Don’t accept less than VEMLIDY

Antiviral efficacy proven in noninferiority trials with TDF[1]

Safety demonstrated in renal and bone effects[1]

Vemlidy®
tenofovir alafenamide 25mg tablets

TDF=tenofovir disoproxil fumarate.

INDICATION

VEMLIDY is indicated for the treatment of chronic hepatitis B virus (HBV) infection in adults with compensated liver disease.

IMPORTANT SAFETY INFORMATION

BOXED 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.**

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Not actual patients.

Patients with chronic hepatitis B (CHB) will need long-term monitoring and disease management.[2] They deserve a therapy that can help them make the journey.

As CHB patients age, their disease progresses and their health can be compromised by comorbidities[3,4]

Progression of disease

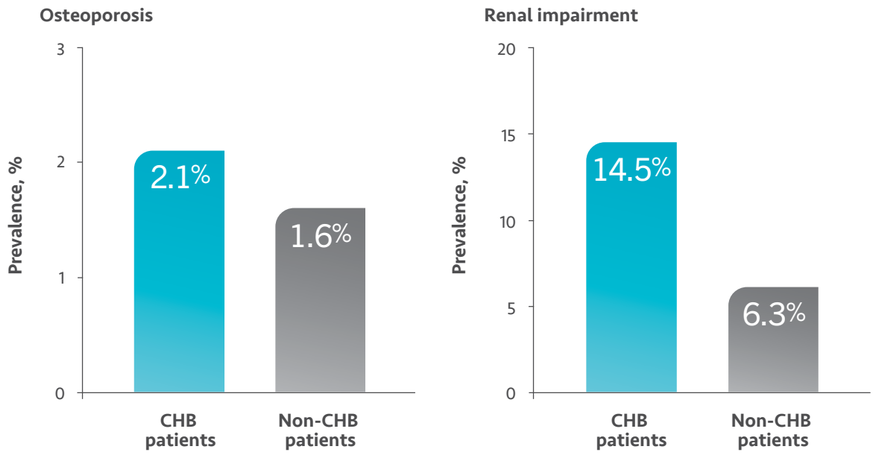
CHB is a lifelong disease that may require long-term or indefinite therapy.[2]

> 20% to 30% of adults with CHB will develop complications such as cirrhosis and hepatocellular carcinoma[2]

Prevalence of comorbidities

CHB patients, compared to the general population, have a higher risk for developing certain comorbidities, including diabetes, metabolic syndrome, and bone and renal conditions.[3-5]

Proportions of CHB patients with comorbidities compared to non-CHB[3] (Commercial, Medicare, and Medicaid, 2015)[a]



Other comorbidities included:

- Hypertension—35.8% for non-CHB patients, 37.3% for CHB patients
- Diabetes—15.1% for non-CHB patients, 17.7% for CHB patients
- Hyperlipidemia—26.4% for non-CHB patients, 24.0% for CHB patients

Renal function naturally declines with age[6]

> Renal abnormalities are common in patients with CHB, with a higher prevalence of chronic kidney disease vs the uninfected population[3,7]

Regular renal monitoring and other considerations may be required during the management of patients with CHB.[8]

As people get older, their bone health deteriorates[9]

> In the US, there is a higher prevalence of osteoporosis and/or bone fracture in patients with CHB when compared to the uninfected population[3,a]

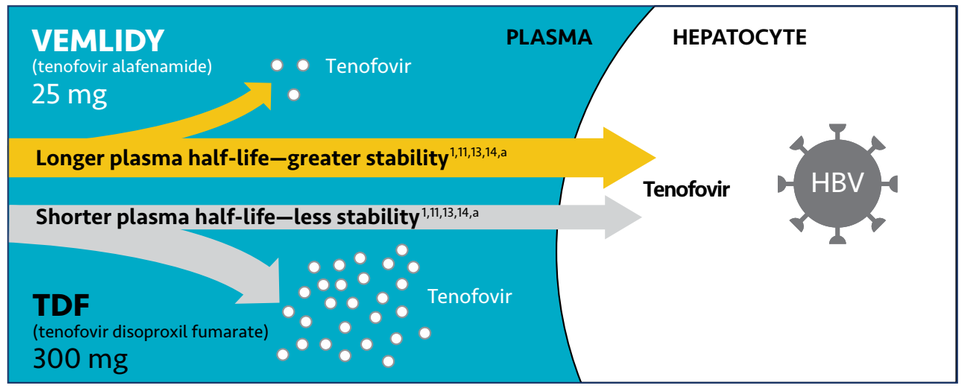
Current risk of bone disease should be considered when managing CHB.[10]

[a]Based on claims from national insurance databases covering Commercial, Medicare, and Medicaid beneficiaries (2006-2015) in 44,026 CHB patients and 121,568 non-CHB patients. The databases contained medical and pharmacy claims for healthcare services performed in both inpatient and outpatient settings. The 2015 cohort included 11,372 CHB patients and 32,110 non-CHB patients.[3]

VEMLIDY optimizes tenofovir delivery to the hepatocyte[11]

Due to enhanced plasma stability, VEMLIDY demonstrates[12]:

- More efficient delivery of tenofovir to the hepatocytes vs TDF[11]
- Reduced systemic exposure, with 89% less tenofovir circulating in the plasma vs TDF[12]



[a]Plasma half-life: VEMLIDY=30.6 minutes (0.51 hour); TDF=0.41 minutes.[1,13]

VEMLIDY: A novel, targeted prodrug of tenofovir[1]

CHB treatment has evolved

Timeline of FDA approvals: Oral antiviral treatments for CHB

1998[15]	2002[16]	2005[17]	2006[18]	2008[19]	2016[1]
LAM (lamivudine)	**ADV** (adefovir dipivoxil)	**ETV** (entecavir)	**LdT** (telbivudine)	**TDF** (tenofovir disoproxil fumarate)	**VEMLIDY** (tenofovir alafenamide)

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

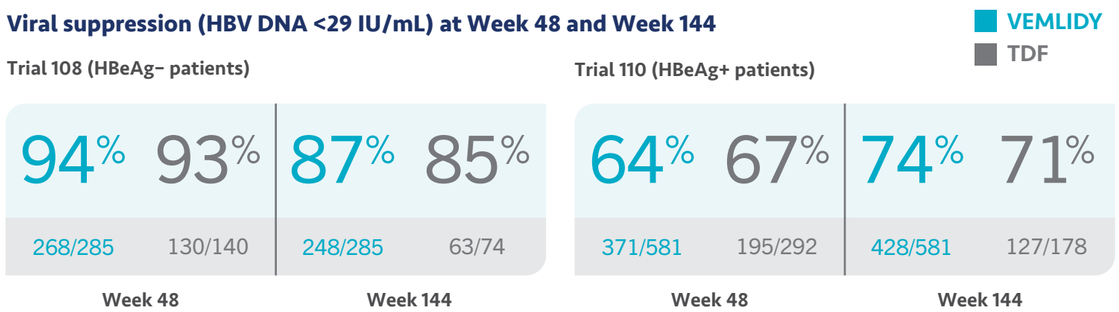
- **Risk of Development of HIV-1 Resistance in HBV/HIV-1 Coinfected Patients:** Due to this risk, VEMLIDY alone should not be used for the treatment of HIV-1 infection. Safety and efficacy of VEMLIDY have not been established in HBV/HIV-1 coinfected patients. HIV antibody testing should be offered to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

VEMLIDY has efficacy you can trust, with no known resistance[1,12,20-22]

Vemlidy® tenofovir alafenamide 25mg tablets

VEMLIDY demonstrated powerful antiviral efficacy in CHB patients with compensated liver disease[1,12,20,21]

Viral suppression (HBV DNA <29 IU/mL) at Week 48 and Week 144



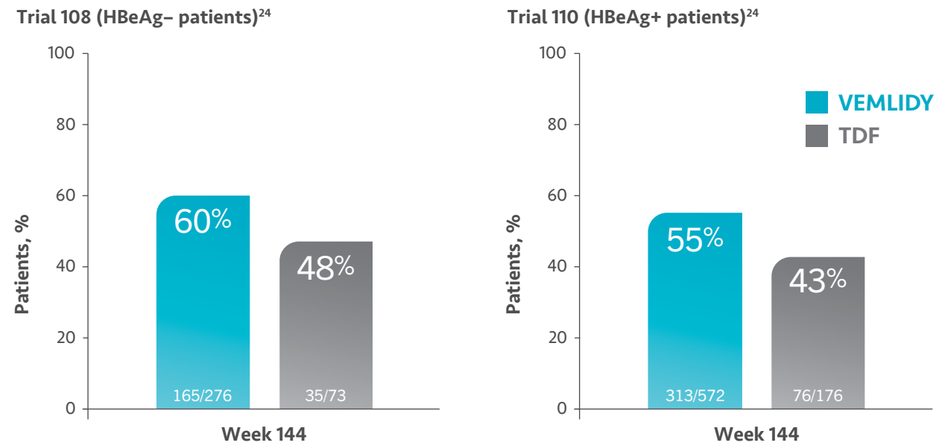
Mean baseline plasma HBV DNA was 5.8 log IU/mL in Trial 108 and 7.6 log IU/mL in Trial 110.[1]

Primary efficacy endpoint: The proportion of patients with HBV DNA <29 IU/mL and noninferiority to TDF (10% margin; 95% CI approach) at Week 48 for both trials.[1,12,21]

0% resistance with VEMLIDY in Trials 108 and 110 through 144 weeks[1,22,23]

VEMLIDY demonstrated improved ALT normalization in CHB patients with compensated liver disease[24]

ALT normalization (2016 AASLD criteria)[a] at Week 144



At Week 48: ALT normalization was 50% (137/276) for VEMLIDY vs 32% (44/138) for TDF in Trial 108 and 45% (257/572) for VEMLIDY vs 36% (105/290) for TDF in Trial 110.[1,12,21]

[a]The population used for analysis of ALT normalization included only patients with ALT above ULN based on the AASLD 2016 criteria (>30 U/L and >19 U/L for males and females, respectively) at baseline.[1]

Please see Trial Designs starting on page 10 for complete details.

AASLD=American Association for the Study of Liver Diseases; CI=confidence interval; ULN=upper limit of normal.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- **New Onset or Worsening Renal Impairment:** Cases of acute renal failure and Fanconi syndrome have been reported with the use of tenofovir prodrugs. In clinical trials of VEMLIDY, there have been no cases of Fanconi syndrome or proximal renal tubulopathy (PRT). Patients with impaired renal function and/or taking nephrotoxic agents (including NSAIDs) are at increased risk of renal-related adverse reactions. Discontinue VEMLIDY in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome. Monitor renal function in all patients – See Dosage and Administration.
- **Lactic Acidosis and Severe Hepatomegaly with Steatosis:** Fatal cases have been reported with the use of nucleoside analogs, including tenofovir DF. Discontinue VEMLIDY if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity develop, including hepatomegaly and steatosis in the absence of marked transaminase elevations.

Adverse Reactions

Most common adverse reactions (incidence ≥5%; all grades) were headache, abdominal pain, cough, back pain, fatigue, nausea, arthralgia, diarrhea, and dyspepsia.

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VEMLIDY has a reduced effect on renal safety parameters and less impact on BMD[24]

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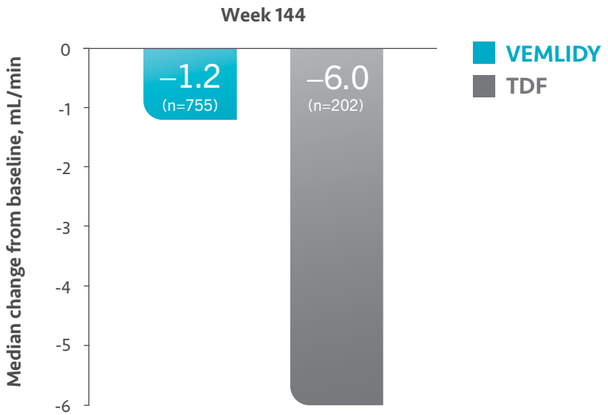
Renal effects of VEMLIDY and TDF were compared in Trials 108 and 110[24]

Change in $eGFR_{CG}$ from baseline at Week 144 (pooled)[24]

Median baseline $eGFR_{CG}$ of 106 mL/min and 105 mL/min, for VEMLIDY and TDF, respectively

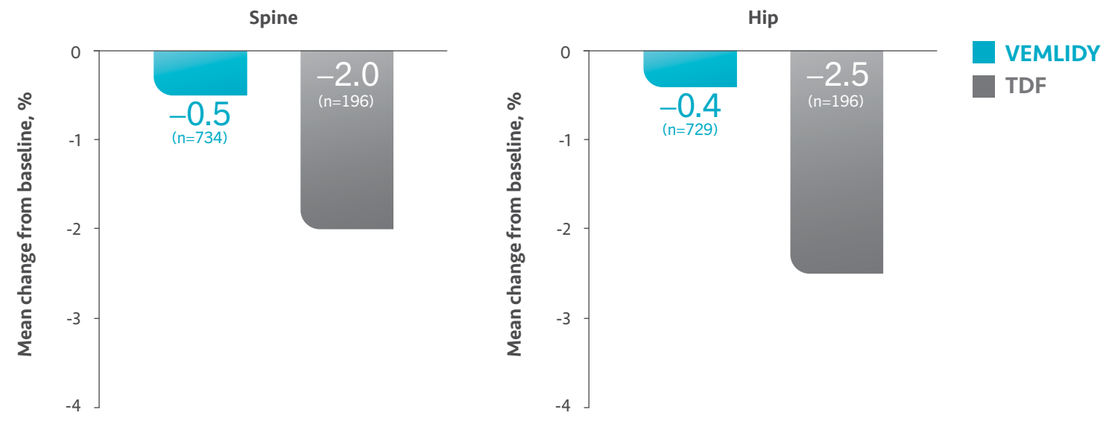


Median change from baseline to **Week 96** in $eGFR_{CG}$ was -1.2 mL/min in the VEMLIDY group (n=790) and -4.8 mL/min in those receiving TDF (n=390).[1,24]

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

Impacts on spine and hip BMD with VEMLIDY and TDF were compared in Trials 108 and 110[24]

Change in BMD from baseline at Week 144 (pooled)[24]



The mean percentage change in BMD from baseline to **Week 96** was -0.7% with VEMLIDY (n=746) compared to -2.6% with TDF (n=371) at the lumbar spine, and -0.3% (n=740) compared to -2.5% (n=369) at the total hip.[1,24]

BMD declines (≥5%) at the lumbar spine[1,24]:
- 11% (VEMLIDY) vs 25% (TDF) at Week 96
- 12% (VEMLIDY) vs 24% (TDF) at Week 144

BMD declines (≥7%) at the femoral neck[1,24]:
- 5% (VEMLIDY) vs 13% (TDF) at Week 96
- 9% (VEMLIDY) vs 16% (TDF) at Week 144

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

Please see Trial Designs starting on page 10 for complete details.

BMD=bone mineral density; $eGFR_{CG}$=estimated glomerular filtration rate by Cockcroft-Gault method, also referred to as eCrCl (estimated creatinine clearance).

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- **New Onset or Worsening Renal Impairment:** Cases of acute renal failure and Fanconi syndrome have been reported with the use of tenofovir prodrugs. In clinical trials of VEMLIDY, there have been no cases of Fanconi syndrome or proximal renal tubulopathy (PRT). Patients with impaired renal function and/or taking nephrotoxic agents (including NSAIDs) are at increased risk of renal-related adverse reactions. Discontinue VEMLIDY in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome. Monitor renal function in all patients – See Dosage and Administration.

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Efficacy with improved renal function and BMD in virologically suppressed CHB patients who switched to VEMLIDY[1,24]

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Patients who switched from TDF to VEMLIDY maintained high rates of viral suppression[1,24]

Trial 4018 (Virologically suppressed CHB patients with compensated liver disease)

Efficacy outcome at Week 48[1,24]

	Switched to VEMLIDY	Continued on TDF
HBV DNA ≥20 IU/mL	<1% (1/243)	<1% (1/245)
HBV DNA <20 IU/mL	96% (234/243)	96% (236/245)
Normal ALT[a]	79% (192/243)	75% (184/245)

At baseline, median duration of prior TDF treatment was 220 weeks (VEMLIDY) and 224 weeks (TDF).[1]

[a]Based on AASLD 2018 criteria for ALT ULN (>35 U/L and >25 U/L for males and females, respectively).[1]

Primary efficacy endpoint: The proportion of patients with plasma HBV DNA ≥20 IU/mL and noninferiority to TDF (4% margin; 95% CI approach) at Week 48.[1,24]

No patients qualified for resistance analysis through 48 weeks of VEMLIDY treatment[1]

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- **New Onset or Worsening Renal Impairment:** Cases of acute renal failure and Fanconi syndrome have been reported with the use of tenofovir prodrugs. In clinical trials of VEMLIDY, there have been no cases of Fanconi syndrome or proximal renal tubulopathy (PRT). Patients with impaired renal function and/or taking nephrotoxic agents (including NSAIDs) are at increased risk of renal-related adverse reactions. Discontinue VEMLIDY in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome. Monitor renal function in all patients – See Dosage and Administration.

Drug Interactions

- Coadministration of VEMLIDY with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of tenofovir and the risk of adverse reactions.
- Coadministration of VEMLIDY is not recommended with the following: oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, or St. John's wort. Such coadministration is expected to decrease the concentration of tenofovir alafenamide, reducing the therapeutic effect of VEMLIDY. Drugs that strongly affect P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) activity may lead to changes in VEMLIDY absorption.

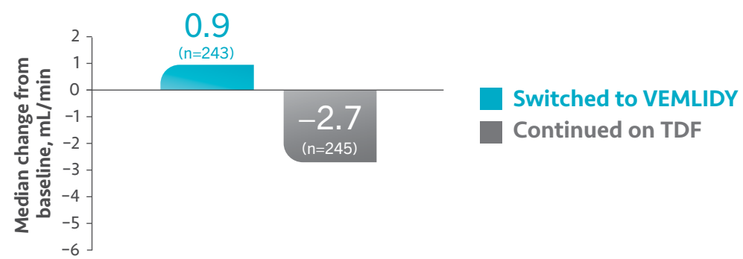
Consult the full Prescribing Information for VEMLIDY for more information on potentially significant drug interactions, including clinical comments.

Patients who switched from TDF to VEMLIDY had improved renal function and BMD[24]

Trial 4018 (Virologically suppressed CHB patients with compensated liver disease)

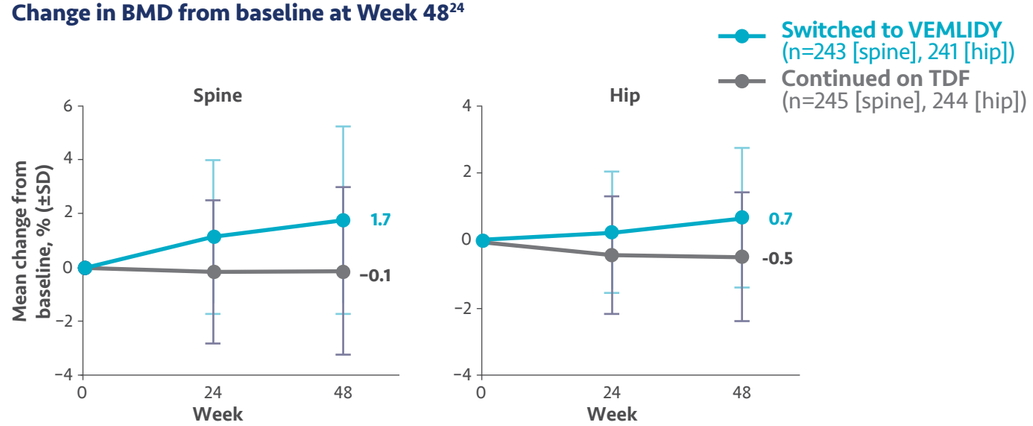
Change in $eGFR_{CG}$ from baseline at Week 48[24]

Median baseline $eGFR_{CG}$ of 90.9 mL/min and 90.3 mL/min, for VEMLIDY and TDF, respectively



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

Change in BMD from baseline at Week 48[24]



BMD declines (>5%) at the lumbar spine: 2% (VEMLIDY) vs 5% (TDF) at Week 48.
BMD declines (>7%) at the hip: 0% (VEMLIDY) vs 0% (TDF) at Week 48.

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

Please see Trial Designs starting on page 10 for complete details.

SD=standard deviation.

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VEMLIDY doesn't compromise on dose adjustment[1,17,25]

Same dose for patients with[1]:

- Mild, moderate, or severe renal impairment (eCrCl ≥15 mL/min) or end stage renal disease (ESRD; eCrCl <15 mL/min) receiving chronic hemodialysis
  - In patients on chronic hemodialysis, on hemodialysis days, administer VEMLIDY after completion of hemodialysis treatment
- Mild hepatic impairment (Child-Pugh A)

VEMLIDY: The only oral antiviral for CHB in adults without required renal dosage adjustment [1,17,25]

VEMLIDY is a pill that's 7.9 mm in diameter

VEMLIDY is a 25-mg pill taken once daily with food[1]

IMPORTANT SAFETY INFORMATION

Dosage and Administration

- **Testing Prior to Initiation:** HIV infection.
- **Prior to or when initiating, and during treatment:** 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.
- **Dosage in Adults:** 1 tablet taken once daily with food.
- **Renal Impairment:** Not recommended in patients with end stage renal disease (ESRD; eCrCl <15 mL/min) who are not receiving chronic hemodialysis; in patients on chronic hemodialysis, on hemodialysis days, administer VEMLIDY after completion of hemodialysis treatment.
- **Hepatic Impairment:** Not recommended in patients with decompensated (Child-Pugh B or C) hepatic impairment

Adverse reactions profile

Proportion of patients who discontinued treatment due to adverse reactions of any severity in Trials 108 and 110[1,24]

Week 96		Week 144	
VEMLIDY	TDF	VEMLIDY	TDF
1.5%	0.9%	1.6%	1.6%
(n=866)	(n=432)	(n=866)	(n=252)

Proportion of patients who discontinued treatment due to adverse reactions of any severity at Week 48 in Trial 4018 was 0.8% (2/243) for VEMLIDY and 0% (0/245) for TDF.[24]

Adverse reactions reported in ≥5% of patients with VEMLIDY in Trials 108 and 110:

- Week 96: Headache, abdominal pain, cough, back pain, fatigue, nausea, arthralgia, diarrhea, and dyspepsia[1]
- Week 144: Headache, upper respiratory tract infection, abdominal pain, cough, back pain, arthralgia, fatigue, nausea, diarrhea, dyspepsia, and pyrexia[24]

Adverse reactions observed with VEMLIDY in Trial 4018 at Week 48 were similar to those in Trials 108 and 110 at Week 96.[1]

Differences were observed between VEMLIDY and TDF in certain lipid parameters.[1,24]

- In Trials 108 and 110[1,24]:
  - Week 96: Mean changes from baseline in low-density lipoprotein cholesterol (LDL-C) (fasted) and triglycerides (TG) (fasted) were +7 mg/dL and +13 mg/dL for VEMLIDY, versus -10 mg/dL and -7 mg/dL for TDF[1]
  - Week 144: Mean changes from baseline in LDL-C (fasted) and TG (fasted) were +8 mg/dL and +18 mg/dL for VEMLIDY, versus -8 mg/dL and -2 mg/dL for TDF[24]
- In Trial 4018, changes from baseline in lipid parameters in the VEMLIDY and TDF groups at Week 48 were similar to those observed in Trials 108 and 110 at Week 96[1]

USE IN SPECIFIC POPULATIONS—PREGNANCY[1]

- 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
- 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 US reference population of the Metropolitan Atlanta Congenital Defects Program
- Based on prospective reports to the APR of exposures to TAF-containing regimens during pregnancy resulting in live births, the prevalence of birth defects in live births was 5.2% and 1.2% following first (n>200) and second/third (n>80) trimester exposure, respectively

Trial designs and baseline characteristics

Vemlidy® tenofovir alafenamide 25mg tablets

PIVOTAL TRIALS: 108 AND 110

The efficacy and safety of VEMLIDY 25 mg once daily in the treatment of CHB in adults with compensated liver disease were evaluated in 2 randomized, double-blind, active-controlled, noninferiority trials: Trial 108 (N=425 HBeAg– treatment-naïve and treatment-experienced patients) and Trial 110 (N=873 HBeAg+ treatment-naïve and treatment-experienced patients).[1,12,21,a] The primary efficacy endpoint for both trials was the proportion of patients with plasma HBV DNA levels below 29 IU/mL at Week 48. Additional efficacy endpoints evaluated at Week 48, Week 96, and Week 144 for both studies include the proportion of patients with HBV DNA <29 IU/mL, alanine aminotransferase (ALT) normalization, and hepatitis B surface antigen (HBsAg) loss and seroconversion. Hepatitis B envelope antigen (HBeAg) loss and seroconversion were also assessed in Trial 110.[1,12,21,24] In the original protocol, patients were randomized to VEMLIDY or TDF 300 mg once daily in the double-blind phase for 96 weeks, followed by an open-label VEMLIDY phase through Week 144.[24] The original protocol was amended to extend the double-blind phase from 96 weeks to 144 weeks, followed by an open-label phase through Week 384.[23] However, before implementation of the amendment protocol, 540 patients entered the open-label phase at Week 96 (n=360 remained on VEMLIDY and n=180 switched from TDF to VEMLIDY).[b] At Week 144, all 1,137 remaining HBeAg– and HBeAg+ patients (out of the original 1,298) entered the open-label VEMLIDY phase for an extension trial that is still ongoing.[26]

Not actual patients.

	Pooled population	
Baseline characteristics[23,24]	**VEMLIDY** (n=866)	**TDF** (n=432)
Mean age, y (range)	**40** (18-80)	**41** (18-72)
Male, n (%)	**544** (63)	**275** (64)
Asian, n (%)	**687** (79)	**333** (77)
HBV genotype A, B, C, D (%)	**6,18,48,26**	**7,20,46,24**
Mean HBV DNA, log_{10} IU/mL (range)	**7.0** (1.8-9.9)	**7.0** (1.4-9.9)
Median ALT, U/L (Q1, Q3)	**80** (56, 123)	**80** (53, 130)
Treatment-experienced, n (%)	**211** (24)	**108** (25)
Prior oral antiviral therapy, n (%)[c]		
Entecavir	**109** (13)	**49** (11)
Lamivudine	**86** (10)	**40** (9)
Adefovir dipivoxil	**35** (4)	**14** (3)
Telbivudine	**21** (2)	**12** (3)
Other[d]	**14** (2)	**6** (1)
History of cirrhosis, n (%)[e]	**65/636** (10)	**38/326** (12)
Hip BMD status, n (%)		
Normal	**570** (67)	**285** (67)
Osteopenia	**256** (30)	**131** (31)
Osteoporosis	**12** (1)	**2** (<1)
Not determined	**13** (2)	**8** (2)
Spine BMD status, n (%)		
Normal	**477** (55)	**237** (56)
Osteopenia	**309** (36)	**152** (36)
Osteoporosis	**57** (7)	**29** (7)
Not determined	**13** (2)	**8** (2)

[a]Key inclusion criteria: HBV DNA >20,000 IU/mL; ALT >60 U/L for men and >38 U/L for women (2x ULN based on the 2016 AASLD criteria).[12,21]
[b]The numbers of patients listed after Week 96 refer to those who entered the open-label phase or remained in the double-blind phase, and exclude patients who prematurely discontinued double-blind trial treatment by Week 96.[26]
[c]Excluding interferon and TDF.[24]
[d]Includes clevudine, tenofovir alafenamide, and other oral nucleoside/nucleotide agents.[24]
[e]Excludes patients with missing values.[23]

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Trial designs and baseline characteristics

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SWITCH TRIAL 4018

The efficacy and safety of switching from TDF 300 mg once daily to VEMLIDY 25 mg once daily in virologically suppressed adults with CHB infection were evaluated in a randomized, double-blind, active-controlled noninferiority trial: Trial 4018 (N=488). Patients must have been taking TDF 300 mg once daily for ≥12 months, with HBV DNA less than the Lower Limit of Quantitation by local laboratory assessment for ≥12 weeks prior to screening and HBV DNA <20 IU/mL at screening. Patients were randomized in a 1:1 ratio to either switch to VEMLIDY (n=243) or stay on TDF (n=245). At baseline, the median duration of exposure to TDF prior to the trial was similar in both treatment groups (TAF=220.0 weeks, TDF=224.3 weeks). The primary efficacy endpoint was the proportion of patients with plasma HBV DNA ≥20 IU/mL at Week 48. Additional efficacy endpoints included the proportion of patients with HBV DNA <20 IU/mL, ALT normal and normalization, HBsAg loss and seroconversion, and HBeAg loss and seroconversion.[1]

Baseline characteristics[24]	**VEMLIDY** (n=243)	**TDF** (n=245)
Mean age, y (SD)	**51** (10.5)	**51** (10.8)
Male, n (%)	**179** (74)	**166** (68)
Asian, n (%)	**195** (80)	**205** (84)
HBeAg+, n (%)	**78** (32)	**79** (32)
History of cirrhosis, n (%)[a]	**32/233** (14)	**45/235** (19)
Prior oral antiviral therapy, n (%)[b]		
Lamivudine	**95** (39)	**96** (39)
Adefovir dipivoxil	**94** (39)	**91** (37)
Entecavir	**47** (19)	**52** (21)
Telbivudine	**21** (9)	**27** (11)
Other[c]	**13** (5)	**11** (4)
Hip BMD status, n (%)		
Normal	**143** (59)	**124** (51)
Osteopenia	**89** (37)	**116** (48)
Osteoporosis	**9** (4)	**4** (2)
Spine BMD status, n (%)		
Normal	**125** (51)	**120** (49)
Osteopenia	**90** (37)	**97** (40)
Osteoporosis	**28** (12)	**28** (11)

[a]Excludes patients with missing values.
[b]Excludes TDF.
[c]Includes clevudine, emtricitabine/TDF, and tenofovir alafenamide.

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For the treatment of chronic hepatitis B virus (HBV) infection in adults with compensated liver disease[1]

Don’t accept less than VEMLIDY

No compromises on dose adjustment with VEMLIDY[1,17,25,a]

0% resistance in a broad range of CHB patients (TN, TE, and virologically suppressed)[1,22,23]

Consider switching your patients to VEMLIDY based on proven efficacy and less impact on renal and bone safety parameters vs TDF[1,24,b]

[a]Not recommended in patients with ESRD who are not receiving chronic hemodialysis or in patients with decompensated hepatic impairment.[1]

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

TE=treatment-experienced; TN=treatment-naïve.

Eligible patients with commercial insurance can save on out-of-pocket costs with the VEMLIDY Co-pay Coupon Program. **For more information, call 1-877-627-0415 or visit VEMLIDYhcp.com**

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IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- **New Onset or Worsening Renal Impairment:** Prior to or when initiating VEMLIDY, and during treatment on a clinically appropriate schedule, assess serum creatinine, eCrCl, urine glucose, and urine protein in all patients. Also assess serum phosphorus in patients with chronic kidney disease (CKD).

Adverse Reactions

Most common adverse reactions (incidence ≥5%; all grades) were headache, abdominal pain, cough, back pain, fatigue, nausea, arthralgia, diarrhea, and dyspepsia.

Click here for VEMLIDY full Prescribing Information, including **BOXED WARNING** on **posttreatment severe acute exacerbation of hepatitis B**, and visit VEMLIDYhcp.com.

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