

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

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

See full prescribing information for complete boxed warning.

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

INDICATIONS AND USAGE

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

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. Assess serum creatinine, serum phosphorous, estimated creatinine clearance, urine glucose, and urine protein before initiating VEMLIDY and during therapy in all patients as clinically appropriate. (2.1)
- Recommended dosage: 25 mg (one tablet) taken orally once daily with food. (2.2)

- Renal Impairment: VEMLIDY is not recommended in patients with estimated creatinine clearance below 15 mL per minute. (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. (5.3)
- New onset or worsening renal impairment: Assessment of serum creatinine, serum phosphorus, estimated creatinine clearance, urine glucose, and urine protein is recommended before initiating VEMLIDY therapy and during therapy as clinically appropriate. (5.4)

ADVERSE REACTIONS

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

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

DRUG INTERACTIONS

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

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

Revised: 11/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Testing Prior to Initiation of VEMLIDY
- 2.2 Recommended Dosage in Adults
- 2.3 Dosage in Patients with Renal Impairment
- 2.4 Dosage in Patients with Hepatic Impairment

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Lactic Acidosis/Severe Hepatomegaly with Steatosis
- 5.2 Severe Exacerbation of Hepatitis B after Discontinuation of Treatment
- 5.3 Risk of Development of HIV-1 Resistance in Patients Coinfected with HBV and HIV-1
- 5.4 New Onset or Worsening Renal Impairment

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience

7 DRUG INTERACTIONS

- 7.1 Potential for Other Drugs to Affect VEMLIDY
- 7.2 Drugs Affecting Renal Function
- 7.3 Established and Other Potentially Significant Interactions
- 7.4 Drugs without Clinically Significant Interactions with VEMLIDY

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

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

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

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

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

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

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Testing Prior to Initiation of VEMLIDY

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

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

2.2 Recommended Dosage in Adults

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

2.3 Dosage in Patients with Renal Impairment

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

2.4 Dosage in Patients with Hepatic Impairment

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis/Severe Hepatomegaly with Steatosis

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

5.2 Severe Acute Exacerbation of Hepatitis B after Discontinuation of Treatment

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

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

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

5.4 New Onset or Worsening Renal Impairment

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir prodrugs in both animal toxicology studies and human trials. In clinical trials of VEMLIDY, there have been no cases of Fanconi syndrome or Proximal Renal Tubulopathy (PRT).

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

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

6 ADVERSE REACTIONS

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

- Lactic Acidosis/Severe Hepatomegaly with Steatosis [see *Boxed Warning and Warnings and Precautions (5.1)*]
- Severe Acute Exacerbation of Hepatitis B [see *Boxed Warning and Warnings and Precautions (5.2)*]
- New Onset or Worsening of Renal Impairment [see *Warnings and Precautions (5.4)*]

6.1 Clinical Trials Experience

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

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

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

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

Table 1 Adverse Reactions^a (All Grades) Reported in ≥5% of Subjects with Chronic HBV Infection and Compensated Liver Disease in Studies 108 and 110 (Week 48 analysis)

| | VEMLIDY (N=866) | Tenofovir Disoproxil Fumarate (N=432) |
|----------------|----------------------------|--|
| Headache | 9% | 8% |
| Abdominal pain | 7% | 6% |
| Fatigue | 6% | 5% |
| Cough | 6% | 6% |
| Nausea | 5% | 5% |
| Back pain | 5% | 4% |

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

Renal Laboratory Tests

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

Decrease in Bone Mineral Density

In a pooled analysis of Studies 108 and 110, the mean percentage change in bone mineral density (BMD) from baseline to Week 48 as assessed by dual-energy X-ray absorptiometry (DXA) was -0.6% with VEMLIDY compared to -2.4% with TDF at the lumbar spine and -0.2% compared to -1.9% at the total hip. BMD declines of 5% or

greater at the lumbar spine were experienced by 6% of VEMLIDY subjects and 20% of TDF subjects. BMD declines of 7% or greater at the femoral neck were experienced by 3% of VEMLIDY subjects and 6% of TDF subjects. The long-term clinical significance of these BMD changes is not known.

Laboratory Abnormalities

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

Table 2 Laboratory Abnormalities (Grades 3–4) Reported in ≥2% of Subjects with Chronic HBV Infection and Compensated Liver Disease in Studies 108 and 110 (Week 48 analysis)

| Laboratory Parameter Abnormality ^a | VEMLIDY (N=866) | Tenofovir Disoproxil Fumarate (N=432) |
|---|--------------------|--|
| ALT (>5 x ULN) | 8% | 9% |
| Glycosuria (≥3+) | 5% | 1% |
| LDL-cholesterol (fasted) (>190 mg/dL) | 4% | <1% |
| AST (>5 x ULN) | 3% | 5% |
| Creatine Kinase (≥10 x ULN) | 3% | 3% |
| Serum Amylase (>2.0 x ULN) | 3% | 2% |

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

Amylase and Lipase Elevations and Pancreatitis

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

Serum Lipids

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

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

| | VEMLIDY (N=866) | | Tenofovir Disoproxil Fumarate (N=432) | |
|--------------------------------|--------------------|---------------------|---|---------------------|
| | Baseline | Week 48 | Baseline | Week 48 |
| | mg/dL | Change ^a | mg/dL | Change ^a |
| Total Cholesterol (fasted) | 188 [n=835] | 0 [n=772] | 193 [n=423] | -25 [n=394] |
| HDL-Cholesterol (fasted) | 60 [n=835] | -4 [n=771] | 61 [n=423] | -10 [n=394] |
| LDL-Cholesterol (fasted) | 116 [n=835] | +6 [n=772] | 120 [n=423] | -11 [n=394] |
| Triglycerides (fasted) | 102 [n=836] | +11 [n=773] | 102 [n=423] | -10 [n=394] |
| Total Cholesterol to HDL ratio | 3 [n=835] | 0 [n=771] | 3 [n=423] | 0 [n=394] |

a. The change from baseline is the mean of within-subject changes from baseline for subjects with both baseline and Week 48 values.

7 DRUG INTERACTIONS

7.1 Potential for Other Drugs to Affect VEMLIDY

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

7.2 Drugs Affecting Renal Function

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

7.3 Established and Other Potentially Significant Interactions

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

prescribing information for emtricitabine/tenofovir alafenamide for interactions with HIV antiretrovirals). The table includes potentially significant interactions but is not all inclusive.

Table 4 Established and Other Potentially Significant Drug Interactions^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. |
| Antimycobacterial: 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, itraconazole, ketoconazole, ledipasvir/sofosbuvir, midazolam, norgestimate, sertraline, sofosbuvir, and sofosbuvir/velpatasvir.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

There are no human data on the use of VEMLIDY in pregnant women to inform a drug-associated risks of adverse fetal developmental outcome. In animal studies, no adverse developmental effects were observed when tenofovir alafenamide was administered during the period of organogenesis at exposure equal to or 51 times (rats and rabbits, respectively) the tenofovir alafenamide exposure at the recommended daily dose of VEMLIDY [see *Data*]. No adverse effects were observed in the offspring when TDF (tenofovir disoproxil fumarate) was administered through lactation at tenofovir exposures of approximately 12 times the exposure at the recommended daily dosage of VEMLIDY.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

Data

Animal Data

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

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

8.2 Lactation

Risk Summary

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

Data

Animal Data

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Renal Impairment

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

8.7 Hepatic Impairment

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

10 OVERDOSAGE

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

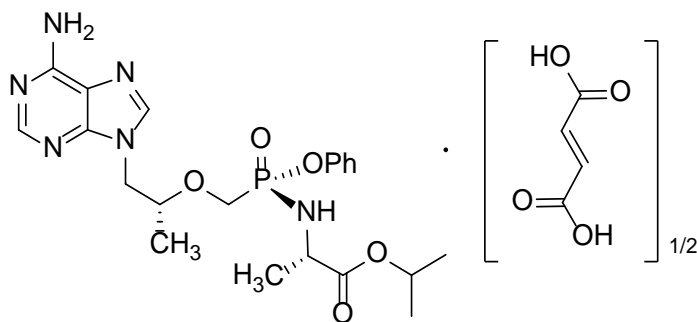
11 DESCRIPTION

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

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

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

- a. Values refer to geometric mean ratio in AUC_{last} [fed/fasted] and (90% confidence interval). High fat meal = ~800 kcal, 50% fat.
- b. *In vivo*, TAF is hydrolyzed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite, tenofovir diphosphate. *In vitro* studies have shown that TAF is metabolized to tenofovir by CES1 in hepatocytes, and by cathepsin A in PBMCs and macrophages.
- c. t_{1/2} values refer to median terminal plasma half-life.
- d. Dosing in mass balance study: TAF 25 mg (single dose administration of [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 Study 108 and Study 110; N = 8.

Specific Populations

Geriatric Patients, Race, and Gender

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

Patients with Renal Impairment

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

Patients with Hepatic Impairment

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

HIV and/or Hepatitis C Virus Coinfection

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

Table 7 Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir Alafenamide in the Presence of the Coadministered Drug^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 (1.24, 1.40) | NC |
| Sertraline | 50 once daily | 10 once daily ^f | 19 | 1.00 (0.86, 1.16) | 0.96 (0.89, 1.03) | NC |
| Sofosbuvir/ Velpatasvir | 400/100 once daily | 10 once daily ^f | 24 | 0.80 (0.68, 0.94) | 0.87 (0.81, 0.94) | 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.

Table 8 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 once daily orally | 25 once daily | 18 | 1.02 (0.92, 1.13) | 1.12 (1.03, 1.22) | NC |
| | 1 once daily IV | | | 0.99 (0.89, 1.11) | 1.08 (1.04, 1.14) | NC |
| Norgestromin | 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) | 1.09 (0.90, 1.32) | NC |
| Sofosbuvir | 400 once daily | 10 once daily ^g | 23 | 1.23 (1.07, 1.42) | 1.37 (1.24, 1.52) | NC |
| GS-331007 ^c | | | | 1.29 (1.25, 1.33) | 1.48 (1.43, 1.53) | 1.58 (1.52, 1.65) |
| Velpatasvir | 100 once daily | | | 15 | 1.30 (1.17, 1.45) | 1.50 (1.35, 1.66) |

NC = not calculated

- All interaction studies conducted in healthy subjects.
- All no effect boundaries are 70%–143%.
- The predominant circulating nucleoside metabolite of sofosbuvir.
- Study conducted with emtricitabine/rilpivirine/tenofovir alafenamide.
- A sensitive CYP3A4 substrate.
- Study conducted with emtricitabine/tenofovir alafenamide.
- Study conducted with elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide.

12.4 Microbiology

Mechanism of Action

Tenofovir alafenamide is a 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

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

Cross-Resistance

The antiviral activity of tenofovir alafenamide was evaluated against a panel of isolates containing substitutions associated with HBV nucleoside reverse transcriptase inhibitor resistance in a transient transfection assay using HepG2 cells. HBV isolates expressing the lamivudine resistance-associated substitutions rtM204V/I (\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 tenofovir disoproxil fumarate administration, carcinogenicity studies were conducted only with tenofovir disoproxil fumarate. Long-term oral carcinogenicity studies of tenofovir disoproxil fumarate in mice and rats were carried out at exposures up to approximately 10 times (mice) and 4 times (rats) those observed in humans at the 300 mg therapeutic dose of tenofovir disoproxil fumarate for chronic hepatitis B. The tenofovir exposure in these studies was approximately 151 times (mice) and 50 times (rat) those observed in humans after administration of VEMLIDY treatment. At the high dose in female mice, liver adenomas were increased at tenofovir exposures approximately 151 times those observed after VEMLIDY administration in humans. In rats, the study was negative for carcinogenic findings.

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

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

13.2 Animal Toxicology and/or Pharmacology

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

14 CLINICAL STUDIES

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

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

In Study 108, HBeAg-negative treatment-naïve and treatment-experienced subjects with compensated liver disease (no evidence of ascites, hepatic encephalopathy, variceal bleeding, INR <1.5x ULN, total bilirubin <2.5x ULN, and albumin >3.0 mg/dL) were randomized in a 2:1 ratio to receive VEMLIDY 25 mg (N=285) once daily or tenofovir disoproxil fumarate 300 mg (N=140) once daily for 48 weeks. The mean age was 46 years, 61% were male, 72% were Asian, 25% were White, 2% were Black, and 1% were other races. 24%, 38%, and 31% had HBV genotype B, C, and D, respectively. 21% were treatment experienced [previous treatment with oral antivirals, including entecavir (N=41), lamivudine (N=42), tenofovir disoproxil fumarate (N=21), or other (N=18)]. At baseline, mean plasma HBV DNA was 5.8 log₁₀ IU/mL, mean serum ALT was 94 U/L, and 9% of subjects had a history of cirrhosis.

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

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

Treatment outcomes of Studies 108 and 110 at Week 48 are presented in Table 9 and Table 10.

Table 9 Studies 108 and 110: HBV DNA Virologic Outcome at Week 48^a in Patients with Chronic HBV Infection and Compensated Liver Disease

| | Study 108 (HBeAg-Negative) | | Study 110 (HBeAg-Positive) | |
|---|-------------------------------|---------------------------------------|--------------------------------|---------------------------------------|
| | VEMLIDY (N=285) | Tenofovir Disoproxil Fumarate (N=140) | VEMLIDY (N=581) | Tenofovir Disoproxil Fumarate (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 | 96% (221/230) | 92% (107/116) | N/A | N/A |
| Baseline HBV DNA ≥7 log ₁₀ IU/mL | 85% (47/55) | 96% (23/24) | | |
| Baseline HBV DNA <8 log ₁₀ IU/mL | N/A | N/A | 82% (254/309) | 82% (123/150) |
| Baseline HBV DNA ≥8 log ₁₀ IU/mL | | | 43% (117/272) | 51% (72/142) |
| Nucleoside Naïve ^c | 94% (212/225) | 93% (102/110) | 68% (302/444) | 70% (156/223) |
| Nucleoside Experienced | 93% (56/60) | 93% (28/30) | 50% (69/137) | 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 Study 108, the proportion of subjects with cirrhosis who achieved HBV DNA <29 IU/mL at Week 48 was 92% (22/24) in the VEMLIDY group and 93% (13/14) in the TDF group. The corresponding proportions in Study 110 were 63% (26/41) and 67% (16/24) in the VEMLIDY and TDF groups, respectively.

Table 10 Additional Efficacy Parameters at Week 48^a

| | Study 108 (HBeAg-Negative) | | Study 110 (HBeAg-Positive) | |
|---|----------------------------|--|----------------------------|--|
| | VEMLIDY (N=285) | Tenofovir Disoproxil Fumarate (N=140) | VEMLIDY (N=581) | Tenofovir Disoproxil Fumarate (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

- Missing = failure analysis
- The population used for analysis of ALT normalization included only subjects with ALT above upper limit of normal (ULN) of the central laboratory range (>43 U/L for males aged 18 to <69 years and >35 U/L for males ≥69 years; >34 U/L for females 18 to <69 years and >32 U/L for females ≥69 years) at baseline.
- The population used for analysis of ALT normalization included only subjects with ALT above ULN of the American Association of the Study of Liver Diseases (AASLD) criteria (>30 U/L males and >19 U/L females) at baseline.
- The population used for serology analysis included only subjects with antigen (HBeAg) positive and antibody (HBeAb) negative or missing at baseline.

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).

Lactic Acidosis and Severe Hepatomegaly

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

Severe Acute Exacerbation of Hepatitis after Discontinuation of Treatment

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

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

Inform patients that if they have or develop HIV infection and are not receiving effective HIV treatment, VEMLIDY may increase the risk of development of resistance to HIV medication [see *Dosage and Administration (2.1)* and *Warnings and Precautions (5.3)*].

New Onset or Worsening Renal Impairment

Advise patients that renal impairment, including cases of acute renal failure, has been reported in association with the use of tenofovir prodrugs [see *Warnings and Precautions (5.4)*].

Drug Interactions

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

Missed Dosage

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

Pregnancy Registry

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

Manufactured and distributed by: Gilead Sciences, Inc. Foster City, CA 94404

© 2016 Gilead Sciences, Inc. All rights reserved.

Patient Information

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

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

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

VEMLIDY can cause serious side effects, including:

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

Lactic acidosis can be hard to identify early, because the symptoms could seem like symptoms of other health problems. **Call your healthcare provider right away if you get any of the following symptoms which could be signs of lactic acidosis:**

- feel very weak or tired
- have unusual (not normal) muscle pain
- have trouble breathing
- have stomach pain with nausea or vomiting
- feel cold, especially in your arms and legs
- feel dizzy or lightheaded
- have a fast or irregular heartbeat

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

Call your healthcare provider right away if you get any of the following symptoms of liver problems:

- your skin or the white part of your eyes turns yellow (jaundice)
- dark “tea-colored” urine
- light-colored bowel movements (stools)
- loss of appetite
- nausea
- pain, aching, or tenderness in the right side of your stomach area

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

- **Worsening of hepatitis B infection.** Your hepatitis B (HBV) infection may become worse (flare-up) if you take VEMLIDY and then stop taking it. A “flare-up” is when your HBV infection suddenly returns in a worse way than before.
 - **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 HBV infection. Tell your healthcare provider about any new or unusual symptoms you may have after you stop taking VEMLIDY.

For more information about side effects, see the section “What are the possible side effects of VEMLIDY?”

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.

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

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

What should I tell my healthcare provider before taking VEMLIDY?

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

- have HIV-1 infection. Your healthcare provider may test you for HIV infection before starting VEMLIDY. If you have HIV and take VEMLIDY, the HIV virus may develop resistance and become

harder to treat.

- have end stage renal disease (ESRD).
 - are pregnant or plan to become pregnant. It is not known if VEMLIDY will harm your unborn baby. Tell your healthcare provider if you become pregnant during treatment with VEMLIDY.
- Pregnancy Registry:** There is a pregnancy registry for women who take antiviral medicines during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk with your healthcare provider about how you can take part in this registry.
- are breastfeeding or plan to breastfeed. It is not known if VEMLIDY passes into your breast milk. Talk with your healthcare provider about the best way to feed your baby.

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

Some medicines may affect how VEMLIDY works.

- Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine. You can ask your healthcare provider or pharmacist for a list of medicines that interact with VEMLIDY.
- **Do not start a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take VEMLIDY with other medicines.

How should I take VEMLIDY?

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

What are the possible side effects of VEMLIDY?

VEMLIDY may cause serious side effects, including:

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

The most common side effects of VEMLIDY are:

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

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

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

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

How should I store VEMLIDY?

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

Keep VEMLIDY and all medicines out of reach of children.

General information about the safe and effective use of VEMLIDY.

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

What are the ingredients in VEMLIDY?

Active ingredients: tenofovir alafenamide

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

Manufactured and distributed by: Gilead Sciences, Inc. Foster City, CA 94404

VEMLIDY is a trademark of Gilead Sciences, Inc., or its related companies. © 2016 Gilead Sciences, Inc. All rights reserved.

208464-GS-000

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

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

Issued: 11/2016