

### 1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

S4

#### SCHEDULING STATUS

##### 1 NAME OF THE MEDICINE

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) with compensated hepatic disease/function (see section 5.1).

###### 4.2 Posology and method of administration

Therapy should be initiated by a medical practitioner 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)  $\geq$  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).

Vemlidy is not recommended for use in 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 mild or moderate hepatic impairment (see sections 4.4 and 5.2). Vemlidy is not recommended for use in patients with severe hepatic impairment (Child Pugh C).

#### *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.

Concomitant use with medicines containing tenofovir alafenamide, tenofovir disoproxil fumarate and adefovir dipivoxil.

#### **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, no dose recommendation can be made and Vemlidy is not recommended for use in these patients

##### Lactic acidosis and severe hepatomegaly

Lactic acidosis and severe hepatomegaly, including fatal cases have been reported with the use of nucleoside analogues, including tenofovir disoproxil fumarate, another prodrug of tenofovir, alone or in combination with other antiretrovirals. Treatment with Vemlidy should be discontinued in patients who develop clinical and/or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity, which may include hepatomegaly and steatosis even in the absence of a marked increase in transaminases.

Clinical features of lactic acidosis are non-specific and include nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss. In patients with suspicious symptoms or biochemistry, measure the venous lactate level (normal < 2mmol/l), and the serum bicarbonate and respond as follows:

- Lactate 2-5 mmol/l with minimum symptoms: switch to medicines that are less likely to cause lactic acidosis
- Lactate 5-10 mmol/l with symptoms and/or with reduced standard bicarbonate. Stop NRTIs and change treatment option. Once the lactate has settled, use medicines that are less likely to cause lactic acidosis.

Exclude other causes (e.g. sepsis, uraemia, diabetic keto acidosis, thyrotoxicosis/hyperthyroidism

- Lactate > 10mmol/l. STOP all therapy (80% mortality)

The above values may not be applicable to paediatric patients.

Caution should be exercised when administering VEMLIDY to patients with known risk factors for liver disease.

### 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 medicines

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

Co administration of Vemlidy with certain anticonvulsants (e.g. carbamazepine, oxcarbazepine, phenobarbitone 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: Patients with rare hereditary conditions of galactose intolerance e.g. total lactase deficiency, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take Vemlidy.

## **4.5 Interaction with other medicines and other forms of interaction**

Interaction studies have only been performed in adults.

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

### Medicines that may affect tenofovir alafenamide

Tenofovir alafenamide is transported by P-gp and breast cancer resistance protein (BCRP).

Medicines 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 medicines with Vemlidy is not recommended.

Co-administration of Vemlidy with medicines that inhibit P-gp and BCRP may increase plasma concentrations 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 medicines

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 medicines 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 medicines**

Medicine by therapeutic areas	Effects on drug levels. <sup>a,b</sup> Mean ratio (90 % confidence interval) for AUC, C <sub>max</sub> , C <sub>min</sub>	Recommendation concerning co-administration with Vemlidy
<b>ANTICONVULSANTS</b>		
Carbamazepine (300 mg orally, b.i.d.)  Tenofovir alafenamide <sup>c</sup> (25 mg orally, s.d.)	<i>Tenofovir alafenamide</i>  ↓ C <sub>max</sub> 0,43 (0,36, 0,51)  ↓ AUC 0,45 (0,40; 0,51)	Co-administration is not recommended.

Medicine by therapeutic areas	Effects on drug levels. <sup>a,b</sup>  Mean ratio (90 % confidence interval) for AUC, C <sub>max</sub> , C <sub>min</sub>	Recommendation concerning co-administration with Vemlidy
	<i>Tenofovir</i> ↓ C <sub>max</sub> 0,70 (0,65; 0,74) ↔ AUC 0,77 (0,74; 0,81)	
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 <sup>d</sup> (2,5 mg orally, s.d.)  Tenofovir alafenamide <sup>c</sup> (25 mg orally, q.d.)	<i>Midazolam</i> ↔ C <sub>max</sub> 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 <sup>d</sup> (1 mg IV, s.d.)  Tenofovir alafenamide <sup>c</sup> (25 mg orally, q.d.)	<i>Midazolam</i> ↔ C <sub>max</sub> 0,99 (0,89; 1,11)  ↔ AUC 1,08 (1,04; 1,14)	

Medicine by therapeutic areas	Effects on drug levels. <sup>a,b</sup>  Mean ratio (90 % confidence interval) for AUC, C <sub>max</sub> , C <sub>min</sub>	Recommendation concerning co-administration with Vemlidy
<b>ANTIDEPRESSANTS</b>		
Sertraline (50 mg orally, s.d.)  Tenofovir alafenamide <sup>e</sup> (10 mg orally, q.d.)	<i>Tenofovir alafenamide</i>  ↔ C <sub>max</sub> 1,00 (0,86; 1,16)  ↔ AUC 0,96 (0,89; 1,03)  <i>Tenofovir</i>  ↔ C <sub>max</sub> 1,10 (1,00; 1,21)  ↔ AUC 1,02 (1,00; 1,04)  ↔ C <sub>min</sub> 1,01 (0,99; 1,03)	No dose adjustment of Vemlidy or sertraline is required.
Sertraline (50 mg orally, s.d.)  Tenofovir alafenamide <sup>e</sup> (10 mg orally, q.d.)	<i>Sertraline</i>  ↔ C <sub>max</sub> 1,14 (0,94; 1,38)  ↔ AUC 0,93 (0,77; 1,13)	

Medicine by therapeutic areas	Effects on drug levels. <sup>a,b</sup>  Mean ratio (90 % confidence interval) for AUC, C <sub>max</sub> , C <sub>min</sub>	Recommendation concerning co-administration with Vemlidy
<b>ANTIFUNGALS</b>		
Itraconazole Ketoconazole	Interaction not studied.  <i>Expected:</i> ↑ Tenofovir alafenamide	Co-administration is not recommended.
<b>ANTIMYCOBACTERIALS</b>		
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.
<b>HCV ANTIVIRAL AGENTS</b>		
Sofosbuvir (400 mg orally, q.d.)	Interaction not studied.  <i>Expected:</i> ↔ Sofosbuvir ↔ GS-331007	No dose adjustment of Vemlidy or sofosbuvir is required.

<b>Medicine by therapeutic areas</b>	<b>Effects on drug levels.<sup>a,b</sup></b>  <b>Mean ratio (90 % confidence interval) for AUC, C<sub>max</sub>, C<sub>min</sub></b>	<b>Recommendation concerning co-administration with Vemlidy</b>
<p>Ledipasvir/sofosbuvir (90 mg/400 mg orally, q.d.)</p> <p>Tenofovir alafenamide<sup>f</sup> (25 mg orally, q.d.)</p>	<p><b>Ledipasvir</b></p> <p>↔ C<sub>max</sub> 1,01 (0,97; 1,05)</p> <p>↔ AUC 1,02 (0,97; 1,06)</p> <p>↔ C<sub>min</sub> 1,02 (0,98; 1,07)</p> <p><i>Sofosbuvir</i></p> <p>↔ C<sub>max</sub> 0,96 (0,89; 1,04)</p> <p>↔ AUC 1,05 (1,01; 1,09)</p> <p><i>GS-331007<sup>g</sup></i></p> <p>↔ C<sub>max</sub> 1,08 (1,05; 1,11)</p> <p>↔ AUC 1,08 (1,06; 1,10)</p> <p>↔ C<sub>min</sub> 1,10 (1,07; 1,12)</p> <p><i>Tenofovir alafenamide</i></p> <p>↔ C<sub>max</sub> 1,03 (0,94; 1,14)</p> <p>↔ AUC 1,32 (1,25; 1,40)</p>	<p>No dose adjustment of Vemlidy or ledipasvir/sofosbuvir is required.</p>

Medicine by therapeutic areas	Effects on drug levels. <sup>a,b</sup>  Mean ratio (90 % confidence interval) for AUC, C <sub>max</sub> , C <sub>min</sub>	Recommendation concerning co-administration with Vemlidy
	<p><i>Tenofovir</i></p> <p>↑ C<sub>max</sub> 1,62 (1,56; 1,68)</p> <p>↑ AUC 1,75 (1,69; 1,81)</p> <p>↑ C<sub>min</sub> 1,85 (1,78; 1,92)</p>	
Sofosbuvir/velpatasvir (400 mg/100 mg orally, q.d.)	<p>Interaction not studied.</p> <p><i>Expected:</i></p> <p>↔ Sofosbuvir</p> <p>↔ GS-331007</p> <p>↔ Velpatasvir</p> <p>↑ Tenofovir alafenamide</p>	No dose adjustment of Vemlidy or sofosbuvir/velpatasvir is required.
Sofosbuvir/velpatasvir/voxiclaprevir (400 mg/100 mg/100 mg + 100 mg <sup>i</sup> orally, q.d.)  Tenofovir alafenamide <sup>f</sup> (25 mg orally, q.d.)	<p>Sofosbuvir</p> <p>↔ C<sub>max</sub> 0,95 (0,86; 1,05)</p> <p>↔ AUC 1,01 (0,97; 1,06)</p> <p><i>GS-331007<sup>g</sup></i></p> <p>↔ C<sub>max</sub> 1,02 (0,98; 1,06)</p> <p>↔ AUC 1,04 (1,01; 1,06)</p> <p><i>Velpatasvir</i></p>	No dose adjustment of Vemlidy or sofosbuvir/velpatasvir/voxiclaprevir is required.

Medicine by therapeutic areas	Effects on drug levels. <sup>a,b</sup>  Mean ratio (90 % confidence interval) for AUC, C <sub>max</sub> , C <sub>min</sub>	Recommendation concerning co-administration with Vemlidy
	<p>↔ C<sub>max</sub> 1,05 (0,96; 1,16)</p> <p>↔ AUC 1,01 (0,94; 1,07)</p> <p>↔ C<sub>min</sub> 1,01 (0,95; 1,09)</p> <p><i>Voxilaprevir</i></p> <p>↔ C<sub>max</sub> 0,96 (0,84; 1,11)</p> <p>↔ AUC 0,94 (0,84; 1,05)</p> <p>↔ C<sub>min</sub> 1,02 (0,92; 1,12)</p> <p><i>Tenofovir alafenamide</i></p> <p>↑ C<sub>max</sub> 1,32 (1,17; 1,48)</p> <p>↑ AUC 1,52 (1,43; 1,61)</p>	
<b>HIV ANTIRETROVIRAL AGENTS – PROTEASE INHIBITORS</b>		
<p>Atazanavir/cobicistat (300 mg/150 mg orally, q.d.)</p> <p>Tenofovir alafenamide<sup>c</sup> (10 mg orally, q.d.)</p>	<p><i>Tenofovir alafenamide</i></p> <p>↑ C<sub>max</sub> 1,80 (1,48; 2,18)</p> <p>↑ AUC 1,75 (1,55; 1,98)</p>	<p>Co-administration is not recommended.</p>

Medicine by therapeutic areas	Effects on drug levels. <sup>a,b</sup>  Mean ratio (90 % confidence interval) for AUC, C <sub>max</sub> , C <sub>min</sub>	Recommendation concerning co-administration with Vemlidy
	<p><i>Tenofovir</i></p> <p>↑ C<sub>max</sub> 3,16 (3,00; 3,33)</p> <p>↑ AUC 3,47 (3,29; 3,67)</p> <p>↑ C<sub>min</sub> 3,73 (3,54; 3,93)</p> <p><i>Atazanavir</i></p> <p>↔ C<sub>max</sub> 0,98 (0,94; 1,02)</p> <p>↔ AUC 1,06 (1,01; 1,11)</p> <p>↔ C<sub>min</sub> 1,18 (1,06; 1,31)</p> <p><i>Cobicistat</i></p> <p>↔ C<sub>max</sub> 0,96 (0,92; 1,00)</p> <p>↔ AUC 1,05 (1,00; 1,09)</p> <p>↑ C<sub>min</sub> 1,35 (1,21; 1,51)</p>	
<p>Atazanavir/ritonavir (300 mg/100 mg orally, q.d.)</p> <p>Tenofovir alafenamide<sup>c</sup> (10 mg orally, s.d.)</p>	<p><i>Tenofovir alafenamide</i></p> <p>↑ C<sub>max</sub> 1,77 (1,28; 2,44)</p> <p>↑ AUC 1,91 (1,55; 2,35)</p>	<p>Co-administration is not recommended.</p>

Medicine by therapeutic areas	Effects on drug levels. <sup>a,b</sup> Mean ratio (90 % confidence interval) for AUC, C <sub>max</sub> , C <sub>min</sub>	Recommendation concerning co-administration with Vemlidy
	<p><i>Tenofovir</i></p> <p>↑ C<sub>max</sub> 2,12 (1,86; 2,43)</p> <p>↑ AUC 2,62 (2,14; 3,20)</p> <p><i>Atazanavir</i></p> <p>↔ C<sub>max</sub> 0,98 (0,89; 1,07)</p> <p>↔ AUC 0,99 (0,96; 1,01)</p> <p>↔ C<sub>min</sub> 1,00 (0,96; 1,04)</p>	

Medicine by therapeutic areas	Effects on drug levels. <sup>a,b</sup>  Mean ratio (90 % confidence interval) for AUC, C <sub>max</sub> , C <sub>min</sub>	Recommendation concerning co-administration with Vemlidy
<p>Darunavir/cobicistat (800 mg/150 mg orally, q.d.)</p> <p>Tenofovir alafenamide<sup>c</sup> (25 mg orally, q.d.)</p>	<p><i>Tenofovir alafenamide</i></p> <p>↔ C<sub>max</sub> 0,93 (0,72; 1,21)          ↔ AUC 0,98 (0,80; 1,19)</p> <p><i>Tenofovir</i></p> <p>↑ C<sub>max</sub> 3,16 (3,00; 3,33)          ↑ AUC 3,24 (3,02; 3,47)          ↑ C<sub>min</sub> 3,21 (2,90; 3,54)</p> <p><i>Darunavir</i></p> <p>↔ C<sub>max</sub> 1.02 (0.96, 1.09)          ↔ AUC 0.99 (0.92, 1.07)          ↔ C<sub>min</sub> 0.97 (0.82, 1.15)</p> <p><i>Cobicistat</i></p> <p>↔ C<sub>max</sub> 1,06 (1,00; 1,12)          ↔ AUC 1,09 (1,03; 1,15)</p>	<p>Co-administration is not recommended.</p>

Medicine by therapeutic areas	Effects on drug levels. <sup>a,b</sup>  Mean ratio (90 % confidence interval) for AUC, C <sub>max</sub> , C <sub>min</sub>	Recommendation concerning co-administration with Vemlidy
	↔ C <sub>min</sub> 1,11 (0,98; 1,25)	
<p>Darunavir/ritonavir (800 mg/100 mg orally, q.d.)</p> <p>Tenofovir alafenamide<sup>c</sup> (10 mg orally, s.d.)</p>	<p><i>Tenofovir alafenamide</i></p> <p>↑ C<sub>max</sub> 1,42 (0,96; 2,09)</p> <p>↔ AUC 1,06 (0,84; 1,35)</p> <p><i>Tenofovir</i></p> <p>↑ C<sub>max</sub> 2,42 (1,98; 2,95)</p> <p>↑ AUC 2,05 (1,54; 2,72)</p> <p><i>Darunavir</i></p> <p>↔ C<sub>max</sub> 0,99 (0,91; 1,08)</p> <p>↔ AUC 1,01 (0,96; 1,06)</p> <p>↔ C<sub>min</sub> 1,13 (0,95; 1,34)</p>	<p><i>Co-administration</i> is not recommended.</p>

Medicine by therapeutic areas	Effects on drug levels. <sup>a,b</sup>  Mean ratio (90 % confidence interval) for AUC, C <sub>max</sub> , C <sub>min</sub>	Recommendation concerning co-administration with Vemlidy
Lopinavir/ritonavir (800 mg/200 mg orally, q.d.)  Tenofovir alafenamide <sup>c</sup> (10 mg orally, s.d.)	<p><i>Tenofovir alafenamide</i></p> <p>↑ C<sub>max</sub> 2,19 (1,72; 2,79)            ↑ AUC 1,47 (1,17; 1,85)</p> <p><i>Tenofovir</i></p> <p>↑ C<sub>max</sub> 3,75 (3,19; 4,39)            ↑ AUC 4,16 (3,50; 4,96)</p> <p><i>Lopinavir</i></p> <p>↔ C<sub>max</sub> 1,00 (0,95; 1,06)            ↔ AUC 1,00 (0,92; 1,09)            ↔ C<sub>min</sub> 0,98 (0,85; 1,12)</p>	<p>Co-administration is not recommended.</p>
Tipranavir/ritonavir	<p>Interaction not studied.</p> <p><i>Expected:</i></p> <p>↓ Tenofovir alafenamide</p>	<p>Co-administration is not recommended.</p>

Medicine by therapeutic areas	Effects on drug levels. <sup>a,b</sup>  Mean ratio (90 % confidence interval) for AUC, C <sub>max</sub> , C <sub>min</sub>	Recommendation concerning co-administration with Vemlidy
<b>HIV ANTIRETROVIRAL AGENTS – INTEGRASE INHIBITORS</b>		
Dolutegravir (50 mg orally, q.d.)  Tenofovir alafenamide <sup>c</sup> (10 mg orally, s.d.)	<p><i>Tenofovir alafenamide</i></p> <p>↑ C<sub>max</sub> 1,24 (0,88; 1,74)            ↑ AUC 1,19 (0,96; 1,48)</p> <p><i>Tenofovir</i></p> <p>↔ C<sub>max</sub> 1,10 (0,96; 1,25)            ↑ AUC 1,25 (1,06; 1,47)</p> <p><i>Dolutegravir</i></p> <p>↔ C<sub>max</sub> 1,15 (1,04; 1,27)            ↔ AUC 1,02 (0,97; 1,08)            ↔ C<sub>min</sub> 1,05 (0,97; 1,13)</p>	No dose adjustment of Vemlidy or dolutegravir is required.
Raltegravir	<p><i>Interaction</i> not studied.</p> <p><i>Expected:</i></p> <p>↔ Tenofovir alafenamide            ↔ Raltegravir</p>	No dose adjustment of Vemlidy or raltegravir is required.

Medicine by therapeutic areas	Effects on drug levels. <sup>a,b</sup>  Mean ratio (90 % confidence interval) for AUC, C <sub>max</sub> , C <sub>min</sub>	Recommendation concerning co-administration with Vemlidy
<b>HIV ANTIRETROVIRAL AGENTS – NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS</b>		
Efavirenz (600 mg orally, q.d.)  Tenofovir alafenamideh (40 mg orally, q.d.)	Tenofovir alafenamide ↓ C <sub>max</sub> 0,78 (0,58; 1,05) ↔ AUC 0,86 (0,72; 1,02)  Tenofovir ↓ C <sub>max</sub> 0,75 (0,67; 0,86) ↔ AUC 0,80 (0,73; 0,87) ↔ C <sub>min</sub> 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.

Medicine by therapeutic areas	Effects on drug levels. <sup>a,b</sup>  Mean ratio (90 % confidence interval) for AUC, C <sub>max</sub> , C <sub>min</sub>	Recommendation concerning co-administration with Vemlidy
<p>Rilpivirine (25 mg orally, q.d.)</p> <p>Tenofovir alafenamide (25 mg orally, q.d.)</p>	<p><i>Tenofovir alafenamide</i></p> <p>↔ C<sub>max</sub> 1,01 (0,84; 1,22)</p> <p>↔ AUC 1,01 (0,94; 1,09)</p> <p><i>Tenofovir</i></p> <p>↔ C<sub>max</sub> 1,13 (1,02; 1,23)</p> <p>↔ AUC 1,11 (1,07; 1,14)</p> <p>↔ C<sub>min</sub> 1,18 (1,13; 1,23)</p> <p><i>Rilpivirine</i></p> <p>↔ C<sub>max</sub> 0,93 (0,87; 0,99)</p> <p>↔ AUC 1,01 (0,96; 1,06)</p> <p>↔ C<sub>min</sub> 1,13 (1,04; 1,23)</p>	<p>No dose adjustment of Vemlidy or rilpivirine is required.</p>

Medicine by therapeutic areas	Effects on drug levels. <sup>a,b</sup>  Mean ratio (90 % confidence interval) for AUC, C <sub>max</sub> , C <sub>min</sub>	Recommendation concerning co-administration with Vemlidy
<b>HIV ANTIRETROVIRAL AGENTS – CCR5 RECEPTOR ANTAGONIST</b>		
Maraviroc	Interaction not studied.  <i>Expected:</i> ↔ Tenofovir alafenamide ↔ Maraviroc	No dose adjustment of Vemlidy or maraviroc is required.
<b>HERBAL SUPPLEMENTS</b>		
St. John's wort ( <i>Hypericum perforatum</i> )	Interaction not studied.  <i>Expected:</i> ↓ Tenofovir alafenamide	Co-administration is not recommended.
<b>ORAL CONTRACEPTIVES</b>		
Norgestimate (0.180 mg/0.215 mg/ 0.250 mg orally, q.d.)  Ethinylestradiol (0.025 mg orally, q.d.)  Tenofovir alafenamide <sup>c</sup> (25 mg orally, q.d.)	Norelgestromin ↔ C <sub>max</sub> 1,17 (1,07; 1,26) ↔ AUC 1,12 (1,07; 1,17) ↔ C <sub>min</sub> 1,16 (1,08; 1,24)  <i>Norgestrel</i> ↔ C <sub>max</sub> 1,10 (1,02; 1,18) ↔ AUC 1,09 (1,01; 1,18)	No dose adjustment of Vemlidy or norgestimate/ethinyl estradiol is required.

Medicine by therapeutic areas	Effects on drug levels. <sup>a,b</sup>  Mean ratio (90 % confidence interval) for AUC, C <sub>max</sub> , C <sub>min</sub>	Recommendation concerning co-administration with Vemlidy
	↔ C <sub>min</sub> 1,11 (1,03; 1,20)  <i>Ethinylestradiol</i>  ↔ C <sub>max</sub> 1,22 (1,15; 1,29)  ↔ AUC 1,11 (1,07; 1,16)  ↔ C <sub>min</sub> 1,02 (0,93; 1,12)	

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**

##### Women of childbearing potential / contraception in males and females

The use of Vemlidy should be accompanied by the use of effective contraception.

##### Pregnancy

Safety in pregnancy has not been established and possible harm to the embryo/developing foetus cannot be excluded.

The use of Vemlidy is not recommended in pregnancy unless no other appropriate medicine that is known to be safe in pregnancy is available, not tolerated or has failed.

##### Breast-feeding

Women on treatment with Vemlidy should not breastfeed their babies as harm to the newborn baby/infant cannot be excluded.

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

##### 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 may affect the ability to drive and use machines. Patients should not drive and use machines until they know how treatment with Vemlidy affects them. Patients should be informed that dizziness, fatigue, nausea and headache have 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) and from post-marketing experience.

The most frequently reported adverse reactions were headache (12 %), nausea (6 %), and fatigue (6 %). After Week 96, patients either remained on their original blinded treatment or received open-label 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 list of adverse events

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  $< 1/10$ ) or uncommon ( $\geq 1/1\ 000$  to  $< 1/100$ ).

**Table 2: Adverse reactions identified with tenofovir alafenamide**

<b>System organ class</b>	
<b>Frequency</b>	<b>Adverse reaction</b>
<i>Nervous system disorders</i>	
Very common	Headache
Common	Dizziness
<i>Gastrointestinal disorders</i>	
Common	Diarrhoea, vomiting, nausea, abdominal pain, abdominal distension, flatulence
<i>Hepatobiliary disorders</i>	
Common	Increased ALT
<i>Skin and subcutaneous tissue disorders</i>	
Common	Rash, pruritus
Uncommon	Angioedema <sup>1</sup> , urticaria <sup>1</sup>
<i>Musculoskeletal and connective tissue disorders</i>	
Common	Arthralgia
<i>General disorders and administration site conditions</i>	
Common	Fatigue

<sup>1</sup> Adverse reaction identified through post-marketing surveillance for tenofovir alafenamide-containing products.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form” found online under SAHPRA’s publications: <https://www.sahpra.org.za/Publications/Index/8>.

#### 4.9 Overdose

If overdose occurs, the patient must be monitored for evidence of toxicity (see section 4.8), as side effects can be precipitated and/or be of increased severity.

Treatment of overdose with Vemlidy consists of symptomatic and 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

Pharmacological classification: A 20.2.8 Antiviral Agents.

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 hydrolysed to form tenofovir by carboxylesterase 1 in primary hepatocytes. Intracellular tenofovir is subsequently phosphorylated to the pharmacologically active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HBV replication through incorporation into viral DNA by the HBV reverse transcriptase, which results in DNA chain termination.

Tenofovir has activity that is specific to hepatitis B virus and human immunodeficiency virus (HIV 1 and HIV 2). Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase  $\gamma$  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<sub>50</sub> (50 % effective concentration) values for tenofovir alafenamide ranged from 34,7 to 134,4 nm, with an overall mean EC<sub>50</sub> of 86,6 nm. The CC<sub>50</sub> (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 log<sub>10</sub> 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 randomised, 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 randomised 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 log<sub>10</sub> 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 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 log<sub>10</sub> 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 (60). 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<sup>a</sup>**

	<b>Study 108 (HBeAg-Negative)</b>		<b>Study 110 (HBeAg-Positive)</b>	
	<b>Vemlidy</b> (N = 285)	<b>TDF</b> (N = 140)	<b>Vemlidy</b> (N = 581)	<b>TDF</b> (N = 292)
<b>HBV DNA &lt; 29 IU/mL</b>	94 %	93 %	64 %	67 %
Treatment difference <sup>b</sup>	1,8 % (95 % CI = -3,6 % to 7,2 %)		-3,6 % (95 % CI = -9,8 % to 2,6 %)	
<b>HBV DNA ≥ 29 IU/mL</b>	2 %	3 %	31 %	30 %
<b>Baseline HBV DNA</b>				
< 7 log <sub>10</sub> IU/mL	96 % (221/230)	92 % (107/116)	N/A	N/A
≥ 7 log <sub>10</sub> IU/mL	85 % (47/55)	96 % (23/24)		
<b>Baseline HBV DNA</b>				
< 8 log <sub>10</sub> IU/mL	N/A	N/A	82 % (254/309)	82 % (123/150)
≥ 8 log <sub>10</sub> IU/mL			43 % (117/272)	51 % (72/142)
<b>Nucleoside naïve<sup>c</sup></b>	94 % (212/225)	93 % (102/110)	68 % (302/444)	70 % (156/223)
<b>Nucleoside experienced</b>	93 % (56/60)	93 % (28/30)	50 % (69/137)	57 % (39/69)

	<b>Study 108 (HBeAg-Negative)</b>		<b>Study 110 (HBeAg-Positive)</b>	
	<b>Vemlidy</b> (N = 285)	<b>TDF</b> (N = 140)	<b>Vemlidy</b> (N = 581)	<b>TDF</b> (N = 292)
<b>No Virologic data at Week 48</b>	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 <sup>d</sup>	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 analogue including tenofovir disoproxil fumarate 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<sup>a</sup>**

	<b>Study 108 (HBeAg-Negative)</b>		<b>Study 110 (HBeAg-Positive)</b>	
	<b>Vemlidy</b> (N = 285)	<b>TDF</b> (N = 140)	<b>Vemlidy</b> (N = 581)	<b>TDF</b> (N = 292)
<b>ALT</b>				
Normalised ALT (Central lab) <sup>b</sup>	83 %	75 %	72 %	67 %
Normalised ALT (AASLD) <sup>c</sup>	50 %	32 %	45 %	36 %
<b>Serology</b>				
HBeAg loss / seroconversion <sup>d</sup>	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 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 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<sup>a</sup>**

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

N/A = not applicable

TDF = tenofovir disoproxil 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 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 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, changes 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 ( $\pm$ 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 in patients who switched from tenofovir disoproxil fumarate to Vemlidy at Week 96.

## **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 chronic hepatitis B, mean steady state AUC<sub>0-24</sub> for tenofovir alafenamide (N = 698) and tenofovir (N = 856) were 0,22  $\mu\text{g}\cdot\text{h}/\text{mL}$  and 0,32  $\mu\text{g}\cdot\text{h}/\text{mL}$ , 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 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 studies was approximately 80 %. The binding of tenofovir to human plasma proteins is less than 0.7 % and is independent of concentration over the range of 0,01 25 µg/mL.

#### Biotransformation

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

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

#### Elimination

Renal excretion of intact tenofovir alafenamide is a minor pathway with < 1 % of the dose eliminated in urine.

Tenofovir alafenamide is mainly eliminated following metabolism to tenofovir. Tenofovir alafenamide and tenofovir have a median plasma half-life of 0,51 and 32,37 hours, respectively. Tenofovir is renally eliminated from the body by the kidneys by both glomerular filtration and active tubular secretion.

#### Linearity/non-linearity

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

#### Pharmacokinetics in special populations

##### *Age, gender and ethnicity*

No clinically relevant differences in pharmacokinetics according to age or ethnicity have been identified.

Differences in pharmacokinetics according to gender were not considered to be clinically relevant.

### *Hepatic impairment*

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

### *Renal impairment*

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

### *Paediatric population*

The pharmacokinetics of tenofovir alafenamide and tenofovir were evaluated in HIV-1 infected, treatment-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) in Study GS-US-292-0106. No clinically relevant differences in tenofovir alafenamide or tenofovir pharmacokinetics were observed between adolescent and adult HIV-1 infected subjects.

Table 6: Pharmacokinetics of tenofovir and tenofovir alafenamide in antiretroviral-naïve adolescents and adults

	Adolescents aged 12 to < 18 years, ≥ 35 kg		Adults	
	Genvoya <sup>a</sup>		Genvoya <sup>a</sup>	
	TAF <sup>b</sup>	TFV <sup>b</sup>	TAF <sup>c</sup>	TFV <sup>c</sup>
<b>AUC<sub>tau</sub></b> <b>(ng·h/mL)</b>	242.8 <sup>c</sup> (57.8)	275.8 (18.4)	206.4 (71.8)	292.6 (27.4)
<b>C<sub>max</sub></b> <b>(ng/mL)</b>	121.7 (46.2)	14.6 (20.0)	162.2 (51.1)	15.2 (26.1)
<b>C<sub>tau</sub></b> <b>(ng/mL)</b>	N/A	10.0 (19.6)	N/A	10.6 (28.5)

TAF = tenofovir alafenamide fumarate; TFV = tenofovir

N/A = not applicable

Data are presented as mean (% coefficient of variation).

a elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF).

b n = 23 adolescents.

c AUC<sub>last</sub>.

d n = 539 (TAF) or 841 (TFV) adults.

### 5.3 Preclinical safety data

Non-clinical studies in rats and dogs revealed bone and kidney as the primary target organs of toxicity. 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.

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. 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.  
Store at or below 30 °C.

#### **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 desiccant and polyester coil.

The following pack sizes are available: outer cartons containing 1 bottle of 30 film-coated tablets.

#### **6.6 Special precautions for disposal**

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

### **7 HOLDER OF THE CERTIFICATE OF REGISTRATION**

Gilead Sciences South Africa (Pty) Ltd,  
Ground Floor,  
West Wing,  
No. 6 Kikuyu Road,  
Sunninghill Extension 56,  
Johannesburg, 2191

### **8 REGISTRATION NUMBER**

To be allocated.

### **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

To be confirmed.

### **10 DATE OF REVISION OF THE TEXT**