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 hepatitis 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

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

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

<table>
<thead>
<tr>
<th></th>
<th>VEMLIDY (N=243)</th>
<th>TDF (N=245)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNA ≥20 IU/mL²</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Treatment Difference³</td>
<td>0.0% (95% CI = -1.9% to 2.0%)</td>
<td></td>
</tr>
<tr>
<td>HBV DNA &lt;20 IU/mL</td>
<td>96%</td>
<td>96%</td>
</tr>
<tr>
<td>Treatment Difference³</td>
<td>0.0% (95% CI = -3.1% to 3.7%)</td>
<td></td>
</tr>
</tbody>
</table>

- No virologic data at Week 48
- Discontinued study drug due to AE or death
- Discontinued study drug due to other reasons and last available HBV DNA <20 IU/mL

a. Week 48 window was between Day 395 and Day 3/6 (inclusive).

b. No subject discontinued treatment due to lack of efficacy.

c. Adjusted by baseline age group (<50, ≥50 years) and baseline HBSAg status strat.

d. Includes subjects who discontinued for reasons other than AE, death, or lack of efficacy, e.g., withdrew consent, less to follow-up, etc.

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

<table>
<thead>
<tr>
<th></th>
<th>VEMLIDY (N=243)</th>
<th>TDF (N=245)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>89%</td>
<td>85%</td>
</tr>
<tr>
<td>Normal ALT (Central Lab)</td>
<td>79%</td>
<td>75%</td>
</tr>
<tr>
<td>Normal ALT (AASLD)</td>
<td>79%</td>
<td>75%</td>
</tr>
<tr>
<td>Normalized ALT (Central Lab)ⁱ</td>
<td>50%</td>
<td>37%</td>
</tr>
<tr>
<td>Normalized ALT (AASLD)ⁱ</td>
<td>50%</td>
<td>26%</td>
</tr>
</tbody>
</table>

- **Serology**
  - HBSAg Loss / Seroconversion¹: 8% / 3%
  - 6% / 0

- HBSAg Loss / Seroconversion:
  - 0 / 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) at the central laboratory range (>43 ULN for males 18 to <65 years and >35 ULN for males ≥66 years; >34 ULN for females 18 to <65 years and >25 ULN for females ≥66 years) at baseline.

c. Proportion of subjects at Week 48 VEMLIDY, TDF: 70/76; TDF: 70%

d. The population used for analysis of ALT normalization included only subjects with ALT above ULN of the 2018 American Association for the Study of the Liver Clinicians (AASLD) criteria (35 ULN males and 25 ULN females) at baseline.

e. Proportion of subjects at Week 48 VEMLIDY: 26/45; TDF: 25/43.

f. The population used for serology analysis included only subjects with antigen (HBSAg) positive and antibody (Anti-HBS) negative or missing at baseline.

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