ספטמבר 21

הודעה על עדכון עלונים:

Vemlidy film coated tablets

(tenofovir alafenamide fumarate 25 mg)

רופאים ורוקחים נכבדים,

חברת גיליאד סיאנסז ישראל בע"מ מבקשת להודיעכם על עדכון בעלון לרופא של התכשיר בנדון.

ההתוויה הרשומה לתכשיר בישראל:

Vemlidy is indicated for the treatment of chronic hepatitis B in adults and adolescents (aged 12 years and older with body weight at least 35 kg).

השינויים מסומנים בעלון המצורף כאשר הטקסט המודגש באדום הוסף לעלון ואילו הטקסט המחוק ~~בקו~~ ~~חוצה~~ נגרע ממנו. הסימונים בצהוב הינם החמרות במידע הבטיחותי.

העדכונים המשמעותיים ביותר מופיעים במכתב זה, קיימים עדכונים נוספים.

העלונים לרופא ולצרכן נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות:

https://data.health.gov.il/drugs/index.html#/byDrug

כמו כן ,ניתן לקבלם מודפסים על ידי פנייה לבעל הרישום:

גיליאד סיאנסז ישראל בע"מ, רחוב החרש 4 ,ת.ד. 6090, פארק העסקים הוד השרון 4524075, ישראל.

התכשיר משווק ע"י סל"א.

בברכה,

מריה חורגין

רוקחת ממונה

גיליאד סיאנסז ישראל בע"מ

העדכונים המהותיים בעלון לרופא:

4.8 Undesirable effects

Changes in lipid laboratory tests

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In *Study 4018,* median changes in fasting lipid parameters from baseline to Week 48 were observed in both treatment groups. In the group that switched from tenofovir disoproxil to tenofovir alafenamide, increases in median fasting total cholesterol, LDL, HDL, and triglycerides were observed, while the group continuing treatment with tenofovir disoproxil demonstrated reductions in median fasting total cholesterol, HDL, and triglycerides, and a minimal median increase in LDL ($p < 0.001$ for the difference between treatment groups in all parameters, Table 9 section 5.1). ~~Median (Q1, Q3) change from baseline at Week 48 in total cholesterol to HDL ratio was 0.2 (-0.1, 0.5) in the tenofovir alafenamide group and 0.0 (-0.3, 0.3) in the tenofovir disoproxil group ($p < 0.001$ for the difference between treatment groups).~~

In the open-label phase of *Study 4018*, where patients switched to tenofovir alafenamide at Week 48, lipid parameters at Week 96 in patients who remained on tenofovir alafenamide were comparable to those at Week 48, whereas at Week 96 median increases in fasting total cholesterol, direct LDL, HDL, and triglycerides were observed in patients who switched from tenofovir disoproxil to tenofovir alafenamide at Week 48 (Table 9 section 5.1).

5.1 Pharmacodynamic properties

Resistance

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In virologically suppressed patients receiving tenofovir alafenamide following switch from tenofovir disoproxil treatment in *Study 4018*, ~~no patient experienced a virologic blip (one visit with HBV DNA ≥ 69 IU/mL), virologic breakthrough or persistent viremia during treatment, and 0 of 243 (0.0%) patients qualified for resistance analysis through 48 weeks of tenofovir alafenamide treatment.~~through 96 weeks of tenofovir alafenamide treatment one patient in the TAF-TAF group experienced a virologic blip (one visit with HBV DNA ≥ 69 IU/mL) and one patient in the TDF-TAF group experienced a virologic breakthrough. No HBV amino acid substitutions associated with resistance to TAF or TDF were detected through 96 weeks of treatment.

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Virologically suppressed adult patients in Study 4018

The efficacy and safety of tenofovir alafenamide in virologically suppressed adults with chronic hepatitis B is based on 48-week data from ~~an ongoing~~ a randomized, double-blind, active-controlled study, *Study 4018* (N=243 on tenofovir alafenamide; N=245 on tenofovir disoproxil), including data from patients who participated in the open-label phase of *Study 4018* from Week 48 through Week 96 (N=235 remained on tenofovir alafenamide [TAF-TAF]; N=237 switched from tenofovir disoproxil to tenofovir alafenamide at Week 48 [TDF-TAF]).

Treatment outcomes of *Study 4018* at Week 48 and Week 96 are presented in Table 7 and Table 8.

Table 7: HBV DNA efficacy parameters at Week 48[a,b] and Week 96[b,c]

	TAF (N=243)	TDF (N=245)	TAF-TAF (N=243)	TDF-TAF (N=245)
	Week 48			Week 96
HBV DNA ≥ 20 IU/mL[b,d]	1 (0.4%)	1 (0.4%)	1 (0.4%)	1 (0.4%)
Treatment Difference[e]	0.0% (95% CI = -1.9% to 2.0%)			0.0% (95% CI = -1.9% to 1.9%)
HBV DNA < 20 IU/mL	234 (96.3%)	236 (96.3%)	230 (94.7%)	230 (93.9%)
Treatment Difference[e]	0.0% (95% CI = -3.7% to 3.7%)			0.9% (95% CI = -3.5% to 5.2%)
No Virologic Data	8 (3.3%)	8 (3.3%)	12 (4.9%)	14 (5.7%)
Discontinued Study Drug Due to AE or Death and Last Available HBV DNA < 20 IU/mL	2 (0.8%)	0	3 (1.2%)	1 (0.4%)
Discontinued Study Drug Due to Other Reasons[f] and Last Available HBV DNA < 20 IU/mL	6 (2.5%)	8 (3.3%)	7 (2.9%)	11 (4.5%)
Missing Data During Window but on Study Drug	0	0	2 (0.8%)	2 (0.8%)

TDF = tenofovir disoproxil
TAF = tenofovir alafenamide
a. Week 48 window was between Day 295 and 378 (inclusive).
b. As determined by the modified US FDA-defined snapshot algorithm.
c. Open-label phase, Week 96 window is between Day 589 and 840 (inclusive).
d. No patient discontinued treatment due to lack of efficacy.
e. Adjusted by baseline age groups (< 50, ≥ 50 years) and baseline HBeAg status strata.
f. Includes patients who discontinued for reasons other than an AE, death or lack of efficacy, e.g., withdrew consent, loss to follow-up, etc.

Table 8: Additional efficacy parameters at Week 48 and Week 96[a]

	TAF (N=243)	TDF (N=245)	TAF-TAF (N=243)	TDF-TAF (N=245)
	Week 48		Week 96	
ALT				
Normal ALT (Central Lab)	89%	85%	88%	91%
Normal ALT (AASLD)	79%	75%	81%	87%
Normalized ALT (Central Lab)[b,c,d]	50%	37%	56%	79%
Normalized ALT (AASLD)[e,f,g]	50%	26%	56%	74%
Serology				
HBeAg Loss / Seroconversion[h]	8% / 3%	6% / 0	18% / 5%	9% / 3%
HBsAg Loss / Seroconversion	0 / 0	2% / 0	2% / 1%	2% / < 1%

TDF = tenofovir disoproxil
TAF = tenofovir alafenamide

a. Missing = failure analysis
b. The population used for analysis of ALT normalization included only patients with ALT above upper limit of normal (ULN) of the central laboratory range (> 43 U/L males 18 to < 69 years and > 35 U/L males ≥ 69 years; > 34 U/L females 18 to < 69 years and > 32 U/L females ≥ 69 years) at baseline.
c. Proportion of patients at Week 48: TAF, 16/32; TDF, 7/19.
d. Proportion of patients at Week 96: TAF, 18/32; TDF, 15/19.
e. The population used for analysis of ALT normalization included only patients 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.
f. Proportion of patients at Week 48: TAF, 26/52; TDF, 14/53.
g. Proportion of patients at Week 96: TAF, 29/52; TDF, 39/53
h. The population used for serology analysis included only patients with antigen (HBeAg) positive and anti-body (HBeAb) negative or missing at baseline.

Changes in bone mineral density in Study 4018
The mean percentage change in BMD from baseline to Week 48 as assessed by DXA was +1.7% with tenofovir alafenamide compared to −0.1% with tenofovir disoproxil at the lumbar spine and +0.7% compared to −0.5% at the total hip. BMD declines of greater than 3% at the lumbar spine were experienced by 4% of tenofovir alafenamide patients and 17% of tenofovir disoproxil patients at Week 48. BMD declines of greater than 3% at the total hip were experienced by 2% of tenofovir alafenamide patients and 12% of tenofovir disoproxil patients at Week 48.

In the open-label phase, mean percentage change in BMD from baseline to Week 96 in patients who remained on tenofovir alafenamide was +2.3% at the lumbar spine and +1.2% at the total hip, compared to +1.7% at the lumbar spine and +0.2% at the total hip in those who switched from tenofovir disoproxil to tenofovir alafenamide at Week 48.

Changes in renal laboratory tests in Study 4018
The median change from baseline to Week 48 in eGFR by Cockcroft-Gault method was +~~0.9~~2.2 mL per minute in the tenofovir alafenamide group and −~~2~~1.7 mL per minute in those receiving tenofovir disoproxil. At Week 48, there was a median increase from baseline in serum creatinine among patients randomized to continue treatment with tenofovir disoproxil (0.~~02~~01 mg/dL) compared with ~~no~~ a median ~~change~~ decrease from baseline among those who were switched to tenofovir alafenamide (-0.0~~0~~1 mg/dL). ~~Further, median percentage decreases from baseline were observed in the tenofovir alafenamide group at Week 48 in urine retinol binding protein to creatinine ratio and urine beta-2-microglobulin to creatinine ratio, compared with median percentage increases from baseline for both of these renal parameters in the tenofovir disoproxil group.~~

In the open-label phase, the median change in eGFR from baseline to Week 96 was 1.6 mL/min in patients who remained on tenofovir alafenamide, compared to +0.5 mL/min in patients who switched from tenofovir disoproxil to tenofovir alafenamide at Week 48. The median change in serum creatinine from baseline to Week 96 was −0.02 mg/dL in those who remained on tenofovir alafenamide, compared to −0.01 mg/dL in those who switched from tenofovir disoproxil to tenofovir alafenamide at Week 48.

Changes in lipid laboratory tests in Study 4018
Changes from double-blind baseline to Week 48 and Week 96 in total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, and total cholesterol to HDL ratio ~~among subjects treated with tenofovir alafenamide and tenofovir disoproxil~~ are presented in Table 9.

Table 9: Median changes in lipid laboratory tests at Week 48 and Week 96

	TAF (N=236)	TAF (N=226)	TAF-TAF (N=220)	TDF (N=230)	TDF (N=~~245~~222)	TDF-TAF N=219)
	Baseline	Week 48	Week 96	Baseline	Week 48	Week 96
	(Q1, Q3) (mg/dL)	Median change[a] (Q1, Q3) (mg/dL)	Median change (Q1, Q3) (mg/dL)	(Q1, Q3) (mg/dL)	Median change[a] (Q1, Q3) (mg/dL)	Median change (Q1, Q3) (mg/dL)
Total Cholesterol (fasted)	166 (147, 189)	19 (6, 33)	16 (3, 30)	169 (147, 188)	−4 (−16, 8)	15 (1, 28)
HDL-Cholesterol (fasted)	48 (41, 56)	3 (−1, 8)	4 (−1, 10)	48 (40, 57)	−1 (−5, 2)	4 (0, 9)
LDL-Cholesterol (fasted)	102 (87,123)	16 (5, 27)	17 (6, 28)	103 (87, 120)	1 (−8, 12)	14 (3, 27)
Triglycerides (fasted)[b]	90 (66, 128)	16 (−3, 44)	9 (−8, 28)	89 (68, 126)	−2 (−22, 18)	8 (−8, 38)
Total Cholesterol to HDL ratio	3.4 (2.9, 4.2)	0.2 (−0.1, 0.5)	0.0 (−0.3, 0.3)	3.4 (2.9, 4.2)	0.0 (−0.3, 0.3)	0.0 (−0.3, 0.3)

TDF = tenofovir disoproxil

TAF = tenofovir alafenamide

a. P-value was calculated for the difference between the TAF and TDF groups at Week 48, from Wilcoxon Rank Sum test and was statistically significant ($p < 0.001$) for median changes (Q1, Q3) from baseline in total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides and total cholesterol to HDL ratio.

~~a.~~b. Number of patients for triglycerides (fasted) for TAF group was N=235 at baseline, N=225 at Week 48 and N=218 for TAF-TAF group at Week 96.