

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Vemlidy 25 mg film-coated tablets.

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 in adults and adolescents (aged 12 years and older with body weight at least 35 kg) (see section 5.1).

4.2 Posology and method of administration

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

Posology

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

Treatment discontinuation

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

- In HBeAg-positive patients without cirrhosis, treatment should be administered for at least 6-12 months after HBe seroconversion (HBeAg loss and HBV DNA loss with anti-HBe detection) is confirmed or until HBs seroconversion or until there is loss of efficacy (see section 4.4). Regular reassessment is recommended after treatment discontinuation to detect virological relapse.

- In HBeAg-negative patients without cirrhosis, treatment should be administered at least until HBs seroconversion or until there is evidence of loss of efficacy. With prolonged treatment for more than 2 years, regular reassessment is recommended to confirm that continuing the selected therapy remains appropriate for the patient.

Missed dose

If a dose is missed and less than 18 hours have passed from the time it is usually taken, the patient should take Vemlidy 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 Vemlidy, the patient should take another tablet. If the patient vomits more than 1 hour after taking Vemlidy, the patient does not need to take another tablet.

Special populations

Elderly

No dose adjustment of Vemlidy is required in patients aged 65 years and older (see section 5.2).

Renal impairment

No dose adjustment of Vemlidy 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, Vemlidy 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 Vemlidy 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, or weighing < 35 kg, have not yet been established. No data are available.

Method of administration

Oral administration. Vemlidy film-coated tablets 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 Vemlidy 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 Vemlidy in HBV-infected patients with decompensated liver disease and who have a Child Pugh Turcotte (CPT) score > 9 (i.e. class C). These patients may be at higher risk of experiencing serious hepatic or renal adverse reactions. Therefore, hepatobiliary and renal parameters should be closely monitored in this patient population (see section 5.2).

Exacerbation of hepatitis

Flares on treatment

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

Flares after treatment discontinuation

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

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

Renal impairment

Patients with creatinine clearance < 30 mL/min

The use of Vemlidy once daily in patients with CrCl \geq 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 Vemlidy to treat HBV-infected patients with CrCl < 30 mL/min.

The use of Vemlidy 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 co-infected with HBV and hepatitis C or D virus

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

Hepatitis B and HIV co-infection

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

Co-administration with other medicinal products

Vemlidy should not be co-administered with products containing tenofovir alafenamide, tenofovir disoproxil fumarate or adefovir dipivoxil.

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

Lactose intolerance

Vemlidy contains lactose monohydrate. Consequently, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Vemlidy should not be co-administered with medicinal products containing tenofovir disoproxil fumarate, 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 Vemlidy is not recommended.

Co-administration of Vemlidy with medicinal products that inhibit P-gp and BCRP may increase plasma concentration of tenofovir alafenamide. Co-administration of strong inhibitors of P-gp with Vemlidy 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.”; 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 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.)	<i>Tenofovir alafenamide</i> ↓ C _{max} 0.43 (0.36, 0.51) ↓ AUC 0.45 (0.40, 0.51) <i>Tenofovir</i> ↓ 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. <i>Expected:</i> ↓ Tenofovir alafenamide	Co-administration is not recommended.
Phenytoin	Interaction not studied. <i>Expected:</i> ↓ Tenofovir alafenamide	Co-administration is not recommended.
Midazolam ^d (2.5 mg orally, s.d.) Tenofovir alafenamide ^c (25 mg orally, q.d.)	<i>Midazolam</i> ↔ C _{max} 1.02 (0.92, 1.13) ↔ AUC 1.13 (1.04, 1.23)	No dose adjustment of midazolam (administered orally or IV) is required.
Midazolam ^d (1 mg IV, s.d.) Tenofovir alafenamide ^c (25 mg orally, q.d.)	<i>Midazolam</i> ↔ 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.)	<i>Tenofovir alafenamide</i> ↔ C _{max} 1.00 (0.86, 1.16) ↔ AUC 0.96 (0.89, 1.03) <i>Tenofovir</i> ↔ 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.)	<i>Sertraline</i> ↔ C _{max} 1.14 (0.94, 1.38) ↔ AUC 0.93 (0.77, 1.13)	
ANTIFUNGALS		
Itraconazole Ketoconazole	Interaction not studied. <i>Expected:</i> ↑ Tenofovir alafenamide	Co-administration is not recommended.
ANTIMYCOBACTERIALS		
Rifampicin Rifapentine	Interaction not studied. <i>Expected:</i> ↓ Tenofovir alafenamide	Co-administration is not recommended.
Rifabutin	Interaction not studied. <i>Expected:</i> ↓ Tenofovir alafenamide	Co-administration is not recommended.
HCV ANTIVIRAL AGENTS		
Sofosbuvir (400 mg orally, q.d.)	Interaction not studied. <i>Expected:</i> ↔ Sofosbuvir ↔ GS-331007	No dose adjustment of Vemlidy or sofosbuvir 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
<p>Ledipasvir/sofosbuvir (90 mg/400 mg orally, q.d.)</p> <p>Tenofovir alafenamide^f (25 mg orally, q.d.)</p>	<p><i>Ledipasvir</i></p> <p>↔ C_{max} 1.01 (0.97, 1.05) ↔ AUC 1.02 (0.97, 1.06) ↔ C_{min} 1.02 (0.98, 1.07)</p> <p><i>Sofosbuvir</i></p> <p>↔ C_{max} 0.96 (0.89, 1.04) ↔ AUC 1.05 (1.01, 1.09)</p> <p><i>GS-331007^s</i></p> <p>↔ C_{max} 1.08 (1.05, 1.11) ↔ AUC 1.08 (1.06, 1.10) ↔ C_{min} 1.10 (1.07, 1.12)</p> <p><i>Tenofovir alafenamide</i></p> <p>↔ C_{max} 1.03 (0.94, 1.14) ↔ AUC 1.32 (1.25, 1.40)</p> <p><i>Tenofovir</i></p> <p>↑ C_{max} 1.62 (1.56, 1.68) ↑ AUC 1.75 (1.69, 1.81) ↑ C_{min} 1.85 (1.78, 1.92)</p>	<p>No dose adjustment of Vemlidy or ledipasvir/sofosbuvir is required.</p>
<p>Sofosbuvir/velpatasvir (400 mg/100 mg orally, q.d.)</p>	<p>Interaction not studied.</p> <p><i>Expected:</i></p> <p>↔ Sofosbuvir ↔ GS-331007 ↔ Velpatasvir ↑ Tenofovir alafenamide</p>	<p>No dose adjustment of Vemlidy or sofosbuvir/velpatasvir is required.</p>
<p>Sofosbuvir/velpatasvir/voxilaprevir (400 mg/100 mg/100 mg + 100 mgⁱ orally, q.d.)</p> <p>Tenofovir alafenamide^f (25 mg orally, q.d.)</p>	<p><i>Sofosbuvir</i></p> <p>↔ C_{max} 0.95 (0.86, 1.05) ↔ AUC 1.01 (0.97, 1.06)</p> <p><i>GS-331007^s</i></p> <p>↔ C_{max} 1.02 (0.98, 1.06) ↔ AUC 1.04 (1.01, 1.06)</p> <p><i>Velpatasvir</i></p> <p>↔ C_{max} 1.05 (0.96, 1.16) ↔ AUC 1.01 (0.94, 1.07) ↔ C_{min} 1.01 (0.95, 1.09)</p> <p><i>Voxilaprevir</i></p> <p>↔ C_{max} 0.96 (0.84, 1.11) ↔ AUC 0.94 (0.84, 1.05) ↔ C_{min} 1.02 (0.92, 1.12)</p> <p><i>Tenofovir alafenamide</i></p> <p>↑ C_{max} 1.32 (1.17, 1.48) ↑ AUC 1.52 (1.43, 1.61)</p>	<p>No dose adjustment of Vemlidy or sofosbuvir/velpatasvir/voxilaprevir is required.</p>

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
HIV ANTIRETROVIRAL AGENTS – PROTEASE INHIBITORS		
<p>Atazanavir/cobicistat (300 mg/150 mg orally, q.d.)</p> <p>Tenofovir alafenamide^c (10 mg orally, q.d.)</p>	<p><i>Tenofovir alafenamide</i> ↑ C_{max} 1.80 (1.48, 2.18) ↑ AUC 1.75 (1.55, 1.98)</p> <p><i>Tenofovir</i> ↑ C_{max} 3.16 (3.00, 3.33) ↑ AUC 3.47 (3.29, 3.67) ↑ C_{min} 3.73 (3.54, 3.93)</p> <p><i>Atazanavir</i> ↔ C_{max} 0.98 (0.94, 1.02) ↔ AUC 1.06 (1.01, 1.11) ↔ C_{min} 1.18 (1.06, 1.31)</p> <p><i>Cobicistat</i> ↔ C_{max} 0.96 (0.92, 1.00) ↔ AUC 1.05 (1.00, 1.09) ↑ C_{min} 1.35 (1.21, 1.51)</p>	Co-administration is not recommended.
<p>Atazanavir/ritonavir (300 mg/100 mg orally, q.d.)</p> <p>Tenofovir alafenamide^c (10 mg orally, s.d.)</p>	<p><i>Tenofovir alafenamide</i> ↑ C_{max} 1.77 (1.28, 2.44) ↑ AUC 1.91 (1.55, 2.35)</p> <p><i>Tenofovir</i> ↑ C_{max} 2.12 (1.86, 2.43) ↑ AUC 2.62 (2.14, 3.20)</p> <p><i>Atazanavir</i> ↔ C_{max} 0.98 (0.89, 1.07) ↔ AUC 0.99 (0.96, 1.01) ↔ C_{min} 1.00 (0.96, 1.04)</p>	Co-administration is not recommended.
<p>Darunavir/cobicistat (800 mg/150 mg orally, q.d.)</p> <p>Tenofovir alafenamide^c (25 mg orally, q.d.)</p>	<p><i>Tenofovir alafenamide</i> ↔ C_{max} 0.93 (0.72, 1.21) ↔ AUC 0.98 (0.80, 1.19)</p> <p><i>Tenofovir</i> ↑ C_{max} 3.16 (3.00, 3.33) ↑ AUC 3.24 (3.02, 3.47) ↑ C_{min} 3.21 (2.90, 3.54)</p> <p><i>Darunavir</i> ↔ C_{max} 1.02 (0.96, 1.09) ↔ AUC 0.99 (0.92, 1.07) ↔ C_{min} 0.97 (0.82, 1.15)</p> <p><i>Cobicistat</i> ↔ C_{max} 1.06 (1.00, 1.12) ↔ AUC 1.09 (1.03, 1.15) ↔ C_{min} 1.11 (0.98, 1.25)</p>	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/ritonavir (800 mg/100 mg orally, q.d.) Tenofovir alafenamide ^c (10 mg orally, s.d.)	<i>Tenofovir alafenamide</i> ↑ C _{max} 1.42 (0.96, 2.09) ↔ AUC 1.06 (0.84, 1.35) <i>Tenofovir</i> ↑ C _{max} 2.42 (1.98, 2.95) ↑ AUC 2.05 (1.54, 2.72) <i>Darunavir</i> ↔ 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.)	<i>Tenofovir alafenamide</i> ↑ C _{max} 2.19 (1.72, 2.79) ↑ AUC 1.47 (1.17, 1.85) <i>Tenofovir</i> ↑ C _{max} 3.75 (3.19, 4.39) ↑ AUC 4.16 (3.50, 4.96) <i>Lopinavir</i> ↔ 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. <i>Expected:</i> ↓ 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.)	<i>Tenofovir alafenamide</i> ↑ C _{max} 1.24 (0.88, 1.74) ↑ AUC 1.19 (0.96, 1.48) <i>Tenofovir</i> ↔ C _{max} 1.10 (0.96, 1.25) ↑ AUC 1.25 (1.06, 1.47) <i>Dolutegravir</i> ↔ 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.
Raltegravir	Interaction not studied. <i>Expected:</i> ↔ 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.)	<i>Tenofovir alafenamide</i> ↓ C _{max} 0.78 (0.58, 1.05) ↔ AUC 0.86 (0.72, 1.02) <i>Tenofovir</i> ↓ C _{max} 0.75 (0.67, 0.86) ↔ AUC 0.80 (0.73, 0.87) ↔ C _{min} 0.82 (0.75, 0.89) <i>Expected:</i> ↔ Efavirenz	No dose adjustment of Vemlidy or efavirenz 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
Nevirapine	Interaction not studied. <i>Expected:</i> ↔ 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.)	<i>Tenofovir alafenamide</i> ↔ C _{max} 1.01 (0.84, 1.22) ↔ AUC 1.01 (0.94, 1.09) <i>Tenofovir</i> ↔ C _{max} 1.13 (1.02, 1.23) ↔ AUC 1.11 (1.07, 1.14) ↔ C _{min} 1.18 (1.13, 1.23) <i>Rilpivirine</i> ↔ 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. <i>Expected:</i> ↔ Tenofovir alafenamide ↔ Maraviroc	No dose adjustment of Vemlidy or maraviroc is required.
HERBAL SUPPLEMENTS		
St. John's wort (<i>hypericum perforatum</i>)	Interaction not studied. <i>Expected:</i> ↓ Tenofovir alafenamide	Co-administration is not recommended.
ORAL CONTRACEPTIVES		
Norgestimate (0.180 mg/0.215 mg/ 0.250 mg orally, q.d.) Ethinyl estradiol (0.025 mg orally, q.d.) Tenofovir alafenamide ^c (25 mg orally, q.d.)	<i>Norelgestromin</i> ↔ C _{max} 1.17 (1.07, 1.26) ↔ AUC 1.12 (1.07, 1.17) ↔ C _{min} 1.16 (1.08, 1.24) <i>Norgestrel</i> ↔ C _{max} 1.10 (1.02, 1.18) ↔ AUC 1.09 (1.01, 1.18) ↔ C _{min} 1.11 (1.03, 1.20) <i>Ethinyl estradiol</i> ↔ 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

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 Vemlidy 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 breastfed child cannot be excluded; therefore, Vemlidy should not be used during breast-feeding.

Fertility

No human data on the effect of Vemlidy 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 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 Vemlidy.

4.8 Undesirable effects

Summary of the safety profile

Assessment of adverse reactions is based on pooled safety data from 2 controlled Phase 3 studies in which 866 HBV-infected patients received tenofovir alafenamide 25 mg once daily in a double-blind fashion through Week 96 (median duration of blinded study drug exposure of 104 weeks). The most frequently reported adverse reactions were headache (12%), nausea (6%), and fatigue (6%). After Week 96, patients either remained on their original blinded treatment or received open-label Vemlidy. No additional adverse reactions to Vemlidy were identified from Week 96 through Week 120 in the double-blind phase and in the subset of subjects receiving open-label Vemlidy treatment (see Section 5.1).

Tabulated summary of adverse reactions

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

Table 2: Adverse drug reactions identified with tenofovir alafenamide

<i>System organ class</i>	
Frequency	Adverse reaction
<i>Gastrointestinal disorders</i>	
Common	Diarrhoea, vomiting, nausea, abdominal pain, abdominal distension, flatulence
<i>General disorders and administration site conditions</i>	
Common	Fatigue
<i>Nervous system disorders</i>	

<i>System organ class</i>	
Frequency	Adverse reaction
Very common	Headache
Common	Dizziness
<i>Skin and subcutaneous tissue disorders</i>	
Common	Rash, pruritus
<i>Hepatobiliary disorders</i>	
Common	Increased ALT
<i>Musculoskeletal and connective tissue disorders</i>	
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 listed in Appendix V.

4.9 Overdose

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

Treatment of overdose with Vemlidy 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 phosphoramidate 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 (HIV-1 and HIV-2). Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there is no evidence of mitochondrial toxicity *in vitro* based on several assays including mitochondrial DNA analyses.

Antiviral activity

The antiviral activity of tenofovir alafenamide was assessed in HepG2 cells against a panel of HBV clinical isolates representing genotypes A-H. The EC₅₀ (50% effective concentration) values for tenofovir alafenamide ranged from 34.7 to 134.4 nM, with an overall mean EC₅₀ of 86.6 nM. The CC₅₀ (50% cytotoxicity concentration) in HepG2 cells was > 44400 nM.

Resistance

In a pooled analysis of patients receiving Vemlidy, 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 \geq 69 IU/mL after having been $<$ 69 IU/mL, or 1.0 log₁₀ or greater increase in HBV DNA from nadir) or patients with HBV DNA \geq 69 IU/mL at Week 96 or at early discontinuation at or after Week 24. In analyses at Week 48 (N = 20) and Week 96 (N = 72), no amino acid substitutions associated with resistance to Vemlidy were identified in these isolates (genotypic and phenotypic analyses).

Cross-resistance

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

Clinical data

The efficacy and safety of Vemlidy in patients with chronic hepatitis B are based on 48 and 96-week data from two randomized, double-blind, active-controlled studies, GS-US-320-0108 (“*Study 108*”) and GS-US-320-0110 (“*Study 110*”). The safety of Vemlidy is also supported by pooled data from patients in Studies *108* and *110* who remained on blinded treatment from Week 96 through Week 120 and additionally from patients in the open-label phase of Studies *108* and *110* from Week 96 through Week 120 (N = 361 remained on Vemlidy; N = 180 switched from tenofovir disoproxil fumarate to Vemlidy at Week 96).

In *Study 108*, HBeAg-negative treatment-naïve and treatment-experienced patients with compensated liver function were randomized in a 2:1 ratio to receive Vemlidy (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 log₁₀ IU/mL, mean serum ALT was 94 U/L, and 9% of patients had a history of cirrhosis.

In *Study 110*, HBeAg-positive treatment-naïve and treatment-experienced patients with compensated liver function were randomized in a 2:1 ratio to receive Vemlidy (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 log₁₀ IU/mL, mean serum ALT was 120 U/L, and 7% of patients had a history of cirrhosis.

The primary efficacy endpoint in both trials was the proportion of patients with plasma HBV DNA levels below 29 IU/mL at Week 48. Vemlidy met the non-inferiority 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.

Table 3: HBV DNA efficacy parameters at Week 48^a

	<i>Study 108 (HBeAg-Negative)</i>		<i>Study 110 (HBeAg-Positive)</i>	
	Vemlidy (N = 285)	TDF (N = 140)	Vemlidy (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	96% (221/230)	92% (107/116)	N/A	N/A
≥ 7 log ₁₀ IU/mL	85% (47/55)	96% (23/24)		
Baseline HBV DNA < 8 log ₁₀ IU/mL	N/A	N/A	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 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 follow-up, etc.

Table 4: Additional efficacy parameters at Week 48^a

	<i>Study 108 (HBeAg-Negative)</i>		<i>Study 110 (HBeAg-Positive)</i>	
	Vemlidy (N = 285)	TDF (N = 140)	Vemlidy (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 (> 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

	<i>Study 108 (HBeAg-Negative)</i>		<i>Study 110 (HBeAg-Positive)</i>	
	Vemlidy (N = 285)	TDF (N = 140)	Vemlidy (N = 581)	TDF (N = 292)
HBV DNA < 29 IU/mL	90%	91%	73%	75%
Baseline HBV DNA < 7 log ₁₀ IU/mL ≥ 7 log ₁₀ IU/mL	90% (207/230) 91% (50/55)	91% (105/116) 92% (22/24)	N/A	N/A
Baseline HBV DNA < 8 log ₁₀ IU/mL ≥ 8 log ₁₀ IU/mL	N/A	N/A	84% (260/309) 60% (163/272)	81% (121/150) 68% (97/142)
Nucleoside naïve ^b Nucleoside experienced	90% (203/225) 90% (54/60)	92% (101/110) 87% (26/30)	75% (331/444) 67% (92/137)	75% (168/223) 72% (50/69)
ALT Normalized ALT (Central lab) ^c Normalized ALT (AASLD) ^d	81% 50%	71% 40%	75% 52%	68% 42%
Serology HBeAg loss / seroconversion ^e HBsAg loss / seroconversion	N/A <1% / <1%	N/A 0 / 0	22% / 18% 1% / 1%	18% / 12% 1% / 0

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 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 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 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 fumarate 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 120 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 120 in patients who remained on Vemlidy was +0.6% at the lumbar spine and 0% at the total hip, compared to +1.7% at the lumbar spine and +0.6% at the total hip in those who switched from tenofovir disoproxil fumarate to Vemlidy at Week 96.

Changes in measures of renal function

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 fumarate 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, change from baseline in renal laboratory parameter values in each group at Week 120 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 120 was -0.002 (0.10) mg/dL in those who remained on Vemlidy, compared to -0.008 (0.09) mg/dL in those who switched from tenofovir disoproxil fumarate to Vemlidy at Week 96. In the open-label phase, the median change in eGFR from Week 96 to Week 120 was -0.6 mL/min in patients who remained on Vemlidy, compared to +1.8 mL/min patients who switched from tenofovir disoproxil fumarate to Vemlidy at Week 96.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Vemlidy 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 Vemlidy 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 CHB, mean steady state AUC_{0-24} for tenofovir alafenamide (N = 698) and tenofovir (N = 856) were $0.22 \mu\text{g}\cdot\text{hr}/\text{mL}$ and $0.32 \mu\text{g}\cdot\text{hr}/\text{mL}$, respectively. Steady state C_{max} for tenofovir alafenamide and tenofovir were 0.18 and $0.02 \mu\text{g}/\text{mL}$, respectively. Relative to fasting conditions, the administration of a single dose of Vemlidy 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 $\mu\text{g}/\text{mL}$.

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 carboxylesterase-1 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/non-linearity

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

Pharmacokinetics in special populations

Age, gender and ethnicity

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

Hepatic impairment

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

Renal impairment

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

Paediatric population

The pharmacokinetics of tenofovir alafenamide and tenofovir were evaluated in HIV-1-infected, treatment-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 HIV-1-infected 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 peri-postnatal 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 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)
Titanium dioxide (E171)
Macrogol (E1521)

Talc (E553b)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture. Keep the bottle tightly closed.

6.5 Nature and contents of container

Vemlidy tablets are packaged in high density polyethylene (HDPE) bottles and enclosed with a polypropylene continuous-thread, child-resistant cap, lined with an induction-activated aluminium foil liner. Each bottle contains silica gel dessicant and polyester coil.

The following pack sizes are available: outer cartons containing 1 bottle of 30 film-coated tablets and outer cartons containing 90 (3 bottles of 30) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1154/001
EU/1/16/1154/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09 January 2017
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Gilead Sciences Ireland UC
IDA Business & Technology Park
Carrigtohill
County Cork
IRELAND

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

BOTTLE AND CARTON LABELLING

1. NAME OF THE MEDICINAL PRODUCT

Vemlidy 25 mg film-coated tablets
tenofovir alafenamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets.

90 (3 bottles of 30) film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

Do not swallow dessicant.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture. Keep the bottle tightly closed.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1154/001 30 film-coated tablets
EU/1/16/1154/002 90 (3 bottles of 30) film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Vemlidy [Outer packaging only]

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Vemlidy 25 mg film-coated tablets

Tenofovir alafenamide

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Vemlidy is and what it is used for
2. What you need to know before you take Vemlidy
3. How to take Vemlidy
4. Possible side effects
5. How to store Vemlidy
6. Contents of the pack and other information

1. What Vemlidy is and what it is used for

Vemlidy contains the active substance *tenofovir alafenamide*. This is an *antiviral medicine*, known as a *nucleotide reverse transcriptase inhibitor* (NtRTI).

Vemlidy is used to **treat chronic (long term) hepatitis B** in adults and adolescents 12 years of age and older, who weigh at least 35 kg. Hepatitis B is an infection affecting the liver, caused by the hepatitis B virus. In patients with hepatitis B, Vemlidy controls the infection by stopping the virus from multiplying.

2. What you need to know before you take Vemlidy

Do not take Vemlidy

- **if you are allergic** to tenofovir alafenamide or any of the other ingredients of this medicine (listed in section 6).

→ If this applies to you, **do not take Vemlidy and tell your doctor immediately.**

Warnings and precautions

- **Take care not to pass on your hepatitis B to other people.** You can still infect others when taking this medicine. Vemlidy does not reduce the risk of passing on hepatitis B to others through sexual contact or blood contamination. You must continue to take precautions to avoid this. Discuss with your doctor the precautions needed to avoid infecting others.

- **Tell your doctor if you have a history of liver disease.** Patients with liver disease, who are treated for hepatitis B with antiviral medicines, have a higher risk of severe and potentially fatal liver complications. Your doctor may need to carry out blood tests to monitor your liver function.
- **Talk to your doctor or pharmacist if you have had kidney disease or if tests have shown problems with your kidneys.** Before starting treatment and during treatment, your doctor may order blood tests to monitor how your kidneys work.
- **Talk to your doctor if you also have hepatitis C or D.** Vemlidy has not been tested on patients who have hepatitis C or D as well as hepatitis B.
- **Talk to your doctor if you also have HIV.** If you are not sure whether you have HIV, your doctor should offer you HIV testing before you start taking Vemlidy for hepatitis B.

→ If any of these apply to you, **talk to your doctor before taking Vemlidy.**

Children and adolescents

Do not give this medicine to children who are under 12 years old or weigh less than 35 kg. Vemlidy has not been tested in children aged less than 12 years old or weighing less than 35 kg.

Other medicines and Vemlidy

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Vemlidy may interact with other medicines. As a result, the amounts of Vemlidy or other medicines in your blood may change. This may stop your medicines from working properly, or may make any side effects worse.

Medicines used in treating hepatitis B infection

Do not take Vemlidy with other medicines containing:

- **tenofovir alafenamide**
- **tenofovir disoproxil fumarate**
- **adefovir dipivoxil**

Other types of medicines

Talk to your doctor if you are taking:

- **antibiotics** used to treat bacterial infections including tuberculosis, containing:
 - rifabutin, rifampicin or rifapentine
- **antiviral medicines used to treat HIV**, such as:
 - ritonavir or cobicistat boosted darunavir, lopinavir or atazanavir
- **anticonvulsants** used to treat epilepsy, such as:
 - carbamazepine, oxcarbazepine, phenobarbital or phenytoin
- **herbal remedies** used to treat depression and anxiety, containing:
 - St. John's wort (*Hypericum perforatum*)
- **antifungal medicines** used to treat fungal infections, containing:
 - ketoconazole or itraconazole

→ **Tell your doctor if you are taking these or any other medicines.**

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

- **Take steps to avoid getting pregnant** during treatment with Vemlidy. You must use an effective method of contraception. Tell your doctor immediately if you become pregnant.
- **Do not breast-feed during treatment with Vemlidy.** It is recommended that you do not breast-feed to avoid passing tenofovir alafenamide or tenofovir to the baby through breast milk.

Driving and using machines

Vemlidy can cause dizziness. If you feel dizzy when taking Vemlidy, do not drive and do not use any tools or machines.

Vemlidy contains lactose

Tell your doctor if you are lactose-intolerant or intolerant to other sugars. Vemlidy contains lactose monohydrate.

3. How to take Vemlidy

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is **one tablet once a day with food**. Treatment should continue for as long as your doctor tells you. Usually this is for at least 6 to 12 months and may be for many years.

If you take more Vemlidy than you should

If you accidentally take more than the recommended dose of Vemlidy you may be at increased risk of experiencing possible side effects with this medicine (see section 4, *Possible side effects*).

Contact your doctor or nearest emergency department immediately for advice. Keep the tablet bottle with you so that you can easily describe what you have taken.

If you forget to take Vemlidy

It is important not to miss a dose of Vemlidy. If you do miss a dose, work out how long since you should have taken it.

- **If it is less than 18 hours** after you usually take Vemlidy, take it as soon as you can, and then take your next dose at its regular time.
- **If it is more than 18 hours** after you usually take Vemlidy, then do not take the missed dose. Wait and take the next dose at the regular time. **Do not take a double dose** to make up for a forgotten tablet.

If you are sick (vomit) less than 1 hour after taking Vemlidy, take another tablet. You do not need to take another tablet if you are sick (vomit) more than 1 hour after taking Vemlidy.

If you stop taking Vemlidy

Do not stop taking Vemlidy without your doctor's advice. Stopping treatment with Vemlidy may cause your hepatitis B to get worse. In some patients with advanced liver disease or cirrhosis, this could be life-threatening. If you stop taking Vemlidy, you will need regular health checks and blood tests for several months to check your hepatitis B infection.

- **Talk to your doctor** before you stop taking Vemlidy for any reason, particularly if you are experiencing any side effects or you have another illness.

- **Tell your doctor immediately** about new or unusual symptoms after you stop treatment, particularly symptoms you associate with hepatitis B infection.
- **Talk to your doctor** before you restart taking Vemlidy tablets.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very common side effects

(may affect more than 1 in 10 people)

- Headache

Common side effects

(may affect up to 1 in 10 people)

- Diarrhoea
- Being sick (*vomiting*)
- Feeling sick (*nausea*)
- Dizziness
- Stomach pain
- Joint pain (*arthralgia*)
- Rash
- Itchiness
- Feeling bloated
- Wind (*flatulence*)
- Feeling tired

Tests may also show:

- Increased level of a liver enzyme (ALT) in the blood

→ **If any of these side effects get serious tell your doctor.**

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly *via* the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Vemlidy

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle and carton after {EXP}. The expiry date refers to the last day of that month.

Store in the original package in order to protect from moisture. Keep the bottle tightly closed.

Do not throw away any medicines *via* wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Vemlidy contains

The active substance is *tenofovir alafenamide*. Each Vemlidy film-coated tablet contains tenofovir alafenamide fumarate, equivalent to 25 mg of tenofovir alafenamide.

The other ingredients are

Tablet core:

Lactose monohydrate, microcrystalline cellulose (E460(i)), croscarmellose sodium (E468), magnesium stearate (E470b).

Film-coating:

Polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol (E1521), talc (E553b), iron oxide yellow (E172).

What Vemlidy looks like and contents of the pack

Vemlidy film-coated tablets are yellow, round, printed (or marked) with “GSI” on one side of the tablet and “25” on the other side of the tablet. Vemlidy comes in bottles of 30 tablets (with a silica gel desiccant that must be kept in the bottle to help protect your tablets). The silica gel desiccant is contained in a separate sachet or canister and should not be swallowed.

The following pack sizes are available: outer cartons containing 1 bottle of 30 film-coated tablets and outer cartons containing 90 (3 bottles of 30) film-coated tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder

Gilead Sciences Ireland UC
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Manufacturer

Gilead Sciences Ireland UC
IDA Business & Technology Park
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.