

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

WARNING: POSTTREATMENT SEVERE ACUTE EXACERBATION OF HEPATITIS B

See full prescribing information for complete boxed warning.

Discontinuation of anti-hepatitis B therapy may result in severe acute exacerbations of hepatitis B. Hepatic function should be monitored closely in patients who discontinue VEMLIDY. If appropriate, resumption of anti-hepatitis B therapy may be warranted. (5.1)

RECENT MAJOR CHANGES

Warnings and Precautions

New Onset or Worsening Renal Impairment (5.3) 03/2021

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

- Testing: Prior to initiation of VEMLIDY, test patients for HIV infection. VEMLIDY alone should not be used in patients with HIV infection. Prior to or when initiating VEMLIDY, and during treatment on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. Also assess serum phosphorus in patients with chronic kidney disease. (2.1)
- Recommended dosage: 25 mg (one tablet) taken orally once daily with food. (2.2)
- Renal Impairment: VEMLIDY is not recommended in patients with estimated creatinine clearance below 15 mL per minute who are not

receiving chronic hemodialysis. In patients on chronic hemodialysis, on hemodialysis days, administer VEMLIDY after hemodialysis. (2.3)

- Hepatic Impairment: VEMLIDY is not recommended in patients with decompensated (Child-Pugh B or C) hepatic impairment. (2.4)

DOSAGE FORMS AND STRENGTHS

Tablets: 25 mg of tenofovir alafenamide. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- HBV and HIV-1 coinfection: VEMLIDY alone is not recommended for the treatment of HIV-1 infection. HIV-1 resistance may develop in these patients. (5.2)
- New onset or worsening renal impairment: Prior to or when initiating VEMLIDY, and during treatment on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. Also assess serum phosphorus in patients with chronic kidney disease. (5.3)
- Lactic acidosis/severe hepatomegaly with steatosis: Discontinue treatment in patients who develop symptoms or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity. (5.4)

ADVERSE REACTIONS

Most common adverse reaction (incidence greater than or equal to 10%, all grades) is headache. (6.1)

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

DRUG INTERACTIONS

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

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

Revised: 03/2021

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FULL PRESCRIBING INFORMATION

WARNING: POSTTREATMENT SEVERE ACUTE EXACERBATION OF HEPATITIS B

Discontinuation of anti-hepatitis B therapy, including VEMLIDY, may result in severe acute exacerbations of hepatitis B. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy, including VEMLIDY. If appropriate, resumption of anti-hepatitis B therapy may be warranted [see *Warnings and Precautions (5.1)*].

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Testing Prior to Initiation of VEMLIDY

Prior to initiation of VEMLIDY, patients should be tested for HIV-1 infection. VEMLIDY alone should not be used in patients with HIV-1 infection [see *Warnings and Precautions (5.2)*].

Prior to or when initiating VEMLIDY, and during treatment with VEMLIDY on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus [see *Warnings and Precautions (5.3)*].

2.2 Recommended Dosage in Adults

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

2.3 Dosage in Patients with Renal Impairment

No dosage adjustment of VEMLIDY is required in patients with estimated creatinine clearance greater than or equal to 15 mL per minute, or in patients with end stage renal disease (ESRD; estimated creatinine clearance below 15 mL per minute) who are receiving chronic hemodialysis. On days of hemodialysis, administer VEMLIDY after completion of hemodialysis treatment.

VEMLIDY is not recommended in patients with ESRD who are not receiving chronic hemodialysis [see *Use in Specific Populations (8.6)* and *Clinical Pharmacology (12.3)*].

2.4 Dosage in Patients with Hepatic Impairment

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Severe Acute Exacerbation of Hepatitis B after Discontinuation of Treatment

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

5.2 Risk of Development of HIV-1 Resistance in Patients Coinfected with HBV and HIV-1

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

5.3 New Onset or Worsening Renal Impairment

Postmarketing cases of renal impairment, including acute renal failure, proximal renal tubulopathy (PRT), and Fanconi syndrome have been reported with TAF-containing products; while most of these cases were characterized by potential confounders that may have contributed to the reported renal events, it is also possible these factors may have predisposed patients to tenofovir-related adverse events [see *Adverse Reactions (6.2)*].

Patients taking tenofovir prodrugs who have impaired renal function and those taking nephrotoxic agents, including non-steroidal anti-inflammatory drugs, are at increased risk of developing renal-related adverse reactions [see *Drug Interactions (7.2)*].

Prior to or when initiating VEMLIDY, and during treatment with VEMLIDY on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus. Discontinue VEMLIDY in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome [see *Adverse Reactions (6.1)* and *Use in Specific Populations (8.6)*].

5.4 Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including tenofovir disoproxil fumarate (TDF), 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).

6 ADVERSE REACTIONS

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

- Severe Acute Exacerbation of Hepatitis B [see *Warnings and Precautions (5.1)*]
- New Onset or Worsening of Renal Impairment [see *Warnings and Precautions (5.3)*]
- Lactic Acidosis/Severe Hepatomegaly with Steatosis [see *Warnings and Precautions (5.4)*]

6.1 Clinical Trials Experience

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

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

The safety assessment of VEMLIDY was based on pooled data through the Week 96 data analysis from 1298 subjects in two randomized, double-blind, active-controlled trials, Trial 108 and Trial 110, in adult subjects with chronic hepatitis B and compensated liver disease. A total of 866 subjects received VEMLIDY 25 mg once daily [see *Clinical Studies (14.2)*]. Further safety assessment was based on pooled data from Trials 108 and 110 from subjects who continued to receive their original blinded treatment through Week 120 and additionally from subjects who received open-label

VEMLIDY from Week 96 through Week 120 (n = 361 remained on VEMLIDY; n = 180 switched from TDF to VEMLIDY at Week 96).

Based on the Week 96 analysis, the most common adverse reaction (all Grades) reported in at least 10% of subjects in the VEMLIDY group was headache. The proportion of subjects who discontinued treatment with VEMLIDY or TDF due to adverse reactions of any severity was 1.5% and 0.9%, respectively. Table 1 displays the frequency of the adverse reactions (all Grades) greater than or equal to 5% in the VEMLIDY group.

Table 1 Adverse Reactions^a (All Grades) Reported in ≥5% of Subjects with Chronic HBV Infection and Compensated Liver Disease in Trials 108 and 110 (Week 96 analysis^b)

	VEMLIDY (N=866)	TDF (N=432)
Headache	12%	10%
Abdominal pain ^c	9%	6%
Cough	8%	8%
Back pain	6%	6%
Fatigue	6%	5%
Nausea	6%	6%
Arthralgia	5%	6%
Diarrhea	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 upper, abdominal pain, abdominal pain lower, and abdominal tenderness.

Additional adverse reactions occurring in less than 5% of subjects in Trials 108 and 110 included vomiting, rash, and flatulence.

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

Renal Laboratory Tests

In a pooled analysis of Trials 108 and 110 in adult subjects with chronic hepatitis B and a median baseline estimated creatinine clearance between 106 and 105 mL per minute (for the VEMLIDY and TDF groups, respectively), mean serum creatinine increased by less than 0.1 mg/dL and median serum phosphorus decreased by 0.1 mg/dL in both treatment groups at Week 96. Median change from baseline to Week 96 in estimated creatinine clearance was -1.2 mL per minute in the VEMLIDY group and -4.8 mL per minute in those receiving TDF.

In subjects who remained on blinded treatment beyond Week 96 in Trials 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, median change in estimated creatinine clearance by Cockcroft-Gault method from Week 96 to Week 120 was -0.6 mL per minute in subjects who remained on VEMLIDY and +1.8 mL per minute in those who switched from TDF to VEMLIDY at Week 96. Mean serum creatinine and median serum phosphorus values at Week 120 were similar to those at Week 96 in subjects who remained on VEMLIDY and in subjects who switched from TDF to VEMLIDY.

The long-term clinical significance of these renal laboratory changes on adverse reaction frequencies between VEMLIDY and TDF is not known.

Bone Mineral Density Effects

In a pooled analysis of Trials 108 and 110, the mean percentage change in bone mineral density (BMD) from baseline to Week 96 as assessed by dual-energy X-ray absorptiometry (DXA) was -0.7% with VEMLIDY compared to -2.6% with TDF at the lumbar spine and -0.3% compared to -2.5% at the total hip. BMD declines of 5% or greater at the lumbar spine were experienced by 11% of VEMLIDY subjects and 25% of TDF subjects at Week 96. BMD declines of 7% or greater at the femoral neck were experienced by 5% of VEMLIDY subjects and 13% of TDF subjects at Week 96.

In subjects who remained on blinded treatment beyond Week 96 in Trials 108 and 110, mean percentage change in BMD in each group at Week 120 was similar to that at Week 96. In the open-label phase, mean percentage change in BMD from Week 96 to Week 120 in subjects 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 TDF to VEMLIDY.

The long-term clinical significance of these BMD changes is not known.

Laboratory Abnormalities

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

Table 2 Laboratory Abnormalities (Grades 3–4) Reported in ≥2% of Subjects with Chronic HBV Infection and Compensated Liver Disease in Trials 108 and 110 (Week 96 analysis^a)

Laboratory Parameter Abnormality ^b	VEMLIDY (N=866)	TDF (N=432)
ALT (>5 × ULN)	8%	10%
LDL-cholesterol (fasted) (>190 mg/dL)	6%	1%
Glycosuria (≥3+)	5%	2%
AST (>5 × ULN)	3%	5%
Creatine Kinase (≥10 × ULN)	3%	3%
Serum Amylase (>2.0 × ULN)	3%	3%

ULN=Upper Limit of Normal

a. Double-blind phase.

b. Frequencies are based on treatment-emergent laboratory abnormalities.

The overall incidence of blinded treatment ALT flares (defined as confirmed serum ALT greater than 2 × baseline and greater than 10 × ULN at 2 consecutive postbaseline visits, with or without associated symptoms) was similar between VEMLIDY (0.6%) and TDF (0.9%) through Week 96. ALT flares generally were not associated with coincident elevations in bilirubin, occurred within the first 12 weeks of treatment, and resolved without recurrence.

Based on the Week 120 analysis, the frequencies of lab abnormalities in subjects who remained on VEMLIDY in the open-label phase were similar to those in subjects who switched from TDF to VEMLIDY at Week 96.

Amylase and Lipase Elevations and Pancreatitis

At Week 96, in Trials 108 and 110, eight subjects treated with VEMLIDY with elevated amylase levels had associated symptoms, such as nausea, low back pain; abdominal tenderness, pain, and distension; and biliary pancreatitis and pancreatitis. Of these eight, two subjects discontinued VEMLIDY due to elevated amylase and/or lipase; one subject experienced recurrence of adverse events when VEMLIDY was restarted. No subject treated with TDF had associated symptoms or discontinued treatment.

From Week 96 to Week 120, one additional subject who continued open-label VEMLIDY and none of the subjects who switched from TDF to VEMLIDY had elevated amylase levels and associated symptoms.

Serum Lipids

Changes from baseline in total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, and total cholesterol to HDL ratio among subjects treated with VEMLIDY and TDF in Trials 108 and 110 are presented in Table 3.

Table 3 Lipid Abnormalities: Mean Change from Baseline in Lipid Parameters in Patients with Chronic HBV Infection and Compensated Liver Disease in Trials 108 and 110 (Week 96 analysis)

	VEMLIDY (N=866)		TDF (N=432)	
	Baseline	Week 96	Baseline	Week 96
	mg/dL	Change ^a	mg/dL	Change ^a
Total Cholesterol (fasted)	188 [n=835]	-1 [n=742]	193 [n=423]	-25 [n=368]
HDL-Cholesterol (fasted)	60 [n=835]	-5 [n=740]	61 [n=423]	-12 [n=368]
LDL-Cholesterol (fasted)	116 [n=835]	+7 [n=741]	120 [n=423]	-10 [n=368]
Triglycerides (fasted)	102 [n=836]	+13 [n=743]	102 [n=423]	-7 [n=368]
Total Cholesterol to HDL ratio	3 [n=835]	0 [n=740]	3 [n=423]	0 [n=368]

a. The change from baseline is the mean of within-subject changes from baseline for subjects with both baseline and Week 96 values.

In the open-label phase, lipid parameters at Week 120 in subjects who remained on VEMLIDY were similar to those at Week 96. In subjects who switched from TDF to VEMLIDY, mean change from Week 96 to Week 120 in total cholesterol was 23 mg/dL, HDL-cholesterol was 5 mg/dL, LDL-cholesterol was 16 mg/dL, triglycerides was 30 mg/dL, and total cholesterol to HDL ratio was 0 mg/dL.

Adverse Reactions in Virologically Suppressed Adult Subjects with Chronic Hepatitis B

The safety of VEMLIDY in virologically suppressed adults is based on Week 48 data from a randomized, double-blind, active-controlled trial (Trial 4018) in which subjects taking TDF at baseline were randomized to switch to VEMLIDY (N=243) or to continue their TDF treatment (N=245). Adverse reactions observed with VEMLIDY in Trial 4018 were similar to those in Trials 108 and 110 [see *Clinical Studies (14.3)*].

Renal Laboratory Tests, Bone Mineral Density Effects, and Serum Lipids

In virologically suppressed adults in Trial 4018, changes from baseline in renal function, BMD, and lipid parameters in the VEMLIDY and TDF groups at Week 48 were similar to those observed in Trials 108 and 110 at Week 96.

Adverse Reactions in Adult Subjects with Chronic Hepatitis B and Renal Impairment

In an open-label trial (Trial 4035) in virologically suppressed adult subjects with chronic hepatitis B switching to VEMLIDY 25 mg, the safety of VEMLIDY was assessed in 78 subjects with moderate to severe renal impairment (estimated creatinine clearance between 15 and 59 mL per minute by Cockcroft-Gault method; Part A, Cohort 1) and 15 subjects with ESRD (estimated creatinine clearance below 15 mL per minute)

receiving chronic hemodialysis (Part A, Cohort 2). The safety of VEMLIDY, including changes from baseline in renal function, BMD, and lipid parameters, was similar to that observed in clinical trials of VEMLIDY in subjects with compensated liver disease but without renal impairment [see *Use in Specific Populations (8.6) and Clinical Studies (14.4)*].

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of VEMLIDY or other products containing tenofovir alafenamide. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and Subcutaneous Tissue Disorders

Angioedema, urticaria

Renal and Urinary Disorders

Acute renal failure, acute tubular necrosis, proximal renal tubulopathy, and Fanconi syndrome

7 DRUG INTERACTIONS

7.1 Potential for Other Drugs to Affect VEMLIDY

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

7.2 Drugs Affecting Renal Function

Because tenofovir is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion, coadministration of VEMLIDY with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of tenofovir and other renally eliminated drugs and this may increase the risk of adverse reactions. Some examples of drugs that are eliminated by active tubular secretion include, but are not limited to, acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs [see *Warnings and Precautions (5.3)*].

7.3 Established and Other Potentially Significant Interactions

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

Table 4 Established and Other Potentially Significant Drug Interactions^a

Concomitant Drug Class: Drug Name	Effect on Concentration ^b	Clinical Comment
Anticonvulsants: Carbamazepine ^{c*} Oxcarbazepine* Phenobarbital* Phenytoin*	↓ tenofovir alafenamide	When coadministered with carbamazepine, the tenofovir alafenamide dose should be increased to two tablets once daily. Coadministration of VEMLIDY with oxcarbazepine, phenobarbital, or phenytoin is not recommended.
Antimycobacterials: Rifabutin* Rifampin* Rifapentine*	↓ tenofovir alafenamide	Coadministration of VEMLIDY with rifabutin, rifampin or rifapentine is not recommended.
Herbal Products: St. John's wort* (<i>Hypericum perforatum</i>)	↓ tenofovir alafenamide	Coadministration of VEMLIDY with St. John's wort is not recommended.

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

7.4 Drugs without Clinically Significant Interactions with VEMLIDY

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

Available data from the APR show no significant difference in the overall risk of birth defects for tenofovir alafenamide (TAF) compared with the background rate for major birth defects of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) (*see Data*). The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15% to 20%.

In animal studies, no adverse developmental effects were observed when tenofovir alafenamide was administered during the period of organogenesis at exposure equal to or 51 times (rats and rabbits, respectively) the tenofovir alafenamide exposure at the recommended daily dose of VEMLIDY (*see Data*). No adverse effects were observed in the offspring when TDF was administered through lactation at tenofovir exposures of approximately 12 times the exposure at the recommended daily dosage of VEMLIDY.

Data

Human Data

Based on prospective reports to the APR of exposures to TAF-containing regimens during pregnancy resulting in live births (including over 200 exposed in the first trimester and over 80 exposed in the second/third trimester), the prevalence of birth defects in live births was 5.2% (95% CI: 2.7% to 8.8%) and 1.2% (95% CI: 0% to 6.5%) following first and second/third trimester exposure, respectively, to TAF-containing regimens. Methodologic limitations of the APR include the use of MACDP as the external comparator group. The MACDP population is not disease-specific, evaluates women and infants from a limited geographic area, and does not include outcomes for births that occurred at <20 weeks gestation.

Animal Data

Embryonic fetal development studies performed in rats and rabbits revealed no evidence of impaired fertility or harm to the fetus. The embryo-fetal NOAELs (no observed adverse effect level) in rats and rabbits occurred at tenofovir alafenamide exposures similar to and 51 times higher than, respectively, the exposure in humans at the recommended daily dose. Tenofovir alafenamide is rapidly converted to tenofovir; the observed tenofovir exposure in rats and rabbits were 54 (rats) and 85 (rabbits) times higher than human tenofovir exposures at the recommended daily dose.

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

8.2 Lactation

Risk Summary

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

Data

Animal Data

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

8.4 Pediatric Use

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

8.5 Geriatric Use

In clinical trials, VEMLIDY was administered to 89 subjects aged 65 and over. No clinically significant differences in safety or efficacy have been observed between elderly subjects and subjects between 18 and less than 65 years of age.

8.6 Renal Impairment

No dosage adjustment of VEMLIDY is required in patients with mild, moderate, or severe renal impairment, or in patients with ESRD (estimated creatinine clearance below 15 mL per minute) who are receiving chronic hemodialysis. On days of hemodialysis, administer VEMLIDY after completion of hemodialysis treatment [see *Dosage and Administration (2.3)*].

The safety and efficacy of VEMLIDY in HBV-infected adult subjects with moderate to severe renal impairment (estimated creatinine clearance between 15 and 59 mL per minute by Cockcroft-Gault method) and ESRD (estimated creatinine clearance of less than 15 mL per minute by Cockcroft-Gault method) receiving chronic hemodialysis were evaluated in 78 and 15 subjects, respectively, in an open-label trial (Trial 4035, Part A). Overall, 98% of subjects achieved HBV DNA <20 IU/mL at Week 24 (Cohort 1, 97%; Cohort 2, 100%) and the safety of VEMLIDY was similar to that observed in clinical trials of VEMLIDY in subjects with compensated liver disease but without renal impairment [see *Adverse Reactions (6.1)* and *Clinical Studies (14.4)*].

The safety and efficacy of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide 150/150/200/10 mg was previously evaluated in 55 virologically suppressed HIV-1 infected subjects with ESRD receiving chronic hemodialysis in an open-label study (Trial 1825). Tenofovir alafenamide exposures are similar when comparing tenofovir alafenamide 25 mg and tenofovir alafenamide 10 mg as part of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide.

Among subjects with ESRD receiving chronic hemodialysis and administered tenofovir alafenamide, higher exposures of tenofovir were observed in HBV-infected subjects (Trial 4035 Part A) compared to HIV-infected subjects (Trial 1825). The clinical significance of these higher exposures is not established [see *Clinical Pharmacology (12.3)*].

VEMLIDY is not recommended in patients with ESRD (estimated creatinine clearance below 15 mL per minute by Cockcroft-Gault method) who are not receiving chronic hemodialysis as the safety of VEMLIDY has not been established in this population [see *Dosage and Administration (2.3)* and *Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

No dosage adjustment of VEMLIDY is required in patients with mild hepatic impairment (Child-Pugh A). The safety and efficacy of VEMLIDY in patients with decompensated cirrhosis (Child-Pugh B or C) have not been established; therefore, VEMLIDY is not

recommended in patients with decompensated (Child-Pugh B or C) hepatic impairment [see *Dosage and Administration (2.4)* and *Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

If overdose occurs, monitor patient for evidence of toxicity. Treatment of overdose with VEMLIDY consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient. Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%.

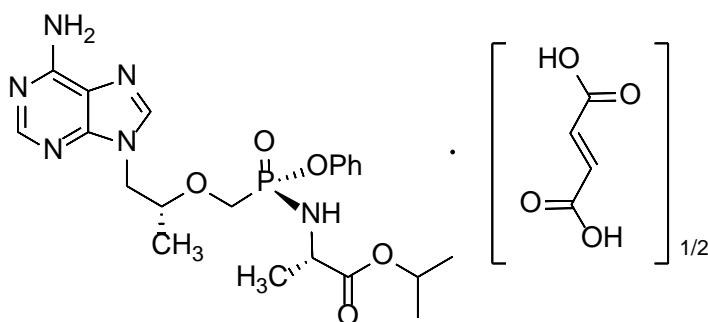
11 DESCRIPTION

VEMLIDY is a tablet containing tenofovir alafenamide for oral administration. Tenofovir alafenamide, a hepatitis B virus (HBV) nucleoside analog reverse transcriptase inhibitor, is converted *in vivo* to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate.

Each tablet contains 25 mg of tenofovir alafenamide (equivalent to 28 mg of tenofovir alafenamide fumarate). The tablets include the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. The tablets are film coated with a coating material containing: iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

The chemical name of tenofovir alafenamide fumarate drug substance is L-alanine, *N*-[[(*S*)-[[[(1*R*)-2-(6-amino-9*H*-purin-9-yl)-1-methylethoxy]methyl]phenoxyphosphinyl]-, 1-methylethyl ester, (2*E*)-2-butenedioate (2:1).

It has an empirical formula of $C_{21}H_{29}O_5N_6P \cdot \frac{1}{2}(C_4H_4O_4)$ and a formula weight of 534.50. It has the following structural formula:



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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tenofovir alafenamide is an antiviral drug against the hepatitis B virus [see *Microbiology (12.4)*].

12.2 Pharmacodynamics

Cardiac Electrophysiology

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

12.3 Pharmacokinetics

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

Table 5 Pharmacokinetic Properties of VEMLIDY

	Tenofovir Alafenamide
Absorption	
T _{max} (h)	0.48
Effect of high fat meal (relative to fasting): AUC _{last} Ratio ^a	1.65 (1.51, 1.81)
Distribution	
% Bound to human plasma proteins	80%
Source of protein binding data	<i>Ex vivo</i>
Blood-to-plasma ratio	1.0
Metabolism	
Metabolism ^b	CES1 (hepatocytes) Cathepsin A (PBMCs) CYP3A (minimal)
Elimination	
Major route of elimination	Metabolism (>80% of oral dose)
t _{1/2} (h) ^c	0.51
% Of dose excreted in urine ^d	<1
% Of dose excreted in feces ^d	31.7

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

- Values refer to geometric mean ratio in AUC_{last} [fed/fasted] and (90% confidence interval). High fat meal = ~800 kcal, 50% fat.
- In vivo, TAF is hydrolyzed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite, tenofovir diphosphate. In vitro studies have shown that TAF is metabolized to tenofovir by CES1 in hepatocytes, and by cathepsin A in PBMCs and macrophages.
- t_{1/2} values refer to median terminal plasma half-life.
- Dosing in mass balance study: TAF 25 mg (single dose administration of [¹⁴C] TAF).

Table 6 Multiple Dose PK Parameters of Tenofovir Alafenamide and its Metabolite Tenofovir Following Oral Administration in Adults with Chronic Hepatitis B

Parameter Mean (CV%)	Tenofovir Alafenamide ^a	Tenofovir ^a
C _{max} (microgram per mL)	0.27 (63.3)	0.03 (24.6)
AUC _{tau} (microgram•hour per mL)	0.27 (47.8)	0.40 (35.2)
C _{trough} (microgram per mL)	NA	0.01 (39.6)

CV = coefficient of variation; NA = not applicable

a. From Intensive PK analyses in Trial 108 and Trial 110; N = 8.

Specific Populations

Geriatric Patients, Race, and Gender

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

Patients with Renal Impairment

In a Phase 1, open-label study, tenofovir alafenamide and tenofovir systemic exposures (AUC_{inf}) were evaluated in subjects with severe renal impairment and in subjects with normal renal function (Table 7). In an open-label trial of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide 150/150/200/10 mg, tenofovir alafenamide and tenofovir AUC were evaluated in a subset of virologically suppressed HIV-1 infected subjects with ESRD receiving chronic hemodialysis (Table 7). In a Phase 2, open-label trial, tenofovir alafenamide and tenofovir AUC were evaluated in a subset of virologically suppressed HBV-infected subjects with ESRD receiving chronic hemodialysis (Table 7) [see *Use in Specific Populations (8.6)*]. The pharmacokinetics of tenofovir alafenamide were similar among subjects with normal renal function, subjects with severe renal impairment, and subjects with ESRD receiving chronic hemodialysis. Relative to those with normal renal function, increased tenofovir exposures were observed in subjects with severe renal impairment and subjects with ESRD receiving chronic hemodialysis. Within the chronic hemodialysis population, increased tenofovir exposures were observed in subjects with HBV relative to those with HIV.

Table 7 Pharmacokinetics of Tenofovir Alafenamide and its Metabolite Tenofovir in Subjects with Renal Impairment as Compared to Subjects with Normal Renal Function

Estimated Creatinine Clearance ^a Mean (CV%)	≥90 mL per minute 25 mg TAF (N=13) ^b	15–29 mL per minute 25 mg TAF (N=14) ^b	<15 mL per minute 25 mg TAF ^c (N=5)	<15 mL per minute 10 mg TAF ^d (N=12)
Tenofovir alafenamide				
AUC (mcg•hour per mL)	0.27 (49.2) ^e	0.51 (47.3) ^e	0.30 (26.7) ^f	0.23 (53.2) ^f
C _{max} (mcg per mL)	0.20 (62.1)	0.36 (65.7)	0.23 (48.4)	0.25 (75.4)
Tenofovir				
AUC (mcg•hour per mL)	0.34 (27.2) ^e	2.07 (47.1) ^e	18.8 (30.4) ^g	8.72 (39.4) ^{g,h}
C _{max} (mcg per mL)	0.01 (36.5)	0.03 (32.4)	0.89 (26.4)	0.44 (40.9)
C _{24h} (mcg per mL)	0.004 (25.6)	0.02 (41.9)	0.89 (26.4)	0.26 (73.2) ^h

CV = coefficient of variation

- a. By Cockcroft-Gault method.
- b. PK assessed on a single dose of TAF 25 mg in subjects with normal renal function and in subjects with severe renal impairment.
- c. PK assessed on the day prior to hemodialysis of TAF 25 mg. These subjects from Study 4035 had a median baseline eGFR by Cockcroft-Gault of 7.2 mL/min (range, 4.8 to 12.0).
- d. Exposures from TAF 25 mg = exposures from TAF 10 mg as part of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide. PK assessed on the day prior to hemodialysis following 3 consecutive daily doses of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide. These subjects from Study 1825 had a median baseline eGFR by Cockcroft-Gault of 10.2 mL/min (range, 6.8 to 19.2) .
- e. AUC_{inf}.
- f. AUC_{last}.
- g. AUC_{tau}.
- h. N=10.

Patients with Hepatic Impairment

Tenofovir alafenamide and tenofovir pharmacokinetics are similar in subjects with mild (Child-Pugh Class A) hepatic impairment and in subjects with normal hepatic function.

HIV and/or Hepatitis C Virus Coinfection

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

Drug Interaction Studies

[see Drug Interactions (7)]

The effects of coadministered drugs on the exposure of tenofovir alafenamide are shown in Table 8. The effects of tenofovir alafenamide on the exposure of coadministered drugs are shown in Table 9 [For information regarding clinical recommendations, see Drug Interactions (7)]. Information regarding potential drug-drug interactions with HIV antiretrovirals is not provided (see the prescribing information for emtricitabine/tenofovir alafenamide for interactions with HIV antiretrovirals).

Table 8 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	Geometric Mean Ratio of TAF 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 (0.40, 0.51)	NC
Cobicistat ^d	150 once 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 ^e	42	1.03 (0.94, 1.14)	1.32 (1.25, 1.40)	NC
Sertraline	50 single dose	10 once daily ^f	19	1.00 (0.86, 1.16)	0.96 (0.89, 1.03)	NC
Sofosbuvir/ Velpatasvir/ Voxilaprevir	400/100/100+ 100 voxilaprevir ^g once daily	25 once daily ^e	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%.
- c. Study conducted with emtricitabine/tenofovir alafenamide.
- d. A representative inhibitor of P-glycoprotein.
- e. Study conducted with emtricitabine/rilpivirine/tenofovir alafenamide.
- f. Study conducted with elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide.
- g. Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

Table 9 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	Geometric 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 ^h	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 ⁱ once daily			0.96 (0.84, 1.11)	0.94 (0.84, 1.05)	1.02 (0.92, 1.12)

NC = not calculated

- All interaction studies conducted in healthy subjects.
- All no effect boundaries are 70%–143%.
- The predominant circulating nucleoside metabolite of sofosbuvir.
- Study conducted with emtricitabine/rilpivirine/tenofovir alafenamide.
- A sensitive CYP3A4 substrate.
- Study conducted with emtricitabine/tenofovir alafenamide.
- Study conducted with elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide.
- Study conducted with emtricitabine/rilpivirine/tenofovir alafenamide.
- Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

12.4 Microbiology

Mechanism of Action

Tenofovir alafenamide is a phosphoramidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analog). Tenofovir alafenamide as a lipophilic cell-permeant compound enters primary hepatocytes by passive diffusion and by the hepatic uptake transporters OATP1B1 and OATP1B3. Tenofovir alafenamide is then converted to tenofovir through hydrolysis primarily by carboxylesterase 1 (CES1) in primary hepatocytes. Intracellular tenofovir is subsequently phosphorylated by cellular kinases to the pharmacologically active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HBV replication through incorporation into viral DNA by the HBV reverse transcriptase, which results in DNA chain-termination.

Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there is no evidence of toxicity to mitochondria in cell culture.

Antiviral Activity in Cell Culture

The antiviral activity of tenofovir alafenamide was assessed in a transient transfection assay using HepG2 cells against a panel of HBV clinical isolates representing genotypes A-H. The EC₅₀ (50% effective concentration) values for tenofovir alafenamide ranged from 34.7 to 134.4 nM, with an overall mean EC₅₀ value of 86.6 nM. The CC₅₀ (50% cytotoxicity concentration) values in HepG2 cells were greater than 44,400 nM. In cell culture combination antiviral activity studies of tenofovir with the HBV nucleoside reverse transcriptase inhibitors entecavir, lamivudine, and telbivudine, no antagonistic activity was observed.

Resistance in Clinical Trials

Genotypic resistance analysis was performed on paired baseline and on-treatment HBV isolates for subjects who either experienced virologic breakthrough (2 consecutive visits with HBV DNA greater than or equal to 69 IU/mL [400 copies/mL] after having been less than 69 IU/mL, or 1.0-log₁₀ or greater increase in HBV DNA from nadir) through Week 48, or had HBV DNA greater than or equal to 69 IU/mL at early discontinuation at or after Week 24.

In a pooled analysis of treatment-naïve and treatment-experienced subjects receiving VEMLIDY in Trials 108 and 110 [see *Clinical Studies (14.2)*], treatment-emergent amino acid substitutions in the HBV reverse transcriptase domain, all occurring at polymorphic positions, were observed in some HBV isolates evaluated (5/20); however, no specific substitutions occurred at a sufficient frequency to be associated with resistance to VEMLIDY.

In virologically suppressed subjects receiving VEMLIDY in Trial 4018 [see *Clinical Studies (14.3)*], no subjects qualified for resistance analysis through 48 weeks of VEMLIDY treatment.

Cross-Resistance

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Since tenofovir alafenamide is rapidly converted to tenofovir and a lower tenofovir exposure in rats and mice was observed after tenofovir alafenamide administration compared to TDF administration, carcinogenicity studies were conducted only with TDF. Long-term oral carcinogenicity studies of TDF 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 TDF for chronic hepatitis B. The tenofovir exposure in these studies was approximately 151 times (mice) and 50 times (rat) those observed in humans after administration of VEMLIDY treatment. At the high dose in female mice, liver adenomas were increased at tenofovir exposures approximately 151 times those observed after VEMLIDY administration in humans. In rats, the study was negative for carcinogenic findings.

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

There were no effects on fertility, mating performance or early embryonic development when tenofovir alafenamide was administered to male rats at a dose equivalent to 155 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 14 days prior to mating through Day 7 of gestation.

13.2 Animal Toxicology and/or Pharmacology

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

14 CLINICAL STUDIES

14.1 Description of Clinical Trials

The efficacy and safety of VEMLIDY were evaluated in the trials summarized in Table 10.

Table 10 Trials Conducted with VEMLIDY in Adults with Chronic HBV Infection

Trial	Population	Trial Arms (N)	Primary Endpoint (Week)
Trial 108 ^a (NCT01940341)	HBeAg-negative TN and TE adults with compensated liver disease	VEMLIDY (285) TDF (140)	48
Trial 110 ^a (NCT01940471)	HBeAg-positive TN and TE adults with compensated liver disease	VEMLIDY (581) TDF (292)	48
Trial 4018 ^a (NCT02979613)	HBeAg-negative and HBeAg-positive virologically suppressed ^b adults with compensated liver disease	VEMLIDY (243) TDF (245)	48
Trial 4035 (Part A, Cohort 1) ^c (NCT03180619)	Virologically suppressed ^b adults with moderate to severe renal impairment ^d	VEMLIDY (78)	24
Trial 4035 (Part A, Cohort 2) ^c (NCT03180619)	Virologically suppressed ^b adults with ESRD ^e receiving chronic hemodialysis	VEMLIDY (15)	24

TE = treatment-experienced, TN = treatment-naïve

- Randomized, double blind, active controlled trial.
- HBV DNA <20 IU/mL at screening.
- Open-label trial.
- Estimated creatinine clearance between 15 and 59 mL per minute by Cockcroft-Gault method.
- End stage renal disease (estimated creatinine clearance of below 15 mL per minute by Cockcroft-Gault method).

14.2 Clinical Trials in Adults with Chronic Hepatitis B Virus Infection and Compensated Liver Disease

The efficacy and safety of VEMLIDY in the treatment of adults with chronic hepatitis B virus infection with compensated liver disease are based on 48-week data from two randomized, double-blind, active-controlled trials, Trial 108 (N=425) and Trial 110 (N=873). In both trials, besides trial treatment, subjects were not allowed to receive other nucleosides, nucleotides, or interferon.

In Trial 108, HBeAg-negative treatment-naïve and treatment-experienced subjects with compensated liver disease (no evidence of ascites, hepatic encephalopathy, variceal bleeding, INR <1.5x ULN, total bilirubin <2.5x ULN, and albumin >3.0 mg/dL) were

randomized in a 2:1 ratio to receive VEMSIDY 25 mg (N=285) once daily or TDF 300 mg (N=140) once daily for 48 weeks. The mean age was 46 years, 61% were male, 72% were Asian, 25% were White, 2% were Black, and 1% were other races. 24%, 38%, and 31% had HBV genotype B, C, and D, respectively. 21% were treatment experienced [previous treatment with oral antivirals, including entecavir (N=41), lamivudine (N=42), TDF (N=21), or other (N=18)]. At baseline, mean plasma HBV DNA was 5.8 log₁₀ IU/mL, mean serum ALT was 94 U/L, and 9% of subjects had a history of cirrhosis.

In Trial 110, HBeAg-positive treatment-naïve and treatment-experienced subjects with compensated liver disease were randomized in a 2:1 ratio to receive VEMSIDY 25 mg (N=581) once daily or TDF 300 mg (N=292) once daily for 48 weeks. The mean age was 38 years, 64% were male, 82% were Asian, 17% were White, and 1% were Black or other races. 17%, 52%, and 23% had HBV genotype B, C, and D, respectively. 26% were treatment experienced [previous treatment with oral antivirals, including adefovir (N=42), entecavir (N=117), lamivudine (N=84), telbivudine (N=25), TDF (N=70), or other (n=17)]. At baseline, mean plasma HBV DNA was 7.6 log₁₀ IU/mL, mean serum ALT was 120 U/L, and 7% of subjects had a history of cirrhosis.

In both trials, randomization was stratified on prior treatment history (nucleoside naïve or experienced) and baseline HBV DNA (<7, ≥7 to <8, and ≥8 log₁₀ IU/mL in Trial 108; and <8 and ≥8 log₁₀ IU/mL in Trial 110). The efficacy endpoint in both trials was the proportion of subjects with plasma HBV DNA levels below 29 IU/mL at Week 48. Additional efficacy endpoints include the proportion of subjects with ALT normalization, HBsAg loss and seroconversion, and HBeAg loss and seroconversion in Trial 110.

Treatment outcomes of Trials 108 and 110 at Week 48 are presented in Table 11 and Table 12.

Table 11 Trials 108 and 110: HBV DNA Virologic Outcome at Week 48^a in Patients with Chronic HBV Infection and Compensated Liver Disease

	Trial 108 (HBeAg-Negative)		Trial 110 (HBeAg-Positive)	
	VEMLIDY (N=285)	TDF (N=140)	VEMLIDY (N=581)	TDF (N=292)
HBV DNA <29 IU/mL	94%	93%	64%	67%
Treatment Difference ^b	1.8% (95% CI = -3.6% to 7.2%)		-3.6% (95% CI = -9.8% to 2.6%)	
HBV DNA ≥29 IU/mL	2%	3%	31%	30%
Baseline HBV DNA <7 log ₁₀ IU/mL ≥7 log ₁₀ IU/mL	96% (221/230) 85% (47/55)	92% (107/116) 96% (23/24)	N/A	N/A
Baseline HBV DNA <8 log ₁₀ IU/mL ≥8 log ₁₀ IU/mL	N/A	N/A	82% (254/309) 43% (117/272)	82% (123/150) 51% (72/142)
Nucleoside Naïve ^c Nucleoside Experienced	94% (212/225) 93% (56/60)	93% (102/110) 93% (28/30)	68% (302/444) 50% (69/137)	70% (156/223) 57% (39/69)
No Virologic Data at Week 48 ^d	4%	4%	5%	3%

- Missing = failure analysis.
- Adjusted by baseline plasma HBV DNA categories and oral antiviral treatment status strata.
- Treatment-naïve subjects received <12 weeks of oral antiviral treatment with any nucleoside or nucleotide analog including TDF or VEMLIDY.
- Includes subjects who discontinued due to lack of efficacy, adverse event or death, for reasons other than an AE, death or lack or loss of efficacy, e.g., withdrew consent, loss to follow-up, etc., or missing data during Week 48 window but still on study drug.

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

Table 12 Additional Efficacy Parameters at Week 48^a

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

N/A = not applicable

- a. Missing = failure analysis.
- b. The population used for analysis of ALT normalization included only subjects with ALT above upper limit of normal (ULN) of the central laboratory range (>43 U/L for males aged 18 to <69 years and >35 U/L for males ≥69 years; >34 U/L for females 18 to <69 years and >32 U/L for females ≥69 years) at baseline.
- c. The population used for analysis of ALT normalization included only subjects with ALT above ULN of the 2016 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 subjects with antigen (HBeAg) positive and anti-body (HBeAb) negative or missing at baseline.

14.3 Clinical Trials in Virologically Suppressed Adults with Chronic Hepatitis B Virus Infection Who Switched to VEMLIDY

The efficacy and safety of switching from TDF to VEMLIDY in virologically suppressed adults with chronic hepatitis B virus infection is based on 48-week data from a randomized, double-blind, active-controlled trial, Trial 4018 (N=488). Subjects must have been taking TDF 300 mg once daily for at least 12 months, with HBV DNA less than the Lower Limit of Quantitation by local laboratory assessment for at least 12 weeks prior to screening and HBV DNA <20 IU/mL at screening. Subjects 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 25 mg once daily (N=243) or stay on TDF 300 mg once daily (N=245). The 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, median duration of prior TDF treatment was 220 and 224 weeks in the VEMLIDY and TDF groups, respectively. At baseline, mean serum ALT was 27 U/L, and 16% of patients had a history of cirrhosis.

The primary efficacy endpoint was the proportion of subjects with plasma HBV DNA levels ≥20 IU/mL at Week 48. Additional efficacy endpoints in Trial 4018 included the proportion of subjects with HBV DNA <20 IU/mL, ALT normal and normalization, HBsAg loss and seroconversion, and HBeAg loss and seroconversion.

Treatment outcomes of Trial 4018 at Week 48 are presented in Table 13 and Table 14.

Table 13 Trial 4018: HBV DNA Virologic Outcome at Week 48^a in Virologically Suppressed Subjects with Chronic HBV Infection

	VEMLIDY (N=243)	TDF (N=245)
HBV DNA \geq 20 IU/mL ^b	<1%	<1%
Treatment Difference ^c	0.0% (95% CI = -1.9% to 2.0%)	
HBV DNA <20 IU/mL	96%	96%
Treatment Difference ^c	0.0% (95% CI = -3.7% to 3.7%)	
No Virologic Data at Week 48	3%	3%
Discontinued Study Drug Due to AE or Death and Last Available HBV DNA <20 IU/mL	1%	0
Discontinued Study Drug Due to Other Reasons ^d and Last Available HBV DNA <20 IU/mL	2%	3%

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

Table 14 Additional Efficacy Parameters at Week 48^a (Trial 4018)

	VEMLIDY (N=243)	TDF (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 subjects with ALT above upper limit of normal (ULN) of the central laboratory range (>43 U/L for males 18 to <69 years and >35 U/L for males \geq 69 years; >34 U/L for females 18 to <69 years and >32 U/L for females \geq 69 years) at baseline.
c. Proportion of subjects at Week 48: VEMLIDY, 16/32; TDF, 7/19.
d. The population used for analysis of ALT normalization included only subjects 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 subjects at Week 48: VEMLIDY, 26/52; TDF, 14/53.
f. The population used for serology analysis included only subjects with antigen (HBeAg) positive and anti-body (HBeAb) negative or missing at baseline.

14.4 Clinical Trial in Adults with Chronic Hepatitis B Virus Infection and Renal Impairment

In Trial 4035, Part A, the efficacy and safety of switching from TDF and/or other antivirals to VEMLIDY were evaluated in an open-label clinical trial of virologically suppressed chronic hepatitis B infected adults with moderate to severe renal

impairment (estimated creatinine clearance between 15 and 59 mL per minute by Cockcroft-Gault method) (Cohort 1, N=78) or ESRD (estimated creatinine clearance below 15 mL per minute by Cockcroft-Gault method) on hemodialysis (Cohort 2, N=15). At baseline, 98% of subjects in Part A had baseline HBV DNA <20 IU/mL. 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 subjects had ALT \leq ULN based on central laboratory criteria and 2018 AASLD criteria, respectively; median estimated creatinine clearance by Cockcroft-Gault was 43 mL per minute (45 mL per minute in Cohort 1 and 7 mL per minute in Cohort 2); and 34% of subjects had a history of cirrhosis.

Overall, 98% of subjects achieved HBV DNA <20 IU/mL at Week 24 (Cohort 1, 97%; Cohort 2, 100%). Two subjects in Cohort 1 discontinued treatment early (due to subject decision); last available HBV DNA for both of these subjects 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. No patient had HBeAg or HBsAg loss 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

VEMLIDY tablets containing 25 mg of tenofovir alafenamide are yellow, round, film-coated, debossed with "GSI" on one side and "25" on the other side. Each bottle contains 30 tablets (NDC 61958-2301-1), a silica gel desiccant, polyester coil, and is closed with a child-resistant closure.

Store below 30 °C (86 °F).

- Keep container tightly closed.
- Dispense only in original container.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Severe Acute Exacerbation of Hepatitis after Discontinuation of Treatment

Inform patients that discontinuation of anti-hepatitis B therapy, including VEMLIDY, may result in severe acute exacerbations of hepatitis B. Advise the patient to not discontinue VEMLIDY without first informing their healthcare provider [see *Warnings and Precautions* (5.1)].

Risk of Development of HIV-1 Resistance in Patients with HIV-1 Coinfection

Inform patients that if they have or develop HIV infection and are not receiving effective HIV treatment, VEMOLIDY may increase the risk of development of resistance to HIV medication [see *Dosage and Administration (2.1)* and *Warnings and Precautions (5.2)*].

New Onset or Worsening Renal Impairment

Postmarketing cases of renal impairment, including acute renal failure, have been reported [see *Warnings and Precautions (5.3)*].

Lactic Acidosis and Severe Hepatomegaly

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with use of drugs similar to VEMOLIDY. Advise patients to contact their healthcare provider immediately and stop VEMOLIDY if they develop clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity [see *Warnings and Precautions (5.4)*].

Drug Interactions

Advise patients to report to their healthcare provider the use of any other prescription or non-prescription medication or herbal products including St. John's wort, as VEMOLIDY may interact with other drugs [see *Drug Interactions (7)*].

Missed Dosage

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

Pregnancy Registry

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

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<p style="text-align: center;">Patient Information VEMLIDY® (VEM-lih-dee) (tenofovir alafenamide) tablets</p>
<p>What is the most important information I should know about VEMLIDY? VEMLIDY can cause serious side effects, including:</p> <ul style="list-style-type: none">• Worsening of hepatitis B virus (HBV) infection. Your HBV infection may get worse (flare-up) if you take VEMLIDY and then stop taking it. A “flare-up” is when your HBV infection suddenly returns in a worse way than before.<ul style="list-style-type: none">○ Do not run out of VEMLIDY. Refill your prescription or talk to your healthcare provider before your VEMLIDY is all gone.○ Do not stop taking VEMLIDY without first talking to your healthcare provider.○ If you stop taking VEMLIDY, your healthcare provider will need to check your health often and do blood tests regularly for several months to check your liver. Tell your healthcare provider about any new or unusual symptoms you may have after you stop taking VEMLIDY. <p>For more information about side effects, see the section “What are the possible side effects of VEMLIDY?”</p>
<p>What is VEMLIDY? VEMLIDY is a prescription medicine used to treat chronic (long-lasting) hepatitis B virus (HBV) in adults with stable (compensated) liver disease.</p> <ul style="list-style-type: none">• VEMLIDY may lower the amount of HBV in your body.• VEMLIDY may improve the condition of your liver. <p>It is not known if VEMLIDY is safe and effective in children under 18 years of age.</p>
<p>What should I tell my healthcare provider before taking VEMLIDY? Before taking VEMLIDY, tell your healthcare provider about all of your medical conditions, including if you:</p> <ul style="list-style-type: none">• have HIV-1 infection. Your healthcare provider may test you for HIV-1 infection before you start VEMLIDY. If you have both HBV and HIV-1, and you only take VEMLIDY, the HIV-1 virus may develop resistance and become harder to treat.• have end stage renal disease (ESRD).• are pregnant or plan to become pregnant. It is not known if VEMLIDY will harm your unborn baby. Tell your healthcare provider if you become pregnant during treatment with VEMLIDY. Pregnancy Exposure Registry: There is a pregnancy registry for women who take antiviral medicines during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk with your healthcare provider about how you can take part in this registry.• are breastfeeding or plan to breastfeed. It is not known if VEMLIDY passes into your breast milk. Talk with your healthcare provider about the best way to feed your baby. <p>Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Some medicines may affect how VEMLIDY works.</p> <ul style="list-style-type: none">• Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine. You can ask your healthcare provider or pharmacist for a list of medicines that interact with VEMLIDY.• Do not start a new medicine without telling your healthcare provider. Your healthcare provider can tell you if it is safe to take VEMLIDY with other medicines.
<p>How should I take VEMLIDY?</p> <ul style="list-style-type: none">• Take VEMLIDY exactly as your healthcare provider tells you to take it.• Take VEMLIDY 1 time each day.• Take VEMLIDY with food.• If you are on dialysis, on your dialysis days, take your daily dose of VEMLIDY following dialysis.

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

What are the possible side effects of VEMLIDY?

VEMLIDY may cause serious side effects, including:

- **See “What is the most important information I should know about VEMLIDY?”**
- **New or worse kidney problems, including kidney failure.** Your healthcare provider should do blood and urine tests to check your kidneys when starting and during treatment with VEMLIDY. Your healthcare provider may tell you to stop taking VEMLIDY if you develop new or worse kidney problems.
- **Too much lactic acid in your blood (lactic acidosis).** Too much lactic acid is a serious but rare medical emergency that can lead to death. Tell your healthcare provider right away if you get these symptoms: weakness or being more tired than usual, unusual muscle pain, being short of breath or fast breathing, stomach pain with nausea and vomiting, cold or blue hands and feet, feel dizzy or lightheaded, or a fast or abnormal heartbeat.
- **Severe liver problems.** In rare cases, severe liver problems can happen that can lead to death. Tell your healthcare provider right away if you get these symptoms: skin or the white part of your eyes turns yellow, dark “tea-colored” urine, light-colored stools, loss of appetite for several days or longer, nausea, or stomach-area pain.

The most common side effect of VEMLIDY is headache. Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

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

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

How should I store VEMLIDY?

- Store VEMLIDY below 86 °F (30 °C).
- Keep VEMLIDY in its original container.
- Keep the container tightly closed.
- VEMLIDY comes in a child-resistant package.

Keep VEMLIDY and all medicines out of reach of children.

General information about the safe and effective use of VEMLIDY.

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

What are the ingredients in VEMLIDY?

Active ingredients: tenofovir alafenamide

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

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

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

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