פברואר 2022

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:

4.4 Special warnings and precautions for use

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Renal impairment

Patients with creatinine clearance < 30 mL/min

The use of tenofovir alafenamide ~~Vemlidy~~ once daily in patients with CrCl ≥ 15 mL/min and < 30 mL/min is based on Week ~~24 interim~~ 96 data on the efficacy and safety of switching from another antiviral regimen to tenofovir alafenamide in an ~~ongoing~~ open-label clinical study of virologically suppressed chronic ~~HBV-infected~~HBV infected patients (see sections 4.8 and 5.1). ~~-~~There are very limited data on the safety and efficacy of tenofovir alafenamide ~~Vemlidy~~ in ~~HBV-infected~~HBV infected patients with CrCl < 15 mL/min on chronic haemodialysis (see sections 4.8, 5.1 and 5.2).

The use of this medicinal product ~~Vemlidy~~ is not recommended in patients with CrCl < 15 mL/min who are not receiving haemodialysis (see section 4.2).

4.7 Effects on ability to drive and use machines

Vemlidy may have minor ~~has no or negligible~~ influence on the ability to drive and use machines. Patients should be informed that dizziness has been reported during treatment with tenofovir alafenamide.

4.8 Undesirable effects

Summary of the safety profile

Assessment of adverse reactions is based on clinical study data and postmarketing data. In pooled safety data from 2 controlled Phase 3 studies (GS-US-320-0108 and GS-US-320-0110; "*Study 108*" and "*Study 110*", respectively), ~~, in which 866 HBV-infected viremic patients with elevated serum ALT levels received 25 mg tenofovir alafenamide once daily in a double-blind fashion through Week 96 (median duration of blinded study drug exposure of 104 weeks) and from post-marketing experience. The~~ the most frequently reported adverse reactions at Week 96 analysis were headache (12%), nausea (6%), and fatigue (6%). ~~-~~After Week 96, patients either remained on their original blinded treatment up to Week 144 or received open-label tenofovir alafenamide.

The safety profile of tenofovir alafenamide was similar in virologically suppressed patients switching from tenofovir disoproxil to tenofovir alafenamide in *Study 108*, *Study 110* and a controlled Phase 3 study GS-US-320-4018 *(Study 4018).* Changes in lipid laboratory tests were observed in these studies following a switch from tenofovir disoproxil (see section 5.1). ~~*Study 108* and *Study 110*. No additional adverse reactions to tenofovir alafenamide were identified from Week 96 through Week 144 in the double-blind phase and in the subset of subjects receiving open-label tenofovir alafenamide treatment (see section 5.1).~~

~~In a double-blind, randomized, active-controlled study (GS-US-320-4018; "*Study 4018*") in virologically suppressed subjects who switched from tenofovir disoproxil to 25 mg tenofovir alafenamide (N=243), changes in lipid laboratory tests were observed.~~

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~~*Changes in lipid laboratory tests*~~

~~In a pooled analysis of *Studies 108* and *110*, median changes in fasting lipid parameters from baseline to Week 96 were observed in both treatment groups. In the tenofovir alafenamide group, decreases in median fasting total cholesterol and HDL, and increases in median fasting direct LDL and triglycerides were observed, while the tenofovir disoproxil group demonstrated median reductions in all parameters (see Table 6). In patients randomised initially to tenofovir alafenamide and switched to receive open-label tenofovir alafenamide at Week 96, the median (Q1, Q3) changes from double-blind baseline to Week 144 were as follows (mg/dL): total cholesterol was 0 (-16, 18); LDL was 8 (-6, 24); HDL was -5 (-12, 2); triglycerides were 11 (-11, 40); total cholesterol to HDL ratio was 0.3 (0.0, 0.7). In patients randomised initially to tenofovir disoproxil and switched to open-label tenofovir alafenamide at Week 96, the median (Q1, Q3) changes from double-blind baseline to Week 144 were as follows (mg/dL): total cholesterol was 1 (17, 20); LDL was 9 (5, 26); HDL was 8 (15, 1); triglycerides were 14 (10, 43); total cholesterol to HDL ratio was 0.4 (0.0, 1.0).~~

~~In the open-label phase of *Studies 108* and *110*, where patients switched to open-label tenofovir alafenamide at Week 96, lipid parameters at Week 144 in patients who remained on tenofovir alafenamide were similar to those at Week 96, whereas 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 96. In the open label phase, median (Q1, Q3) change from Week 96 to Week 144 in total cholesterol to HDL ratio was 0.0 (-0.2, 0.4) in patients who remained on tenofovir alafenamide and 0.2 (-0.2, 0.6) in patients who switched from tenofovir disoproxil to tenofovir alafenamide at Week 96.~~

~~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).~~

~~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).~~

In the open-label Phase 2 study (GS-US-320-4035; "*Study 4035*") to evaluate the efficacy and safety of switching from another antiviral regimen to tenofovir alafenamide in virologically suppressed chronic HBV infected patients, small median increases in fasting total cholesterol, direct LDL, HDL, and triglycerides from baseline to Week 96 were observed in subjects with moderate or severe renal impairment (Part A Cohort 1) and subjects with moderate or severe hepatic impairment (Part B), consistent with changes observed in *Studies 108 and 110*. Small median decreases in total cholesterol, LDL and triglycerides were observed in subjects with ESRD on hemodialysis in Part A Cohort 2, while small median increases were observed in HDL from baseline to Week 96. Median (Q1, Q3) change from baseline at Week 96 in total cholesterol to HDL ratio was 0.1 (-0.4, 0.4) in the moderate or severe renal impairment group, and -0.4 (-0.8,-0.1) in subjects with ESRD on hemodialysis and 0.1 (-0.2, 0.4) in subjects with moderate or severe hepatic impairment.

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Other ~~S~~special ~~P~~populations

In ~~an ongoing open-label Phase 2 study (GS-US-320-4035; "~~*Study 4035*~~")~~ in virologically suppressed patients with moderate to severe renal impairment (eGFR by Cockcroft-Gault method 15 to 59 mL/min;

Part A, Cohort 1, N = 78), end stage renal disease (ESRD) (eGFR < 15 mL/min) on haemodialysis (Part A, Cohort 2, N = 15), and/or moderate to severe hepatic impairment (Child-Pugh Class B or C at screening or by history; Part B, N = 31) who switched from another antiviral regimen to tenofovir alafenamide, no additional adverse reactions to tenofovir alafenamide were identified through Week ~~24~~96.

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5.1 Pharmacodynamic properties

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Changes in lipid laboratory tests in Study 108 and Study 110

In a pooled analysis of *Studies 108* and *110*, median changes in fasting lipid parameters from baseline to Week 96 were observed in both treatment groups. For patients who switched to open label tenofovir alafenamide at Week 96, changes from double-blind baseline for patients randomised initially to tenofovir alafenamide and tenofovir disoproxil at Week 96 and Week 144 in total cholesterol, high density lipid (HDL)-cholesterol, low density lipid (LDL)-cholesterol, triglycerides, and total cholesterol to HDL ratio are presented in Table 6. At Week 96, the end of the double-blind phase, decreases in median fasting total cholesterol and HDL, and increases in median fasting direct LDL and triglycerides were observed in the tenofovir alafenamide group, while the tenofovir disoproxil group demonstrated median reductions in all parameters.

In the open-label phase of *Studies 108* and *110*, where patients switched to open-label tenofovir alafenamide at Week 96, lipid parameters at Week 144 in patients who remained on tenofovir alafenamide were similar to those at Week 96, whereas 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 96. In the open label phase, median (Q1, Q3) change from Week 96 to Week 144 in total cholesterol to HDL ratio was 0.0 (-0.2, 0.4) in patients who remained on tenofovir alafenamide and 0.2 (-0.2, 0.6) in patients who switched from tenofovir disoproxil to tenofovir alafenamide at Week 96.

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Renal and/or hepatic impairment Study 4035

Study 4035 ~~is~~was an ~~ongoing~~ open-label clinical study to evaluate the efficacy and safety of switching from another antiviral regimen to tenofovir alafenamide in virologically suppressed chronic ~~HBV-infected~~HBV infected patients. ~~-~~Part A of the study include~~s~~d patients with moderate to severe renal impairment (eGFR by Cockcroft-Gault method between 15 and 59 mL/min; Cohort 1, N = 78) or ESRD (eGFR by Cockcroft-Gault method < 15 mL/min) on hemodialysis (Cohort 2, N = 15). ~~-~~Part B of the study include~~ds~~ patients (N = 31) with moderate ~~to~~ or severe hepatic impairment (Child-Pugh Class B or C at screening or a history of CPT score ≥ 7 with any CPT score ≤ 12 at screening). ~~The final clinical and laboratory outcomes will be reported following study completion at Week 96.~~

The primary endpoint was the proportion of subjects with HBV DNA < 20 IU/mL at Week 24. Secondary efficacy endpoints at Weeks 24 and 96 included the proportion of subjects with HBV DNA < 20 IU/mL and target detected/not detected (ie, < LLOD), the proportion of subjects with biochemical response (normal ALT and normalized ALT), the proportion of subjects with serological response (loss of HBsAg and seroconversion to anti-HBs and loss of HBeAg and seroconversion to anti-HBe in HBeAg-positive subjects) and change from baseline in CPT and Model for End Stage Liver Disease (MELD) scores for hepatically impaired subjects in Part B.

Renally impaired adult patients in Study 4035, Part A

At baseline, 98% (91/93) of patients in Part A had HBV DNA < 20 IU/mL and 66% (61/93) had an undetectable HBV DNA level. Median age was 65 years, 74% were male, 77% were Asian, 16% were White, and 83% were HBeAg-negative. The most commonly used HBV medication oral antivirals included TDF (N = 58), lamivudine (N = 46), adefovir dipivoxil (N = 46), and entecavir (N = 43). At baseline, 97% and 95% of patients had ALT ≤ ULN based on central laboratory criteria and 2018 AASLD

criteria, respectively; median eGFR by Cockcroft-Gault was 43.7 mL/min (45.7 mL/min in Cohort 1 and 7.32 mL/min in Cohort 2); and 34% of patients had a history of cirrhosis.

Treatment outcomes of *Study 4035* Part A at Weeks 24 and 96 are presented in Table 10.

Table 10: Efficacy parameters for Renally Impaired Patients at Weeks 24 and 96

	Cohort 1[a] (N=78)		Cohort 2[b] (N= 15)		Total (N=93)	
	Week 24	Week 96	Week 24	Week 96	Week 24	Week 96[d]
HBV DNA[c]						
HBV DNA < 20 IU/mL	76/78 (97.4%)	65/78 (83.3%)	15/15 (100.0%)	13/15 (86.7%)	91/93 (97.8%)	78/93 (83.9%)
ALT[c]						
Normal ALT (Central Lab)	72/78 (92.3%)	64/78 (82.1%)	14/15 (93.3%)	13/15 (86.7%)	86/93 (92.5%)	77/93 (82.8%)
Normal ALT (AASLD)[e]	68/78 (87.2%)	58/78 (74.4%)	14/15 (93.3%)	13/15 (86.7%)	82/93 (88.2%)	71/93 (76.3%)

a. Part A Cohort 1 includes patients with moderate or severe renal impairment
b. Part A Cohort 2 includes patients with ESRD on hemodialysis
c. Missing = Failure analysis
d. The denominator includes 12 subjects (11 for Cohort 1 and 1 for Cohort 2) who prematurely discontinued study drug.
e. 2018 American Association of the Study of Liver Diseases (AASLD) criteria

Hepatically impaired adult patients in Study 4035, Part B

At baseline, 100% (31/31) of patients in Part B had baseline HBV DNA < 20 IU/mL and 65% (20/31) had an undetectable HBV DNA level. Median age was 57 years (19% ≥ 65 years), 68% were male, 81% were Asian, 13% were White, and 90% were HBeAg-negative. The most commonly used HBV medication oral antivirals included TDF (N = 21), lamivudine (N = 14), entecavir (N = 14), and adefovir dipivoxil (N = 10). At baseline, 87% and 68% of patients had ALT ≤ ULN based on central laboratory criteria and 2018 AASLD criteria, respectively; median eGFR by Cockcroft-Gault was 98.5 mL/min; 97% of patients had a history of cirrhosis, median (range) CPT score was 6 (5–10), and median (range) MELD score was 10 (6–17).

Treatment outcomes of *Study 4035* Part B at Weeks 24 and 96 are presented in Table 11.

Table 11: Efficacy parameters for Hepatically Impaired Patients at Weeks 24 and 96

	Part B (N=31)	
	Week 24	Week 96[b]
HBV DNA[a]		
HBV DNA < 20 IU/mL	31/31 (100.0%)	24/31 (77.4%)
ALT[a]		
Normal ALT (Central Lab)	26/31 (83.9%)	22/31 (71.0%)
Normal ALT (AASLD)[c]	25/31 (80.6%)	18/31 (58.1%)
CPT and MELD Score		
Mean change from Baseline in CPT Score (SD)	0 (1.1)	0 (1.2)
Mean Change from Baseline in MELD Score (SD)	-0.6 (1.94)	-1.0 (1.61)

CPT = Child-Pugh Turcotte;

MELD = Model for End-Stage Liver Disease

a. Missing = Failure analysis

b. The denominator includes 6 subjects who prematurely discontinued study drug
c. 2018 American Association of the Study of Liver Diseases (AASLD) criteria

Changes in lipid laboratory tests in Study 4035
Small median increases from baseline to Week 24 and Week 96 in total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, and total cholesterol to HDL ratio among patients with renal or hepatic impairment are consistent when compared with results observed from other studies involving switch to TAF (see section 5.1 for *Studies 0108, 0110 and 4018*), whereas decreases from baseline in total cholesterol, LDL-cholesterol, triglycerides, and total cholesterol to HDL ratio were observed in patients with ESRD on haemodialysis at Week 24 and Week 96.

העדכונים המהותיים בעלון לצרכן:

(עדכוני עריכה וניסוח ללא השפעה על תוכן קליני)