Product Monograph

INCLUDING PATIENT MEDICATION INFORMATION

PrVEMLIDY®

(tenofovir alafenamide) tablets

25 mg tenofovir alafenamide*

*as 28.0 mg tenofovir alafenamide hemifumarate

Antiviral Agent

Gilead Sciences Canada, Inc.
Mississauga, ON L5N 2W3

www.gilead.ca

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet 25 mg tenofovir alafenamide* *as 28.0 mg tenofovir alafenamide hemifumarate	lactose monohydrate *For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.*

INDICATIONS AND CLINICAL USE

VEMLIDY is indicated for the treatment of chronic hepatitis B in adults with compensated liver disease (see **WARNINGS AND PRECAUTIONS**).

Geriatrics (≥ 65 years of age)

Clinical trials of VEMLIDY did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients (see **ACTION AND CLINICAL PHARMACOLOGY**).

Pediatrics (< 18 years of age)

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

CONTRAINDICATIONS

VEMLIDY is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the product. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING**.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Post-treatment Exacerbation of Hepatitis B**

Discontinuation of anti-hepatitis B therapy, including VEMLIDY, may be associated with 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, Hepatic**).

General

VEMLIDY should not be coadministered with products containing tenofovir alafenamide (GENVOYA®, DESCOVY®, ODEFSEY®, BIKTARVY®, Symtuza®), tenofovir disoproxil fumarate (ATRIPLA®, COMPLERA®, STRIBILD®, TRUVADA®, VIREAD®), or adefovir dipivoxil (HEPSERA®) (see **DRUG INTERACTIONS**, **Drug-Drug Interactions**).

Hepatic/Biliary/Pancreatic

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 **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY**).

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.

Lactic acidosis and 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, another prodrug of tenofovir, alone or in combination with other antiretrovirals. 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).

Renal

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.

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 **DOSAGE AND ADMINISTRATION**, **Testing Prior to Initiation and During Treatment with VEMLIDY**).

No dosage adjustment of VEMLIDY is required in patients with mild, moderate, or severe renal impairment (estimated creatinine clearance of ≥ 15 mL/min).

VEMLIDY is not recommended in patients with end stage renal disease (estimated creatinine clearance of < 15 mL/min) (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY, Special Populations**).

Special Populations

Patients Coinfected with HBV and HIV-1

Due to the risk of development of HIV 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 HIV-1 and HBV. 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.

Patients should be informed that if they have HIV infection and are not receiving effective HIV treatment, VEMLIDY may increase the risk of development of resistance to HIV treatment (see **DOSAGE AND ADMINISTRATION**).

Pregnant Women

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, VEMLIDY should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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 53 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.

Antiretroviral Pregnancy Registry:

To monitor fetal outcomes of pregnant women exposed to VEMLIDY, an Antiretroviral Pregnancy Registry has been established. Healthcare professionals are encouraged to register patients,
http://www.apregistry.com
Telephone: 1-800-258-4263
Fax: (800) 800-1052

Nursing Women

Animal studies have demonstrated that tenofovir is secreted in milk after administration of tenofovir disoproxil fumarate. There is no information regarding the presence of tenofovir alafenamide in human 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.

Geriatrics (≥ 65 years of age)

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

Pediatrics (< 18 years of age)

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The following adverse drug reactions are discussed in other sections of the Product Monograph:

- Severe Acute Exacerbation of Hepatitis B (see **Serious Warnings and Precautions Box** under **WARNINGS AND PRECAUTIONS**).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information

from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Clinical Trials in Adult Patients with Chronic Hepatitis B

The safety assessment of VEMLIDY was based on pooled data through Week 96 from 1298 patients in two randomized, double-blind, active-controlled trials, GS-US-320-0108 (Study 108) and GS-US-320-0110 (Study 110), in adult patients with chronic hepatitis B. A total of 866 patients received one tablet of VEMLIDY once daily (see **CLINICAL TRIALS**).

Based on the Week 48 and Week 96 analysis (double-blind phase), the most common adverse reaction (all Grades, attributed to study drugs by the investigator) reported in at least 2% of patients in the VEMLIDY group was nausea. The proportion of patients who discontinued treatment with VEMLIDY or VIREAD due to adverse events, regardless of severity, was 1.5% and 0.9% at the Week 96 analysis, respectively. Table 1 displays the frequency of the adverse drug reaction (all Grades) greater than or equal to 2% in the VEMLIDY group.

Table 1 Adverse Drug Reaction[a] (All Grades) Reported in ≥ 2% of Patients Receiving VEMLIDY in Studies 108 and 110 (Week 48 and Week 96 analysis[b])

	Weeks 48 and 96[c]	
	VEMLIDY (N=866)	**VIREAD** (N=432)
GASTROINTESTINAL DISORDERS		
Nausea	2%	4%

a. Frequency of adverse reaction is based on all adverse events attributed to study drugs by the investigator.
b. Double-blind phase
c. Frequencies of adverse reaction at Week 48 and Week 96 were the same.

Based on the Week 96 analysis, additional adverse reactions (based on all treatment-emergent adverse events) included headache, abdominal pain, fatigue, diarrhea, vomiting, rash and flatulence.

Laboratory Abnormalities

The frequency of selected laboratory abnormalities (Grades 3-4) occurring in at least 2% of patients receiving VEMLIDY in Studies 108 and 110 are presented in Table 2.

Table 2 Selected Laboratory Abnormalities (Grades 3-4) Reported in ≥ 2% of Patients Receiving VEMLIDY in Studies 108 and 110 (Week 48 analysis[a])

Laboratory Parameter Abnormality[b]	VEMLIDY (N=866)	VIREAD (N=432)
ALT (>5.0 x ULN)	8%	9%
LDL-cholesterol (fasted) (>4.91 mmol/L)	4%	<1%
Glycosuria (≥3+)	5%	1%
AST (>5.0 x ULN)	3%	5%
Creatine Kinase (≥10.0 x ULN)	3%	3%
Serum Amylase (>2.0 x ULN)	3%	2%

a. Double-blind phase
b. Frequencies are based on treatment-emergent laboratory abnormalities.

At Week 96, laboratory abnormalities (Grades 3-4) in patients who received VEMLIDY in Studies 108 and 110 were consistent with those observed at Week 48.

Post-Market Adverse Drug Reactions

In addition to adverse reactions from clinical studies, the following adverse reactions have been identified during post-approval 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

DRUG INTERACTIONS

Drug-Drug Interactions

Drugs Inducing or Inhibiting P-glycoprotein and BCRP

VEMLIDY is transported by P glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Drugs that strongly affect P-gp and BCRP activity may lead to changes in tenofovir alafenamide absorption (see Table 3). 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. Co-administration of VEMLIDY with other drugs that inhibit P-gp and BCRP may increase the absorption and plasma concentration of tenofovir alafenamide.

Established and Other Potentially Significant Interactions

Drug interaction information for VEMLIDY with potential concomitant drugs is summarized in

Table 3. The drug interactions described are based on studies conducted with tenofovir alafenamide or are potential drug interactions that may occur with VEMLIDY. The table is not all-inclusive (see Table 4 and Table 5 below).

Table 3. Established and Other Potentially Significant[a] Drug Interactions

Concomitant Drug Class: Drug Name	Effect[b]	Clinical Comment
Anticonvulsants: carbamazepine[c] oxcarbazepine phenobarbital phenytoin	↓ tenofovir alafenamide	Coadministration of carbamazepine, oxcarbazepine, phenobarbital, or phenytoin, all of which are P-gp inducers, may decrease tenofovir alafenamide plasma concentrations. Based on tenofovir alafenamide population pharmacokinetic and pharmacodynamic analyses, no dose adjustment is required.
Antifungals: itraconazole ketoconazole	↑ tenofovir alafenamide	Coadministration of itraconazole or ketoconazole, both of which are P-gp inhibitors, may increase plasma concentrations of tenofovir alafenamide. No dose adjustment is required.
Antimycobacterial: rifabutin rifampin rifapentine	↓ tenofovir alafenamide	Coadministration of rifampin, rifabutin, and rifapentine, all of which are P-gp inducers, may decrease tenofovir alafenamide plasma concentrations. Coadministration of VEMLIDY with rifabutin, rifampin, or rifapentine is not recommended.
Herbal Products: St. John's wort (*Hypericum perforatum*)	↓ tenofovir alafenamide	Coadministration of St. John's wort, a P-gp inducer, may decrease tenofovir alafenamide plasma concentrations, which may result in loss of therapeutic effect. Coadministration of VEMLIDY with St. John's wort is not recommended.

a. This table is not all inclusive.
b. ↑ = increase, ↓ = decrease
c. Indicates that a drug interaction study was conducted

Drugs without Clinically Significant Interactions with VEMLIDY

Based on drug interaction studies conducted with VEMLIDY, no clinically significant drug interactions have been observed or are expected with: ethinyl estradiol, ledipasvir/sofosbuvir, midazolam, norgestimate, sertraline, sofosbuvir, sofosbuvir/velpatasvir, and sofosbuvir/velpatasvir/voxilaprevir.

Assessment of Drug Interactions

Tenofovir alafenamide 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.

In vitro and clinical pharmacokinetic drug-drug interaction studies have shown that the potential for CYP-mediated interactions involving tenofovir alafenamide with other medicinal products is low.

Tenofovir alafenamide is not an inhibitor or inducer of CYP3A in vivo.

Drug Interaction Studies

The effects of coadministered drugs on the exposure of tenofovir alafenamide are shown in Table 4. The effects of VEMLIDY on the exposure of coadministered drugs are shown in Table 5.

Table 4 Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir Alafenamide in the Presence of the Coadministered Drug[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	Tenofovir Alafenamide (mg)	N	Mean Ratio of Tenofovir Alafenamide Pharmacokinetic Parameters (90% CI)[b]; No effect = 1.00		
				C_{max}	AUC	C_{min}
Carbamazepine	300 twice daily	25 once daily[c]	26	0.43 (0.36, 0.51)	0.45[d] (0.40, 0.51)	NC
Cobicistat[e]	150 mg daily	8 once daily	12	2.83 (2.20,3.65)	2.65 (2.29,3.07)	NC
Ledipasvir/ Sofosbuvir	90/400 once daily	25 once daily[f]	42	1.03 (0.94, 1.14)	1.32 (1.25, 1.40)	NC
Sertraline	50 single dose	10 once daily[g]	19	1.00 (0.86,1.16)	0.96 (0.89,1.03)	NC
Sofosbuvir/ Velpatasvir/ Voxilaprevir	400/100/100+100 voxilaprevir[h] once daily	25 once daily[f]	30	1.32 (1.17, 1.48)	1.52 (1.43, 1.61)	NC

NC = Not Calculated

a. All interaction studies conducted in healthy subjects.
b. All No Effect Boundaries are 70% -143% unless otherwise specified.
c. Study conducted with DESCOVY (emtricitabine/tenofovir alafenamide).
d. Based on tenofovir alafenamide population pharmacokinetic and pharmacodynamic analyses, no dose adjustment is required
e. A representative inhibitor of P-glycoprotein.
f. Study conducted with ODEFSEY (emtricitabine/rilpivirine/tenofovir alafenamide).
g. Study conducted with GENVOYA (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide).
h. Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

Table 5 Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Tenofovir Alafenamide[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	Tenofovir Alafenamide (mg)	N	Mean Ratio of Coadministered Drug Pharmacokinetic Parameters (90% CI)[b]; No effect = 1.00		
				C_{max}	AUC	C_{min}
Ledipasvir	90 ledipasvir / 400 sofosbuvir once daily	25 once daily[d]	41	1.01 (0.97, 1.05)	1.02 (0.97, 1.06)	1.02 (0.98, 1.07)
Sofosbuvir				0.96 (0.89, 1.04)	1.05 (1.01, 1.09)	NC
GS-331007[c]				1.08 (1.05, 1.11)	1.08 (1.06, 1.10)	1.10 (1.07, 1.12)
Midazolam[e]	2.5 single dose, orally	25 once daily	18	1.02 (0.92, 1.13)	1.13 (1.04, 1.23)	NC
	1 single dose, IV			0.99 (0.89, 1.11)	1.08 (1.04, 1.14)	NC
Norelgestromin	norgestimate 0.180/0.215/0.250 once daily / ethinyl estradiol 0.025 once daily	25 once daily[f]	29	1.17 (1.07,1.26)	1.12 (1.07,1.17)	1.16 (1.08, 1.24)
Norgestrel				1.10 (1.02, 1.18)	1.09 (1.01, 1.18)	1.11 (1.03, 1.20)
Ethinyl estradiol				1.22 (1.15, 1.29)	1.11 (1.07, 1.16)	1.02 (0.93, 1.12)
Sertraline	50 single dose	10 once daily[g]	19	1.14 (0.94, 1.38)	0.93 (0.77, 1.13)	NC
Sofosbuvir	400 once daily	25 once daily[d]	30	0.95 (0.86, 1.05)	1.01 (0.97, 1.06)	NC
GS-331007[c]				1.02 (0.98, 1.06)	1.04 (1.01, 1.06)	NC
Velpatasvir	100 once daily			1.05 (0.96, 1.16)	1.01 (0.94, 1.07)	1.01 (0.95, 1.09)
Voxilaprevir	100 +100[h] once daily			0.96 (0.84, 1.11)	0.94 (0.84, 1.05)	1.02 (0.92, 1.12)

NC = Not Calculated

a. All interaction studies conducted in healthy subjects.
b. All No Effect Boundaries are 70% -143% unless otherwise specified.
c. The predominant circulating nucleoside metabolite of sofosbuvir.
d. Study conducted with ODEFSEY (emtricitabine/rilpivirine/tenofovir alafenamide).
e. A sensitive CYP3A4 substrate.
f. Study conducted with DESCOVY (emtricitabine/tenofovir alafenamide).
g. Study conducted with GENVOYA (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide).
h. Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

Drug-Food Interactions

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.

Drug-Herb Interactions

Coadministration of St. John's wort, a potent CYP3A inducer, may significantly decrease TAF plasma concentrations, which may result in loss of therapeutic effect.

Coadministration of VEMLIDY with St. John's wort is not recommended.

Drug-Laboratory Interactions

Interactions of VEMLIDY with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Testing Prior to Initiation and During Treatment with VEMLIDY

Prior to initiation of VEMLIDY, patients should be tested for HIV-1 infection (see **WARNINGS AND PRECAUTIONS**).

Prior to or when initiating VEMLIDY, and during treatment with VEMLIDY, assess serum creatinine, estimated creatinine clearance (CrCl), urine glucose and urine protein in all patients on a clinically appropriate schedule. In patients with chronic kidney disease, also assess serum phosphorus (see **WARNINGS AND PRECAUTIONS**, **Renal**).

Recommended Dose and Dose Adjustment

Adults

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

Pediatrics (< 18 years of age)

No clinical data in patients with chronic hepatitis B are available on which to make a dose recommendation for patients younger than 18 years.

Geriatrics (≥ 65 years of age)

No dose adjustment is required in patients over the age of 65 years.

Hepatic Impairment

No dose adjustment of VEMLIDY is required in patients with mild hepatic impairment.

VEMLIDY is not recommended in patients with decompensated (Child-Pugh B or C) hepatic impairment (see **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**).

Renal Impairment

No dosage adjustment of VEMLIDY is required in patients with mild, moderate, or severe renal impairment (estimated creatinine clearance of ≥ 15 mL/min).

VEMLIDY is not recommended in patients with end stage renal disease (estimated creatinine clearance of < 15 ml/min)(see **ACTION AND CLINICAL PHARMACOLOGY**).

Missed Dose

If a dose is missed and less than 18 hours have passed from the time it is usually taken, the patient should take VEMLIDY as soon as possible and then resume their normal dosing schedule. If more than 18 hours have passed from the time it is usually taken, the patient should not take the missed dose. The dose should not be doubled to make up for a missed dose.

If the patient vomits within 1 hour of taking VEMLIDY, the patient should take another tablet. If the patient vomits more than 1 hour after taking VEMLIDY, the patient does not need to take another tablet.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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 hemodialysis with an extraction coefficient of approximately 54%.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Tenofovir alafenamide is a phosphonamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analogue). Tenofovir alafenamide enters primary hepatocytes by passive diffusion and by the hepatic uptake transporters OATP1B1 and OATP1B3. Tenofovir

alafenamide is primarily hydrolyzed by carboxylesterase 1 in primary hepatocytes; and by cathepsin A in 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.

Pharmacodynamics

Effects on Electrocardiogram

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

Pharmacokinetics

Absorption and Bioavailability

Following oral administration of VEMLIDY under fasted conditions in adult patients with chronic hepatitis B, peak plasma concentrations of tenofovir alafenamide were observed approximately 0.48 hours post-dose. 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.

Effect of Food on Oral Absorption

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 micrograms per 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 metabolized to tenofovir (major metabolite) by carboxylesterase-1 in hepatocytes, and by cathepsin A in peripheral blood mononuclear cells (PBMCs) and macrophages. In vivo, tenofovir alafenamide is hydrolyzed 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 metabolized by CYP1A2, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. Tenofovir alafenamide is minimally metabolized by CYP3A4. Upon coadministration with the strong CYP3A inducer probe carbamazepine, tenofovir alafenamide exposure was not affected to a clinically meaningful 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 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 mg to 125 mg.

Special Populations and Conditions

Pediatrics (< 18 years of age)

The pharmacokinetics of tenofovir have not been evaluated in pediatric patients (<18 years of age) (see **INDICATIONS AND CLINICAL USE** and **WARNINGS AND PRECAUTIONS**).

Geriatrics (≥ 65 years of age)

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 (see **INDICATIONS AND CLINICAL USE** and **WARNINGS AND PRECAUTIONS**).

Race

No clinically relevant pharmacokinetic differences due to race have been identified.

Gender

No clinically relevant pharmacokinetic differences have been observed between men and women.

Hepatic Impairment

In non-HBV-infected patients with severe hepatic impairment, total plasma concentrations of tenofovir alafenamide and tenofovir are lower than those seen in subjects with normal hepatic function. Administration of TAF 25 mg in Study GS-US-320-1615 to subjects with severe hepatic impairment Child-Pugh-Turcotte [CPT] Class C achieved 46% lower total TAF AUC_{inf} and 55% lower C_{max} as compared to matched controls with normal liver function. When corrected for protein binding, unbound (free) plasma concentrations of tenofovir alafenamide in non-HBV-infected patients with severe hepatic impairment and normal hepatic function are similar. The clinical relevance of this is unknown. The clinical efficacy and safety of VEMLIDY in HBV infected patients with severe hepatic impairment has not been established.

No dosage adjustment 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 **DOSAGE AND ADMINISTRATION** and **WARNINGS AND PRECAUTIONS**).

Renal Impairment

No clinically relevant differences in tenofovir alafenamide or tenofovir pharmacokinetics were observed between healthy subjects and subjects with severe renal impairment (estimated creatinine clearance from 15 to less than 30 mL per minute). 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 tenofovir exposure observed was in or below the range of that following administration of tenofovir disoproxil fumarate in subjects with normal renal function. The pharmacokinetics of tenofovir alafenamide have not been evaluated in patients with creatinine clearance less than 15 mL per minute. Population pharmacokinetic modeling in subjects with end stage renal disease on chronic hemodialysis predicts no clinically relevant changes in tenofovir alafenamide or tenofovir exposure. No dose adjustment is required in patients with renal 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.

STORAGE AND STABILITY

Store below 30°C (86°F).

- Keep container tightly closed.
- Dispense only in original container.
- Do not use if seal over bottle opening is broken or missing.

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each VEMLIDY tablet contains 25 mg of tenofovir alafenamide (equivalent to 28.0 mg of tenofovir alafenamide hemifumarate).

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.

VEMLIDY tablets are yellow, round, film-coated, debossed with “GSI” on one side and “25” on the other side. VEMLIDY tablets are packaged in white, high density polyethylene (HDPE) bottles and enclosed with a polypropylene continuous-thread, child-resistant cap, lined with an induction activated aluminum foil liner. Each bottle contains silica gel desiccant and polyester coil. Each bottle contains 30 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

VEMLIDY is a tablet containing tenofovir alafenamide (as tenofovir alafenamide hemifumarate) for oral administration. Tenofovir alafenamide 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 28.0 mg of tenofovir alafenamide hemifumarate). 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.

Drug Substance

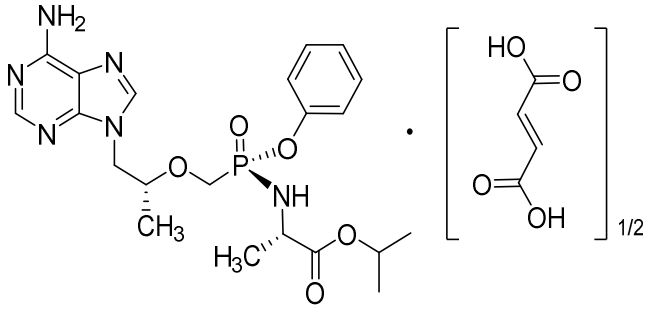
Common Name: **Tenofovir alafenamide hemifumarate**
Tenofovir alafenamide fumarate (USAN)

Chemical Name: Propan-2-yl N-[(S)-({[(2R)-1-(6-amino-9H-purin-9-yl)propan-2-yl]-oxy}methyl)(phenoxy)phosphoryl]-l-alaninate, (2E)-but-2-enedioate

Empirical Formula: $C_{21}H_{29}O_5N_6P \bullet 1/2(C_4H_4O_4)$

Molecular Weight: 534.5

Structural Formula:



Physicochemical Properties:

Description TAF hemifumarate is a white to off-white or tan powder.

Solubility The solubility of TAF hemifumarate in water, pH 8.0 (50 mM phosphate buffer) at 20°C is 4.86 mg/mL. The partition coefficient (log P) is 1.6 and the pKa is 3.96.

CLINICAL TRIALS

The efficacy and safety of VEMLIDY in patients with chronic hepatitis B are based on 48 and 96-week data from two randomized, double-blind, active-controlled studies, GS-US-320-0108 ("Study 108") and GS-US-320-0110 ("Study 110").

Adult Patients with Compensated Liver Disease

Study Demographics and Trial Design

In Study 108, HBeAg-negative treatment-naïve and treatment-experienced patients with compensated liver function were randomized in a 2:1 ratio to receive VEMLIDY (N=285) once daily or VIREAD (tenofovir disoproxil fumarate 300 mg; N=140) once daily. 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)).

In Study 110, HBeAg-positive treatment-naïve and treatment-experienced patients with compensated liver function were randomized in a 2:1 ratio to receive VEMLIDY (N=581) once daily or VIREAD (300 mg; N=292) once daily. 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).

The demographics and baseline characteristics for the patients in Studies 108 and 110 are summarized in Table 6. The baseline disease characteristics are summarized in Table 7.

Table 6 Studies 108 and 110: Demographic and Baseline Characteristics

	Study 108 (HBeAg-Negative)		Study 110 (HBeAg-Positive)	
	VEMLIDY (N = 285)	VIREAD (N = 140)	VEMLIDY (N = 581)	VIREAD (N = 292)
Age, years				
Mean (Range)	45 (19-80)	48 (25-72)	38 (18-69)	38 (18-68)
Sex, n (%)				
Male	173 (61%)	86 (61%)	371 (64%)	189 (65%)
Female	112 (39%)	54 (39%)	210 (36%)	103 (35%)
Race, n (%)				
Asian	205 (72%)	101 (72%)	482 (83%)	232 (79%)
Black or African American	5 (2%)	3 (2%)	2 (<1%)	3 (1%)
Native Hawaiian or Pacific Islander	2 (<1%)	0	1 (<1%)	3 (1%)
White	71 (25%)	35 (25%)	96 (17%)	53 (18%)
Other	2 (<1%)	1 (<1%)	0	1 (<1%)

The denominator for percentages is based on the number of patients in the Safety Analysis Set.

Body Mass Index (BMI) = [Weight (kg) / Height $(m)^2$].

Table 7 Studies 108 and 110: Baseline Disease Characteristics

	Study 108 (HBeAg-Negative)		Study 110 (HBeAg-Positive)	
	VEMLIDY (N = 287)	**VIREAD (N = 138)**	**VEMLIDY (N = 581)**	**VIREAD (N = 292)**
HBV DNA, log_{10} IU/mL				
N	285	140	581	292
Mean (SD)	5.7 (1.34)	5.8 (1.32)	7.6 (1.34)	7.6 (1.41)
HBV DNA Category, n (%)				
< 7 log_{10} IU/mL	230 (81%)	116 (83%)	NA	NA
≥ 7 and < 8 log_{10} IU/mL	42 (15%)	20 (14%)	NA	NA
< 8 log_{10} IU/mL	NA	NA	309 (53%)	150 (51%)
≥ 8 log_{10} IU/mL	13 (5%)	4 (3%)	272 (47%)	142 (49%)
ALT, U/L[a]				
N	285	140	581	292
Median (Q1, Q3SD)	67 (44, 102)	67 (47, 102)	85 (61, 139)	86 (57, 137)
HBV Genotype, n (%)				
A	15 (5%)	6 (4%)	39 (7%)	25 (9%)
B	60 (21%)	40 (29%)	100 (17%)	48 (16%)
C	115 (40%)	47 (34%)	303 (52%)	152 (52%)
D	90 (32%)	42 (30%)	134 (23%)	63 (22%)
E	5 (2%)	2 (1%)	2 (<1%)	1 (<1%)
F	–	–	3 (<1%)	2 (<1%)
H	0	2 (1%)	–	–
Unknown	0	1 (<1%)	0	1 (<1%)
Previous Oral Nucleoside/Nucleotide Treatment, n (%)[b]				
Yes	60 (21%)	31 (22%)	151 (26%)	77 (26%)
Previous Interferon Experience, n (%)				
Yes	29 (10%)	19 (14%)	78 (13%)	28 (10%)
Fibrosis Stage by FibroTest Score, n (%)				
0.75 to 1.00	31 (11%)	20 (14%)	45 (8%)	22 (8%)

NA = Not Applicable
a ALT level was based on central laboratory normal range.
b Previous oral nucleoside/nucleotide treatment status was categorized by "Yes" or "No" irrespective of treatment duration.

Study Results

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 Week 48 are presented in Table 8 and Table 9.

Table 8 HBV DNA Efficacy Parameters at Week 48[a]

	Study 108 (HBeAg-Negative)		Study 110 (HBeAg-Positive)	
	VEMLIDY (N=285)	**Comparator** (N=140)	**VEMLIDY** (N=581)	**Comparator** (N=292)
HBV DNA <29 IU/mL	94%	93%	64%	67%
Treatment Difference[b]	1.8% (95% CI = -3.6% to 7.2%)		-3.6% (95% CI = -9.8% to 2.6%)	
HBV DNA ≥ 29 IU/mL	2%	3%	31%	30%
No Virologic Data at Week 48	4%	4%	5%	3%
Discontinued Study Drug Due to Lack of Efficacy	0	0	<1%	0
Discontinued Study Drug Due to AE or Death	1%	1%	1%	1%
Discontinued Study Drug Due to Other Reasons[c]	2%	3%	3%	2%
Missing Data During Window but on Study Drug	<1%	1%	<1%	0

Comparator = VIREAD (tenofovir disoproxil fumarate)

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 noninferiority criteria in achieving HBV DNA less than 29 IU/mL versus the comparator at Week 48. At Week 96, similar antiviral efficacy was demonstrated with VEMLIDY versus the comparator.

Table 9 Additional Efficacy Parameters at Week 48[a]

	Study 108 (HBeAg-Negative)		Study 110 (HBeAg-Positive)	
	VEMLIDY (N=285)	**Comparator** (N=140)	**VEMLIDY** (N=581)	**Comparator** (N=292)
ALT				
Normalized ALT (Central Lab)[b]	83%	75%	72%	67%
Normalized ALT (AASLD)[c]	50%	32%	45%	36%
Serology				
HBeAg Loss / Seroconversion[d]	N/A	N/A	14% / 10%	12% / 8%
HBsAg Loss / Seroconversion	0 / 0	0 / 0	1% / 1%	<1% / 0

N/A = not applicable
Comparator = VIREAD (tenofovir disoproxil fumarate)

a. Missing = failure analysis
b. The population used for analysis of ALT normalization included only patients with ALT above upper limit of normal (ULN) of the central laboratory range (> 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, which is consistent with the Canadian Association for the Study of the Liver (CASL) criteria.
d. The population used for serology analysis included only patients with antigen positive and anti-body negative or missing at baseline.

The rates of ALT normalization by both central laboratory and AASLD criteria in the VEMLIDY group and the comparator group were similar at Week 96 compared to Week 48. In both studies, the rates of HBsAg loss and seroconversion to anti-HBs were low through Week 96. In Study 110, rates of HBeAg loss and HBeAg loss with seroconversion increased at Week 96 compared with Week 48 in both treatment groups.

Bone Mineral Density*:* In a pooled analysis of Studies 108 and 110, the effects of VEMLIDY versus the comparator on bone mineral density (BMD) percent change from baseline to Week 48 was assessed by dual-energy X-ray absorptiometry (DXA). As shown in Table 10, in patients with both baseline and Week 48 measurements (N=807 and 814 in the VEMLIDY group and N=404 and 407 in the comparator group, for hip and spine, respectively), there were smaller decreases in BMD in the VEMLIDY group versus the comparator group at Week 48.

Table 10 Measures of Bone Mineral Density in Studies 108 and 110 (Week 48 analysis)

	VEMLIDY	Comparator	Treatment Difference
Hip DXA Analysis	N=807	N=404	
Mean Percent Change in BMD	-0.2%	-1.9%	1.7% p < 0.001
Patients with Categorical Change: > 3% Decrease in BMD > 3% Increase in BMD	 8% 7%	 27% 2%	--
Patients with No Decrease (≥ zero % change) in BMD	47%	21%	--
Lumbar Spine DXA Analysis	N=814	N=407	
Mean Percent Change in BMD	-0.6%	-2.4%	1.8% p < 0.001
Patients with Categorical Change: > 3% Decrease in BMD > 3% Increase in BMD	 20% 11%	 38% 3%	--
Patients with No Decrease (≥ zero % change) in BMD	41%	22%	--

Comparator = VIREAD (tenofovir disoproxil fumarate)

Based on the Week 96 analysis, the mean percent changes in BMD at the hip and spine were consistent with data at Week 48; smaller decreases in BMD were observed in the VEMLIDY group versus the comparator group.

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 the comparator on renal laboratory parameters. As shown in Table 11, statistically significant differences were observed between treatment groups for mean changes in serum creatinine, and median changes in estimated glomerular filtration rate (eGFR), 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 Week 48.

Table 11 Change from Baseline in Renal Laboratory Tests in Studies 108 and 110 (Week 48 analysis)

	VEMLIDY (N=866)	Comparator (N=432)	Treatment Difference
Serum Creatinine (µmol/L)[a]	1 ± 10.1	2 ± 8.6	-1.4, p = 0.01
Estimated Glomerular Filtration Rate [eGFR] (mL/min)[b,c]	-1.2	-5.4	p < 0.001
Proteinuria by Urine Dipstick (%)[d]	24.7%	21.4%	p = 0.26
Urine Protein to Creatinine Ratio [UPCR] (%)[e]	6%	16.5%	p = 0.01
Urine Albumin to Creatinine Ratio [UACR] (%)[e]	6.9%	12.2%	p = 0.073
Urine RBP to Creatinine Ratio[e]	-0.3%	25.1%	p < 0.001
Urine Beta-2-Microglobulin to Creatinine Ratio[e]	-3.5%	37.9%	p < 0.001

Comparator = VIREAD (tenofovir disoproxil fumarate)
a. Mean change ± SD.
b. By Cockcroft-Gault method.
c. Median change from baseline.
d. Includes all severity grades (1-3).
e. Median percent change.

Based on the Week 96 analysis, with the exception to the median change in UPCR, the statistically significant changes in renal laboratory tests observed between the treatment groups were consistent with those observed at Week 48.

Changes in Lipid Laboratory Tests: In a pooled analysis of Studies 108 and 110, median changes in most fasting lipid parameters from baseline to Week 96 were observed in both treatment groups. In the VEMLIDY group, no change or decreases in median fasting total cholesterol and HDL, and increases in median fasting direct LDL and triglycerides were observed, while the comparator 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 comparator group ($p = 0.14$ for the difference between treatment groups).

DETAILED PHARMACOLOGY

See **ACTION AND CLINICAL PHARMACOLOGY**.

MICROBIOLOGY

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

In Clinical Trials

In a pooled analysis of treatment-naive and treatment-experienced patients receiving VEMLIDY in Study 108 and Study 110, sequence analysis was performed on paired baseline and on-treatment HBV isolates for patients who 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 96 or at early discontinuation at or after Week 24. In analyses at Week 48 (n=20) and Week 96 (n=72), no amino acid substitutions associated with resistance to VEMLIDY were identified in these isolates (genotypic and phenotypic analyses).

Cross Resistance

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

NONCLINICAL TOXICOLOGY

General

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

Carcinogenesis

Since tenofovir alafenamide is rapidly converted to tenofovir and a lower tenofovir exposure in rats and mice is observed 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 55 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 10 times (300 mg tenofovir disoproxil fumarate) and 167 times VEMLIDY that in humans. In rats, the study was negative for carcinogenic findings.

Mutagenesis

Tenofovir alafenamide was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or rat micronucleus assays.

Reproductive Toxicology

There were no effects on fertility when TAF 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 seven of gestation.

REFERENCES

1. World Health Organization (WHO). Guidelines for the Prevention, Care and Treatment of Persons with Chronic Hepatitis B Infection. 2015.

2. Coffin C.S., Fung S.K., Ma M.M., Canadian Association for the Study of the L. Management of chronic hepatitis B: Canadian Association for the Study of the Liver consensus guidelines. Can J Gastroenterol 2012;26 (12):917-38.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PART III: PATIENT MEDICATION INFORMATION

PrVemlidy®
(tenofovir alafenamide*) tablets
***as tenofovir alafenamide hemifumarate**

Read this carefully before you start taking **Vemlidy.** Read it each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your doctor about your medical condition and treatment. Ask if there is any new information about **Vemlidy**.

Serious Warnings and Precautions

- **"Flare-ups" of Hepatitis B Virus infection** can occur if you stop taking **Vemlidy**. In these cases, your infection may return and become worse than it was before. Do not stop taking **Vemlidy** without your doctor's advice. If you stop taking **Vemlidy**, tell your doctor right away. Tell your doctor about any unusual or worsening symptoms that you notice after stopping treatment. After you stop taking **Vemlidy**, your doctor will still need to check your health and take blood tests regularly for several months to check your HBV infection.

What is Vemlidy used for?
Vemlidy is used to treat chronic (long-lasting) hepatitis B in adults. Hepatitis B is caused by an infection with the hepatitis B virus (HBV).

How does Vemlidy work?
Vemlidy blocks the virus from making more copies of itself in the body. This may help lower the amount of HBV in your body and reduce the infection.

What are the ingredients in Vemlidy?
Each tablet has the following medicines: tenofovir alafenamide*
(*as tenofovir alafenamide hemifumarate)

Each tablet has the following ingredients that are not medicines: croscarmellose sodium, lactose monohydrate, magnesium stearate, and microcrystalline cellulose.

Each tablet is covered with the following ingredients that are not medicines: iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Vemlidy comes in the following dosage forms:
Vemlidy comes in yellow tablets. Each tablet has 25 mg of tenofovir alafenamide (equal to 28.0 mg of tenofovir alafenamide hemifumarate).

Do not use Vemlidy if you:

- have an allergy to tenofovir alafenamide or any of the other ingredients in this product (Read also "**What are the ingredients in Vemlidy?**" above).

To help avoid side effects, make sure you take your medicine correctly. Talk to your doctor before you take Vemlidy. Talk about any health problems you may have, including if you:

- are taking any medicine that is listed under "**Drugs that should not be taken with Vemlidy**".
- have any other health problems, including Human Immunodeficiency Virus (HIV) infection. Your doctor may test you for HIV before starting **Vemlidy**. If you have HIV and take **Vemlidy**, your HIV may become harder to treat.
- have severe liver problems (hepatotoxicity) with an enlarged (hepatomegaly) and fatty liver (steatosis).
- have kidney problems. Kidney problems, including kidney failure, have occurred in patients taking tenofovir. If you have kidney problems and are taking **Vemlidy** along with certain medicines such as non-steroidal anti-inflammatory drugs, your kidney problems could get worse.
- have lactic acid in the blood (lactic acidosis).

Other warnings you should know about:

If you are pregnant or plan to become pregnant:
It is not known if **Vemlidy** can harm your unborn child. Your doctor will decide if you should take **Vemlidy**.

Pregnancy Registry: There is a pregnancy registry for women who take medicines such as **Vemlidy** during pregnancy. This registry collects information about your health and your baby's health. If you become pregnant while taking **Vemlidy**, talk with your doctor about taking part in this Pregnancy Registry.

If you are breast-feeding or plan to breast-feed:
If you are a woman who has or will have a baby, talk with your doctor about the best way to feed your baby.

Tell your doctor about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

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

Drugs that should not be taken with Vemlidy:

- Any other medicines that contain tenofovir alafenamide (GENVOYA®, DESCOVY®, ODEFSEY®, BIKTARVY®, Symtuza®).
- Any other medicines that contain tenofovir disoproxil fumarate (ATRIPLA®,

COMPLERA®, STRIBILD®, TRUVADA®, VIREAD®).
- Adefovir (HEPSERA®).

The following may interact with Vemlidy:

- Antimycobacterials such as rifabutin (Mycobutin®), rifampin (Rifadin®, Rifamate®*, Rifater®*, Rofact®), and rifapentine (*Not available in Canada).
- Herbal products such as *Hypericum perforatum* (St. John's wort).

How to take Vemlidy:

- Stay under a doctor's care when taking **Vemlidy**.
- Do not change your dose or stop taking **Vemlidy** without first talking with your doctor.
- When your **Vemlidy** supply starts to run low, get more from your doctor or pharmacy. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short time. If **Vemlidy** is not taken on a regular basis, the virus may become harder to treat.

Usual adult dose:

- Take one tablet (by mouth) once each day with or without food. Try to take the tablet at the same time each day. Swallow with plenty of water.

Overdose:

If you think you have taken too much **Vemlidy**, contact your doctor, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
It is important to take **Vemlidy** each day.

- **If you miss a dose** of **Vemlidy** and you notice within 18 hours, take a tablet as soon as you can. Then take the next dose at your usual time.
- **If you miss a dose** of **Vemlidy** and you notice after 18 hours, wait and take the next dose at your usual time. Do NOT take a double dose (two doses close together).

What to do if you vomit (throw up):

- If you vomit **less than 1 hour** after taking **Vemlidy,** take another tablet.
- If you vomit more than 1 hour after taking **Vemlidy**, wait. DO NOT take another tablet until you are scheduled to take the next tablet.

Call your doctor or pharmacist if you are not sure what to do.

What are possible side effects from using Vemlidy?

These are not all the possible side effects you may feel when taking **Vemlidy**. If you

experience any side effects not listed here, contact your healthcare professional.

- The most common side effect of **Vemlidy** is nausea.
- Other side effects include headache, abdominal pain, feeling tired, diarrhea, vomiting, rash, flatulence, swelling of the face, lips, tongue or throat (angioedema), and hives (urticaria).
- Please also see "Serious side effects and what to do about them" table, below.

Serious side effects and what to do about them			
Symptoms / effect	**Talk to your doctor**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
RARE **Lactic acidosis (acid in the blood), with symptoms such as:**			
• Feeling very weak or tired		✓	
• Unusual muscle pain		✓	
• Stomach pain with nausea and vomiting		✓	
• Feeling unusually cold especially in arms and legs		✓	
• Feeling dizzy or lightheaded		✓	
• Fast or irregular heartbeat		✓	
• Fast and deep breathing		✓	
VERY RARE **Flare-ups of hepatitis B virus infection following drug discontinuation, with symptoms such as:**			
• Jaundice (skin or the white part of eyes turn yellow)		✓	
• Urine turns dark		✓	
• Bowel movements (stools) turn light in color		✓	
• Loss of appetite for several days or longer		✓	
• Feeling sick to your stomach (nausea)		✓	
• Lower stomach pain		✓	

Serious side effects and what to do about them			
Symptoms / effect	**Talk to your doctor**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY RARE **Hepatotoxicity (severe liver problems) with hepatomegaly (liver enlargement) and steatosis (fat in the liver), with symptoms such as:**			
• Jaundice (skin or the white part of eyes turn yellow)		✓	
• Urine turns dark		✓	
• Bowel movements (stools) turn light in color		✓	
• Loss of appetite for several days or longer		✓	
• Feeling sick to your stomach (nausea)		✓	
• Lower stomach pain		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your doctor.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html)
  for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your doctor if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store **Vemlidy** below 30°C (86°F).
- Keep **Vemlidy** in its original container and keep the container tightly closed.
- Do not use **Vemlidy** if the seal over the bottle opening is broken or missing.
- Keep this medicine where children cannot reach it or see it.

If you want more information about Vemlidy:

- Talk to your doctor.
- Find the full product monograph that is prepared for doctors and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada.html); the manufacturer's website www.gilead.ca, or by calling 1-866-207-4267.

This leaflet was prepared by Gilead Sciences Canada, Inc.

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Gilead Sciences, Inc.
Foster City, CA 94404
USA

Gilead Sciences Canada, Inc.
Mississauga, ON L5N 2W3

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