NEW ZEALAND DATA SHEET

1 VEMLIDY (TENOFOVIR ALAFENAMIDE 25 MG) TABLETS

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tenofovir alafenamide 25 mg.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

VEMLIDY tablets are yellow, round, film-coated, debossed with “GSI” on one side and “25” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

VEMLIDY is indicated for the treatment of chronic hepatitis B in adults.

4.2 Dose and method of administration

The recommended dose of VEMLIDY is one tablet once daily, with or without food.

Special populations

Children and Adolescents up to 18 Years of Age
No data are available on which to make a dose recommendation for patients younger than 18 years.

Elderly
No dose adjustment is required in patients age of 65 years and older. In clinical trials, 89 HBV-infected patients aged 65 years and over received VEMLIDY. No differences in safety or efficacy have been observed between elderly patients and those between 18 and less than 65 years of age (see Section 5.2).

Renal Impairment
No dose adjustment of VEMLIDY is required in patients with renal impairment. VEMLIDY is not recommended in patients with end stage renal disease (estimated creatinine clearance below 15 mL per minute) (see Section 5.2).

Hepatic Impairment
No dose adjustment of VEMLIDY is required in patients with hepatic impairment (see Section 5.2).

4.3 Contraindications
VEMLIDY tablets are contraindicated in patients with known hypersensitivity to the active substance or to any other component of the tablets listed in section 6.1.

4.4 Special warnings and precautions for use

Exacerbation of Hepatitis after Discontinuation of Treatment

Discontinuation of anti-hepatitis B therapy, including VEMLIDY, may be associated with severe acute exacerbations of hepatitis. 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. In patients with advanced liver disease or cirrhosis, discontinuation of anti-hepatitis B therapy is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

Hepatitis B and HIV Coinfection

Due to the risk of development of HIV-1 resistance, VEMLIDY is not recommended for the treatment of HIV-1 infection. The safety and efficacy of VEMLIDY have not been established in patients co-infected 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 co-infected with HIV-1 should be used.

Use with Related Products

VEMLIDY should not be coadministered with products containing tenofovir alafenamide, tenofovir disoproxil fumarate, or adefovir dipivoxil.

Children and Adolescents up to 18 Years of Age
Safety and effectiveness of VEMLIDY in children less than 18 years of age have not been established.

4.5 Interaction with other medicines and other forms of interaction

Interaction studies have only been performed in adults.

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

Medicinal products that may affect tenofovir alafenamide

Tenofovir alafenamide is transported by P-gp and breast cancer resistance protein (BCRP). Medicinal products that are P-gp inducers (e.g., rifampicin, rifabutin, phenobarbital or St. John's wort) are expected to decrease plasma concentrations of tenofovir alafenamide, which may lead to loss of therapeutic effect of Vemlidy. Co-administration of such medicinal products with Vemlidy is not recommended.

Co-administration of Vemlidy with medicinal products that inhibit P-gp and BCRP may increase plasma concentration of tenofovir alafenamide. Vemlidy may be coadministered with P-gp or BCRP inhibitors.

Tenofovir alafenamide is a substrate of OATP1B1 and OATP1B3 *in vitro*. The distribution of tenofovir alafenamide in the body may be affected by the activity of OATP1B1 and/or OATP1B3.

Effect of tenofovir alafenamide on other medicinal products

Tenofovir alafenamide is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 *in vitro*. It is not an inhibitor or inducer of CYP3A *in vivo*.

Tenofovir alafenamide is not an inhibitor of human uridine diphosphate glucuronosyltransferase (UGT) 1A1 *in vitro*. It is not known whether tenofovir alafenamide is an inhibitor of other UGT enzymes.

Drug interaction information for Vemlidy with potential concomitant medicinal products is summarised in Table 1 below (increase is indicated as "↑", decrease as "↓", no change as "↔"; twice daily as "b.i.d.", single dose as "s.d.", once daily as "q.d."; and intravenously as "IV"). The drug interactions described are based on studies conducted with tenofovir alafenamide, or are potential drug interactions that may occur with Vemlidy.

Table 1: Interactions between Vemlidy and other medicinal products

Medicinal product by therapeutic areas	**Effects on drug levels.[a,b] Mean ratio (90% confidence interval) for AUC, C_{max}, C_{min}**	**Recommendation concerning co-administration with Vemlidy**
ANTICONVULSANTS		
Carbamazepine (300 mg orally, b.i.d.) Tenofovir alafenamide[c] (25 mg orally, s.d.)	*Tenofovir alafenamide* ↓ C_{max} 0.43 (0.36, 0.51) ↓ AUC 0.45 (0.40, 0.51) *Tenofovir* ↓ C_{max} 0.70 (0.65, 0.74) ↔ AUC 0.77 (0.74, 0.81)	Increase tenofovir alafenamide dose to two tablets once daily.
Oxcarbazepine Phenobarbital	Interaction not studied. *Expected:* ↓ Tenofovir alafenamide	Co-administration is not recommended.
Phenytoin	Interaction not studied. *Expected:* ↓ Tenofovir alafenamide	Co-administration is not recommended.
Midazolam[d] (2.5 mg orally, s.d.) Tenofovir alafenamide[c] (25 mg orally, q.d.)	*Midazolam* ↔ C_{max} 1.02 (0.92, 1.13) ↔ AUC 1.13 (1.04, 1.23)	No dose adjustment of midazolam (administered orally or IV) is required.

Medicinal product by therapeutic areas	**Effects on drug levels.[a,b] Mean ratio (90% confidence interval) for AUC, C_{max}, C_{min}**	**Recommendation concerning co-administration with Vemlidy**
Midazolam[d] (1 mg IV, s.d.) Tenofovir alafenamide[c] (25 mg orally, q.d.)	*Midazolam* ↔ C_{max} 0.99 (0.89, 1.11) ↔ AUC 1.08 (1.04, 1.14)	
ANTIDEPRESSANTS		
Sertraline (50 mg orally, s.d.) Tenofovir alafenamide[e] (10 mg orally, q.d.)	*Tenofovir alafenamide* ↔ C_{max} 1.00 (0.86, 1.16) ↔ AUC 0.96 (0.89, 1.03) *Tenofovir* ↔ C_{max} 1.10 (1.00, 1.21) ↔ AUC 1.02 (1.00, 1.04) ↔ C_{min} 1.01 (0.99, 1.03)	No dose adjustment of Vemlidy or sertraline is required.
Sertraline (50 mg orally, s.d.) Tenofovir alafenamide[e] (10 mg orally, q.d.)	*Sertraline* ↔ C_{max} 1.14 (0.94, 1.38) ↔ AUC 0.93 (0.77, 1.13)	
ANTIFUNGALS		
Itraconazole Ketoconazole	Interaction not studied. *Expected:* ↑ Tenofovir alafenamide, not clinically relevant.	No dose adjustment of Vemlidy is required.
ANTIMYCOBACTERIALS		
Rifampicin Rifapentine	Interaction not studied. *Expected:* ↓ Tenofovir alafenamide	Co-administration is not recommended.
Rifabutin	Interaction not studied. *Expected:* ↓ Tenofovir alafenamide	Co-administration is not recommended.
HCV ANTIVIRAL AGENTS		
Sofosbuvir (400 mg orally, q.d.)	Interaction not studied. *Expected:* ↔ Sofosbuvir ↔ GS-331007	No dose adjustment of Vemlidy or sofosbuvir is required.

Medicinal product by therapeutic areas	**Effects on drug levels.[a,b] Mean ratio (90% confidence interval) for AUC, C_{max}, C_{min}**	**Recommendation concerning co-administration with Vemlidy**
Ledipasvir/sofosbuvir (90 mg/400 mg orally, q.d.) Tenofovir alafenamide[f] (25 mg orally, q.d.)	*Ledipasvir* ↔ C_{max} 1.01 (0.97, 1.05) ↔ AUC 1.02 (0.97, 1.06) ↔ C_{min} 1.02 (0.98, 1.07) *Sofosbuvir* ↔ C_{max} 0.96 (0.89, 1.04) ↔ AUC 1.05 (1.01, 1.09) *GS-331007*[g] ↔ C_{max} 1.08 (1.05, 1.11) ↔ AUC 1.08 (1.06, 1.10) ↔ C_{min} 1.10 (1.07, 1.12) *Tenofovir alafenamide* ↔ C_{max} 1.03 (0.94, 1.14) ↔ AUC 1.32 (1.25, 1.40) *Tenofovir* ↑ C_{max} 1.62 (1.56, 1.68) ↑ AUC 1.75 (1.69, 1.81) ↑ C_{min} 1.85 (1.78, 1.92)	No dose adjustment of Vemlidy or ledipasvir/sofosbuvir is required.
Sofosbuvir/velpatasvir (400 mg/100 mg orally, q.d.)	Interaction not studied. *Expected:* ↔ Sofosbuvir ↔ GS-331007 ↔ Velpatasvir ↑ Tenofovir alafenamide	No dose adjustment of Vemlidy or sofosbuvir/velpatasvir is required.

Medicinal product by therapeutic areas	**Effects on drug levels.[a,b] Mean ratio (90% confidence interval) for AUC, C_{max}, C_{min}**	**Recommendation concerning co-administration with Vemlidy**
Sofosbuvir/velpatasvir/ voxilaprevir (400 mg/100 mg/ 100 mg + 100 mg[h] orally, q.d.) Tenofovir alafenamide[f] (25 mg orally, q.d.)	*Sofosbuvir* ↔ C_{max} 0.95 (0.86, 1.05) ↔ AUC 1.01 (0.97, 1.06) *GS-331007[g]* ↔ C_{max} 1.02 (0.98, 1.06) ↔ AUC 1.04 (1.01, 1.06) *Velpatasvir* ↔ C_{max} 1.05 (0.96, 1.16) ↔ AUC 1.01 (0.94, 1.07) ↔ C_{min} 1.01 (0.95, 1.09) *Voxilaprevir* ↔ C_{max} 0.96 (0.84, 1.11) ↔ AUC 0.94 (0.84, 1.05) ↔ C_{min} 1.02 (0.92, 1.12) *Tenofovir alafenamide* ↑ C_{max} 1.32 (1.17, 1.48) ↑ AUC 1.52 (1.43, 1.61)	No dose adjustment of Vemlidy or sofosbuvir/velpatasvir/voxilaprevir is required.
HERBAL SUPPLEMENTS		
St. John's wort *(hypericum perforatum)*	Interaction not studied. *Expected:* ↓ Tenofovir alafenamide	Co-administration is not recommended.
ORAL CONTRACEPTIVES		
Norgestimate (0.180 mg/0.215 mg/ 0.250 mg orally, q.d.) Ethinyl estradiol (0.025 mg orally, q.d.) Tenofovir alafenamide[c] (25 mg orally, q.d.)	*Norelgestromin* ↔ C_{max} 1.17 (1.07, 1.26) ↔ AUC 1.12 (1.07, 1.17) ↔ C_{min} 1.16 (1.08, 1.24) *Norgestrel* ↔ C_{max} 1.10 (1.02, 1.18) ↔ AUC 1.09 (1.01, 1.18) ↔ C_{min} 1.11 (1.03, 1.20) *Ethinyl estradiol* ↔ C_{max} 1.22 (1.15, 1.29) ↔ AUC 1.11 (1.07, 1.16) ↔ C_{min} 1.02 (0.93, 1.12)	No dose adjustment of Vemlidy or norgestimate/ethinyl estradiol is required.

a. All interaction studies are conducted in healthy volunteers
b. All No Effect Boundaries are 70% - 143%
c. Study conducted with emtricitabine/tenofovir alafenamide fixed-dose combination tablet
d. A sensitive CYP3A4 substrate
e. Study conducted with elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fixed-dose combination tablet
f. Study conducted with emtricitabine/rilpivirine/tenofovir alafenamide fixed-dose combination tablet
g. The predominant circulating nucleoside metabolite of sofosbuvir
h. Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled studies with VEMLIDY in pregnant women. VEMLIDY should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Studies in animals have shown no evidence of teratogenicity (rats and rabbits) or an effect on reproductive function (rats) due to tenofovir alafenamide.

Embryonic fetal development studies performed in rats and rabbits revealed no evidence of impaired fertility or harm to the fetus. The embryo-fetal NOAELs 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 and 85 times higher than human tenofovir exposures at the recommended daily doses, respectively.

Breast-feeding

In animal studies it has been shown that tenofovir is secreted into milk. It is not known whether tenofovir alafenamide is secreted in human milk.

Fertility

No human data on the effect of VEMLIDY on fertility are available. 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 to Day 7 of gestation.

4.7 Effects on ability to drive and use machines

No studies on the effects of VEMLIDY on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Clinical Trials in Adult Patients with Chronic Hepatitis B

The safety assessment of VEMLIDY was based on pooled data to Week 96 data analysis from 1298 patients in two randomised, double-blind, active-controlled trials, Study 108 and Study 110, in adult patients with chronic hepatitis B. A total of 866 patients received one tablet of VEMLIDY once daily (see Section 5.1). Further safety assessment was based on pooled data from Studies 108 and 110 from patients who continued to receive their original blinded treatment through Week 120 and additionally from patients who received open-label VEMLIDY from Week 96 through Week 120.

Based on the Week 96 analysis, the most common adverse reactions (all Grades) reported in at least 10% of patients in the VEMLIDY group was headache. The proportion of patients who discontinued treatment with VEMLIDY or VIREAD due to adverse reactions, regardless of severity, was 1.5% and 0.9%, respectively. Table 2 displays the frequency of the adverse reactions (all Grades) greater than or equal to 5% in the VEMLIDY group.

Table 2 Adverse Reactions[a] (All Grades) Reported in ≥ 5% of Patients Receiving VEMLIDY in Studies 108 and 110 (Week 96 analysis)[b]

	VEMLIDY (N=866)	VIREAD (N=432)
Headache	12%	10%
Abdominal pain[c]	9%	6%
Cough	8%	8%
Back pain	6%	6%
Fatigue	6%	5%
Nausea	5%	5%
Diarrhoea	5%	5%
Dyspepsia	5%	5%

a.Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.
b.Double-blind phase
c.Grouped term including abdominal pain and abdominal pain upper.

Additional adverse reactions occurring in greater than 1% to less than 5% of patients in Studies 108 and 110 included vomiting, rash, and flatulence.

The safety profile of VEMLIDY in patients who continued to receive blinded treatment to Week 120 was similar to that at Week 96. The safety profile of VEMLIDY in patients who remained on VEMLIDY in the open-label phase to Week 120 was similar to that in patients who switched from VIREAD to VEMLIDY at Week 96.

Virologically Suppressed Patients

No additional adverse reactions to VEMLIDY were identified through Week 48 in a double-blind, randomized, active-controlled Study (GS-US-320-4018) in virologically suppressed subjects who switched from VIREAD to VEMLIDY (N=243).

Patients with Renal and/or Hepatic Impairment

No additional adverse reactions to VEMLIDY were identified through Week 24 in an open-label clinical study (GS-US-320-4035) of virologically suppressed patients with moderate to severe renal impairment (eGFR by Cockcroft-Gault method 15 to 59 mL/min; N=78), end stage renal disease (ESRD) (eGFR <15 mL/min) on hemodialysis (N=15), or moderate to severe hepatic impairment (N=31) who switched from another antiviral regimen to VEMLIDY.

Tabulated summary of adverse reactions

The following adverse drug reactions have been identified with tenofovir alafenamide in patients with chronic hepatitis B (Table 3). The adverse reactions are listed below by body system organ class and frequency based on the Week 96 analysis. Frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) or very rare (< 1/10,000).

Table 3: Adverse drug reactions identified with tenofovir alafenamide

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

Post marketing experience

In addition to adverse reactions from clinical studies, the following adverse reactions were identified during postapproval use of products containing tenofovir alafenamide (TAF). Because these reactions were reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

SKIN AND SUBCUTANEOUS TISSUE DISORDERS

Angioedema, urticaria

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions:
https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

If overdose occurs the patient must 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.

Limited clinical experience is available at doses higher than the therapeutic dose of tenofovir alafenamide. A dose of 120 mg tenofovir alafenamide (4.8 times the dose in VEMLIDY) was administered once daily for 28 days to 10 patients with chronic hepatitis B; no serious adverse reactions were reported. The effects of higher doses are unknown. Tenofovir is efficiently removed by haemodialysis with an extraction coefficient of approximately 54%.

For information on the management of overdose, contact the National Poisons Centre on 0800 764 766.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiviral for systemic use, nucleoside and nucleotide reverse transcriptase inhibitors; ATC code: J05AF13

Mechanism of action

Tenofovir alafenamide is a phosphonamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analogue). Tenofovir alafenamide enters primary hepatocytes by passive diffusion with some contribution by hepatic uptake transporters, OATP1B1 and OATP1B3. Tenofovir alafenamide is primarily hydrolysed by carboxylesterase 1 in primary hepatocytes, and by cathepsin A in peripheral blood mononuclear cells (PBMCs) and other HIV target cells. Intracellular tenofovir is subsequently phosphorylated to the pharmacologically active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HBV replication through incorporation into viral DNA by the HBV reverse transcriptase, which results in DNA chain-termination.

Tenofovir has activity that is specific to hepatitis B virus and human immunodeficiency virus (HIV-1 and HIV-2). Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there is no evidence of mitochondrial toxicity in vitro based on several assays including mitochondrial DNA analyses.

Antiviral activity

The antiviral activity of tenofovir alafenamide was assessed in HepG2 cells against a panel of HBV clinical isolates representing genotypes A-H. The EC_{50} (50% effective concentration) values for tenofovir alafenamide ranged from 34.7 to 134.4 nM, with an overall mean EC_{50} of 86.6 nM. The CC_{50} (50% cytotoxicity concentration) in HepG2 cells was > 44400 nM. In cell culture combination antiviral activity studies of tenofovir with the nucleoside reverse transcriptase inhibitors emtricitabine, entecavir, lamivudine, and telbivudine, no antagonistic activity was observed.

Resistance

Sequence analysis was performed on paired baseline and on-treatment HBV isolates for patients who either experienced virologic breakthrough (2 consecutive visits with HBV DNA ≥ 69 IU/mL after having been < 69 IU/mL, or 1.0-log_{10} or greater increase in HBV DNA from nadir) or patients with HBV DNA ≥ 69 IU/mL at Week 48 or Week 96 or at early discontinuation at or after Week 24.

In a pooled analysis of treatment-naïve and treatment-experienced patients receiving VEMLIDY in Study 108 and Study 110, 27 and 87 patients qualified for resistance analyse at Week 48 and Week 96, respectively. No amino acid substitutions associated with resistance to VEMLIDY were identified in these isolates (genotypic and phenotypic analyses).

In virologically suppressed patients receiving VEMLIDY in Study 4018, no patient experienced a virologic blip (one visit with HBV DNA ≥ 69 IU/mL), virologic breakthrough or persistent viremia during treatment, and 0 of 243 (0.0%) patients qualified for resistance analysis through 48 weeks of VEMLIDY treatment.

In virologically suppressed patients with renal impairment (Part A, Cohorts 1 and 2) and hepatic impairment (Part B) receiving VEMLIDY in Study 4035, no patient experienced a virologic blip, virologic breakthrough, or persistent viremia during treatment, and no patient qualified for virologic resistance analysis through 24 weeks of VEMLIDY treatment.

Cross-resistance
The antiviral activity of tenofovir alafenamide was evaluated against a panel of isolates containing nucleos(t)ide reverse transcriptase inhibitor mutations in HepG2 cells. HBV isolates expressing the rtV173L, rtL180M, and rtM204V/I substitutions associated with resistance to lamivudine remained susceptible to tenofovir alafenamide (< 2-fold change in EC_{50}). HBV isolates expressing the rtL180M, rtM204V plus rtT184G, rtS202G, or rtM250V substitutions associated with resistance to entecavir remained susceptible to tenofovir alafenamide. HBV isolates expressing the rtA181T, rtA181V, or rtN236T single substitutions associated with resistance to adefovir remained susceptible to tenofovir alafenamide; however, the HBV isolate expressing rtA181V plus rtN236T exhibited reduced susceptibility to tenofovir alafenamide (3.7-fold change in EC50). The clinical relevance of these substitutions is not known.

Effects on the electrocardiogram

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

Clinical Data

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

The efficacy and safety of VEMLIDY in virologically suppressed adults with chronic hepatitis B are based on 48-week data from a randomized, double-blind, active-controlled study, GS-US-320-4018 ("Study 4018"). The efficacy and safety of VEMLIDY in virologically suppressed patients with chronic hepatitis B and moderate to severe renal impairment or ESRD on hemodialysis is based on 24-week data from an open-label study, GS-US-320-4035 ("Study 4035"), Part A. The efficacy and safety of VEMLIDY in virologically suppressed patients with chronic hepatitis B and moderate to severe hepatic impairment is based on 24-week data from an open-label study, Study 4035, Part B.

Adult Patients with Compensated Liver Disease

In Study 108, HBeAg-negative treatment-naïve and treatment-experienced patients with compensated liver function were randomised in a 2:1 ratio to receive VEMLIDY (N=285) once daily or VIREAD (tenofovir disoproxil fumarate 300 mg; N=140) once daily. The mean age was 46 years, 61% were male, 72% were Asian, and 25% were White. 24%, 38%, and 31% had HBV genotype B, C, and D, respectively. 21% were treatment experienced (previous treatment with oral antivirals, including entecavir (N=41), lamivudine (N=42), tenofovir disoproxil fumarate (N=21), or other (N=18)). At baseline, mean plasma HBV DNA was 5.8 $\log_{10}$ IU/mL, mean serum ALT was 94 U/L, and 9% of patients had a history of cirrhosis.

In Study 110, HBeAg-positive treatment-naïve and treatment-experienced patients with compensated liver function were randomised in a 2:1 ratio to receive VEMLIDY (N=581) once daily or VIREAD (300 mg; N=292) once daily. The mean age was 38 years, 64% were male, 82% were Asian, and 17% were White. 17%, 52%, and 23% had HBV genotype B, C, and D, respectively. 26% were treatment experienced (previous treatment with oral antivirals, including adefovir (N=42), entecavir (N=117), lamivudine (N=84), telbivudine (N=25), tenofovir disoproxil fumarate (N=70), or other (n=17)). At baseline, mean plasma HBV DNA was 7.6 $\log_{10}$ IU/mL, mean serum ALT was 120 U/L, and 7% of patients had a history of cirrhosis.

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

Treatment outcomes of Studies 108 and 110 at Weeks 48 and 96 are presented in Table 4 and Table 5.

Table 4 HBV DNA Efficacy Parameters at Weeks 48[a] and 96 [a]

	Week 48				Week 96			
	Study 108 (HBeAg-Negative)		Study 110 (HBeAg-Positive)		Study 108 (HBeAg-Negative)		Study 110 (HBeAg-Positive)	
	VEMLIDY (N=285)	**VIREAD** (N=140)	**VEMLIDY** (N=581)	**VIREAD** (N=292)	**VEMLIDY** (N=285)	**VIREAD** (N=140)	**VEMLIDY** (N=581)	**VIREAD** (N=292)
HBV DNA < 29 IU/mL	94%	93%	64%	67%	90%	91%	73%	75%
Treatment Difference[b]	1.8% (95% CI = -3.6% to 7.2%)		-3.6% (95% CI = -9.8% to 2.6%)		-0.6% (95% CI = -7.0% to 5.8%)		-2.2% (95% CI = -8.3% to 3.9%)	
HBV DNA ≥ 29 IU/mL	2%	3%	31%	30%	2%	2%	18%	14%
No Virologic Data at Week 48 or 96	4%	4%	5%	3%	8%	7%	9%	11%
Discontinued Study Drug Due to Lack of Efficacy	0	0	<1%	0	0	0	<1%	<1%
Discontinued Study Drug Due to AE or Death	1%	1%	1%	1%	2%	1%	2%	1%
Discontinued Study Drug Due to Other Reasons[c]	2%	3%	3%	2%	5%	6%	7%	8%
Missing Data During Window but on Study Drug	<1%	1%	<1%	0	1%	0	<1%	1%

a. Missing = failure analysis
b. Adjusted by baseline plasma HBV DNA categories and oral antiviral treatment status strata.
c. Includes patients who discontinued for reasons other than an AE, death or lack or loss of efficacy, e.g., withdrew consent, loss to follow-up, etc.

VEMLIDY met the non-inferiority criteria in achieving HBV DNA less than 29 IU/mL when compared to VIREAD at Week 48. At Week 96, similar efficacy was demonstrated with VEMLIDY compared to VIREAD..

Table 5 Additional Efficacy Parameters at Weeks 48[a] and 96[a]

	Week 48				Week 96			
	Study 108 (HBeAg-Negative)		Study 110 (HBeAg-Positive)		Study 108 (HBeAg-Negative)		Study 110 (HBeAg-Positive)	
	VEMLIDY	VIREAD	VEMLIDY	VIREAD	VEMLIDY	VIREAD	VEMLIDY	VIREAD
ALT Normalised ALT (Central Lab)[b]	83% (196/236)	75% (91/121)	72% (384/537)	67% (179/268)	81% (191/236)	71% (86/121)	75% (405/537)	68% (181/268)
Normalised ALT (AASLD)[c]	50% (137/276)	32% (44/138)	45% (257/572)	36% (105/290)	50% (139/276)	40% (55/138)	52% (299/572)	42%
Serology HBeAg Loss / Seroconversion[d]	N/A	N/A	14% (78/565)/ 10% (58/565)	12% (34/285)/ 8% (23/285)	N/A	N/A	22% (123/565) / 18% (99/565)	18% (51/285)/ 12% (35/285)
HBsAg Loss / Seroconversion	0 (0/281) / 0 (0/281)	0 (0/138)/ 0(0/138)	1% (4/576)/ 1% (3/576)	<1% (1/288)/ 0 (0/288)	<1%(1/281) / <1% (1/281)	0 (0/138)/ 0 (0/138)	1% (7/576)/ 1% (6/576)	1% (4/288)/ 0(0/288)

N/A = not applicable

a. Missing = failure analysis

b. The population used for analysis of ALT normalization included only patients with ALT above upper limit of normal (ULN) of the central laboratory range (> 43 U/L males 18 to < 69 years and > 35 U/L males ≥ 69 years; > 34 U/L females 18 to < 69 years and > 32 U/L females ≥ 69 years at baseline.

c. The population used for analysis of ALT normalization included only patients with ALT above ULN of the American Association of the Study of Liver Diseases (AASLD) criteria (> 30 U/L males and > 19 U/L females) at baseline.

d. The population used for serology analysis included only patients with antigen positive and anti-body negative or missing at baseline.

Bone Mineral Density: In a pooled analysis of Studies 108 and 110, the effects of VEMLIDY compared to that of VIREAD on bone mineral density (BMD) change from baseline to Weeks 48 and 96 was assessed by dual-energy X-ray absorptiometry (DXA). As shown in Table 6, in patients with both baseline and Week 48, and with both baseline and Week 96, measurements in the VEMLIDY group and in the VIREAD group, for hip; and in the VEMLIDY group and in the VIREAD group for spine; at Weeks 48 and 96, respectively), there were smaller decreases in BMD in the VEMLIDY group as compared to VIREAD.

Table 6 Measures of Bone Mineral Density in Studies 108 and 110 (Weeks 48 and 96 analyses)[a]

	Week 48			Week 96		
	VEMLIDY	**VIREAD**	**Treatment Difference[b]**	**VEMLIDY**	**VIREAD**	**Treatment Difference**
Hip DXA Analysis	N=807	N=404		N=740	N=369	
Mean Percent Change in BMD	-0.2%	-1.9%	1.7% p < 0.001	-0.3%	-2.5%	2.2% p < 0.001
Patients with Categorical Change: > 3% Decrease in BMD > 3% Increase in BMD	8% 7%	27% 2%	--	14% 9%	39% 3%	--
Patients with No Decrease (≥ zero % change) in BMD	47%	21%	--	48%	17%	--
Lumbar Spine DXA Analysis	N=814	N=407		N=746	N=371	
Mean Percent Change in BMD	-0.6%	-2.4%	1.8% p < 0.001	-0.7%	-2.6%	1.8% p < 0.001
Patients with Categorical Change: > 3% Decrease in BMD > 3% Increase in BMD	20% 11%	38% 3%	--	25% 13%	45% 7%	--
Patients with No Decrease (≥ zero % change) in BMD	41%	22%	--	41%	25%	--

a. Changes are from baseline; based on observed data
b. The clinical significance of these findings has yet to be established

In patients who remained on blinded treatement beyond Week 96 in Studies 108 and 110, mean percentage change in BMD as assessed by DXA in each group at Week 120 was similar to that at Week 96. In the open-phase of Studies 108 and 110, mean percentage change in BMD from Week 96 to Week 120 in patients who remained on VEMLIDY was +0.6% at the lumbar spine and 0% at the total hip, compared to +1.7% at the lumbar spine and +0.6% at the total hip in those who switched from VIREAD to VEMLIDY at Week 96.

Changes in Renal Laboratory Tests

In a pooled analysis of Studies 108 and 110, laboratory tests were performed to compare the effect of VEMLIDY to that of VIREAD on renal laboratory parameters. As shown in Table 7, statistically significant differences were observed between treatment groups for decreases in creatinine clearance, and changes in urine protein to creatinine ratio (UPCR), urine retinol binding protein (RBP) to creatinine ratio, and urine beta-2-microglobulin to creatinine ratio that favored VEMLIDY at Weeks 48 and 96. There were no cases of Fanconi Syndrome or proximal renal tubulopathy (PRT) in either treatment group up to Week 96.

Table 7 Change from Baseline in Renal Laboratory Tests in Studies 108 and 110 (Weeks 48 and 96 analyses)

	Week 48			**Week 96**		
	VEMLIDY (N=836)	**VIREAD (N=432)**	**Treatment Difference**	**VEMLIDY** (N=866)	**VIREAD** (N=432)	**Treatment Difference**
Creatinine Clearance (mL/min)[a,d]	-1.2 (-8.4, 7.5)	-5.4 (-12.0, 3.0)	p<0.001	-1.2 (-9.0, 7.0)	-4.8 (-13.2, 3.0)	p < 0.001
Proteinuria by Urine Dipstick (%)[b]	24.7%	21.4%	p = 0.26	27.8%	25.1%	p = 0.41
Urine Protein to Creatinine Ratio [UPCR] (%)[c]	6%	16.5%	p = 0.01	2.5%	13.8%	p = 0.07
Urine Albumin to Creatinine Ratio [UACR] (%)[c]	6.9%	12.2%	p = 0.073	23.8%	29%	p = 0.2
Urine RBP to Creatinine Ratio[c]	-0.3%	25.1%	p < 0.001	21.2%	55.4%	p < 0.001
Urine Beta-2-Microglobulin to Creatinine Ratio[c]	-3.5%	37.9%	p < 0.001	10.2%	56.5%	p < 0.001
Serum Creatinine (mg/dL)[e]	0.01 ± 0.11	0.02 ± 0.1	-0.02, p = 0.012	0.003 ± 0.09	0.02 ± 0.09	-0.02, p = 0.001
Estimated Glomerular Filtration Rate [eGFR] (mL/min) [a, d]	-1.2	-5.4	p < 0.001	-1.2	-4.8	p < 0.001

a. Calculated with Cockcroft Gault equation (median Q1, Q3).
b. Includes all severity grades (1-3).
c. Median percent change from baseline.
d. Median change from baseline
e. Mean change ± SD.

In patients who remained on blinded treatment beyond Week 96 in Studies 108 and 110, change from baseline in renal laboratory parameter values in each group at Week 120 were similar to those at Week 96. In the open-label phase of Studies 108 and 110, the mean change

(±SD) in serum creatinine from Week 96 to Week 120 was -0.002 (0.10) mg/dL in those who remained on VEMLIDY, compared to -0.008 (0.09) mg/dL in those who switched from VIREAD to VEMLIDY at Week 96. In the open-label phase, the median change in eGFR from Week 96 to Week 120 was -0.6 mL/min in patients who remained on VEMLIDY, compared to +1.8 mL/min patients who switched from VIREAD to VEMLIDY at Week 96.

Changes in Lipid Laboratory Tests

In a pooled analysis of Studies 108 and 110, median changes in fasting lipid parameters from baseline to Week 96 were observed in both treatment groups. In the VEMLIDY group, decreases in median fasting total cholesterol and HDL, and increases in median fasting direct LDL and triglycerides were observed, while the VIREAD group demonstrated reductions in all parameters ($p < 0.001$ for the difference between treatment groups for fasting total cholesterol, direct LDL, HDL, and triglycerides). Median (Q1, Q3) change from baseline at Week 96 in total cholesterol to HDL ratio was 0.3 (-0.1, 0.6) in the VEMLIDY group and 0.2 (-0.1, 0.6) in the VIREAD group ($p = 0.14$ for the difference between treatment groups).

Virologically Suppressed Adult Patients

The efficacy and safety of switching from VIREAD to VEMLIDY were evaluated in a randomized, double-blind, active-controlled study (Study 4018) of virologically suppressed chronic hepatitis B-infected adults (N=488). Patients must have been taking TDF 300 mg once daily for at least 12 months, with HBV DNA <LLOQ by local laboratory assessment for at least 12 weeks prior to screening and HBV DNA <20 IU/mL at screening. Patients were stratified by HBeAg status (HBeAg-positive or HBeAg-negative) and age (≥50 or <50 years) and randomized in a 1:1 ratio to either switch to VEMLIDY (N=243) or stay on TDF 300 mg once daily (N=245). Mean age was 51 years (22% were ≥60 years), 71% were male, 82% were Asian, 14% were White, and 68% were HBeAg-negative. At baseline, mean serum ALT was 27 U/L, median eGFR by Cockcroft-Gault was 90.5 mL/min; 16% of patients had a history of cirrhosis.

The primary efficacy endpoint was the proportion of patients with plasma HBV DNA levels ≥20 IU/mL at Week 48 (as determined by the modified US FDA Snapshot algorithm). Additional efficacy endpoints included the proportion of subjects with HBV DNA levels <20 IU/mL, ALT normal and ALT normalization, HBsAg loss and seroconversion, and HBeAg loss and seroconversion.

Treatment outcomes of Study 4018 at Week 48 are presented in Table 8 and Table 9.

Table 8. HBV DNA Efficacy Parameters at Week 48[a,b] (Study 4018)

	VEMLIDY (N=243)	VIREAD (N=245)
HBV DNA ≥20 IU/mL[b,c]	1 (0.4%)	1 (0.4%)
Treatment Difference[d]	0.0% (95% CI = -1.9% to 2.0%)	
HBV DNA<20 IU/mL	234 (96.3%)	236 (96.3%)
Treatment Difference[d]	0.0% (95% CI = -3.7% to 3.7%)	
No Virologic Data at Week 48	8 (3.3%)	8 (3.3%)
Discontinued Study Drug Due to AE or Death and Last Available HBV DNA <20 IU/mL	2 (0.8%)	0
Discontinued Study Drug Due to Other Reasons[e] and Last Available HBV DNA <20 IU/mL	6 (2.5%)	8 (3.3%)
Missing Data During Window but on Study Drug	0	0

a Week 48 window was between Day 295 and 378 (inclusive).
b As determined by the modified US FDA-defined snapshot algorithm.
c No subject discontinued treatment due to lack of efficacy.
d Adjusted by baseline age groups (< 50, ≥ 50 years) and baseline HBeAg status strata.
e Includes patients who discontinued for reasons other than an AE, death or lack of efficacy, e.g., withdrew consent, loss to follow-up, etc.

VEMLIDY was noninferior in the proportion of subjects with HBV DNA ≥20 IU/mL at Week 48 when compared to VIREAD as assessed by the modified FDA Snapshot algorithm. Treatment outcomes (HBV DNA <20 IU/mL by missing=failure) at Week 48 between treatment groups were similar across subgroups by age, sex, race, baseline HBeAg status, and ALT.

Table 9. Additional Efficacy Parameters at Week 48[a] (Study 4018)

	VEMLIDY (N=243)	VIREAD (N=245)
ALT		
Normal ALT (Central Lab)	89%	85%
Normal ALT (AASLD)	79%	75%
Normalized ALT (Central Lab)[b,c]	50%	37%
Normalized ALT (AASLD)[d,e]	50%	26%
Serology		
HBeAg Loss / Seroconversion[f]	8% / 3%	6% / 0
HBsAg Loss / Seroconversion	0 / 0	2% / 0

a Missing = failure analysis
b The population used for analysis of ALT normalization included only patients with ALT above upper limit of normal (ULN) of the central laboratory range (> 43 U/L males 18 to < 69 years and > 35 U/L males ≥ 69 years; > 34 U/L females 18 to < 69 years and > 32 U/L females ≥ 69 years) at baseline.
c Proportion of patients at Week 48: VEMLIDY, 16/32; VIREAD, 7/19.
d The population used for analysis of ALT normalization included only patients with ALT above ULN of the 2018 American Association of the Study of Liver Diseases (AASLD) criteria (35 U/L males and 25 U/L females) at baseline.
e Proportion of patients at Week 48: VEMLIDY, 26/52; VIREAD, 14/53.
f The population used for serology analysis included only patients with antigen (HBeAg) positive and anti-body (HBeAb) negative or missing at baseline.

Bone Mineral Density: In Study 4018, the mean percentage change in BMD from baseline to Week 48 as assessed by DXA was +1.7% with VEMLIDY compared to −0.1% with VIREAD at the lumbar spine and +0.7% compared to −0.5% at the total hip. BMD declines of greater than 3% at the lumbar spine were experienced by 4% of VEMLIDY patients and 17% of VIREAD patients at Week 48. BMD declines of greater than 3% at the total hip were experienced by 2% of VEMLIDY patients and 12% of VIREAD patients at Week 48.

Changes in Renal Laboratory Tests*:* In Study 4018, median change from baseline to Week 48 in eGFR by Cockcroft-Gault method was +0.9 mL per minute in the VEMLIDY group and −2.7 mL per minute in those receiving VIREAD.

Changes in Lipid Laboratory Tests: In Study 4018, median changes in fasting lipid parameters from baseline to Week 48 were observed in both treatment groups. In the VEMLIDY group, increases in median fasting total cholesterol, LDL, HDL, and triglycerides were observed, while the VIREAD group demonstrated reductions in median fasting total cholesterol, HDL, and triglycerides, and a minimal median increase in LDL ($p < 0.001$ for the difference between treatment groups in all parameters). Median (Q1, Q3) change from baseline at Week 48 in total cholesterol to HDL ratio was 0.2 (-0.1, 0.5) in the VEMLIDY group and 0.0 (-0.3, 0.3) in the VIREAD group ($p < 0.001$ for the difference between treatment groups).

Adult Patients with Renal and/or Hepatic Impairment

Patients with Renal Impairment (Study 4035, Part A)

In Study 4035, Part A, the efficacy and safety of switching from another antiviral regimen to VEMLIDY were evaluated in an open-label clinical study of virologically suppressed chronic hepatitis B-infected adults with moderate to severe renal impairment (eGFR by Cockcroft-Gault method between 15 and 59 mL/min) (Cohort 1, N=78) or ESRD (eGFR by Cockcroft-Gault method <15 mL/min) on hemodialysis (Cohort 2, N=15). At baseline, 98% (91/93) of patients in Part A had baseline HBV DNA < 20 IU/mL and 66% (61/93) had an undetectable HBV DNA level. Median age was 65 years, 74% were male, 77% were Asian, 16% were White, and 83% were HBeAg-negative. Previous treatment with oral antivirals included TDF (Cohort 1, N=57; Cohort 2, N=1), lamivudine (N=46), adefovir dipivoxil (N=46), and entecavir (N=43). At baseline, 97% and 95% of patients had ALT ≤ ULN based on central laboratory criteria and 2018 AASLD criteria, respectively; median eGFR by Cockcroft-Gault was 43.2 mL/min (45.1 mL/min in Cohort 1 and 7.2 mL/min in Cohort 2); and 34% of patients had a history of cirrhosis.

Overall, 98% (91/93) of patients achieved HBV DNA < 20 IU/mL at Week 24 (Cohort 1, 97% [76/78]; Cohort 2, 100% [15/15]), and 73% (68/93) of patients had undetectable HBV DNA at Week 24 (Cohort 1, 76% [59/78]; Cohort 2, 60% [9/15]). Two patients in Cohort 1 discontinued treatment early (due to patient decision); last available HBV DNA for both of these patients was < 20 IU/mL. The overall mean (SD) change from baseline in ALT values was + 1 (11.3) U/L (Cohort 1, + 1 [11.9] U/L; Cohort 2, + 3 [7.9] U/L) at Week 24. For patients with ALT > ULN at baseline (all Cohort 1), ALT normalization was achieved for 67% (2/3) (central laboratory criteria) and 40% (2/5) (2018 AASLD criteria) at Week 24.

No patient had HBeAg or HBsAg loss or seroconversion at Week 24. The mean (SD) changes in HBsAg level from baseline were −0.05 (0.122) $\log_{10}$ IU/mL (−0.05 [0.124] $\log_{10}$ IU/mL for Cohort 1 and −0.07 [0.115] $\log_{10}$ IU/mL for Cohort 2) at Week 24.

Patients with Hepatic Impairment (Study 4035, Part B)

In Study 4035, Part B, the efficacy and safety of switching from another antiviral regimen to VEMLIDY were evaluated in an open-label clinical study of 31virologically suppressed chronic hepatitis B-infected adults with moderate to severe hepatic impairment (Child-Pugh-Turcotte [CPT] B or C at screening or a history of CPT ≥ 7 with any CPT score ≤ 12 at screening). At baseline, 100% (31/31) of patients in Part B had baseline HBV DNA < 20 IU/mL and 65% (20/31) had an undetectable HBV DNA level. Median age was 57 years (19% ≥ 65 years), 68% were male, 81% were Asian, 13% were White, and 90% were HBeAg-negative. Previous treatment with oral antivirals included TDF (N=21), lamivudine (N=14), entecavir (N=14), and adefovir dipivoxil (N=10). At baseline, 87% and 68% of patients had ALT ≤ ULN based on central laboratory criteria and 2018 AASLD criteria, respectively; median eGFR by Cockcroft-Gault was 98.4 mL/min; 97% of patients had a history of cirrhosis, median (range) CPT score was 6 (5−10), and median (range) Model for End Stage Renal Disease (MELD) score was 10 (6−17).

All 31 patients achieved HBV DNA < 20 IU/mL at Week 24, and 77% (24/31) of patients had undetectable HBV DNA at Week 24. The overall mean (SD) change from baseline in ALT values was −1 (15.9) U/L at Week 24. For patients with ALT > ULN at baseline, ALT normalization was achieved for 50% (2/4) (central laboratory criteria) and 60% (6/10) (2018 AASLD criteria) at Week 24. Median change from baseline in CPT score and MELD score was 0 and −0.7, respectively, at Week 24.

No patients had HBeAg or HBsAg loss or seroconversion at Week 24. The mean (SD) change in HBsAg level from baseline was −0.05 (0.134) $\log_{10}$ IU/mL at Week 24.

Bone Mineral Density: In Study 4035, mean percentage change in BMD at the total hip and lumbar spine from baseline to Week 24 as assessed by DXA was +0.14% and +1.27% in patients with moderate to severe renal impairment (Part A, Cohort 1); +0.33% and +0.69% in patients with ESRD on hemodialysis (Part A, Cohort 2); and +0.32% and +1.26% in patients with moderate to severe hepatic impairment (Part B), respectively.

Changes in Renal Laboratory Tests: In Study 4035, median change from baseline to Week 24 in eGFR by Cockcroft-Gault method was +0.6 mL per minute in Part A, Cohort 1, and +3.0 mL per minute in Part B. In both treatment groups there were decreases from baseline in proteinuria (UPCR), albuminuria (UACR), tubular proteinuria (urine RBP to creatinine ratio and urine beta-2-microglobulin to creatinine ratio), and other measures of proximal renal tubular dysfunction in patients switching to VEMLIDY, collectively indicating the reduced impact of tenofovir alafenamide on proximal renal tubular function. Changes from baseline in renal laboratory tests in Study 4035 are summarized in Table 10.

Table 10 Change from Baseline in Renal Laboratory Tests in Study 4035[a] (Week 24 Analysis)

	VEMLIDY Part A, Cohort 1 (N=78)	VEMLIDY Part B (N=31)
Serum Creatinine (mg/dL)[b]	0.038 ± 0.235	−0.008 ± 0.195
Estimated Glomerular Filtration Rate [eGFR] (mL/min)[c,d]	0.6	3.0
Proteinuria by Urine Dipstick (%)[e]	19%	23%
Urine Protein to Creatinine Ratio [UPCR] (%)[f]	−23%	−8%
Urine Albumin to Creatinine Ratio [UACR] (%)[f]	−20%	−23%
Urine RBP to Creatinine Ratio[f]	-45%	-11%
Urine Beta-2-Microglobulin to Creatinine Ratio[f]	-40%	-21%

a Parameters were not calculated for Part A, Cohort 2.
b Mean change ± SD.
c By Cockcroft-Gault method.
d Median change from baseline.
e Includes all severity grades (1-3).
f Median percent change.

Changes in Lipid Laboratory Tests: In Study 4035, median changes in fasting lipid parameters from baseline to Week 24 were observed in both Part A, Cohorts 1 and 2, as well as Part B. Small increases in median fasting total cholesterol, LDL, HDL, and triglycerides were observed in patients with moderate to severe renal impairment (Part A, Cohort 1) and in patients with moderate to severe hepatic impairment (Part B) while small decreases in median fasting total cholesterol, LDL, HDL, and triglycerides were observed in patients with ESRD on hemodialysis (Part A, Cohort 2). Median (Q1, Q3) change from baseline at Week 24 in total cholesterol to HDL ratio was 0.0 (−0.3, 0.3) and 0.0 (−0.6, 0.2) in patients in Part A, Cohorts 1 and 2, respectively, and 0.1 (−0.1, 0.4) in patients in Part B.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of VEMLIDY under fasted conditions in adult patients with chronic hepatitis B, peak plasma concentrations were observed approximately 0.48 hours post-dose. The steady-state mean C_{max} and AUC_{last} for tenofovir alafenamide were 0.25 ± 0.11 µg/ml and 0.15 ± 0.06 µg•hr/ml, respectively.

Relative to fasting conditions, the administration of a single dose of VEMLIDY with a high fat meal resulted in a 65% increase in tenofovir alafenamide exposure. This difference in exposure is not considered clinically relevant and VEMLIDY may be administered without regard to food.

Distribution

The binding of tenofovir to human plasma proteins is less than 0.7% and is independent of concentration over the range of 0.01–25 µg/ml. The binding of tenofovir alafenamide to human plasma proteins in samples collected during clinical trials was approximately 80%.

Metabolism

Metabolism is a major elimination pathway for tenofovir alafenamide in humans, accounting for > 80% of an oral dose. *In vitro* studies have shown that tenofovir alafenamide is metabolised to tenofovir (major metabolite) by carboxylesterase 1 in hepatocytes; and by cathepsin A in PBMCs and macrophages. *In vivo*, tenofovir alafenamide is hydrolysed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite, tenofovir diphosphate. In clinical studies in patients with chronic hepatitis B, a 25 mg oral dose of tenofovir alafenamide in VEMLIDY resulted in tenofovir diphosphate concentrations 7.6 fold higher in PBMCs and 89% lower concentrations of tenofovir in plasma as compared to a 300 mg oral dose of tenofovir disoproxil fumarate in VIREAD.

In vitro, tenofovir alafenamide is not metabolised by CYP1A2, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. Tenofovir alafenamide is minimally metabolised by CYP3A4. Upon coadministration with the strong CYP3A inducer probe carbamazepine, tenofovir alafenamide exposure was not affected to a clinically significant extent. Tenofovir alafenamide is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or UGT1A1. Tenofovir alafenamide is not an inhibitor or inducer of CYP3A *in vivo*.

Excretion

Tenofovir alafenamide is eliminated following metabolism to tenofovir. Tenofovir alafenamide and tenofovir have a median plasma half-life of 0.51 and 32.37 hours, respectively. Tenofovir is renally eliminated by both glomerular filtration and active tubular secretion. Unlike tenofovir, tenofovir alafenamide is not a substrate for the renal transporters OAT1 and OAT3. Renal excretion of intact tenofovir alafenamide is a minor pathway with less than 1% of the dose eliminated in urine. The pharmacologically active metabolite, tenofovir diphosphate, has a half-life of 150-180 hours within PBMCs.

Linearity/non-linearity

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

Special Populations

Age, Gender, and Ethnicity
No clinically relevant pharmacokinetic differences due to gender or ethnicity have been identified.

Population pharmacokinetics analysis of patients with chronic hepatitis B in Phase 1 and Phase 3 trials of VEMLIDY showed that, within the age range studied (18 to 80 years), age did not have a clinically relevant effect on exposures of tenofovir alafenamide.

Patients with Impaired Renal Function
No clinically relevant differences in tenofovir alafenamide or tenofovir pharmacokinetics were observed between healthy patients and patients with severe renal impairment (estimated creatinine clearance from 15 to less than 30 mL per minute). Relative to patients with normal renal function (estimated creatinine clearance ≥ 90 mL/min), the tenofovir alafenamide and tenofovir systemic exposures in patients with severe renal impairment were 1.9-fold and 5.7-fold higher, respectively; the tenofovir exposure observed was in or below the range of that following administration of tenofovir disoproxil fumarate in patients with normal renal function. No dose adjustment is required in patients with renal impairment.

Exposures of tenofovir in 17 subjects with ESRD (estimated creatinine clearance < 15 mL/min) on chronic hemodialysis who received GENVOYA (elvitegravir/cobicistat/emtricitabine/ tenofovir alafenamide) (N=12) or tenofovir alafenamide (N=5) were substantially higher than in subjects with normal renal function. No clinically relevant differences in tenofovir alafenamide pharmacokinetics were observed in patients with ESRD as compared to those with normal function. The safety profile of tenofovir alafenamide in subjects with ESRD on chronic hemodialysis was similar to that in subjects with normal renal function.

Patients with Hepatic Impairment
Clinically relevant changes in the pharmacokinetics of tenofovir alafenamide or its metabolite tenofovir were not observed in patients with mild, moderate, or severe hepatic impairment; no dosage adjustment is required in patients with hepatic impairment.

HIV and/or Hepatitis C Virus Co-infection
The pharmacokinetics of tenofovir alafenamide have not been fully evaluated in patients coinfected with HIV and/or hepatitis C virus.

5.3 Preclinical safety data

Because there is a lower tenofovir exposure in rats and mice after tenofovir alafenamide administration compared to tenofovir disoproxil fumarate, 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 167 times (mice) and 5 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 of 10 times (300 mg tenofovir disoproxil fumarate) and 167 times (for VEMLIDY) greater than the tenofovir exposures 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate
Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate

Film-coating

Polyvinyl alcohol
Polyethylene glycol
Titanium dioxide
Purified talc
Iron oxide yellow

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

VEMLIDY should be stored below 30 °C.

6.5 Nature and contents of container

VEMLIDY is supplied in high density polyethylene (HDPE) bottles containing 30 tablets and is closed with a child resistant closure.

6.6 Special precautions for disposal

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

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Gilead Sciences (NZ)

c/- Grant Thornton New Zealand Limited,
L4, 152 Fanshawe Street

Auckland 1010
New Zealand

Tel: 0800 443 933

9 DATE OF FIRST APPROVAL

26 October 2017

10 DATE OF REVISION OF THE TEXT

16 September 2020

Summary table of changes

Section changed	Summary of new information
4.2	Revision to geriatric text
4.8, 5.1	Addition of Week 48 safety and efficacy data from Study GS-US-320-4018 in virologically suppressed patients with Chronic Hepatitis B who switched from TDF 300 mg to TAF 25 mg
4.8, 5.1, 5.2	Addition of data from Study GS-US-320-4035 in virologically suppressed patients with renal and/or hepatic impairment