 48.

In the open-label phase, mean percentage change in BMD from baseline to Week 96 in patients who remained on tenofovir alafenamide was +2.3% at the lumbar spine and +1.2% at the total hip, compared to +1.7% at the lumbar spine and +0.2% at the total hip in those who switched from tenofovir disoproxil to tenofovir alafenamide at Week 48.

Changes in renal laboratory tests in Study 4018
The median change from baseline to Week 48 in eGFR by Cockcroft-Gault method was +2.2 mL per minute in the tenofovir alafenamide group and −1.7 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 (0.01 mg/dL) compared with a median decrease from baseline among those who were switched to tenofovir alafenamide (-0.01 mg/dL).

In the open-label phase, the median change in eGFR from baseline to Week 96 was 1.6 mL/min in patients who remained on tenofovir alafenamide, compared to +0.5 mL/min in patients who switched from tenofovir disoproxil to tenofovir alafenamide at Week 48. The median change in serum creatinine from baseline to Week 96 was −0.02 mg/dL in those who remained on tenofovir

alafenamide, compared to −0.01 mg/dL in those who switched from tenofovir disoproxil to tenofovir alafenamide at Week 48.

Changes in lipid laboratory tests in Study 4018
Changes from double-blind baseline to Week 48 and Week 96 in total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, and total cholesterol to HDL ratio are presented in Table 9.

Table 9: Median changes in lipid laboratory tests at Week 48 and Week 96

	TAF (N=236)	**TAF (N=226)**	**TAF-TAF (N=220)**	**TDF (N=230)**	**TDF (N=222)**	**TDF-TAF N=219)**
	Baseline	**Week 48**	**Week 96**	**Baseline**	**Week 48**	**Week 96**
	(Q1, Q3) (mg/dL)	Median change[a] (Q1, Q3) (mg/dL)	Median change (Q1, Q3) (mg/dL)	(Q1, Q3) (mg/dL)	Median change[a] (Q1, Q3) (mg/dL)	Median change (Q1, Q3) (mg/dL)
Total Cholesterol (fasted)	166 (147, 189)	19 (6, 33)	16 (3, 30)	169 (147, 188)	−4 (−16, 8)	15 (1, 28)
HDL-Cholesterol (fasted)	48 (41, 56)	3 (−1, 8)	4 (−1, 10)	48 (40, 57)	−1 (−5, 2)	4 (0, 9)
LDL-Cholesterol (fasted)	102 (87,123)	16 (5, 27)	17 (6, 28)	103 (87, 120)	1 (−8, 12)	14 (3, 27)
Triglycerides (fasted)[b]	90 (66, 128)	16 (−3, 44)	9 (−8, 28)	89 (68, 126)	−2 (−22, 18)	8 (−8, 38)
Total Cholesterol to HDL ratio	3.4 (2.9, 4.2)	0.2 (−0.1, 0.5)	0.0 (−0.3, 0.3)	3.4 (2.9, 4.2)	0.0 (−0.3, 0.3)	0.0 (−0.3, 0.3)

TDF = tenofovir disoproxil

TAF = tenofovir alafenamide

a. P-value was calculated for the difference between the TAF and TDF groups at Week 48, 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.

b. Number of patients for triglycerides (fasted) for TAF group was N=235 at baseline, N=225 at Week 48 and N=218 for TAF-TAF group at Week 96.

Renal and/or hepatic impairment Study 4035
Study 4035 was an open-label clinical study to evaluate the efficacy and safety of switching from another antiviral regimen to tenofovir alafenamide in virologically suppressed chronic HBV infected patients. Part A of the study included patients with moderate to severe renal impairment (eGFR by Cockcroft-Gault method between 15 and 59 mL/min; Cohort 1, N = 78) or ESRD (eGFR by Cockcroft-Gault method < 15 mL/min) on hemodialysis (Cohort 2, N = 15). Part B of the study included patients (N = 31) with moderate or severe hepatic impairment (Child-Pugh Class B or C at screening or a history of CPT score ≥ 7 with any CPT score ≤ 12 at screening).

The primary endpoint was the proportion of subjects with HBV DNA < 20 IU/mL at Week 24. Secondary efficacy endpoints at Weeks 24 and 96 included the proportion of subjects with HBV DNA < 20 IU/mL and target detected/not detected (ie, < LLOD), the proportion of subjects with biochemical response (normal ALT and normalized ALT), the proportion of subjects with serological response (loss of HBsAg and seroconversion to anti-HBs and loss of HBeAg and seroconversion to anti-HBe in HBeAg-positive subjects) and change from baseline in CPT and Model for End Stage Liver Disease (MELD) scores for hepatically impaired subjects in Part B.

Renally impaired adult patients in Study 4035, Part A
At baseline, 98% (91/93) of patients in Part A had HBV DNA < 20 IU/mL and 66% (61/93) had an undetectable HBV DNA level. Median age was 65 years, 74% were male, 77% were Asian, 16% were White, and 83% were HBeAg-negative. The most commonly used HBV medication oral antivirals included TDF (N = 58), lamivudine (N = 46), adefovir dipivoxil (N = 46), and entecavir (N = 43). At baseline, 97% and 95% of patients had ALT ≤ ULN based on central laboratory criteria and 2018 AASLD criteria, respectively; median eGFR by Cockcroft-Gault was 43.7 mL/min (45.7 mL/min in Cohort 1 and 7.32 mL/min in Cohort 2); and 34% of patients had a history of cirrhosis.

Treatment outcomes of *Study 4035* Part A at Weeks 24 and 96 are presented in Table 10.

Table 10: Efficacy parameters for Renally Impaired Patients at Weeks 24 and 96

	Cohort 1[a] (N=78)		**Cohort 2[b] (N= 15)**		**Total (N=93)**	
	Week 24	Week 96	Week 24	Week 96	Week 24	Week 96[d]
HBV DNA[c]						
HBV DNA < 20 IU/mL	76/78 (97.4%)	65/78 (83.3%)	15/15 (100.0%)	13/15 (86.7%)	91/93 (97.8%)	78/93 (83.9%)
ALT[c]						
Normal ALT (Central Lab)	72/78 (92.3%)	64/78 (82.1%)	14/15 (93.3%)	13/15 (86.7%)	86/93 (92.5%)	77/93 (82.8%)
Normal ALT (AASLD)[e]	68/78 (87.2%)	58/78 (74.4%)	14/15 (93.3%)	13/15 (86.7%)	82/93 (88.2%)	71/93 (76.3%)

a. Part A Cohort 1 includes patients with moderate or severe renal impairment
b. Part A Cohort 2 includes patients with ESRD on hemodialysis
c. Missing = Failure analysis
d. The denominator includes 12 subjects (11 for Cohort 1 and 1 for Cohort 2) who prematurely discontinued study drug.
e. 2018 American Association of the Study of Liver Diseases (AASLD) criteria

Hepatically impaired adult patients in Study 4035, Part B
At baseline, 100% (31/31) of patients in Part B had baseline HBV DNA < 20 IU/mL and 65% (20/31) had an undetectable HBV DNA level. Median age was 57 years (19% ≥ 65 years), 68% were male, 81% were Asian, 13% were White, and 90% were HBeAg-negative. The most commonly used HBV medication oral antivirals included TDF (N = 21), lamivudine (N = 14), entecavir (N = 14), and adefovir dipivoxil (N = 10). At baseline, 87% and 68% of patients had ALT ≤ ULN based on central laboratory criteria and 2018 AASLD criteria, respectively; median eGFR by Cockcroft-Gault was 98.5 mL/min; 97% of patients had a history of cirrhosis, median (range) CPT score was 6 (5−10), and median (range) MELD score was 10 (6−17).

Treatment outcomes of *Study 4035* Part B at Weeks 24 and 96 are presented in Table 11.

Table 11: Efficacy parameters for Hepatically Impaired Patients at Weeks 24 and 96

	Part B (N=31)	
	Week 24	Week 96[b]
HBV DNA[a]		
HBV DNA < 20 IU/mL	31/31 (100.0%)	24/31 (77.4%)
ALT[a]		
Normal ALT (Central Lab)	26/31 (83.9%)	22/31 (71.0%)
Normal ALT (AASLD)[c]	25/31 (80.6%)	18/31 (58.1%)
CPT and MELD Score		
Mean change from Baseline in CPT Score (SD)	0 (1.1)	0 (1.2)
Mean Change from Baseline in MELD Score (SD)	-0.6 (1.94)	-1.0 (1.61)

CPT = Child-Pugh Turcotte;

MELD = Model for End-Stage Liver Disease

a. Missing = Failure analysis
b. The denominator includes 6 subjects who prematurely discontinued study drug
c. 2018 American Association of the Study of Liver Diseases (AASLD) criteria

Changes in lipid laboratory tests in Study 4035
Small median increases from baseline to Week 24 and Week 96 in total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, and total cholesterol to HDL ratio among patients with renal or hepatic impairment are consistent when compared with results observed from other studies involving switch to TAF (see section 5.1 for *Studies 0108, 0110 and 4018*), whereas decreases from baseline in total

cholesterol, LDL-cholesterol, triglycerides, and total cholesterol to HDL ratio were observed in patients with ESRD on haemodialysis at Week 24 and Week 96.

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 AUC_{0-24} for tenofovir alafenamide (N = 698) and tenofovir (N = 856) were 0.22 μg•h/mL and 0.32 μg•h/mL, respectively. Steady state C_{max} 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 (Table 12).

Exposures of tenofovir in subjects with ESRD (estimated creatinine clearance < 15 mL/min) on chronic haemodialysis who received tenofovir alafenamide (N = 5) were substantially higher than in subjects with normal renal function (Table 12). No clinically relevant differences in tenofovir alafenamide pharmacokinetics were observed in patients with ESRD on chronic haemodialysis as compared to those with normal renal function.

Table 12: Pharmacokinetics of tenofovir alafenamide and its metabolite tenofovir in subjects with renal impairment as compared to subjects with normal renal function

	AUC (mcg•hour per mL) Mean (CV%)		
Estimated Creatinine Clearance[a]	**Normal renal function ≥ 90 mL per minute (N = 13)[b]**	**Severe renal impairment 15–29 mL per minute (N = 14)[b]**	**ESRD on haemodialysis < 15 mL per minute (N = 5)[c]**
Tenofovir alafenamide	0.27 (49.2)[d]	0.51 (47.3)[d]	0.30 (26.7)[e]
Tenofovir	0.34 (27.2)[d]	2.07 (47.1)[d]	18.8 (30.4)[f]

CV = coefficient of variation
a. By Cockcroft-Gault method.
b. PK assessed on a single dose of TAF 25 mg in subjects with normal renal function and in subjects with severe renal impairment in Study GS-US-120-0108.
c. PK assessed prior to haemodialysis following multiple-dose administration of TAF 25 mg in 5 HBV infected subjects in Study GS-US-320-4035. These subjects had a median baseline eGFR by Cockcroft-Gault of 7.2 mL/min (range, 4.8 to 12.0).
d. AUC_{inf}.
e. AUC_{last}.
f. AUC_{tau}

Paediatric population
The pharmacokinetics of tenofovir alafenamide and tenofovir were evaluated in HIV-1-infected, 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; Gendevra). 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 (E460(i))
Croscarmellose sodium (E468)
Magnesium stearate (E470b)

Film-coating

Polyvinyl alcohol (E1203)
Talc (E553b)
Macrogol/PEG (E1521)
Titanium dioxide (E171)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
In use: 90 days after first opening.

6.4 Special precautions for storage

Store below 30°C.
Store in the original package in order to protect from moisture. Keep the bottle tightly closed.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottles, enclosed with a polypropylene continuous-thread, child-resistant cap, lined with an induction-activated aluminium foil liner. Each bottle contains silica gel desiccant and polyester coil.

The following pack size is available: outer carton containing 1 bottle of 30 film-coated tablets.

6.6 Special precautions for disposal

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

7. **MANUFACTURER**

Gilead Sciences Ireland UC
IDA Business & Technology Park
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Ireland

8. **REGISTRATION HOLDER**

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