Application for inclusion of tenofovir alafenamide (Vemlidy®) tablets on the WHO Model List of Essential Medicines

Submitted by

Gilead Sciences Inc.

December 2016

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Gilead Submission Reference number: GSI-VMY-161201
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1. Summary statement of the proposal for inclusion

Vemlidy® (tenofovir alafenamide; TAF) is a once-daily (QD) oral nucleotide analog (NA) reverse transcriptase inhibitor that blocks reverse transcriptase, a crucial enzyme in chronic hepatitis B virus (CHB) infection and human immunodeficiency virus-1 (HIV) infection. It is proposed for inclusion in the World Health Organization (WHO) Model List of Essential Medicines as a potent treatment for CHB in adults with compensated liver disease. The use of Vemlidy® is based upon pivotal data from two large, international, randomized, Phase 3 studies – GS-US-320-0108 (Study 108; hepatitis B e antigen [HBeAg]-negative patients) and GS-US-320-0110 (Study 110; HBeAg-positive patients), where Vemlidy® was shown to be non-inferior to tenofovir disoproxil fumarate (TDF) in the suppression of HBV DNA while being associated with improved rates of alanine aminotransferase (ALT) normalization and a favorable safety profile, including improvements in bone and renal safety parameters [Buti et al, 2016; Chan et al, 2016; Agarwal et al, 2016; Chuang et al, 2016; Seto et al, 2016; Lim et al, 2016; Brunetto et al, 2016; Gane et al, 2016].

The principal reasons for requesting this inclusion are as follows:

- CHB continues to be a major public health issue despite the availability of an effective vaccine and potent antiviral treatments [WHO 2016]
- A large proportion of CHB patients remain undiagnosed and only 2.5% of patients in the USA are estimated to be actually receiving antiviral therapy [Cohen et al, 2011]
- CHB patients are at considerable risk of developing cirrhosis, hepatocellular carcinoma (HCC) and hepatic decompensation [Fattovich et al, 2008], and have an increased risk of multiple comorbidities [Chen et al, 2015a; Chen et al, 2015b; Khalili M, et al 2015]
- Vemlidy®, as a novel prodrug of tenofovir, has increased plasma stability, allowing it to be delivered more efficiently to the hepatocytes, relative to TDF [Agarwal et al, 2015]
- Treatment with Vemlidy® resulted in non-inferior HBV DNA suppression and higher rates of ALT normalization compared with TDF in a broad patient population [Buti et al, 2016; Chan et al, 2016; Brunetto et al, 2016; Gane et al, 2016].
Vemlidy® provides an improved renal and bone safety profile compared with TDF [Buti et al, 2016; Chan et al, 2016; Agarwal et al, 2016; Chuang et al, 2016; Seto et al, 2016; Lim et al, 2016]

Vemlidy® is well-tolerated with low rates of discontinuation [Buti et al, 2016; Chan et al, 2016]

Vemlidy® can be administered without renal dose adjustments down to a creatinine clearance (CrCl) of 15 mL/min [Vemlidy® PI]

Vemlidy® is not associated with any detectable resistance to date [Buti et al, 2016; Chan et al, 2016]

As there is currently no cure for HBV, CHB patients must be treated with long-term – even life-long – courses of therapy [WHO 2016]. It is essential that any such treatment is effective and well-tolerated – an important unmet medical that is addressed by Vemlidy® [Buti et al, 2016; Chan et al, 2016]

CHB patients, particularly those who are older, will benefit substantially from a therapy that does not compromise renal or bone safety, which is a recognized challenge with TDF [Viread® PI]

2. Name of the focal point in WHO submitting or supporting the application

Betty Chiang.

3. Name of the organization(s) consulted and/or supporting the application

World Hepatitis Alliance.

4. International Nonproprietary Name (INN, generic name) of the medicine

Tenofovir alafenamide.

5. Formulation proposed for inclusion
Application for inclusion of Vemlidy® tablets in the WHO Model List of Essential Medicines: December 2016

Vemlidy® is a once-daily oral medication indicated for the treatment of CHB infection in adults with compensated liver disease, at a dose of 25 mg orally QD, with food. Each tablet includes 25 mg of tenofovir alafenamide (equivalent to 28 mg of tenofovir alafenamide fumarate). The tablets are yellow, round and film-coated, debossed with GSI on one side of the tablet and 25 on the other side.

Vemlidy® tablets should be stored below 30°C (86°F). Further information on appropriate storage and stability of Vemlidy® can be found in the supporting document ‘Storage and stability information for tenofovir alafenamide’. The qualitative composition of Vemlidy® tablets is as described in Table 1.

<table>
<thead>
<tr>
<th>Tablet core</th>
<th>Film coating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose monohydrate</td>
<td>Polyvinyl alcohol</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>Titanium dioxide</td>
</tr>
<tr>
<td>Croscarmellose sodium</td>
<td>Polyethylene glycol</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>Talc</td>
</tr>
<tr>
<td></td>
<td>Iron oxide yellow</td>
</tr>
</tbody>
</table>

6. International availability

Vemlidy® is a registered trademark of Gilead Sciences, Inc, or its related companies in the US and other countries.

Vemlidy® tablets are currently manufactured, packaged, labeled and tested for Gilead Sciences, Inc. at the facilities listed in Table 2. All of the sites are currently approved and listed in the USA New Drug Application (NDA). The manufacturing steps conducted at all facilities are in compliance with European Union (EU) and Food and Drug Administration (FDA) Good Manufacturing Practice (GMP) guidelines.
Table 2: Manufacturing, packaging, labeling and testing facilities for Vemlidy® tablets

<table>
<thead>
<tr>
<th>Manufacturing site</th>
<th>Function(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patheon Inc.</td>
<td>Manufacturing, packaging, labeling, release testing and stability testing</td>
</tr>
<tr>
<td>Toronto Regional Operations</td>
<td>2100 Syntex Court Mississauga, Ontario L5N 7K9, Canada</td>
</tr>
<tr>
<td>Gilead Sciences, Inc.</td>
<td>Release testing, stability testing and drug product release</td>
</tr>
<tr>
<td>333 Lakeside Drive Foster City, California 94404, USA</td>
<td></td>
</tr>
<tr>
<td>Gilead Sciences, Inc.</td>
<td>Packaging, labeling and drug product release</td>
</tr>
<tr>
<td>650 Cliffside Drive San Dimas, California 91773, USA</td>
<td></td>
</tr>
<tr>
<td>Eurofins Lancaster Laboratories, Inc.</td>
<td>Release testing and stability testing</td>
</tr>
<tr>
<td>2425 New Holland Pike Lancaster, Pennsylvania 17601, USA</td>
<td></td>
</tr>
<tr>
<td>Gilead Sciences Ireland UC</td>
<td>Packaging, labeling and drug product release</td>
</tr>
<tr>
<td>IDA Business and Technology Park Carrigtoghill County Cork, Ireland</td>
<td></td>
</tr>
<tr>
<td>Millmount Healthcare Ltd.</td>
<td>Packaging and labeling</td>
</tr>
<tr>
<td>Block 7, City North Business Campus, Stamullen, Co. Meath, Ireland</td>
<td></td>
</tr>
<tr>
<td>AndersonBrecon, Inc.</td>
<td>Packaging and labeling</td>
</tr>
<tr>
<td>4545 Assembly Drive Rockford, Illinois 61109, USA</td>
<td></td>
</tr>
</tbody>
</table>
7. Listing type requested

Listing is requested on the Model List of Essential Medicines as an example of a: ‘Nucleoside/Nucleotide reverse transcriptase inhibitor’ under ‘Medicines for hepatitis B’ (Section 6).

8. Information supporting the public health relevance

8.1 Epidemiological information on disease burden

Worldwide, an estimated 2 billion people have evidence of past or present infection with HBV and an estimated 240 million people suffer from CHB [WHO 2015]. The estimated global number of annual deaths from CHB is 686,000 [WHO 2016]. Specifically, the number of CHB infections has been estimated at 13 million in Europe [WHO 2015] and up to 2.2 million in the USA [CDC 2016]. Age-specific HBsAg seroprevalence varies markedly by geographical region, with the highest prevalence (>5%) in sub-Saharan Africa, East Asia, some parts of the Balkan regions, the Pacific Islands and the Amazon Basin of South America. Prevalence <2% is seen in regions such as Central Latin America, North America and Western Europe [WHO 2015].

Because HBV vaccination is universally recommended in the USA for all infants and children [CDC 2015], foreign-born persons in the USA account for a disproportionate number of HBV cases. Of the estimated 1.32 million CHB cases in the USA among foreign-born persons, 89% were in persons born in countries with high or intermediate HBV endemicity [Kowdley et al, 2012; WHO 2015]. A CHB surveillance program (2001–2010) funded by the Centers for Disease Control and Prevention (CDC) showed that the frequency of CHB in foreign-born cases was ~9.2 times higher than in USA-born cases [Liu et al, 2015]. Among cases originating in the USA, the vast majority are associated with high-risk sexual activity or injection drug use [CDC 2008]. CHB has become more prevalent among people of older age, which may lead to an increased risk of comorbidities [Carrion et al, 2012; Loustaud-Ratti 2016]. In 2009, people ≥55 years of age accounted for 17.9% of CHB cases reported to the CDC, but by 2013, this had increased to 25.7% of reported CHB cases [CDC 2009; CDC 2013]. In addition,
patients with delayed HBeAg seroconversion after the age of 40 have significantly higher incidences of HBeAg-negative hepatitis, cirrhosis, and HCC [Chen et al, 2010].

CHB patients are at considerable risk of developing cirrhosis, HCC and hepatic decompensation [Fattovich et al, 2008], while physiologic changes and accumulating comorbidities can also influence disease progression [Carrion et al, 2012]. Those with CHB have an increased risk of comorbidities, including hyperlipidemia, hypertension, nephrolithiasis, diabetes and osteoporosis [Chen et al, 2015a; Chen et al, 2015b; Khalili et al, 2015]. HBV infection is responsible for more than 50% of HCC cases worldwide and as many as 70–80% of HCC cases in highly endemic HBV regions [Davis et al, 2008; Nguyen et al, 2009]. Importantly, HBV is also thought to increase the risk of non-HCC malignancy [Kwok et al, 2016].

Since up to 60% of patients with CHB have no symptoms, it is not surprising that a large proportion remain undiagnosed and only a small percentage (2.5%) of patients in the USA are thought to actually receive antiviral therapy. There are approximately 200,000 people in the USA who are potentially eligible for treatment but not receiving care [Cohen et al, 2011]. This emphasizes not only the urgent need for effective treatment, but also the need to extend treatment to all eligible CHB patients in an effort to prevent further liver-related complications and help maintain a good quality of life.

8.2 Assessment of current use

In the USA, Vemlidy® is indicated for the treatment of CHB in adults with compensated liver disease. The safety and effectiveness of Vemlidy® in pediatric patients <18 years of age have not been established [Vemlidy® PI].

Vemlidy® was approved for use in CHB by the FDA in November 2016. At the same time, a positive opinion was adopted by the Committee for Medicinal Products for Human Use (CHMP) for Vemlidy® marketing authorization for the treatment of CHB infection in adults and adolescents (≥12 years and ≥35 kg body weight) in Europe [European Medicines Agency 2016].

9. Treatment details
9.1 Indications and usage

Vemlidy® is indicated for the treatment of CHB in adults with compensated liver disease.

9.2 Dosage and administration

The recommended dose of Vemlidy® in adults is 25 mg QD taken orally with food.

Metabolism is a major elimination pathway for Vemlidy® (>80% of oral dose) while renal excretion is a minor pathway (<1% eliminated in urine). If overdose occurs, the patient should be monitored for evidence of toxicity. 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 hemodialysis with an extraction coefficient of approximately 54% [Viread® PI]. There are no studies evaluating the pharmacokinetic parameters of the crushed or split Vemlidy® tablet versus the whole tablet. Please refer to supporting documentation ‘Crushing or splitting of tenofovir alafenamide tablets’ for further information.

9.2.1 Special populations

Pregnancy: There are no data on the use of Vemlidy® in pregnant women to inform on the drug-associated risks of adverse fetal developmental outcome. An antiretroviral pregnancy registry is in place to monitor fetal outcomes of pregnant women exposed to Vemlidy® [Vemlidy® PI].

Lactation: It is not known whether Vemlidy® and its metabolites are present in human breast milk, affect human milk production, or have effects on the breastfed infant. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for Vemlidy® and any potential adverse effects on the breastfed infant from Vemlidy® or from the underlying maternal condition [Vemlidy® PI].

Pediatric use: The safety and efficacy of Vemlidy® have not been established in pediatric patients <18 years of age [Vemlidy® PI].
Geriatric use: Clinical trials of Vemlidy® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently to younger subjects [Vemlidy® PI].

Renal impairment: No dosage adjustment of Vemlidy® is required in patients with mild, moderate or severe renal impairment. Vemlidy® is not recommended in patients with end stage renal disease (estimated CrCl below 15 mL per minute) [Vemlidy® PI].

Hepatic impairment: No dosage adjustment of Vemlidy® is required in patients with mild hepatic impairment (Child–Pugh A). The safety and efficacy of Vemlidy® in patients with decompensated cirrhosis (Child–Pugh B or C) have not been established; therefore Vemlidy® is not recommended in patients with decompensated (Child–Pugh B or C) hepatic impairment [Vemlidy® PI].

9.3 Reference to existing WHO and other clinical guidelines

Evidence-based guidelines on the management of CHB have been issued by a number of internationally recognized bodies, including the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver (EASL), WHO and the Asian Pacific Association for the Study of the Liver (APASL) [Terrault et al, 2016; EASL 2012; WHO 2015; Sarin et al, 2016]. The first WHO guidelines for CHB management were released in March 2015, owing to the continued global burden imposed by CHB and a need for simple guidance in limited resource settings [WHO 2015]. Current guidelines recommend TDF and entecavir as first-line therapeutic options for the treatment of CHB, owing to their high potency and low barriers to resistance [Terrault et al, 2016; EASL 2012; WHO 2015; Sarin et al, 2016]. However, entecavir is not a valid treatment option for those who have previously failed treatment with lamivudine (LAM) [Terrault et al, 2016; EASL 2012; WHO 2015] and there have been concerns with bone and renal safety with TDF, along with a requirement for renal monitoring [Viread® PI].
10. Summary of comparative effectiveness in a variety of clinical settings

10.1 Identification of clinical evidence

The benefits of Vemlidy® for the treatment of CHB infection in compensated liver disease is based on virologic, biochemical, and serologic responses in patients with HBeAg-positive or HBeAg-negative CHB. Key studies that have investigated Vemlidy® in the treatment of CHB include one Phase 1b study of 51 patients [Agarwal et al, 2015] and two global Phase 3 studies in HBeAg-negative and HBeAg-positive patients (N=1298 patients collectively) [Buti et al, 2016; Chan et al, 2016]. A number of analyses have subsequently been performed using the Phase 3 datasets to produce robust clinical evidence that both supports and expands upon the initial findings [Agarwal et al, 2016; Brunetto et al, 2016; Chuang et al, 2016; Gane et al, 2016; Lim et al, 2016; Seto et al, AASLD 2016].

A Phase 3b, open-label, switch study (N=72) investigated TAF as part of a single tablet regimen (STR; elvitegravir/cobicistat/emtricitabine/TAF [E/C/F/TAF]; Genvoya®) in HIV/HBV coinfection [Gallant et al, 2016], a population who are at significant risk of liver-related complications and rapid disease progression [WHO 2015].

10.2 Summary of available data on comparative effectiveness of Vemlidy® in patients with CHB

This section will focus primarily on the outcomes from two pivotal Phase 3 clinical studies – GS-US-320-0108 (Study 108) and GS-US-320-0110 (Study 110) – that formed the basis of the regulatory submissions for Vemlidy® as well as subsequent pooled analyses and follow-up data. In addition, an early-phase study of Vemlidy® in CHB is described below, along with a Phase 3b study of patients coinfected with CHB and HIV.

10.2.1 Phase 1b study background and design

A dose-ranging Phase 1b study was performed to evaluate the safety, antiviral activity, and pharmacokinetics of Vemlidy® versus TDF in treatment-naïve subjects with CHB [Agarwal et al, 2015]. This was a randomized, open-label, multicenter, international
study of 51 non-cirrhotic, treatment-naïve subjects with CHB who were randomized (1:1:1:1:1) to receive Vemlidy® (8 mg, 25 mg, 40 mg, or 120 mg QD), or TDF (300 mg QD) for 28 days. They were assessed for safety, antiviral response, and pharmacokinetics, and followed up for another 4 weeks. The primary antiviral endpoint was the log change from baseline (Day 1) to Day 29 in serum HBV DNA. Other efficacy endpoints included time-weighted change in HBV DNA through Week 4, and estimation of the slope of viral decay from baseline to Week 4. Other measures of efficacy included change in ALT and change in quantitative hepatitis B surface antigen (HBsAg) levels from baseline to Day 29 [Agarwal et al, 2015].

10.2.2 Results from a Phase 1b study of Vemlidy® in CHB
A total of 34/51 (66%) subjects were male. Overall, 29/51 (57%) of subjects were of Asian descent and 27/51 (53%) were HBeAg-negative; all the common HBV genotypes (A–E) were well represented with similar distribution across groups [Agarwal et al, 2015]. Across the Vemlidy® groups (8 mg, 25 mg, 40 mg, or 120 mg), similar mean changes in serum HBV DNA were found at Week 4, which were similar to those achieved with TDF 300 mg. Kinetics of viral decline were also similar among groups. Vemlidy® pharmacokinetics were linear and proportional to the dose, reaching maximum concentrations within 30–40 minutes. Vemlidy® plasma concentrations were below the limit of quantification 6–8 hours following dosing. Pharmacokinetic results demonstrated reduced mean plasma tenofovir concentrations following administration of Vemlidy® at all doses studied, which were substantially lower than those observed with TDF dosing [Agarwal et al, 2015]. Based on these findings, TAF 25 mg QD was chosen for further clinical investigation in the Phase 3 program.

10.2.3 Phase 3 study background and design
GS-US-320-0108 (Study 108) and GS-US-320-0110 (Study 110) were global, Phase 3, double-blind, non-inferiority studies, designed to investigate the efficacy and safety of Vemlidy® 25 mg QD versus TDF 300 mg QD in treatment-naïve and treatment-experienced patients with immune-active HBeAg-negative and HBeAg-positive CHB, respectively (Figures 1 and 2). A total of 1298 patients were enrolled across the two
Application for inclusion of Vemlidy® tablets in the WHO Model List of Essential Medicines: December 2016

studies and eligibility criteria are summarised in Table 3 [Buti et al, 2016; Chan et al, 2016].

The primary endpoint in both studies was the proportion of patients with HBV DNA <29 IU/mL at Week 48 in all randomly assigned patients who received at least one dose of the study drug. The prespecified non-inferiority margin was 10%. A key prespecified secondary efficacy endpoint was the proportion of patients with HBsAg or HBeAg loss (Studies 108 and 110, respectively) and with HBsAg or HBeAg seroconversion (Studies 108 and 110, respectively) to anti-HBe at Week 48. Key prespecified secondary safety endpoints at Week 48 included percent change in hip bone mineral density (BMD), percent change in spine BMD, and change from baseline in serum creatinine levels. Other outcomes measured included the proportion of patients with ALT normalization at Week 48, fibrosis regression, adverse events (AEs), laboratory abnormalities and resistance [Buti et al, 2016; Chan et al, 2016].

Figure 1: Study 108 design [Buti et al, 2016]
Figure 2: Study 110 design [Chan et al, 2016]

- Double-blind, active-controlled, Phase 3 study
- Key inclusion criteria
  - HBeAg-positive at screening
  - HBV DNA ≥20,000 IU/mL; ALT >60 U/L (males), >38 U/L (females)
- 2:1 randomization
  - Stratified by HBV DNA level and treatment status (naïve vs experienced)

*Amendment to extend double blind to Week 144 and open-label to Week 384 (Year 8) is currently underway
Table 3: Eligibility criteria for enrollment [Buti et al, 2016; Chan et al, 2016]

<table>
<thead>
<tr>
<th></th>
<th>Study 108 HBeAg-negative</th>
<th>Study 110 HBeAg-positive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Specific inclusion criteria</strong></td>
<td>Patients &gt;18 years with HBeAg-negative chronic HBV (HBV DNA &gt;20,000 IU/mL)</td>
<td>Patients &gt;18 years with HBeAg-positive chronic HBV (HBV DNA ≥20,000 IU/mL)</td>
</tr>
<tr>
<td><strong>General inclusion criteria</strong></td>
<td>ALT concentrations of &gt;60 U/L in men or &gt;38 U/L in women and no more than 10 x ULN; and an estimated CrCl of ≥50 mL/min (Cockcroft-Gault)</td>
<td></td>
</tr>
<tr>
<td><strong>Exclusion criteria</strong></td>
<td>• Platelet counts of ≤50,000 cells/µL</td>
<td>• Platelet counts of ≤50,000 cells/µL</td>
</tr>
<tr>
<td></td>
<td>• Hemoglobin &lt;10 g/dL</td>
<td>• Hemoglobin &lt;10 g/dL</td>
</tr>
<tr>
<td></td>
<td>• Albumin &lt;3 g/dL</td>
<td>• Albumin &lt;3 g/dL</td>
</tr>
<tr>
<td></td>
<td>• Total bilirubin &gt;2.5 x ULN</td>
<td>• Total bilirubin &gt;2.5 x ULN</td>
</tr>
<tr>
<td></td>
<td>• AST or ALT &gt;10 x ULN</td>
<td>• AST or ALT &gt;10 x ULN</td>
</tr>
<tr>
<td></td>
<td>• Evidence of decompensation and/or HCC</td>
<td>• Evidence of decompensation and/or HCC</td>
</tr>
<tr>
<td></td>
<td>• Coinfection with HBV and HCV, HDV or HIV</td>
<td>• Coinfection with HBV and HCV, HDV or HIV</td>
</tr>
</tbody>
</table>

ALT: alanine aminotransferase; CrCl: creatinine clearance; HCC: hepatocellular carcinoma; HBeAg: hepatitis B e antigen; HBV: hepatitis B virus; HCV: hepatitis C virus; HDV: hepatitis D virus; HIV: human immunodeficiency virus; ULN: upper limit of normal

10.2.4 Phase 3b study background and design: E/C/F/TAF in HIV/HBV coinfection

Of the 34 million HIV-infected people worldwide, it is estimated that 5–15% are coinfectected with CHB [WHO 2015]. CHB patients who are coinfectected with HIV are at risk of rapid HBV disease progression and HCC, higher liver-related mortality and decreased treatment response, compared with those infected with CHB alone [WHO 2015]. Furthermore, there is a risk of progression to acquired immune deficiency syndrome (AIDS)-related outcomes and all-cause mortality in those coinfectected with CHB and HIV [WHO 2015].

TAF 10 mg is part of a four-drug formulation, Genvoya® (E/C/F/TAF), which is licensed for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA < 50 copies per mL)
[Genvoya® PI]. A 10 mg dose of TAF – when administered as part of the STR E/C/F/TAF – has been shown to be bioequivalent to a single 25 mg dose of TAF administered without a pharmacokinetic enhancer [Zack et al, 2016]. The efficacy and safety of this regimen was investigated in GS-US-292-1249, a Phase 3b, open-label study conducted in the USA, Canada and Japan, in HIV/HBV coinfected adults who switched from stable antiretroviral therapy (ART) to E/C/F/TAF and who had suppressed HIV (HIV-1 RNA viral load [VL] <50 copies/mL for 6 months before screening). Patients were required to have CD4 count >200 cells/µL, ALT ≤10 x ULN, total bilirubin ≤2.5 mg/dL, international normalized ratio (INR) ≤1.5, albumin >3 g/dL, CrCl by Cockcroft-Gault (CrClCG) ≥50 mL/min. Exclusion criteria for the study were: current or previous use of regimens concurrently containing three active anti-HBV agents; presence of cirrhosis; HCC; or HCV or HDV infection [Gallant et al, 2016].

Primary efficacy endpoints were the percent of patients with (1) VL <50 copies/mL and (2) HBV DNA <29 IU/mL at Week 24. Secondary endpoints included measurements of HIV and HBV VL at Week 48, HBsAg and HBeAg loss at Weeks 24 and 48, seroconversion at Weeks 24 and 48, ALT normalization (of those with baseline abnormal ALT), and change from baseline in FibroTest score at Weeks 24 and 48 [Gallant et al, 2016].

10.2.5 Results from Phase 3 studies of Vemlidy® in CHB
Baseline characteristics between treatment arms were similar in both studies. Across both studies, ~60–65% were male. Most patients were of Asian origin (72–83%) and HBV genotypes B, C and D were the most common. In Study 108, ~30% had received prior treatment for their CHB, either with interferon or with nucleos(t)ide analogs [Buti et al, 2016; Chan et al, 2016].

Vemlidy® was shown to be non-inferior to TDF in both HBeAg-negative and HBe-positive patients, where similar rates of HBV DNA <29 IU/mL at Week 48 were observed between groups (Table 4). Patients receiving Vemlidy® also achieved significantly higher rates of ALT normalization (as per AASLD criteria; Table 4) [Buti et al, 2016; Chan et al, 2016]. When using less stringent central laboratory cut-off values, the difference was not significant (Table 4) [Buti et al, 2016; Chan et al, 2016].
Table 4: Efficacy outcomes at Week 48 [Buti et al, 2016; Chan et al, 2016]

<table>
<thead>
<tr>
<th></th>
<th>Study 108 (N=425)</th>
<th>Study 110 (N=873)</th>
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<tr>
<td></td>
<td>Vemlidy® n=285</td>
<td>TDF n=140</td>
</tr>
<tr>
<td>HBV DNA &lt;29 IU/mL</td>
<td>94%</td>
<td>93%</td>
</tr>
<tr>
<td>Treatment difference (95% CI)</td>
<td>1.8% (-3.6%, 7.2%); p=0.47</td>
<td>-3.6% (-9.8%, 2.6%); p=0.25</td>
</tr>
<tr>
<td>ALT normalization (AASLD criteria')</td>
<td>50%</td>
<td>32%</td>
</tr>
<tr>
<td>Treatment difference (95% CI)</td>
<td>17.9% (8.0%, 27.7%); p=0.0005</td>
<td>8.7% (1.8%, 15.6%); p=0.014</td>
</tr>
<tr>
<td>ALT normalization (central laboratory criteria')</td>
<td>83%</td>
<td>75%</td>
</tr>
<tr>
<td>Treatment difference (95% CI)</td>
<td>8.0% (-1.3%, 17.2%); p=0.076</td>
<td>4.6% (-2.3%, 11.4%); p=0.18</td>
</tr>
</tbody>
</table>

*AASLD criteria: ≤19 U/L for women and ≤30 U/L for men; 'Central laboratory criteria: ≤43 U/L for men and ≤34 U/L for women <69 years of age; ≤35 U/L for men and ≤32 U/L for women >69 years of age. ALT: alanine aminotransferase; AASLD: American Association for the Study of Liver Diseases; HBV: hepatitis B virus; CI: confidence interval; HBeAg: hepatitis B e antigen; TDF: tenofovir disoproxil fumarate.*

At Week 72, virologic efficacy was similar between the Vemlidy® and TDF treatment groups [Gane et al, 2016], with higher rates of ALT normalization observed with Vemlidy® compared with TDF [Brunetto et al, 2016].

Even as early as Week 12, more Vemlidy® patients were shown to achieve ALT normalization and HBV DNA <29 IU/mL compared with TDF (9% versus 5%) and Vemlidy® was significantly associated with achieving this early treatment response (Odds ratio [OR] 2.78; 95% confidence interval [CI]: 1.44, 5.37; p=0.0022), along with baseline HBV DNA (OR 0.53; 95% CI: 0.43, 0.64; p<0.0001), HBeAg negative status (OR 3.12; 95% CI: 1.63, 5.98; p=0.0006), male gender (OR 2.48; 95% CI: 1.38, 4.45; p=0.0023) and no history of cirrhosis (OR 7.35; 95% CI: 1.70, 31.87; p=0.0077) [Brunetto et al, 2016].
10.2.6 Results from a Phase 3b study of E/C/F/TAF in HIV/HBV coinfection

Enrolled patients had a median age of 51 years and were mostly male (92%), with a median CD4 count of 605 cells/mm$^3$ and a median duration of HIV infection that was 18 years. A total of 96% of patients had been receiving TDF-based regimens prior to the switch. The median duration of known HBV infection was 12 years, and 99% were HBsAg positive, with 42% being HBeAg positive. A total of 60% had moderate-to-severe fibrosis as measured by FibroTest [Gallant et al, 2016].

Of the 100 adults screened, 74 and 72 were included in the safety and efficacy analysis, respectively. One year after switching to E/C/F/TAF, participants maintained high rates of HIV and HBV suppression (Figure 3), Seroconversion occurred in 1.4% of HBsAg-positive participants and 3.3% of HBeAg-positive participants at Week 24. A total of 10 patients had ALT values >upper limit of normal (ULN) at baseline; of these, five (50%) achieved ALT normalization by Week 24 and four (40%) by Week 48. With regard to fibrosis response, nine were shown to improve, 45 had no change, and six worsened (assessment performed in 60 patients with paired baseline and Week 48 data) [Gallant et al, 2016].

Figure 3: Virologic response with E/C/F/TAF at Weeks 24 and 48 in HIV/HBV coinfected patients [Gallant et al, 2016]

10.3 Summary of the resistance profile of Vemlidy® in patients with CHB

The potential for the development of viral mutations that are resistant to treatment with nucleos(t)ide analogs is an important consideration in patients receiving oral antiviral
agents for CHB infection. In Study 110, a total of 34 patients qualified for resistance testing, where 14/22 in the Vemlidy® group and 12/12 in the TDF group had virologic breakthrough at Week 48 (defined as HBV DNA ≥69 IU/mL after achieving <69 IU/mL, or >1 log_{10} IU/mL increase in HBV DNA from nadir). Resistance was not detected in either treatment group [Chan et al, 2016].

In Study 108, four patients qualified for resistance testing – two in each treatment arm. Both Vemlidy® patients experienced virologic breakthrough but showed no sequence changes from baseline. One TDF patient experienced virologic breakthrough while the other was viremic when they discontinued from the study. The virus could not be sequenced in either TDF patient. No resistance was detected in either treatment group [Buti et al, 2016].

10.4 Effect of Vemlidy® therapy on long-term patient outcomes
Long-term follow-up data are not yet available for Vemlidy® in patients with CHB. Outcomes show that the efficacy and safety outcomes observed with Vemlidy® are sustained at treatment Week 72, while exhibiting non-inferiority to TDF [Buti et al, 2016; Chan et al, 2016; Gane et al, 2016; Seto et al, 2016; Agarwal et al, 2016; Brunetto et al, 2016]. Longer follow-up (up to 8 years) is planned for both Studies 108 and 110, to determine whether the short-term improvements in bone and renal parameters will be maintained, leading to a reduced incidence of bone and renal events over the long term [Buti et al, 2016; Chan et al, 2016].

10.5 Summary of available estimates of comparative effectiveness
Pivotal Phase 3 studies in HBeAg-negative and HBeAg-positive patients have provided evidence that Vemlidy® is non-inferior to TDF in terms of HBV viral suppression up to Week 72. In addition, Vemlidy® was associated with higher rates of ALT normalization compared with TDF and showed a favorable resistance profile. In CHB patients coinfected with HIV, E/C/F/TAF provided an efficacious regimen in terms of both HBV and HIV suppression. Together these data suggest that Vemlidy® presents a highly effective treatment option for CHB, including for those infected with HIV. Safety outcomes will be summarized in the next section.
11. Summary of comparative evidence on safety

11.1 Estimate of total patient exposure to Vemlidy®

To date, a total of 51 patients have been enrolled in a Phase 1b study; 1298 in two registrational Phase 3 studies; and 100 in a Phase 3b study of HIV/HBV coinfection. Patients with a range of characteristics have been included in these investigations, e.g. HBeAg-negative and HBeAg-positive CHB; HIV-coinfected patients; treatment-naïve and treatment-experienced; cirrhosis; and comorbidities such as diabetes, hypertension and cardiovascular disease. Vemlidy® only recently received licensing approval in the USA (November 2016); therefore, post-marketing data are not yet available.

11.2 Description of adverse effects/reactions

A safety analysis from a key Phase 1b study showed that Vemlidy® was associated with a favorable safety and tolerability profile. All AEs were mild or moderate in intensity. No subject experienced an AE that was serious or severe (Grade 3/4) and there were no withdrawals from the study. Headache, fatigue, nausea, constipation, and cough were the most frequently reported AEs in the Vemlidy® arm. Three subjects in the Vemlidy® 120 mg group experienced moderate (Grade 2) fatigue, vomiting and influenza (one subject each), which were considered to be related to the study drug [Agarwal et al, 2015].

Two pivotal Phase 3 studies demonstrated the safety and tolerability of Vemlidy® in the treatment of HBeAg-negative (Study 108) and HBeAg-positive (Study 110) patients (Table 5). Vemlidy® was well tolerated in Phase 3 studies. The majority of AEs were mild to moderate in intensity. The most common AEs across both studies were headache, nasopharyngitis and upper respiratory tract infection. Only 1% of patients in each group discontinued treatment owing to AEs. The incidence of serious adverse events (SAEs) was similar between Vemlidy® and TDF groups – none of these events were considered to be related to study treatment (Table 5) [Buti et al, 2016; Chan et al, 2016].
No deaths occurred in either study, although in Study 108, a cirrhotic patient discontinued TDF treatment at Week 54 owing to a diagnosis of HCC, which was the cause of death 9 days later [Buti et al, 2016]. In Study 110, one death occurred in a cirrhotic patient who went into a coma on Day 98 and subsequently discontinued Vemlidy® treatment. She died 2 days later from cardio-respiratory arrest, which was attributed to influenza complications [Chan et al, 2016].

Table 5: Phase 3 safety overview [Buti et al, 2016; Chan et al, 2016]

<table>
<thead>
<tr>
<th></th>
<th>Study 108* HBeAg-negative</th>
<th>Study 110† HBeAg-positive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vemlidy® n=285</td>
<td>TDF n=140</td>
</tr>
<tr>
<td>AEs, patients (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any AE</td>
<td>210 (74)</td>
<td>99 (71)</td>
</tr>
<tr>
<td>Grade 3–4 AE</td>
<td>12 (4)</td>
<td>6 (4)</td>
</tr>
<tr>
<td>SAE</td>
<td>14 (5)</td>
<td>9 (6)</td>
</tr>
<tr>
<td>Discontinuation due to AE</td>
<td>3 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>AEs in ≥5% of patients in any treatment group (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>11 (4)</td>
<td>10 (7)</td>
</tr>
<tr>
<td>Back pain</td>
<td>14 (5)</td>
<td>7 (5)</td>
</tr>
<tr>
<td>Cough</td>
<td>18 (6)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Fatigue</td>
<td>16 (6)</td>
<td>9 (6)</td>
</tr>
<tr>
<td>Headache</td>
<td>40 (14)</td>
<td>14 (10)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>30 (11)</td>
<td>15 (11)</td>
</tr>
<tr>
<td>Nausea</td>
<td>15 (5)</td>
<td>9 (6)</td>
</tr>
<tr>
<td>Upper abdominal pain</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>
### Study 108*  
**HBeAg-negative**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Vemlidy&lt;sup&gt;®&lt;/sup&gt; <strong>n=285</strong></th>
<th>TDF <strong>n=140</strong></th>
<th>Vemlidy&lt;sup&gt;®&lt;/sup&gt; <strong>n=581</strong></th>
<th>TDF <strong>n=492</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>35 (12)</td>
<td>10 (7)</td>
<td>51 (9)</td>
<td>22 (8)</td>
</tr>
</tbody>
</table>

### Study 110†  
**HBeAg-positive**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Vemlidy&lt;sup&gt;®&lt;/sup&gt; <strong>n=581</strong></th>
<th>TDF <strong>n=492</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>51 (9)</td>
<td>22 (8)</td>
</tr>
</tbody>
</table>

### Grade 3–4 laboratory abnormalities in ≥1% of any treatment group, patients (%)<sup>a</sup>

<table>
<thead>
<tr>
<th>Any Grade 3–4 laboratory abnormality</th>
<th>Study 108*</th>
<th>Study 110†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute neutrophil count &lt;750 cells/µL</td>
<td>NR</td>
<td>7 (1)</td>
</tr>
<tr>
<td>ALT &gt;5 x ULN</td>
<td>8 (3)</td>
<td>62 (11)</td>
</tr>
<tr>
<td>AST &gt;5 x ULN</td>
<td>8 (3)</td>
<td>20 (3)</td>
</tr>
<tr>
<td>Amylase &gt;2 x ULN</td>
<td>14 (5)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>GGT &gt;5 x ULN</td>
<td>0</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Blood glucose &gt;250 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>4/280 (1)</td>
<td>NR</td>
</tr>
<tr>
<td>Non-fasting</td>
<td>10 (4)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Total cholesterol &gt;300 mg/dL</td>
<td>3/280 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Fasting LDL cholesterol &gt;300 mg/dL</td>
<td>14/277 (5)</td>
<td>23/560 (4)</td>
</tr>
<tr>
<td>CK ≥10 x ULN</td>
<td>7 (2)</td>
<td>18 (3)</td>
</tr>
<tr>
<td>Occult blood</td>
<td>17 (6)</td>
<td>49 (8)</td>
</tr>
<tr>
<td>Urine erythrocytes</td>
<td>17/252 (7)</td>
<td>42/516 (8)</td>
</tr>
<tr>
<td>Urine glucose</td>
<td>15 (5)</td>
<td>26 (5)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Laboratory results are based on 282 TAF patients and 140 TDF patients unless otherwise noted;

<sup>†</sup>Laboratory results are based on 577 TAF patients and 288 TDF patients unless otherwise noted.

AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CK: creatinine kinase; GGT: gamma-glutamyl transferase; HBeAg: hepatitis B e antigen; LDL: low-density lipoprotein;
In a Phase 3b study of HIV/HBV coinfectcd patients, E/C/F/TAF was well tolerated with no discontinuations due to renal events. The most frequent drug-related AEs were diarrhea (4.1%) and increased appetite (2.7%). SAEs occurred in 8.1% of patients and none were reported as being related to the study drug. There were no deaths or ALT flares, and assessments of other liver-related parameters did not suggest increased hepatic risk. Two patients had ALT or AST >3 x ULN during the study and one patient had ALT or AST >5 x ULN (during acute HCV infection) [Gallant et al, 2016].

11.3 The effect of Vemlidy® on renal safety in CHB

There is an increased risk of renal comorbidities in the CHB population owing to the large proportion of aging patients [Carrion et al, 2012], and HBV infection may also increase the risk of comorbid renal disease [Chen et al, 2015a].

Study 110 showed that Vemlidy® was associated with a significantly smaller increase in serum creatinine (SCr) from baseline to Week 48 compared with TDF (Table 6). While a difference was also noted between Vemlidy® and TDF in Study 108, this was not statistically significant. Decreases in estimated glomerular filtration rates (eGFR) were significantly smaller with Vemlidy® in both studies, compared with those who received TDF (Table 6) [Buti et al, 2016; Chan et al, 2016]. A pooled analysis of renal safety outcomes showed that findings were in line with those from the primary analyses, where Vemlidy® had significantly less impact on both eGFR_{CG} (p≤0.001) and SCr levels (p<0.05) than TDF up to treatment Week 72 [Agarwal et al, 2016]. Smaller eGFR declines were consistently noted with Vemlidy® versus TDF regardless of age, gender or the presence of comorbidities (cardiovascular disease, diabetes or hypertension) (Figure 4). TDF, along with FibroTest score >0.75 and a higher baseline eGFR_{CG}, were shown to be significantly associated with a ≥25% decline in eGFR_{CG} [Agarwal et al, 2016].

Other markers of renal safety (retinol binding protein:creatinine ratio [RBP:Cr]; beta-2 microglobulin:creatinine ratio [β2M:Cr]; urine protein-to-creatinine ratio [UPCR]; urinary albumin-creatinine ratio [UACR]) showed similar or improved outcomes with Vemlidy®
Application for inclusion of Vemlidy® tablets in the WHO Model List of Essential Medicines: December 2016

versus TDF. No patient in either group experienced a serious renal AE; a renal AE resulting in discontinuation of study drugs; or a renal AE associated with proximal tubulopathy or renal failure. No cases of Fanconi syndrome were identified [Buti et al, 2016; Chan et al, 2016].

**Table 6: Renal safety outcomes at Week 48 in Phase 3 studies [Buti et al, 2016; Chan et al, 2016]**

<table>
<thead>
<tr>
<th>Renal parameter</th>
<th>Study 108 HBeAg-negative</th>
<th></th>
<th>Study 110 HBeAg-positive</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean SCr change, mg/dL (95% CI)</td>
<td>Vemlidy® n=285</td>
<td>TDF n=140</td>
<td>p value</td>
<td>Vemlidy® n=581</td>
</tr>
<tr>
<td></td>
<td>0.01 (0.00, 0.02)</td>
<td>0.02 (0.00, 0.04)</td>
<td>0.32</td>
<td>0.01 (0.00, 0.02)</td>
</tr>
<tr>
<td>Median eGFR$_{CG}$ change, mL/min (IQR)</td>
<td>-1.8 (-7.8, 6.0)</td>
<td>-4.8 (-12.0, 3.0)</td>
<td>0.004</td>
<td>-0.6 (-8.4, 7.8)</td>
</tr>
</tbody>
</table>

CI: confidence interval; eGFR$_{CG}$: estimated glomerular filtration rate using Cockcroft-Gault; HBeAg: hepatitis B e antigen; IQR: interquartile range; SCr: serum creatinine; TDF: tenofovir disoproxil fumarate.

Fewer Vemlidy® patients experienced chronic kidney disease (CKD) disease worsening than TDF patients, as measured by the Kidney Disease Improving Global Outcomes (KDIGO) Guidelines [Agarwal et al, 2016]. Further information can be found in the supporting document ‘Tenofovir alafenamide renal safety in patients with chronic hepatitis B virus infection’.
Figure 4: Change in eGFR at Week 48 by baseline CKD risk factors in Studies 108 and 110 combined [Agarwal et al, 2016]

CVD: cardiovascular disease; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; HTN: hypertension; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate.

Vemlidy® was associated with smaller changes in proteinuria markers compared with TDF, a difference that was significant for markers of tubular function (RBP:Cr; β2M:Cr; UPCR; UACR) [Lim et al, 2016]. Changes in RBP:Cr and β2M:Cr at Week 48 in Vemlidy® patients were unaffected by the presence of baseline CKD risk factors (older age, gender, eGFR <90 mL/min, hypertension, diabetes mellitus and cardiovascular disease), compared with TDF (Figure 5) [Lim et al, 2016].
Figure 5: Change in tubular biomarkers at Week 48 by baseline CKD risk factors in Studies 108 and 110 combined [Lim et al, 2016]

*\(p<0.05; \dagger p<0.01; \ddagger p<0.001; \S\) As determined by medical history or concomitant medication. \(\beta 2\text{M:Cr: beta-2 microglobulin:creatinine ratio; CKD: chronic kidney disease; CVD: cardiovascular disease; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; HTN: hypertension; RBP:Cr: retinol-binding protein:creatinine ratio; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate.}

E/C/F/TAF was associated with improved renal function as measured by CrCl (Cockcroft-Gault) in a Phase 3b study of HIV/HBV coinfected patients who had switched from stable ART. There was no proximal tubulopathy or drug discontinuation due to renal AEs. There were declines in markers of proximal tubular proteinuria (RBP:Cr and \(\beta 2\text{M:Cr} \)) and in clinically significant proteinuria (UPCR \(\geq 200 \text{ mg/g} \)) and albuminuria (UACR \(\geq 30 \text{ mg/g} \)) [Gallant et al, 2016].

11.4 The effect of Vemlidy\textsuperscript{®} on bone safety outcomes in CHB

Chronic liver disease is associated with low BMD and an increased risk of fracture [Collier et al, 2007]. Osteoporosis and osteopenia are common comorbidities of patients with liver disease, particularly in longer duration or more severe liver disease [Javed et al, 2009; Mahmoudi et al, 2011; Schiefke et al, 2005]. A modest but significant overall increase in risk (13%) in osteoporosis has been observed in CHB.
patients versus non-CHB patients, which was shown to increase with age [Chen et al, 2015b].

Vemlidy® was associated with significantly smaller decreases in hip and spine BMD compared with TDF, in both Study 108 and 110 (Table 7).

**Table 7: Bone safety outcomes at Week 48 in Phase 3 studies [Buti et al, 2016; Chan et al, 2016]**

<table>
<thead>
<tr>
<th>Bone parameter</th>
<th>Study 108 HBeAg-negative</th>
<th>Study 110 HBeAg-positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vemlidy® n=285</td>
<td>TDF n=140</td>
<td></td>
</tr>
<tr>
<td>Mean change in spine BMD from baseline, %</td>
<td>-0.88%</td>
<td>-2.51%</td>
</tr>
<tr>
<td>Mean change in hip BMD from baseline, %</td>
<td>-0.29%</td>
<td>-2.16%</td>
</tr>
<tr>
<td>Vemlidy® n=581</td>
<td>TDF n=292</td>
<td></td>
</tr>
<tr>
<td>Mean change in spine BMD from baseline, %</td>
<td>-0.42%</td>
<td>-2.29%</td>
</tr>
<tr>
<td>Mean change in hip BMD from baseline, %</td>
<td>-0.10%</td>
<td>-1.72%</td>
</tr>
</tbody>
</table>

BMD: bone mineral density; HBeAg: hepatitis B e antigen; TDF: tenofovir disoproxil fumarate.

Two pooled analyses of Phase 3 data from Studies 108 and 110 were undertaken to further investigate bone safety with Vemlidy® versus TDF [Chuang et al, 2016; Seto et al, 2016].

Fewer Vemlidy® patients showed worsening T-score status at Week 48 [Seto et al, 2016]. In addition, fewer Vemlidy® patients had hip and spine BMD decline compared with TDF patients – this was independent of the level of fracture risk, as measured by Fracture Risk Assessment (FRAX®) score quartile (Q1: p=0.0214; Q2, 3 and 4: p<0.001). Vemlidy® was also associated with fewer >3% declines in hip BMD compared with TDF, which was independent of the number of risk factors (female gender, age ≥50 years, Asian race, baseline eGFR<sub>CC</sub> <90 mL/min) for osteoporosis (Figure 6). Data from Seto et al. supported the initial findings from Study 108 and Study 110 at Week 48, while also showing that BMD reductions were sustained through to Week 72 with Vemlidy® compared with TDF (mean percent change in spine BMD: -0.60
versus -2.52, respectively, p<0.001; mean percent change in hip BMD: -0.29 versus -2.43, respectively, p<0.001) [Seto et al, 2016].

**Figure 6: Association between hip BMD decline and number of risk factors in Studies 108 and 110 combined [Seto et al, 2016]**

![Graph showing association between hip BMD decline and number of risk factors]

BMD: bone mineral density; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate.

In Studies 108 and 110, Vemlidy® was associated with significantly smaller changes in a number of biomarkers of bone resorption and formation compared with TDF from baseline to Week 48 (C-type collagen sequence, pro-collagen type 1 N-terminal propeptide [P1NP], osteocalcin [OC], and bone-specific alkaline phosphatase [BAP]; p<0.001 for all) [Buti et al, 2016; Chan et al, 2016].

Bone biomarkers were studied in further detail in another pooled analysis [Chuang et al, 2016], where Vemlidy® was associated with smaller mean changes in markers of bone formation (OC and P1NP) and bone resorption (C-terminal cross-linking telopeptide of type I collagen [CTX]), compared with TDF. Changes in P1NP and OC levels in the Vemlidy® group remained consistent regardless of FRAX® score quartile (Figure 7), as was the case for bone resorption markers. In HIV/HBV coinfected patients who had switched from stable ART, E/C/F/TAF was shown to be associated with significant reductions in biomarkers of bone turnover (serum CTX and P1NP) [Gallant et al, 2016].
11.5 Drug interactions

Vemlidy® is a substrate of P glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Drugs that strongly affect P-gp and BCRP activity may lead to changes in Vemlidy® absorption. Drugs that induce P-gp activity are expected to decrease the absorption of TAF, resulting in decreased plasma concentrations of TAF, which may lead to loss of therapeutic effect of Vemlidy®. Co-administration of Vemlidy® with other drugs that inhibit P-gp and BCRP may increase the absorption and plasma concentration of TAF [Vemlidy® PI].

Because tenofovir is primarily excreted via the kidneys by a combination of glomerular filtration and active tubular secretion, coadministration of Vemlidy® with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of tenofovir and other renally eliminated drugs and this may increase the risk of adverse reactions. This list includes, but is not limited to, acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g. gentamicin), and high-dose or multiple nonsteroidal anti-inflammatory drugs (NSAIDs) [Vemlidy® PI].

Clinically relevant drug–drug interactions with Vemlidy® as described in the Vemlidy® PI are summarized in Table 8.
### Table 8: Established and other potentially significant drug Interactions between Vemlidy® and other agents [Vemlidy® PI]

<table>
<thead>
<tr>
<th>Coadministered drug</th>
<th>Effect on concentration†</th>
<th>Clinical comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anticonvulsants:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine†§</td>
<td>↓ TAF</td>
<td>When coadministered with carbamazepine, the TAF dose should be increased to two tablets QD. Coadministration of Vemlidy® with oxcarbazepine, phenobarbital, or phenytoin is not recommended</td>
</tr>
<tr>
<td>Oxcarbazepine§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenobarbital§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenytoin§</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antimycobacterial:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifabutin§</td>
<td>↓ TAF</td>
<td>Coadministration of Vemlidy® with rifabutin, rifampin or rifapentine is not recommended</td>
</tr>
<tr>
<td>Rifampin§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifapentine§</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Herbal products:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>St. John’s wort§</td>
<td>↓ TAF</td>
<td>Coadministration of Vemlidy® with St John’s wort is not recommended</td>
</tr>
</tbody>
</table>

*This table is not all inclusive; †↓ = decrease; ‡Indicates that a drug interaction study was conducted; §P-gp inducer. QD: once daily.

### 11.6 Summary of comparative safety

Phase 3 studies of Vemlidy in CHB infection conducted to date have demonstrated that it is a well-tolerated therapy with a favorable safety profile that is similar to – or in some cases better than – TDF.

The most common AEs observed were headache, nasopharyngitis and upper respiratory tract infection, while the incidence of SAEs was low and unrelated to study treatment. Only a small proportion (1%) of patients discontinued treatment owing to AEs.

While the benefits of TDF are long-established in the treatment of CHB, long-term use is associated with renal toxicity, reductions in BMD and increases in markers of bone turnover in a small proportion of patients. Renal safety outcomes with Vemlidy were associated with improvements in SCr and glomerular filtration rates compared with
TDF up to Week 72, and benefits were maintained regardless of age, gender or the presence of comorbidities. Fewer Vemlidy® patients experienced CKD disease worsening than TDF patients and Vemlidy® was associated with significantly smaller changes in tubular biomarkers – a finding that was unaffected by the presence of risk factors. Furthermore, in clinical trials of Vemlidy®, there have been no cases of Fanconi syndrome.

Vemlidy® was associated with significantly smaller decreases in hip and spine BMD when compared with TDF – reductions that were sustained through to Week 72. Smaller mean changes in markers of bone formation and bone resorption were noted with Vemlidy® versus TDF, along with fewer >3% declines in hip BMD, which was irrespective of the level of fracture risk. Observations to date suggest that Vemlidy® therapy may overcome the limitations of TDF by minimizing the risk of bone or renal side effects in patients with CHB. Long-term follow-up data from Studies 108 and 110 will provide further insight into these outcomes.

12. Summary of available data on comparative cost and cost-effectiveness within the pharmacologic class or therapeutic group

12.1 Range of costs of the proposed medicine

12.1.1 USA

The FDA approved Vemlidy® in November 2016 for the treatment of CHB infection in adults with compensated liver disease [Vemlidy® PI].

The wholesale cost of Vemlidy® in access markets is shown in Table 9.
Table 9: Wholesale access costs of Vemlidy®

<table>
<thead>
<tr>
<th>Dosage form and product strength</th>
<th>Package size</th>
<th>Wholesale acquisition cost (US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablet containing:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 mg tenofovir alafenamide</td>
<td>30 tablets</td>
<td>Please contact Gilead Sciences, Inc.</td>
</tr>
</tbody>
</table>

12.1.2 Developing countries

Gilead works with regional business partners on local country regulatory submissions to provide branded HBV drugs at reduced prices in 125 low- and middle-income countries. Gilead has also established licensing agreements with 19 generic drug manufacturers in India, South Africa and China, as well as the Medicines Patent Pool, granting them rights to produce and sell high-quality, low-cost generic versions of Gilead HBV medicines in 112 developing countries. Partners set their own process and may also create fixed-dose combinations with TAF for ART. Vemlidy® is already an integrated component of the company’s generic licensing agreements, and with FDA approval, manufacturing partners may begin production and distribution of a generic version of this medicine.

Gilead’s no-profit price for a 30-day supply of Vemlidy® to our in-country Access Program distribution partners is **US$10**. Vemlidy® will be made available to Governments at this no-profit transfer price in addition to distribution and other related costs (these may vary from country to country).

12.2 Cost-effectiveness of medicines for CHB

The cost-effectiveness of medicines for CHB infection and the cost effectiveness of Vemlidy® is not yet available, however analyses are currently underway.

13. Summary of regulatory status of the medicine

The countries where Vemlidy® is approved for use in patients with CHB are shown in Table 10.
Table 10: Countries with Marketing Authorization status for Vemlidy® tablets

<table>
<thead>
<tr>
<th>Territory</th>
<th>Approval date</th>
<th>Trade name</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States of America</td>
<td>November 11, 2016</td>
<td>Vemlidy®</td>
</tr>
</tbody>
</table>


14.1 Specifications of Vemlidy® tablets

None available.
15. Proposed (new/adapted) text for the WHO Model Formulary

15.1 Other antivirals

Tenofovir alafenamide

**Tablet:** 25 mg tenofovir alafenamide.
Also known as Vemlidy®.

*Uses:* Vemlidy® is licensed in the USA for the treatment of chronic hepatitis B in adults with compensated liver disease.

*Precautions:* In those with HBV and HIV-1 coinfection, Vemlidy® alone is not recommended for the treatment of HIV-1 infection. HIV-1 resistance may develop in these patients. In cases of new onset or worsening renal impairment, assessment of serum creatinine, serum phosphorus, estimated creatinine clearance, urine glucose, and urine protein are recommended in all patients before initiating Vemlidy® therapy and monitoring during therapy as clinically appropriate. Treatment with Vemlidy® should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations). Discontinuation of anti-hepatitis B therapy, including Vemlidy®, may result in severe acute exacerbations of hepatitis B. Patients who discontinue Vemlidy® should be closely monitored with both clinical and laboratory follow-ups for at least several months after stopping treatment. If appropriate, resumption of anti-hepatitis B therapy may be warranted.

*Dose:* One tablet taken orally once daily, with food.

*Adverse effects:* The most common adverse reactions (≥5%, all grades) are headache, abdominal pain, fatigue, cough, nausea, and back pain.

Please refer to the Prescribing Information appropriate to the Gilead Access Program contained in Appendix 1 for further details on Vemlidy®.
16. References


Baraclude® Prescribing information. August 2015.


Gilead Sciences


Chen YC, Su YC, Li CY, Wu CP, Lee MS. A nationwide cohort study suggests chronic hepatitis B virus infection increases the risk of end-stage renal disease among patients in Taiwan. Kidney Int. 2015a;87:1030–38.


Genvoya® Prescribing Information. September 2016.


Appendix 1. Vemlidy® prescribing information

**HIGHLIGHTS OF PRESCRIBING INFORMATION**
These highlights do not include all the information needed to use VEMLIDY safely and effectively. See full prescribing information for VEMLIDY.

**VEMLIDY** (tenofovir alafenamide) tablets, for oral use
Initial U.S. Approval: 2015

**WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS AND POST TREATMENT SEVERE ACUTE EXACERBATION OF HEPATITIS B**
See full prescribing information for complete boxed warning.

- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs. (5.1)
- Discontinuation of anti-hepatitis B therapy may result in severe acute exacerbations of hepatitis B. Hepatic function should be monitored closely in patients who discontinue VEMLIDY. If appropriate, resumption of anti-hepatitis B therapy may be warranted. (5.2)

**INDICATIONS AND USAGE**
VEMLIDY is a hepatitis B virus (HBV) nucleoside analog reverse transcriptase inhibitor and is indicated for the treatment of chronic hepatitis B virus infection in adults with compensated liver disease. (1)

**DOSE AND ADMINISTRATION**
- Testing: Prior to initiation of VEMLIDY, test patients for HIV infection. VEMLIDY alone should not be used in patients with HIV infection. Assess serum creatinine, serum phosphorus, estimated creatinine clearance, urine glucose, and urine protein before initiating VEMLIDY and during therapy in all patients as clinically appropriate. (2.1)
- Recommended dosage: 25 mg (one tablet) taken orally once daily with food. (2.2)

**DOSE FORMS AND STRENGTHS**
Tablets: 25 mg of tenofovir alafenamide. (3)

**CONTRAINDICATIONS**
None. (4)

**WARNINGS AND PRECAUTIONS**
- HBV and HIV-1 coinfection: VEMLIDY alone is not recommended for the treatment of HIV-1 infection. HIV-1 resistance may develop in these patients. (5.3)
- New onset or worsening renal impairment: Assessment of serum creatinine, serum phosphorus, estimated creatinine clearance, urine glucose, and urine protein is recommended before initiating VEMLIDY therapy and during therapy as clinically appropriate. (5.4)

**ADVERSE REACTIONS**
Most common adverse reactions (incidence greater than or equal to 5%, all grades) are headache, abdominal pain, fatigue, cough, nausea, and back pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Gilead Sciences, Inc. at 1-800-GILEAD-5 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

**DRUG INTERACTIONS**
VEMLIDY is a substrate of P-glycoprotein (P-gp) and BCRP. Drugs that strongly affect P-gp and BCRP activity may lead to changes in VEMLIDY absorption. Consult the full prescribing information prior to and during treatment for potential drug-drug interactions. (7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2016

Gilead Sciences 42
FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT SEVERE ACUTE EXACERBATION OF HEPATITIS B

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs [see Warnings and Precautions (5.1)].

Discontinuation of anti-hepatitis B therapy, including VEMLIDY, may result in severe acute exacerbations of hepatitis B. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy, including VEMLIDY. If appropriate, resumption of anti-hepatitis B therapy may be warranted [see Warnings and Precautions (5.2)].

1 INDICATIONS AND USAGE

VEMLIDY is indicated for the treatment of chronic hepatitis B virus (HBV) infection in adults with compensated liver disease [see Clinical Studies (14)].

2 DOSAGE AND ADMINISTRATION

2.1 Testing Prior to Initiation of VEMLIDY

Prior to initiation of VEMLIDY, patients should be tested for HIV-1 infection. VEMLIDY alone should not be used in patients with HIV infection [see Warnings and Precautions (5.3)].

It is recommended that serum creatinine, serum phosphorous, estimated creatinine clearance, urine glucose, and urine protein be assessed before initiating VEMLIDY and during therapy in all patients as clinically appropriate [see Warnings and Precautions (5.4)].

2.2 Recommended Dosage in Adults
The recommended dosage of VEMLIDY is 25 mg (one tablet) taken orally once daily with food [see Clinical Pharmacology (12.3)].

2.3 Dosage in Patients with Renal Impairment

No dosage adjustment of VEMLIDY is required in patients with mild, moderate, or severe renal impairment. VEMLIDY is not recommended in patients with end stage renal disease (estimated creatinine clearance below 15 mL per minute) [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].

2.4 Dosage in Patients with Hepatic Impairment

No dosage adjustment of VEMLIDY is required in patients with mild hepatic impairment (Child-Pugh A). VEMLIDY is not recommended in patients with decompensated (Child-Pugh B or C) hepatic impairment [see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)].

3 DOSAGE FORMS AND STRENGTHS

Tablets: 25 mg of tenofovir alafenamide (equivalent to 28 mg of tenofovir alafenamide fumarate) — yellow, round, film-coated tablets, debossed with “GSI” on one side of the tablet and “25” on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including tenofovir disoproxil fumarate in combination with other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with
known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with VEMLIDY should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

5.2 Severe Acute Exacerbation of Hepatitis B after Discontinuation of Treatment
Discontinuation of anti-hepatitis B therapy, including VEMLIDY, may result in severe acute exacerbations of hepatitis B. Patients who discontinue VEMLIDY should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, resumption of anti-hepatitis B therapy may be warranted.

5.3 Risk of Development of HIV-1 Resistance in Patients Coinfected with HBV and HIV-1
Due to the risk of development of HIV-1 resistance, VEMLIDY alone is not recommended for the treatment of HIV-1 infection. The safety and efficacy of VEMLIDY have not been established in patients coinfected with HBV and HIV-1. HIV antibody testing should be offered to all HBV-infected patients before initiating therapy with VEMLIDY, and, if positive, an appropriate antiretroviral combination regimen that is recommended for patients coinfected with HIV-1 should be used.

5.4 New Onset or Worsening Renal Impairment
Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir prodrugs in both animal toxicology studies and human trials. In clinical trials of VEMLIDY, there have been no cases of Fanconi syndrome or Proximal Renal Tubulopathy (PRT).
Patients taking tenofovir prodrugs who have impaired renal function and those taking nephrotoxic agents, including non-steroidal anti-inflammatory drugs, are at increased risk of developing renal-related adverse reactions [see Drug Interactions (7.2)].

It is recommended that serum creatinine, serum phosphorous, estimated creatinine clearance, urine glucose, and urine protein be assessed before initiating VEMLIDY and during therapy in all patients as clinically appropriate. Discontinue VEMLIDY in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in other sections of the labeling:

Lactic Acidosis/Severe Hepatomegaly with Steatosis [see Boxed Warning and Warnings and Precautions (5.1)]

Severe Acute Exacerbation of Hepatitis B [see Boxed Warning and Warnings and Precautions (5.2)]

New Onset or Worsening of Renal Impairment [see Warnings and Precautions (5.4)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions in Adult Subjects with Chronic Hepatitis B and Compensated Liver Disease

The safety assessment of VEMLIDY was based on pooled data through the Week 48 data analysis from 1298 subjects in two randomized, double-blind, active-controlled trials, Study 108 and Study 110, in adult subjects with chronic
hepatitis B and compensated liver disease. A total of 866 subjects received VEMLIDY 25 mg once daily [see Clinical Studies (14.1)].

The proportion of subjects who discontinued treatment with VEMLIDY or tenofovir disoproxil fumarate due to adverse reactions of any severity was 1.0% and 1.2%, respectively. Table 1 displays the frequency of the adverse reaction (all Grades) greater than or equal to 5% in the VEMLIDY group.

**Table 1 Adverse Reactions**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>VEMLIDY (N=866)</th>
<th>Tenofovir Disoproxil Fumarate (N=432)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Cough</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Nausea</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Back pain</td>
<td>5%</td>
<td>4%</td>
</tr>
</tbody>
</table>

a. Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.

**Renal Laboratory Tests**

In a pooled analysis of Studies 108 and 110 in adult subjects with chronic hepatitis B and a median baseline eGFR of 106 and 105 mL per minute (for the VEMLIDY and tenofovir disoproxil fumarate [TDF] groups, respectively), mean serum creatinine increased by less than 0.1 mg/dL and median serum phosphorus decreased by 0.1 mg/dL in both treatment groups. Median change from baseline in eGFR was -1.2 mL per minute in the VEMLIDY group and -5.4 mL per minute in those receiving TDF. The long-term clinical significance of
these renal laboratory changes on adverse reaction frequencies between VEMLIDY and TDF is not known.

Decrease in Bone Mineral Density
In a pooled analysis of Studies 108 and 110, the mean percentage change in bone mineral density (BMD) from baseline to Week 48 as assessed by dual-energy X-ray absorptiometry (DXA) was -0.6% with VEMLIDY compared to -2.4% with TDF at the lumbar spine and -0.2% compared to -1.9% at the total hip. BMD declines of 5% or greater at the lumbar spine were experienced by 6% of VEMLIDY subjects and 20% of TDF subjects. BMD declines of 7% or greater at the femoral neck were experienced by 3% of VEMLIDY subjects and 6% of TDF subjects. The long-term clinical significance of these BMD changes is not known.

Laboratory Abnormalities
The frequency of laboratory abnormalities (Grades 3–4) occurring in at least 2% of subjects receiving VEMLIDY in Studies 108 and 110 are presented in Table 2.

<table>
<thead>
<tr>
<th>Laboratory Parameter Abnormality</th>
<th>VEMLIDY (N=866)</th>
<th>Tenofovir Disoproxil Fumarate (N=432)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT (&gt;5 x ULN)</td>
<td>8%</td>
<td>9%</td>
</tr>
<tr>
<td>Glycosuria (≥3+)</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>LDL-cholesterol (fasted) (&gt;190 mg/dL)</td>
<td>4%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>AST (&gt;5 x ULN)</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>Creatine Kinase (≥10 x ULN)</td>
<td>3%</td>
<td>3%</td>
</tr>
</tbody>
</table>
Serum Amylase (≥2.0 x ULN)  | 3%  | 2%
---|---|---

Frequencies are based on treatment-emergent laboratory abnormalities.

**Amylase and Lipase Elevations and Pancreatitis**

In Studies 108 and 110, seven subjects treated with VEMLIDY with elevated amylase levels had associated symptoms, such as nausea, low back pain, abdominal tenderness, biliary pancreatitis and pancreatitis. Of these seven, two subjects discontinued VEMLIDY due to elevated amylase and/or lipase; one subject experienced recurrence of adverse events when VEMLIDY was restarted. No subject treated with tenofovir disoproxil fumarate had associated symptoms or discontinued treatment.

**Serum Lipids**

Changes from baseline in total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, and total cholesterol to HDL ratio among subjects treated with VEMLIDY and tenofovir disoproxil fumarate are presented in Table 3.

**Table 3. Lipid Abnormalities: Mean Change from Baseline in Lipid Parameters in Patients with Chronic HBV Infection and Compensated Liver Disease in Studies 108 and 110 (Week 48 Analysis)**

<table>
<thead>
<tr>
<th></th>
<th>VEMLIDY (N=866)</th>
<th>Tenofovir Disoproxil Fumarate (N=432)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Week 48</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>188 [n=835]</td>
<td>0 [n=772]</td>
</tr>
<tr>
<td>(fasted)</td>
<td>mg/dL</td>
<td>mg/dL</td>
</tr>
<tr>
<td>HDL-Cholesterol (fasted)</td>
<td>60 [n=835]</td>
<td>-4 [n=771]</td>
</tr>
</tbody>
</table>
7 DRUG INTERACTIONS

7.1 Potential for Other Drugs to Affect VEMLIDY

VEMLIDY is a substrate of P-glycoprotein (P-gp) and BCRP. Drugs that strongly affect P-gp and BCRP activity may lead to changes in tenofovir alafenamide absorption (see Table 4). Drugs that induce P-gp activity are expected to decrease the absorption of tenofovir alafenamide, resulting in decreased plasma concentrations of tenofovir alafenamide, which may lead to loss of therapeutic effect of VEMLIDY. Coadministration of VEMLIDY with other drugs that inhibit P-gp and BCRP may increase the absorption and plasma concentration of tenofovir alafenamide.

7.2 Drugs Affecting Renal Function

Because tenofovir is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion, coadministration of VEMLIDY with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of tenofovir and other renally eliminated drugs and this may increase the risk of adverse reactions. Some examples of drugs that are eliminated by active tubular secretion include, but are not limited to, acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs [see Warnings and Precautions (5.4)].

7.3 Established and Other Potentially Significant Interactions
Table 4 provides a listing of established or potentially clinically significant drug interactions. The drug interactions described are based on studies conducted with tenofovir alafenamide or are predicted drug interactions that may occur with VEMLIDY. [For magnitude of interaction, see Clinical Pharmacology (12.3)]. Information regarding potential drug-drug interactions with HIV antiretrovirals is not provided (see the prescribing information for emtricitabine/tenofovir alafenamide for interactions with HIV antiretrovirals). The table includes potentially significant interactions but is not all inclusive.
Table 4. Established and Other Potentially Significant Drug Interactions

<table>
<thead>
<tr>
<th>Concomitant Drug Class: Drug Name</th>
<th>Effect on Concentration</th>
<th>Clinical Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anticonvulsants:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>carbamazepine&lt;sup&gt;c*&lt;/sup&gt;</td>
<td>↓ tenofovir alafenamide</td>
<td></td>
</tr>
<tr>
<td>oxcarbazepine*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>phenobarbital*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>phenytoin*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>When coadministered with carbamazepine, the tenofovir alafenamide dose should be increased to two tablets once daily. Coadministration of VEMLIDY with oxcarbazepine, phenobarbital, or phenytoin is not recommended.</td>
</tr>
<tr>
<td><strong>Antimycobacterial:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifabutin*</td>
<td>↓ tenofovir alafenamide</td>
<td></td>
</tr>
<tr>
<td>Rifampin*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifapentine*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Coadministration of VEMLIDY with rifabutin, rifampin or rifapentine is not recommended.</td>
</tr>
<tr>
<td><strong>Herbal Products:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>St. John’s wort*</td>
<td>↓ tenofovir alafenamide</td>
<td></td>
</tr>
<tr>
<td><em>(Hypericum perforatum)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Coadministration of VEMLIDY with St. John’s wort is not recommended.</td>
</tr>
</tbody>
</table>

a. This table is not all inclusive.
b. ↓ = decrease.
c. Indicates that a drug interaction study was conducted.
* P-gp inducer

7.4 Drugs without Clinically Significant Interactions with VEMLIDY

**Based on drug interaction studies conducted with VEMLIDY, no clinically significant drug interactions have been observed with:** ethinyl estradiol, itraconazole, ketoconazole, ledipasvir/sofosbuvir, midazolam, norgestimate, sertraline, sofosbuvir, and sofosbuvir/velpatasvir.
8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to VEMLIDY during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary
There are no human data on the use of VEMLIDY in pregnant women to inform a drug-associated risks of adverse fetal developmental outcome. In animal studies, no adverse developmental effects were observed when tenofovir alafenamide was administered during the period of organogenesis at exposure equal to or 51 times (rats and rabbits, respectively) the tenofovir alafenamide exposure at the recommended daily dose of VEMLIDY [see Data]. No adverse effects were observed in the offspring when TDF (tenofovir disoproxil fumarate) was administered through lactation at tenofovir exposures of approximately 12 times the exposure at the recommended daily dosage of VEMLIDY. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

Data

Animal Data
Embryonic fetal development studies performed in rats and rabbits revealed no evidence of impaired fertility or harm to the fetus. The embryo-fetal NOAELs (no observed adverse effect level) in rats and rabbits occurred at tenofovir alafenamide exposures similar to and 51 times higher than, respectively, the
exposure in humans at the recommended daily dose. Tenofovir alafenamide is rapidly converted to tenofovir; the observed tenofovir exposure in rats and rabbits were 54 (rats) and 85 (rabbits) times higher than human tenofovir exposures at the recommended daily dose. Tenofovir alafenamide was administered orally to pregnant rats (25, 100, or 250 mg/kg/day) and rabbits (10, 30, or 100 mg/kg/day) through organogenesis (on gestation days 6 through 17, and 7 through 20, respectively). No adverse embryo-fetal effects were observed in rats and rabbits at tenofovir alafenamide exposures approximately similar to (rats) and 51 (rabbits) times higher than the exposure in humans at the recommended daily dose of VEMLIDY. Tenofovir alafenamide is rapidly converted to tenofovir; the observed tenofovir exposures in rats and rabbits were 54 (rats) and 85 (rabbits) times higher than human tenofovir exposures at the recommended daily dose. Since tenofovir alafenamide is rapidly converted to tenofovir and a lower tenofovir exposure in rats and mice was observed after tenofovir alafenamide administration compared to TDF, another prodrug for tenofovir administration, a pre/postnatal development study in rats was conducted only with TDF. Doses up to 600 mg/kg/day were administered through lactation; no adverse effects were observed in the offspring on gestation day 7 [and lactation day 20] at tenofovir exposures of approximately 12 [18] times higher than the exposures in humans at the recommended daily dose of VEMLIDY.

8.2 Lactation

**Risk Summary**

It is not known whether VEMLIDY and its metabolites are present in human breast milk, affect human milk production, or have effects on the breastfed infant. Tenofovir has been shown to be present in the milk of lactating rats and rhesus monkeys after administration of TDF [see Data]. It is not known if tenofovir alafenamide can be present in animal milk. The developmental and health benefits of breastfeeding should be considered along with the mother’s
clinical need for VEMLIDY and any potential adverse effects on the breastfed infant from VEMLIDY or from the underlying maternal condition.

Data

Animal Data

Studies in rats and monkeys have demonstrated that tenofovir is secreted in milk. Tenofovir was excreted into the milk of lactating rats following oral administration of TDF (up to 600 mg/kg/day) at up to approximately 24% of the median plasma concentration in the highest dosed animals at lactation day 11 [see Data (8.1)]. Tenofovir was excreted into the milk of lactating monkeys following a single subcutaneous (30 mg/kg) dose of tenofovir at concentrations up to approximately 4% of plasma concentration, resulting in exposure (AUC) of approximately 20% of plasma exposure.

8.4 Pediatric Use

Safety and effectiveness of VEMLIDY in pediatric patients less than 18 years of age have not been established.

8.5 Geriatric Use

Clinical trials of VEMLIDY did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

8.6 Renal Impairment

No dosage adjustment of VEMLIDY is required in patients with mild, moderate, or severe renal impairment. VEMLIDY is not recommended in patients with end stage renal disease (estimated creatinine clearance below 15 mL per minute) [see Clinical Pharmacology (12.3)].

8.7 Hepatic Impairment
No dosage adjustment of VEMLIDY is required in patients with mild hepatic impairment (Child-Pugh A). The safety and efficacy of VEMLIDY in patients with decompensated cirrhosis (Child-Pugh B or C) have not been established; therefore VEMLIDY is not recommended in patients with decompensated (Child-Pugh B or C) hepatic impairment [see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)].

10 OVERDOSAGE

If overdose occurs, monitor patient for evidence of toxicity. 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 hemodialysis with an extraction coefficient of approximately 54%.

11 DESCRIPTION

VEMLIDY is a tablet containing tenofovir alafenamide for oral administration. Tenofovir alafenamide, a hepatitis B virus (HBV) nucleoside analog reverse transcriptase inhibitor, is converted in vivo to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5’-monophosphate. Each tablet contains 25 mg of tenofovir alafenamide (equivalent to 28 mg of tenofovir alafenamide fumarate). The tablets include the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. The tablets are film coated with a coating material containing: iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

The chemical name of tenofovir alafenamide fumarate drug substance is L-alanine, N-[(S)-[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]phenoxyphosphinyl]-, 1-methylethyl ester, (2E)-2-butenedioate (2:1).
It has an empirical formula of $\text{C}_{21}\text{H}_{29}\text{O}_5\text{N}_6\text{P} \cdot \frac{1}{2}(\text{C}_4\text{H}_4\text{O}_4)$ and a formula weight of 534.50. It has the following structural formula:

![Structural formula of Tenofovir alafenamide fumarate](image)

Tenofovir alafenamide fumarate is a white to off-white or tan powder with a solubility of 4.7 mg per mL in water at 20 °C.

### 12 CLINICAL PHARMACOLOGY

#### 12.1 Mechanism of Action
Tenofovir alafenamide is an antiviral drug against the hepatitis B virus [see Microbiology (12.4)].

#### 12.2 Pharmacodynamics

**Cardiac Electrophysiology**

In a thorough QT/QTc study in 48 healthy subjects, tenofovir alafenamide at the recommended dose or at a dose 5 times the recommended dose did not affect the QT/QTc interval and did not prolong the PR interval.

#### 12.3 Pharmacokinetics

The pharmacokinetic properties of VEMLIDY are provided in Table 5. The multiple dose PK parameters of tenofovir alafenamide and its metabolite tenofovir are provided in Table 6.
Table 5  Pharmacokinetic Properties of VEMLIDY

<table>
<thead>
<tr>
<th></th>
<th>Tenofovir Alafenamide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absorption</strong></td>
<td></td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>0.48</td>
</tr>
<tr>
<td>Effect of high fat meal (relative to fasting): AUC$_{\text{last}}$ Ratio$^a$</td>
<td>1.65 (1.51, 1.81)</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td></td>
</tr>
<tr>
<td>% Bound to human plasma proteins</td>
<td>80%</td>
</tr>
<tr>
<td>Source of protein binding data</td>
<td><em>Ex vivo</em></td>
</tr>
<tr>
<td>Blood-to-plasma ratio</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td></td>
</tr>
<tr>
<td>Metabolism$^b$</td>
<td>CES1 (hepatocytes)</td>
</tr>
<tr>
<td></td>
<td>Cathepsin A (PBMCs)</td>
</tr>
<tr>
<td></td>
<td>CYP3A (minimal)</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td></td>
</tr>
<tr>
<td>Major route of elimination</td>
<td>Metabolism (&gt;80% of oral dose)</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)$^c$</td>
<td>0.51</td>
</tr>
<tr>
<td>% Of dose excreted in urine$^d$</td>
<td>&lt;1</td>
</tr>
<tr>
<td>% Of dose excreted in feces$^d$</td>
<td>31.7</td>
</tr>
</tbody>
</table>

CES1 = carboxylesterase 1; PBMCs = peripheral blood mononuclear cells.

a. Values refer to geometric mean ratio in AUC$_{\text{last}}$ [fed/fasted] and (90% confidence interval). High fat meal = ~800 kcal, 50% fat.

b. *In vivo*, TAF is hydrolyzed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite, tenofovir diphosphate. *In vitro* studies have shown that TAF is metabolized to tenofovir by CES1 in hepatocytes, and by cathepsin A in PBMCs and macrophages.

c. $t_{1/2}$ values refer to median terminal plasma half-life.

d. Dosing in mass balance study: TAF 25 mg (single dose administration of [$^{14}$C] TAF).
## Table 6  Multiple Dose PK Parameters of Tenofovir Alafenamide and its Metabolite Tenofovir Following Oral Administration in Adults with Chronic Hepatitis B

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Tenofovir Alafenamide&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Tenofovir&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (microgram per mL)</td>
<td>0.27 (63.3)</td>
<td>0.03 (24.6)</td>
</tr>
<tr>
<td>$AUC_{\text{tau}}$ (microgram•hour per mL)</td>
<td>0.27 (47.8)</td>
<td>0.40 (35.2)</td>
</tr>
<tr>
<td>$C_{\text{trough}}$ (microgram per mL)</td>
<td>NA</td>
<td>0.01 (39.6)</td>
</tr>
</tbody>
</table>

CV = coefficient of variation; NA = not applicable

<sup>a</sup> From Intensive PK analyses in Study 108 and Study 110; N = 8.
Specific Populations

Geriatric Patients, Race, and Gender
No clinically relevant differences in tenofovir alafenamide or tenofovir pharmacokinetics due to race or gender have been identified. Limited data in subjects aged 65 and over suggest a lack of clinically relevant differences in tenofovir alafenamide or tenofovir pharmacokinetics [see Use in Specific Populations (8.5)].

Patients with Renal Impairment
Relative to subjects with normal renal function (estimated creatinine clearance ≥90 mL/min), the tenofovir alafenamide and tenofovir systemic exposures in subjects with severe renal impairment were 1.9-fold and 5.7-fold higher, respectively. The pharmacokinetics of tenofovir alafenamide have not been evaluated in patients with creatinine clearance less than 15 mL per minute.

Patients with Hepatic Impairment
Relative to subjects with normal hepatic function, tenofovir alafenamide and tenofovir systemic exposures were 7.5% and 11% lower in subjects with mild hepatic impairment, respectively.

HIV and/or Hepatitis C Virus Coinfection
The pharmacokinetics of tenofovir alafenamide have not been fully evaluated in subjects coinfected with HIV and/or hepatitis C virus.

Drug Interaction Studies
[see Drug Interactions (7)]
The effects of coadministered drugs on the exposure of tenofovir alafenamide are shown in Table 7. The effects of tenofovir alafenamide on the exposure of coadministered drugs are shown in Table 8 [For information regarding clinical
recommendations, see Drug Interactions (7)]. Information regarding potential
drug-drug interactions with HIV antiretrovirals is not provided (see the
prescribing information for emtricitabine/tenofovir alafenamide for interactions
with HIV antiretrovirals).

Table 7  Drug Interactions: Changes in Pharmacokinetic Parameters
for Tenofovir Alafenamide in the Presence of the Coadministered Drug

<table>
<thead>
<tr>
<th>Coadministered Drug</th>
<th>Dose of Coadministered Drug (mg)</th>
<th>Tenofovir Alafenamide (mg)</th>
<th>N</th>
<th>Geometric Mean Ratio of TAF Pharmacokinetic Parameters (90% CI)b; No effect = 1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C_{max}</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>300 twice daily</td>
<td>25 once dailyc</td>
<td>26</td>
<td>0.43 (0.36, 0.51)</td>
</tr>
<tr>
<td>Cobicistatd</td>
<td>150 once daily</td>
<td>8 once daily</td>
<td>12</td>
<td>2.83 (2.20, 3.65)</td>
</tr>
<tr>
<td>Ledipasvir/Sofosbuvir</td>
<td>90/400 once daily</td>
<td>25 once dailyg</td>
<td>42</td>
<td>1.03 (0.94, 1.14)</td>
</tr>
<tr>
<td>Sertraline</td>
<td>50 once daily</td>
<td>10 once dailyf</td>
<td>19</td>
<td>1.00 (0.86, 1.16)</td>
</tr>
<tr>
<td>Sofosbuvir/Velpatasvir</td>
<td>400/100 once daily</td>
<td>10 once dailyf</td>
<td>24</td>
<td>0.80 (0.68, 0.94)</td>
</tr>
</tbody>
</table>

NC = not calculated
All interaction studies conducted in healthy subjects.
All no effect boundaries are 70%–143%.
Study conducted with emtricitabine/tenofovir alafenamide.
A representative inhibitor of P-glycoprotein.
Study conducted with emtricitabine/rilpivirine/tenofovir alafenamide.
Study conducted with elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide.
### Table 8  Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Tenofovir Alafenamide

<table>
<thead>
<tr>
<th>Coadministered Drug</th>
<th>Dose of Coadministered Drug (mg)</th>
<th>Tenofovir Alafenamide (mg)</th>
<th>N</th>
<th>Geometric Mean Ratio of Coadministered Drug Pharmacokinetic Parameters (90% CI); No effect = 1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ledipasvir</td>
<td>90 ledipasvir / 25 once daily</td>
<td></td>
<td></td>
<td>$C_{\text{max}}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>41</td>
<td>1.01 (0.97, 1.05)</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>400 sofosbuvir once daily</td>
<td></td>
<td></td>
<td>0.96 (0.89, 1.04)</td>
</tr>
<tr>
<td>GS-331007</td>
<td></td>
<td></td>
<td></td>
<td>1.08 (1.05, 1.11)</td>
</tr>
<tr>
<td>Midazolame</td>
<td>2.5 once daily orally</td>
<td></td>
<td>18</td>
<td>1.02 (0.92, 1.13)</td>
</tr>
<tr>
<td></td>
<td>1 once daily IV</td>
<td></td>
<td></td>
<td>0.99 (0.89, 1.11)</td>
</tr>
<tr>
<td>Norgestromin</td>
<td>norgestimate 0.180/0.215/0.250</td>
<td></td>
<td></td>
<td>1.17 (1.07, 1.26)</td>
</tr>
<tr>
<td>Norgestrel</td>
<td>250 once daily / ethinyl estradiol 0.025</td>
<td></td>
<td>29</td>
<td>1.10 (1.02, 1.18)</td>
</tr>
<tr>
<td>Ethinyl estradiol</td>
<td>once daily</td>
<td></td>
<td></td>
<td>1.22 (1.15, 1.29)</td>
</tr>
<tr>
<td>Coadministered Drug</td>
<td>Dose of Coadministered Drug (mg)</td>
<td>Tenofovir Alafenamide (mg)</td>
<td>N</td>
<td>Geometric Mean Ratio of Coadministered Drug Pharmacokinetic Parameters (90% CI)b; No effect = 1.00</td>
</tr>
<tr>
<td>---------------------</td>
<td>---------------------------------</td>
<td>---------------------------</td>
<td>----</td>
<td>--------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td>50 single dose</td>
<td>10 once daily</td>
<td>19</td>
<td>C&lt;sub&gt;max&lt;/sub&gt; (1.14) (0.94, 1.38) (\bar{C}&lt;sub&gt;max&lt;/sub&gt;) 1.09 (0.90, 1.32) NC</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>400 once daily</td>
<td>10 once daily</td>
<td>23</td>
<td>C&lt;sub&gt;max&lt;/sub&gt; (1.23) (1.07, 1.42) (\bar{C}&lt;sub&gt;max&lt;/sub&gt;) 1.37 (1.24, 1.52) NC</td>
</tr>
<tr>
<td>GS-331007&lt;sup&gt;c&lt;/sup&gt;</td>
<td>100 once daily</td>
<td>15</td>
<td></td>
<td>C&lt;sub&gt;max&lt;/sub&gt; (1.30) (1.17, 1.45) (\bar{C}&lt;sub&gt;max&lt;/sub&gt;) 1.50 (1.35, 1.66) 1.60 (1.44, 1.78)</td>
</tr>
<tr>
<td>Velpatasvir</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NC = not calculated

All interaction studies conducted in healthy subjects.

All no effect boundaries are 70%–143%.

The predominant circulating nucleoside metabolite of sofosbuvir.

Study conducted with emtricitabine/rilpivirine/tenofovir alafenamide.

A sensitive CYP3A4 substrate.

Study conducted with emtricitabine/tenofovir alafenamide.

Study conducted with elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide.
12.4 Microbiology

Mechanism of Action
Tenofovir alafenamide is a phosphonamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analog). Tenofovir alafenamide as a lipophilic cell-permeant compound enters primary hepatocytes by passive diffusion and by the hepatic uptake transporters OATP1B1 and OATP1B3. Tenofovir alafenamide is then converted to tenofovir through hydrolysis primarily by carboxylesterase 1 (CES1) in primary hepatocytes. Intracellular tenofovir is subsequently phosphorylated by cellular kinases 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 diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there is no evidence of toxicity to mitochondria in cell culture.

Antiviral Activity in Cell Culture
The antiviral activity of tenofovir alafenamide was assessed in a transient transfection assay using 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 value of 86.6 nM. The CC50 (50% cytotoxicity concentration) values in HepG2 cells were greater than 44,400 nM. In cell culture combination antiviral activity studies of tenofovir with the HBV nucleoside reverse transcriptase inhibitors entecavir, lamivudine, and telbivudine, no antagonistic activity was observed.

Resistance in Clinical Trials
In a pooled analysis of treatment-naïve and treatment-experienced subjects receiving VEMLIDY in Studies 108 and 110, genotypic resistance analysis was
performed on paired baseline and on-treatment HBV isolates for subjects who either experienced virologic breakthrough (2 consecutive visits with HBV DNA greater than or equal to 69 IU/mL [400 copies/mL] after having been less than 69 IU/mL, or 1.0-log10 or greater increase in HBV DNA from nadir) through Week 48, or had HBV DNA greater than or equal to 69 IU/mL at early discontinuation at or after Week 24. Treatment-emergent amino acid substitutions in the HBV reverse transcriptase domain, all occurring at polymorphic positions, were observed in some HBV isolates evaluated (5/20); however, no specific substitutions occurred at a sufficient frequency to be associated with resistance to VEMLIDY.

Cross-Resistance
The antiviral activity of tenofovir alafenamide was evaluated against a panel of isolates containing substitutions associated with HBV nucleoside reverse transcriptase inhibitor resistance in a transient transfection assay using HepG2 cells. HBV isolates expressing the lamivudine resistance-associated substitutions rtM204V/I (±rtL180M±rtV173L) and expressing the entecavir resistance-associated substitutions rtT184G, rtS202G, or rtM250V in the presence of rtL180M and rtM204V showed less than 2-fold reduced susceptibility (within the inter-assay variability) to tenofovir alafenamide. HBV isolates expressing the rtA181T, rtA181V, or rtN236T single substitutions associated with resistance to adefovir also had less than 2-fold changes in EC50 values; however, the HBV isolate expressing the rtA181V plus rtN236T double substitutions exhibited reduced susceptibility (3.7-fold) to tenofovir alafenamide. The clinical relevance of these substitutions is not known.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Since tenofovir alafenamide is rapidly converted to tenofovir and a lower tenofovir exposure in rats and mice was observed after tenofovir alafenamide administration compared to tenofovir disoproxil fumarate administration,
carcinogenicity studies were conducted only with tenofovir disoproxil fumarate. Long-term oral carcinogenicity studies of tenofovir disoproxil fumarate in mice and rats were carried out at exposures up to approximately 10 times (mice) and 4 times (rats) those observed in humans at the 300 mg therapeutic dose of tenofovir disoproxil fumarate for chronic hepatitis B. The tenofovir exposure in these studies was approximately 151 times (mice) and 50 times (rat) those observed in humans after administration of VEMLIDY treatment. At the high dose in female mice, liver adenomas were increased at tenofovir exposures approximately 151 times those observed after VEMLIDY administration in humans. In rats, the study was negative for carcinogenic findings. Tenofovir alafenamide was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or rat micronucleus assays. There were no effects on fertility, mating performance or early embryonic development when tenofovir alafenamide was administered to male rats at a dose equivalent to 155 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 14 days prior to mating through Day 7 of gestation.

13.2 Animal Toxicology and/or Pharmacology

Minimal to slight infiltration of mononuclear cells in the posterior uvea was observed in dogs with similar severity after three- and nine-month administration of tenofovir alafenamide; reversibility was seen after a three month recovery period. At the NOAEL for eye toxicity, the systemic exposure in dogs was 5 (tenofovir alafenamide) and 14 (tenofovir) times the exposure seen in humans at the recommended daily VEMLIDY dosage.

14 CLINICAL STUDIES

14.1 Clinical Trials in Adults with Chronic Hepatitis B Virus Infection and Compensated Liver Disease
The efficacy and safety of VEMLIDY® in the treatment of adults with chronic hepatitis B virus infection with compensated liver disease are based on 48-week data from two randomized, double-blind, active-controlled studies, Study 108 (N=425) and Study 110 (N=873). In both studies, besides study treatment, patients were not allowed to receive other nucleosides, nucleotides, or interferon.

In Study 108, HBeAg-negative treatment-naïve and treatment-experienced subjects with compensated liver disease (no evidence of ascites, hepatic encephalopathy, variceal bleeding, INR <1.5x ULN, total bilirubin <2.5x ULN, and albumin >3.0 mg/dL) 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 for 48 weeks. The mean age was 46 years, 61% were male, 72% were Asian, 25% were White, 2% were Black, and 1% were other races. 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 subjects had a history of cirrhosis.

In Study 110, HBeAg-positive treatment-naïve and treatment-experienced subjects with compensated liver disease 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 for 48 weeks. The mean age was 38 years, 64% were male, 82% were Asian, 17% were White, and 1% were Black or other races. 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 subjects had a history of cirrhosis.
In both studies, randomization was stratified on prior treatment history (nucleoside naïve or experienced) and baseline HBV DNA (<7, ≥7 to <8, and ≥8 log10 IU/mL in Study 108; and <8 and ≥8 log10 IU/mL in Study 110). The efficacy endpoint in both trials was the proportion of subjects with plasma HBV DNA levels below 29 IU/mL at Week 48. Additional efficacy endpoints include the proportion of subjects with ALT normalization, HBsAg loss and seroconversion, and HBeAg loss and seroconversion in Study 110. Treatment outcomes of Studies 108 and 110 at Week 48 are presented in Table 9 and Table 10.
Table 9  Studies 108 and 110: HBV DNA Virologic Outcome at Week 48a in Patients with Chronic HBV Infection and Compensated Liver Disease

<table>
<thead>
<tr>
<th></th>
<th>Study 108 (HBeAg-Negative)</th>
<th>Study 110 (HBeAg-Positive)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VEMLIDY (N=285)</td>
<td>VEMLIDY (N=581)</td>
</tr>
<tr>
<td></td>
<td>Tenofovir Disoproxil Fumarate (N=140)</td>
<td>Tenofovir Disoproxil Fumarate (N=292)</td>
</tr>
<tr>
<td>HBV DNA &lt;29 IU/mL</td>
<td>94%</td>
<td>93%</td>
</tr>
<tr>
<td>Treatment Differenceb</td>
<td>1.8% (95% CI = -3.6% to 7.2%)</td>
<td>-3.6% (95% CI = -9.8% to 2.6%)</td>
</tr>
<tr>
<td>HBV DNA ≥ 29 IU/mL</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Baseline HBV DNA &lt;7 log10 IU/mL</td>
<td>96% (221/230)</td>
<td>92% (107/116)</td>
</tr>
<tr>
<td></td>
<td>85% (47/55)</td>
<td>96% (23/24)</td>
</tr>
<tr>
<td>Baseline HBV DNA ≥7 log10 IU/mL</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Baseline HBV DNA &lt;8 log10 IU/mL</td>
<td>N/A</td>
<td>82% (254/309)</td>
</tr>
<tr>
<td></td>
<td>43% (117/272)</td>
<td>82% (123/150)</td>
</tr>
<tr>
<td></td>
<td>51% (72/142)</td>
<td>57% (39/69)</td>
</tr>
<tr>
<td>Nucleoside Naïvec</td>
<td>94% (212/225)</td>
<td>93% (102/110)</td>
</tr>
<tr>
<td></td>
<td>93% (56/60)</td>
<td>93% (28/30)</td>
</tr>
<tr>
<td>Nucleoside Experienced</td>
<td>68% (302/444)</td>
<td>50% (69/137)</td>
</tr>
<tr>
<td></td>
<td>70% (156/223)</td>
<td>77% (39/69)</td>
</tr>
<tr>
<td>No Virologic Data at</td>
<td>4%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Gilead Sciences 69
Week 48<sup>d</sup>

Missing = failure analysis

Adjusted by baseline plasma HBV DNA categories and oral antiviral treatment status strata.

Treatment-naïve subjects received <12 weeks of oral antiviral treatment with any nucleoside or nucleotide analog including TDF or VEMLIDY.

Includes subjects who discontinued due to lack of efficacy, adverse event or death, for reasons other than an AE, death or lack or loss of efficacy, e.g., withdrew consent, loss to follow-up, etc., or missing data during Week 48 window but still on study drug.

In Study 108, the proportion of subjects with cirrhosis who achieved HBV DNA <29 IU/mL at Week 48 was 92% (22/24) in the VEMLIDY group and 93% (13/14) in the TDF group. The corresponding proportions in Study 110 were 63% (26/41) and 67% (16/24) in the VEMLIDY and TDF groups, respectively.
### Table 10  Additional Efficacy Parameters at Week 48

<table>
<thead>
<tr>
<th>Study 108 (HBeAg-Negative)</th>
<th>Study 110 (HBeAg-Positive)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEMLIDY (N=285)</td>
<td>VEMLIDY (N=581)</td>
</tr>
<tr>
<td>Tenofovir Disoproxil Fumarate (N=140)</td>
<td>Tenofovir Disoproxil Fumarate (N=292)</td>
</tr>
</tbody>
</table>

#### ALT
- Normalized ALT (Central Lab)<sup>b</sup>  
  - Study 108: 83%  
  - Study 110: 75%  
  - Study 110 (HBeAg-Positive): 72%  
  - Study 110 (HBeAg-Negative): 67%
- Normalized ALT (AASLD)<sup>c</sup>  
  - Study 108: 50%  
  - Study 110: 32%  
  - Study 110 (HBeAg-Positive): 45%  
  - Study 110 (HBeAg-Negative): 36%

#### Serology
- HBeAg Loss / Seroconversion<sup>d</sup>  
  - Study 108: N/A  
  - Study 110: N/A  
  - Study 110 (HBeAg-Positive): 14% / 10%  
  - Study 110 (HBeAg-Negative): 12% / 8%
- HBsAg Loss / Seroconversion  
  - Study 108: 0 / 0  
  - Study 110: 0 / 0  
  - Study 110 (HBeAg-Positive): 1% / 1%  
  - Study 110 (HBeAg-Negative): <1% / 0%

N/A = not applicable

The population used for analysis of ALT normalization included only subjects with ALT above upper limit of normal (ULN) of the central laboratory range (>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) at baseline.

The population used for analysis of ALT normalization included only subjects 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.

The population used for serology analysis included only subjects with antigen (HBeAg) positive and anti-body (HBeAb) negative or missing at baseline.

### 16  HOW SUPPLIED/STORAGE AND HANDLING

Gilead Sciences
VEMLIDY tablets containing 25 mg of tenofovir alafenamide are yellow, round, film-coated, debossed with “GSI” on one side and “25” on the other side. Each bottle contains 30 tablets (NDC 61958-2301-1), a silica gel desiccant, polyester coil, and is closed with a child-resistant closure.
Store below 30 °C (86 °F).
Keep container tightly closed.
Dispense only in original container.

17 PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Patient Information).

Lactic Acidosis and Severe Hepatomegaly
Advise patients that lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with use of drugs similar to VEMLIDY. Advise patients to contact their healthcare provider immediately and stop VEMLIDY if they develop clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity [see Warnings and Precautions (5.1)].

Severe Acute Exacerbation of Hepatitis after Discontinuation of Treatment
Inform patients that discontinuation of anti-hepatitis B therapy, including VEMLIDY, may result in severe acute exacerbations of hepatitis B. Advise the patient to not discontinue VEMLIDY without first informing their healthcare provider [see Warnings and Precautions (5.2)].

Risk of Development of HIV-1 Resistance in Patients with HIV-1 Coinfection
Inform patients that if they have or develop HIV infection and are not receiving effective HIV treatment, VEMLIDY may increase the risk of development of resistance to HIV medication [see Dosage and Administration (2.1) and Warnings and Precautions (5.3)].

New Onset or Worsening Renal Impairment
Advise patients that renal impairment, including cases of acute renal failure, has been reported in association with the use of tenofovir prodrugs [see Warnings and Precautions (5.4)].
Drug Interactions
Advise patients to report to their healthcare provider the use of any other prescription or non-prescription medication or herbal products including St. John’s wort, as VEMLIDY may interact with other drugs [see Drug Interactions (7)].

Missed Dosage
Inform patients that it is important to take VEMLIDY on a regular dosing schedule with food and to avoid missing doses, as it can result in development of resistance [see Dosage and Administration (2.2)].

Pregnancy Registry
Inform patients that there is an antiretroviral pregnancy registry to monitor fetal outcomes of pregnant women exposed to VEMLIDY [see Use in Specific Populations (8.1)].

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Patient Information

VEMLIDY® (VEM-lih-dee)
(tenofovir alafenamide)
tablets

Read this Patient Information before you start taking VEMLIDY and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is the most important information I should know about VEMLIDY?

VEMLIDY can cause serious side effects, including:

• **Build-up of lactic acid in your blood (lactic acidosis).** Lactic acidosis may happen in some people who take VEMLIDY or similar medicines. Lactic acidosis is a serious medical emergency that can lead to death.

  Lactic acidosis can be hard to identify early, because the symptoms could seem like symptoms of other health problems. **Call your healthcare provider right away if you get any of the following symptoms which could be signs of lactic acidosis:**
  
  - feel very weak or tired
  - have unusual (not normal) muscle pain
  - have trouble breathing
  - have stomach pain with nausea or vomiting
  - feel cold, especially in your arms and legs
  - feel dizzy or lightheaded
  - have a fast or irregular heartbeat

• **Severe liver problems.** Severe liver problems may happen in people who take VEMLIDY. In some cases, these liver problems can lead to death. Your liver may become large (hepatomegaly) and you may develop fat in your liver (steatosis).

  **Call your healthcare provider right away if you get any of the following symptoms of liver problems:**
  
  - your skin or the white part of your eyes turns yellow (jaundice)
  - dark “tea-colored” urine
  - light-colored bowel movements (stools)
  - loss of appetite
  - nausea
  - pain, aching, or tenderness in the right side of your stomach area

  **You may be more likely to get lactic acidosis or severe liver problems if you are female, very overweight (obese), or have been taking VEMLIDY or a similar medicine for a long time.**

• **Worsening of hepatitis B infection.** Your hepatitis B (HBV) infection may become worse (flare-up) if you take VEMLIDY and then stop taking it. A “flare-up” is when your HBV
infection suddenly returns in a worse way than before.
  o **Do not** run out of VEMILIDY. Refill your prescription or talk to your healthcare provider before your VEMILIDY is all gone.
  o **Do not** stop taking VEMILIDY without first talking to your healthcare provider.
  o If you stop taking VEMILIDY, your healthcare provider will need to check your health often and do blood tests regularly for several months to check your HBV infection. Tell your healthcare provider about any new or unusual symptoms you may have after you stop taking VEMILIDY.

_for more information about side effects, see the section “what are the possible side effects of VEMILIDY?”_

**What is VEMILIDY?**

VEMILIDY is a prescription medicine used to treat chronic (long-lasting) hepatitis B virus (HBV) in adults with stable (compensated) liver disease.

- VEMILIDY may lower the amount of HBV in your body.
- VEMILIDY may improve the condition of your liver.

It is not known if VEMILIDY is safe and effective in children under 18 years of age.

**What should I tell my healthcare provider before taking VEMILIDY?**

Before you take VEMILIDY, tell your healthcare provider about all of your medical conditions, including if you:

- have HIV-1 infection. Your healthcare provider may test you for HIV infection before starting VEMILIDY. If you have HIV and take VEMILIDY, the HIV virus may develop resistance and become harder to treat.
- have end stage renal disease (ESRD).
- are pregnant or plan to become pregnant. It is not known if VEMILIDY will harm your unborn baby. Tell your healthcare provider if you become pregnant during treatment with VEMILIDY.

**Pregnancy Registry:** There is a pregnancy registry for women who take antiviral medicines during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk with your healthcare provider about how you can take part in this registry.

- are breastfeeding or plan to breastfeed. It is not known if VEMILIDY passes into your breast milk. Talk with your healthcare provider about the best way to feed your baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Some medicines may affect how VEMILIDY works.

- Keep a list of your medicines and show it to your healthcare provider and pharmacist when
you get a new medicine. You can ask your healthcare provider or pharmacist for a list of medicines that interact with VEMLIDY.

- **Do not start a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take VEMLIDY with other medicines.

### How should I take VEMLIDY?

- Take VEMLIDY exactly as your healthcare provider tells you to take it.
- Take VEMLIDY 1 time each day.
- Take VEMLIDY with food.
- Do not change your dose or stop taking VEMLIDY without first talking with your healthcare provider. Stay under a healthcare provider’s care when taking VEMLIDY.
- **Do not miss a dose of VEMLIDY.**
- If you take too much VEMLIDY, call your healthcare provider or go to the nearest hospital emergency room right away.
- When your VEMLIDY supply starts to run low, get more from your healthcare provider or pharmacy. This is very important because your HBV infection may get worse (flare-up) if you stop taking VEMLIDY.

### What are the possible side effects of VEMLIDY?

VEMLIDY may cause serious side effects, including:

- **See “What is the most important information I should know about VEMLIDY?”**
- **New or worse kidney problems, including kidney failure.** Your healthcare provider may do blood and urine tests to check your kidneys before you start and while you are taking VEMLIDY. Your healthcare provider may tell you to stop taking VEMLIDY if you develop new or worse kidney problems.

The most common side effects of VEMLIDY are:

- headache
- stomach pain
- tiredness
- cough
- nausea
- back pain

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of VEMLIDY. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

### How should I store VEMLIDY?

- Store VEMLIDY below 86 °F (30 °C).
- Keep VEMLIDY in its original container.
• Keep the container tightly closed.

Keep VEMLIDY and all medicines out of reach of children.

General information about the safe and effective use of VEMLIDY.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use VEMLIDY for a condition for which it was not prescribed. Do not give VEMLIDY to other people, even if they have the same symptoms you have. It may harm them. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about VEMLIDY that is written for health professionals.

What are the ingredients in VEMLIDY?

Active ingredients: tenofovir alafenamide

Inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. The tablets are film-coated with a coating material containing: iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

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208464-GS-000

For more information, call 1-800-445-3235 or go to www.VEMLIDY.com.

This Patient Information has been approved by the U.S. Food and Drug Administration

Issued: 11/2016