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Vemlidy® (tenofovir alafenamide) Effect of Food

This document is in response to your request for information regarding Vemlidy® (tenofovir alafenamide [TAF]) and the effect of food on TAF pharmacokinetics (PK), efficacy, and safety.

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The full indication, important safety information, and boxed warnings are available at: www.gilead.com/-/media/files/pdfs/medicines/liver-disease/vemlidy/vemlidy_pi.

Summary

Product Labeling[1]

The recommended dosage of TAF in adults and pediatric patients ≥6 years of age and weighing ≥25 kg is one 25 mg tablet taken orally once daily with food.

The effect of high fat meal (~800 kcal, 50% fat) relative to fasting as determined by AUC_{last} (fed to fasting ratio; GMR [90% CI]) was 1.65 (1.51, 1.81).

Inform patients that it is important to take TAF on a regular dosing schedule with food and to avoid missing doses, as it can result in development of resistance.

Clinical Data on the Effect of Food on TAF PK, Efficacy, and Safety

- In a phase 1 PK study (N=40), the overall TAF exposures under both fasted and fed conditions were in the range of exposures associated with efficacy and safety in the TAF CHB phase 1 study and phase 3 studies. TAF administered under fasted and fed conditions was well tolerated.[2]
- In a substudy of the phase 3 Study 4018 that evaluated the effect of food intake on the efficacy and safety of TAF, similar rates of viral suppression (HBV DNA <20 IU/mL) at Week 96 were seen in participants who received TAF with or without food. Safety and tolerability through Week 96 were also similar between participants who received TAF with or without food.[3]

Clinical Data on the Effect of Food on TAF PK, Efficacy, and Safety

PK Study: Effect of Food on TAF in Healthy Volunteers[2]

The effect of TAF and food was studied in 40 healthy volunteers in a phase 1, single-center, randomized, open-label, 2-treatment, 2-period, crossover study. Healthy volunteers from both the fasted and fed (high calorie/high fat; ~800 kcal/50% fat) groups were given a single

dose of 25 mg of TAF followed by a washout period; TAF exposures were compared between the two groups (Table 1).

Table 1. PK Study: TAF PK in Fasting and Fed Conditions[2]

TAF PK Parameter	Fasted (n=39)	Fed (n=40)	GMR (90% CI)
AUC_{∞}, mean (%CV), h·ng/mL	172 (34)	289 (39)	168 (154, 183)
AUC_{last}, mean (%CV), h·ng/mL	170 (34)	283 (40)	165 (151, 181)
C_{max}, mean (%CV), ng/mL	266 (47)	253 (46)	94.3 (78.5, 113)
T_{max}, median (Q1, Q3), h	0.5 (0.25, 0.5)	1 (0.5, 1.5)	–

Abbreviations: AUC_{∞}=AUC from time 0 to infinity; AUC_{last}=AUC from time 0 to time of last measurable concentration; C_{max}=peak concentration; CV=coefficient of variation; GMR=geometric mean ratio; T_{max}=time to peak concentration.

The overall TAF exposures in the present study under both fasted and fed conditions were in the range of exposures associated with efficacy and safety in the TAF CHB phase 1 study (n=41; AUC range, 17.3–1630 h·ng/mL; TAF evaluated at 8, 25, 40, and 120 mg) and phase 3 studies (n=698; AUC range, 56.6–2690 h·ng/mL; TAF evaluated at 25 mg). TAF administered under fasted and fed conditions was well tolerated. All AEs observed were mild in severity (Grade 1), and there were no clinically relevant laboratory abnormalities.

Study 4018: Switch From TDF to TAF–Effect of Food in Virologically Suppressed Participants With CHB

Study design and demographics

In a 96-week subanalysis of Study 4018, the effect of food intake on the efficacy and safety of TAF was assessed. Study 4018 was a double-blind, randomized, phase 3 study that evaluated the safety and efficacy of switching from TDF to TAF in virologically suppressed participants with CHB. Participants had been treated with TDF for ≥48 weeks prior to screening and had an $eGFR_{CG}$ ≥50 mL/min at screening. At Week 48, participants who switched to TAF at baseline (n=243), and participants who remained on TDF (n=245) were switched to open-label TAF through Week 96.[4] Study participants received the study drug either with food (TAF to TAF, n=162; TDF to TAF, n=164) or without food (TAF to TAF, n=81; TDF to TAF, n=81) according to their preference, which was self-reported at study entry and maintained throughout the study. Baseline characteristics are provided in Table 2. The efficacy endpoint was the number of participants with HBV DNA ≥20 IU/mL (non-inferiority to TDF) at Week 96. Safety endpoints included changes in renal function and BMD.[3]

Table 2. Study 4018 Subanalysis: Baseline Demographics and Disease Characteristics[3]

Key Demographics and Characteristics	TAF to TAF		TDF to TAF	
	With Food (n=162)	Without Food (n=81)	With Food (n=164)	Without Food (n=81)
Age, mean (SD), years	52 (10)	49 (11)	52 (11)	50 (10)
Male, n (%)	120 (74)	59 (73)	105 (64)	61 (75)
Asian, n (%)	122 (75)	73 (90)	128 (78)	77 (95)
HBeAg-, n (%)	118 (73)	47 (58)	109 (66)	57 (70)
ALT level, mean (SD), U/L	28 (16)	26 (15)	25 (10)	28 (16)
History of cirrhosis, n (%)	24 (15)	8 (10)	32 (20)	13 (16)
$CrCl_{CG}$, median (Q1, Q3), mL/min	89 (76, 108)	96 (80, 113)	88 (73, 106)	95 (82, 110)
Osteoporosis by hip BMD T-score,[a] n (%)	6 (4)	3 (4)	2 (1)	2 (2)

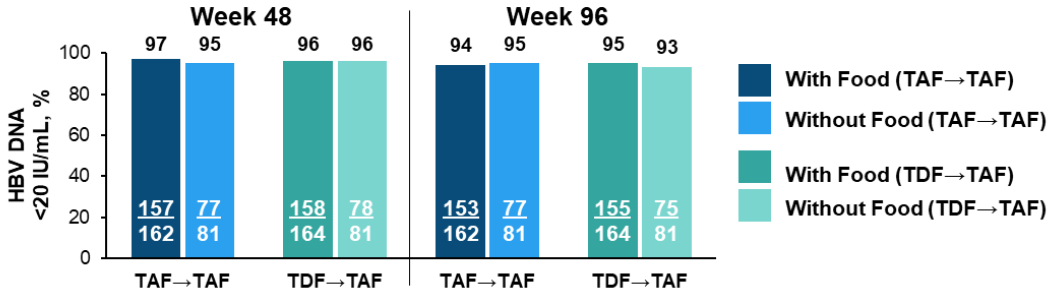
Key Demographics and Characteristics	TAF to TAF		TDF to TAF	
	With Food (n=162)	Without Food (n=81)	With Food (n=164)	Without Food (n=81)
Osteoporosis by spine BMD T-score,[a] n (%)	19 (12)	9 (11)	22 (13)	6 (7)

Abbreviation: HBeAg=hepatitis B envelope antigen.
[a]T-score <-2.5 is indicative of osteoporosis.

Efficacy[3]

Rates of viral suppression in the with food and without food groups were similar between each treatment arm at Weeks 48 and 96 (Figure 1).

Figure 1. Study 4018 Subanalysis: Maintenance of Viral Suppression According to Coadministration With and Without Food[3]



Note: Participants who were missing data were considered to have failed treatment.

Safety[3]

Treatment-emergent safety outcomes through Week 96 were similar between participants who received TAF with food and those who received TAF without food (Table 3). None of the Grade 3 to 4 AEs or serious AEs were considered related to the study drug. Similar improvements from baseline in hip and spine BMD and in CrCl were observed with TAF at Week 96 regardless of whether TAF was administered with or without food.

Table 3. Study 4018: Treatment-Emergent Safety Outcomes Through Week 96[3]

Safety Outcome, n (%)		TAF to TAF		TDF to TAF	
		With Food (n=162)	Without Food (n=81)	With Food (n=164)	Without Food (n=81)
AE		98 (60)	57 (70)	96 (59)	52 (64)
Grade 3–4 AE		13 (8)	3 (4)	5 (3)	5 (6)
Serious AE		14 (9)	5 (6)	4 (2)	4 (5)
Discontinuation due to AE		2 (1)	1 (1)	0	0
Any Grade 3–4 laboratory abnormality		18 (11)	5 (6)[a]	13 (8)[b]	5 (6)
Laboratory abnormalities in ≥2 participants in any group	Increased LDL	6 (4)	3 (4)[a]	3 (2)[c]	1 (1)
	Urine glucose	2 (1)	1 (1)[a]	4 (2)[b]	1 (1)

[a]Percentage calculated using a denominator of 80 participants.
[b]Percentage calculated using a denominator of 162 participants
[c]Percentage calculated using a denominator of 160 participants.

References

1. Enclosed. Gilead Sciences Inc, VEMLIDY® (tenofovir alafenamide) tablets, for oral use. U.S. Prescribing Information. Foster City, CA.
2. Custodio JM, Ma G, Sajwani K, Ling KHJ, Flaherty JF, Kearney BP. Lack of Clinically Relevant Effect of Food on the Pharmacokinetics of Tenofovir Alafenamide [Poster P_46]. Paper presented at: 17th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy; 08-10 June, 2016; Washington, DC.
3. Kao JH, Chuang WL, Chen CY, et al. Impact of Coadministration With or Without Food on the 96-Week Efficacy and Safety of TAF in Virally Suppressed Chronic HBV Patients Switched From Tenofovir Disoproxil Fumarate to TAF [Poster 795]. Paper presented at: American Association for the Study of Liver Diseases (AASLD): The Liver Meeting Digital Experience; 13-16 November, 2020.
4. Lampertico P, Buti M, Fung S, et al. Switching from Tenofovir Disoproxil Fumarate to Tenofovir Alafenamide in Virologically Suppressed Patients with Chronic Hepatitis B: A Randomised, Double-Blind, Phase 3, Multicentre Non-Inferiority Study. *Lancet Gastroenterol Hepatol.* 2020. https://www.ncbi.nlm.nih.gov/pubmed/32087795

Abbreviations

AE=adverse event
AUC=area under the concentration-time curve
BMD=bone mineral density
CG=Cockcroft-Gault
CHB=chronic hepatitis B
PK=pharmacokinetic(s)
Q=quartile
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil fumarate

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Vemlidy US Prescribing Information available at: www.gilead.com/-/media/files/pdfs/medicines/liver-disease/vemlidy/vemlidy_pi.

Follow-Up

For any additional questions, please contact Gilead Medical Information at:

☎1-866-MEDI-GSI (1-866-633-4474) or 🖱 www.askgileadmedical.com

Adverse Event Reporting

Please report all adverse events to:

Gilead Global Patient Safety ☎ 1-800-445-3235, option 3 or
🖱 www.gilead.com/utility/contact/report-an-adverse-event

FDA MedWatch Program by ☎ 1-800-FDA-1088 or ✉MedWatch, FDA, 5600 Fishers Ln, Rockville, MD 20852 or 🖱 www.accessdata.fda.gov/scripts/medwatch

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