U.S. FOOD & DRUG ADMINISTRATION

VEMLIDY: Labeling Updates

February 4, 2020

The VEMLIDY (tenofovir alafenamide) label was updated to include the Week 48 safety and efficacy data from Study GS-US-320-4018, a study in virologically suppressed adults with chronic hepatis B virus infection who switched from tenofovir disoproxil fumarate 300 mg once daily (QD) to tenofovir alafenamide 25 mg QD. In addition, updates to the pregnancy section were made. A summary of the changes is provided below:

Section 6: ADVERSE REACTIONS

6.1 Clinical Trials Experience

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.

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.

Section 8: USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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%.

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.

Section 14: CLINICAL STUDIES

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 ≥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, ≥ 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 ≥69 years; >34 U/L for females 18 to <69 years and >32 U/L for females ≥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.

The updated label will soon be available at Drugs@FDA or DailyMed.

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