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Vemlidy® (tenofovir alafenamide) Serology

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Summary

Clinical Data on Serology From Phase 3 Studies With TAF

Studies 108 and 110 compared TAF with TDF in predominantly nucleos(t)ide-naive HBeAg- and HBeAg+ participants with CHB. Participants received double-blind TAF or TDF for 96 to 144 weeks, followed by OL TAF.[1] The following final serology results were reported at Year 8:

- The rates of HBeAg loss and seroconversion were 46% and 31%, respectively, in participants who received TAF only, 44% and 27% in participants who switched to TAF at Week 96, and 46% and 33% in participants who switched to TAF at Week 144.[1]
- The rates of HBsAg loss and seroconversion were ≤5% across all treatment groups, including those who were HBeAg- and HBeAg+.[1,2]

A subanalysis of Studies 108 and 110, which evaluated the PK of TAF to characterize HBeAg+ or HBeAg- participants who achieved HBsAg loss with up to 8 years of treatment, reported the following findings[3]:

- At Year 8, a shorter median time to HBsAg loss was observed in HBeAg+ participants vs HBeAg- participants (126 vs 300 weeks, respectively; *P*=0.02). In HBeAg+ participants, GTs A and F demonstrated the fastest time to HBsAg loss (48 weeks).
- Among HBeAg+ participants, those with the highest baseline HBsAg levels (>100,000 IU/mL) had the highest rates of HBsAg loss relative to those with the lowest levels (<1000 IU/mL); conversely, among HBeAg- participants those with the lowest HBsAg levels at baseline had the highest rates of HBsAg loss.
- Significant factors for HBsAg loss included White race (*P*=0.0026), FibroTest score >0.48 (*P*=0.0078), a ≥1 $\log_{10}$ IU/mL decline in HBsAg at Week 24 (*P*<0.0001), a ≥75% decline in HBsAg at Week 24 (*P*=0.0004), and elevated ALT levels at Week 24 (*P*=0.0221).

In a post hoc analysis of results from East Asian participants enrolled in Studies 108 and 110 through Year 5, the overall rate of HBeAg loss and seroconversion increased over the course of the study period, and the rate of HBsAg loss was low (<1%).[4]

Study 4108 compared switching from TDF to TAF vs continuing TDF after ≥1 year of treatment with TDF in virologically suppressed participants with CHB.[5]

- A higher rate of HBsAg loss was observed at Week 48 in participants who continued TDF than in participants who switched to TAF. By Week 96, similar rates of HBsAg loss and seroconversion were observed between the TAF continuation and TDF→TAF groups. Additionally, at Weeks 48 and 96, similar rates of HBeAg loss/seroconversion and similar rates of quantitative HBsAg decline were observed between treatment groups.[5,6]

Clinical Data on Serology From Phase 3 Studies With TAF

Studies 108 and 110

Study designs and demographics

Studies 108 and 110 were phase 3 clinical trials that compared outcomes in predominantly nucleos(t)ide-naive participants with CHB who received once-daily oral administration of TAF 25 mg or TDF 300 mg. A total of 1298 HBeAg- and HBeAg+ adult participants with an HBV DNA level ≥20,000 IU/mL, both with and without compensated cirrhosis, were randomly assigned to receive either double-blind TAF 25 mg or TDF 300 mg for 3 years in Studies 108 (HBeAg-; n=425) and 110 (HBeAg+; n=873).[1] The study allowed participants in both treatment groups to switch to OL TAF at Year 2 or Year 3, and the OL TAF phase was extended to Year 8.[1,2]

The primary endpoint was a non-inferiority margin of 10% in the proportion of participants with undetectable HBV DNA (<29 IU/mL) at Week 48.[7,8]

Table 1. Studies 108 and 110: Baseline Demographics and Disease Characteristics[1,8,9]

Key Demographics and Characteristics	TAF8y (n=866)	TDF2y→OL TAF6y (n=207)	TDF3y→OL TAF5y (n=225)
Age, mean ± SD, years	40±11.8	42±12.2	42±12.4
Male, n (%)	544 (63)	126 (61)	149 (66)
Asian, n (%)	687 (79)	167 (81)	166 (74)
ALT, median (Q1, Q3), U/L	80 (56, 123)	81 (53, 136)	79 (51, 121)
Nucleos(t)ide experienced, n (%)	211 (24)	50 (24)	58 (26)
HBV GT, A/B/C/D/other,[a] %	6/19/48/26/1	6/26/45/21/2	8/16/48/28/1
HBV DNA, mean ± SD, $\log_{10}$ IU/mL	7±1.59	7±1.66	7.1±1.6
HBeAg+, n (%)	569 (66)	133 (64)	157 (70)
HBsAg, mean ± SD, $\log_{10}$ IU/mL	3.8±0.81	3.9±0.76	3.8±0.81
FibroTest score 0.75–1,[b] n/N (%)	76/846 (9)	16/200 (8)	26/221 (12)

[a]Other GTs included E, F, H, and unknown.
[b]Assessed with BioPredictive (Paris, France); FibroTest range is suggestive of cirrhosis (ie, METAVIR F4).

Year 8 serology results

Through Year 8, the rates of HBeAg loss and seroconversion were similar among treatment groups during the double-blind phase, and progressively increased during the OL phase.[2] Across treatment groups, HBsAg loss and seroconversion occurred at low rates (≤5%), with small mean declines in levels of HBsAg (Table 2).[1]

Table 2. Studies 108 and 110: Overall Serology Results at Year 8 (M=E Analysis)[1]

Parameter		TAF8y	TDF2y→OL TAF6y	TDF3y→OL TAF5y
HBeAg	Loss, n/N (%)	171/373 (46)	32/73 (44)	50/108 (46)
	Seroconversion, n/N (%)	114/373 (31)	20/73 (27)	36/108 (33)
HBsAg	Loss, n/N (%)	17/583 (3)	4/117 (3)	4/167 (2)
	Seroconversion, n/N (%)	12/583 (2)	4/117 (3)	3/167 (2)
	Change from baseline, mean ± SD, log_{10} IU/mL	−0.8±1.127	−0.88±1.219	−0.93±1.141

HBsAg loss and seroconversion and small mean declines in quantitative HBsAg also occurred at low rates (≤5%) through Year 8 in HBeAg- and HBeAg+ participants who were treated with TAF or switched to OL TAF at Year 2 or Year 3 (Table 3).[2]

Table 3. Studies 108 and 110: Serology at Year 8 According to HBeAg- and HBeAg+ Status (M=E Analysis)[1,2]

Parameter		TAF8y		TDF2y→OL TAF6y		TDF3y→OL TAF5y	
		HBeAg- (n=285)	HBeAg+ (n=581)	HBeAg- (n=74)	HBeAg+ (n=133)	HBeAg- (n=66)	HBeAg+ (n=159)
HBeAg	Loss, n/N (%)	N/A	171/373 (46)	N/A	32/73 (44)	N/A	50/108 (46)
	Seroconversion, n/N (%)	N/A	114/373 (31)	N/A	20/73 (27)	N/A	36/108 (33)
HBsAg	Loss, n/N (%)	8/199 (4)	9/384 (2)	0/41	4/76 (5)	1/58 (2)	3/109 (3)
	Seroconversion, n/N (%)	6/199 (3)	6/384 (2)	0/41	4/76 (5)	0/58	3/109 (3)
	Change from baseline, mean ± SD, log_{10} IU/mL	-0.62±0.924	-0.89±1.211	-0.5±0.526	-1.09±1.424	-0.61±0.758	-1.09±1.268

At Year 8 in an M=E analysis, rates of viral suppression (HBV DNA <29 IU/mL) were high (94–97%) across treatment groups, regardless of HBeAg status, with 57% to 64% achieving HBV DNA <29 IU/mL with target not detected.[1]

High rates of ALT normalization (AASLD criteria, 78%) were observed among participants treated with TAF for 8 years, regardless of HBeAg status, based on an M=E analysis. ALT normalization rates increased after switching to TAF in participants who were initially randomly assigned to receive TDF (AASLD criteria, 71% and 79%).[1]

A total of 8 participants who received TAF throughout the study discontinued treatment due to HBsAg seroconversion in the double-blind (n=4) and OL phases (n=4), and 4 participants who switched to TAF at Week 96 or Week 144 discontinued due to HBsAg seroconversion during the OL phase.[1]

Safety at Year 8

The incidence of AEs was similar between the TAF and TDF→OL TAF groups in the OL safety analysis, and most AEs were Grade 1 or 2 (Table 4).[1]

Table 4. Studies 108 and 110 OL Safety Analysis: AEs Through Year 8[1]

Safety Outcomes, n (%)	TAF8y (n=775)	TDF→OL TAF[a] (n=382)
Any AEs	525 (68)	271 (71)
TRAEs	43 (6)	18 (5)
Grade ≥3 AEs	60 (8)	27 (7)
Treatment-related	2 (<1)[b]	0
SAEs	97 (13)	49 (13)
Treatment-related	4 (1)[c]	0

Safety Outcomes, n (%)		TAF8y (n=775)	TDF→OL TAF[a] (n=382)
Discontinuations due to AEs		9 (1)[d]	3 (<1)[e]
Deaths		1 (<1)[f]	1 (<1)[g]
HCC[h]		7 (<1)	3 (<1)
AEs that occurred in ≥5% of participants	Headache	59 (8)	30 (8)
	Upper respiratory tract infection	55 (7)	27 (7)
	Nasopharyngitis	52 (7)	23 (6)
	Arthralgia	41 (5)	23 (6)
	Hypertension	37 (5)	26 (7)
	Back pain	34 (4)	23 (6)
	Cough	28 (4)	27 (7)

[a]Included all participants who switched to OL TAF at Year 2 and at Year 3.
[b]Cerebrovascular accident and renal neoplasm (each, n=1).
[c] ALT increase, cerebrovascular accident, osteonecrosis, and renal neoplasm (each, n=1).
[d]Cardiopulmonary failure, cerebrovascular accident, γ-glutamyltransferase increased, HCC, myelodysplastic syndrome, osteonecrosis, osteoporosis, pancreatic carcinoma, and proteinuria (each, n=1).
[e]Tuberculosis, ascites, and pemphigoid (each, n=1).
[f]Pancreatic cancer.
[g]Bilateral pneumonia.
[h]Over the course of the entire study, 21 participants (1.8%) developed HCC (TAF, n=12; TDF→TAF, n=9; *P*=0.33); 10 of these events occurred during the OL phase.

Subanalysis: TAF PK and HBsAg loss[3]

Study designs and demographics

A subanalysis of Studies 108 and 110 evaluated the PK of TAF to characterize HBeAg+ or HBeAg- participants who achieved HBsAg loss with up to 8 years of treatment.

Table 5. Subanalysis of Studies 108 and 110: Baseline Demographics and Disease Characteristics[3]

Key Demographics and Characteristics		TAF (N=866)		TDF→OL TAF (N=432)	
		HBeAg- (n=285)	HBeAg+ (n=581)	HBeAg- (n=140)	HBeAg+ (n=292)
Age, mean ± SD, years		45±11.6	38±11	48±10.4	38±11.7
Male, n (%)		173 (61)	371 (64)	86 (61)	189 (65)
Asian, n (%)		205 (72)	482 (83)	101 (72)	232 (80)
Race, n (%)	White	71 (25)	96 (17)	35 (25)	52 (18)
	Black or African American	5 (2)	2 (<1)	3 (2)	3 (1)
ALT, median (Q1, Q3), U/L		67 (44, 102)	85 (61, 139)	67 (47, 102)	86 (57, 137)
Nucleos(t)ide experienced, n (%)		60 (21)	151 (26)	31 (22)	77 (26)
HBV GT, A/B/C/D, %		5/21/40/32	7/17/52/23	4/29/34/30	9/16/52/22
HBV DNA, mean ± SD, $\log_{10}$ IU/mL		5.7±1.34	7.6±1.34	5.8±1.32	7.6±1.41
HBsAg, mean ± SD, $\log_{10}$ IU/mL		3.4±0.66	4±0.79	3.4±0.73	4.1±0.68
FibroTest score ≥0.75,[a] n/N (%)		31/280 (11)	45/566 (8)	20/139 (14)	22/282 (8)

[a]METAVIR F4/cirrhosis.

Results

At Year 8, in participants who received TAF only or switched to TAF during the OL phase, rates of HBsAg loss were similar: HBeAg-, n/N=10/427 (2%); HBeAg+, n/N=27/873 (3%). The median time to HBsAg loss was significantly shorter in HBeAg+ participants than in HBeAg- participants: 126 vs 300 weeks, respectively (*P*=0.02).

Among HBeAg+ participants, those with the highest baseline HBsAg levels (>100,000 IU/mL) had the highest rates of HBsAg loss; among HBeAg- participants, those with the lowest baseline levels (<1000 IU/mL) had the highest rates of HBsAg loss (Table 6). Regardless of HBV GT, HBsAg loss occurred sooner in HBeAg+ participants than in HBeAg- participants, with GTs A and F demonstrating the fastest time to HBsAg loss (approximately 48 weeks) in the HBeAg+ population.

Table 6. Subanalysis of Studies 108 and 110: HBsAg Loss According to Baseline HBsAg Levels and GT[3]

Rates of HBsAg Loss		TAF	
		HBeAg-	HBeAg+
Baseline HBsAg level, %	<1000 IU/mL	7.2	5.2
	>1000 to <10,000 IU/mL	1.4	0.6
	>10,000 to <100,000 IU/mL	0	3.4
	>100,000 IU/mL	-	9.8
HBV GT, n/N (%)	A	7/64 (11)	2/21 (10)
	B	5/148 (3)	1/100 (1)
	C	6/456 (1)	5/163 (3)
	D	8/197 (4)	2/133 (2)
	E	0/3	0/7
	F	2/5 (40)	N/A
	H	N/A	0/2
	Unknown	N/A	0/1

Factors significantly associated with HBsAg loss included baseline characteristics such as White race (HR, 2.98; 95% CI:1.46–6.07; *P*=0.0026) and a FibroTest score of >0.48 (HR, 2.6; 95% CI: 1.29–5.25; *P*=0.0078) and treatment factors such as a ≥1 $\log_{10}$ IU/mL decline in HBsAg at Week 24 (HR, 9.4; 95% CI: 4.29–20.62; *P*<0.0001), a decline in HBsAg levels of ≥75% at Week 24 (HR, 12.41; 95% CI: 3.1–49.66; *P*=0.0004), and elevated ALT levels at Week 24 (HR, 2.28; 95% CI: 1.13–4.62; *P*=0.0221).

Post hoc analysis: Year 5 results in East Asian participants[4]

Study design and demographics

A post hoc analysis was conducted to evaluate outcomes through Year 5 in East Asian participants from Hong Kong, Japan, Singapore, South Korea, and Taiwan in Studies 108 and 110.

Table 7. Post Hoc Analysis of East Asian Participants in Studies 108 and 110: Baseline Demographics and Disease Characteristics[4]

Key Demographics and Characteristics	TAF5y (n=401)	TDF2y→OL TAF3y (n=84)	TDF3y→OL TAF2y (n=106)
Age, mean ± SD, years	43±10.8	45±11.6	45±11.1
Male, n (%)	232 (57.9)	41 (48.8)	67 (63.2)
ALT, median (Q1, Q3), U/L	80 (56, 126)	78 (56, 117)	82 (52, 137)
Nucleos(t)ide experienced, n (%)	100 (24.9)	14 (16.7)	22 (20.8)
HBV GT, B/C/other,[a] %	22.9/76.8/0.2	35.7/61.9/2.4	24.5/71.7/3.8
HBV DNA, mean ± SD, $\log_{10}$ IU/mL	7±1.51	6.9±1.59	6.9±1.51
≥8 $\log_{10}$ IU/mL, n (%)	119 (29.7)	23 (27.4)	30 (28.3)

Key Demographics and Characteristics	TAF5y (n=401)	TDF2y→OL TAF3y (n=84)	TDF3y→OL TAF2y (n=106)
HBeAg+, n (%)	284 (70.8)	53 (63.1)	73 (68.9)
FibroTest score ≥0.75,[b] n/N (%)	40/394 (10.2)	6/82 (7.3)	17/106 (16)

[a]"Other" included other and unknown GTs.
[b]FibroTest score of 0.75–1 corresponds to a histological classification of METAVIR F4 and is consistent with cirrhosis.

Serology results

Overall, through Year 5, the rate of HBeAg loss and seroconversion increased over the course of the study period, and the rate of HBsAg loss was low (<1%; Table 8).

Table 8. Post Hoc Analysis of East Asian Participants in Studies 108 and 110: Serology Results at Year 5 (Missing=Failure Analysis)[4]

Parameter		TAF5y	TDF2y→OL TAF3y	TDF3y→OL TAF2y
HBeAg	Loss, n/N (%)	86/240 (35.8)	15/35 (42.9)	32/72 (44.4)
	Seroconversion, n/N (%)	61/240 (25.4)	12/35 (34.3)	20/72 (27.8)
HBsAg	Loss, n/N (%)	1/339 (0.3)	0/54	1/106 (0.9)[a]
	Change from baseline, median (Q1, Q3), log_{10} IU/mL	n=320 -0.26 (-0.77, 0.03)	n=51 -0.24 (-0.88, 0.13)	n=100 -0.37 (-0.96, -0.09)

[a]This participant also achieved seroconversion.

Safety results

Within this group of participants, the incidences of Grade 3 or 4 AEs, TRAEs, and AEs that led to study drug discontinuation was low during the double-blind and OL phases (Table 9). No deaths occurred during the double-blind or OL phases.

Through Year 5, 12 HCC cases occurred; none were related to study treatment, and 1 participant discontinued TAF due to HCC during the double-blind phase (Table 9). Seven cases (1.7%) of HCC occurred in the TAF5y group (double-blind, n=5; OL, n=2), and 5 cases (2.6%) occurred in the TDF→TAF group (double-blind, n=3; OL, n=2).

Table 9. Post Hoc Analysis of East Asian Participants in Studies 108 and 110: Safety Outcomes During the Double-Blind and OL Phases[4]

Safety Outcomes, n (%)	TAF5y		TDF2y→OL TAF3y		TDF3y→OL TAF2y	
	DB Phase (n=401)	OL Phase (n=373)	DB Phase (n=84)	OL Phase (n=84)	DB Phase (n=106)	OL Phase (n=106)
Any AEs	326 (81.3)	225 (60.3)	61 (72.6)	47 (56)	90 (84.9)	61 (57.5)
Grade 3 and 4 AEs	29 (7.2)	20 (5.4)	5 (6)	6 (7.1)	4 (3.8)	4 (3.8)
Treatment-related	0	1 (0.3)[a]	0	0	0	0
SAEs	44 (11)	42 (11.3)	9 (10.7)	10 (11.9)	13 (12.3)	10 (9.4)
Treatment-related	0	2 (0.5)[b]	0	0	0	0
Discontinuations due to AE	5 (1.2)[c]	2 (0.5)[d]	0	0	0	1 (0.9)[e]

Abbreviation: DB=double-blind.
[a]Renal neoplasm. [b]Renal neoplasm, n=1; osteonecrosis, n=1. [c]Included pancreatic carcinoma (n=2); HCC (n=1); basilar artery occlusion (n=1); dyspepsia, nausea, and vomiting (n=1). [d]Osteonecrosis and pancreatic carcinoma. [e]Pemphigoid.

Serology in Participants Who Switched From TDF to TAF[5,6]

Study design and demographics

Study 4018 was a double-blind, randomized, phase 3 study that evaluated the safety and efficacy of switching from TDF to TAF (n=243) vs continuing TDF (n=245) in virologically suppressed participants with CHB. All participants had been treated with TDF for ≥48 weeks prior to screening, with $eGFR_{CG}$ ≥50 mL/min at screening. At Week 48, all participants were eligible to receive OL TAF and were either switched to TAF from TDF (TDF→TAF) or continued TAF (TAF→TAF) to Week 96 (Figure 1). The primary endpoint was the number of participants with HBV DNA ≥20 IU/mL (non-inferiority to TDF) at Week 48.

Figure 1. Study 4018: Study Design[5]

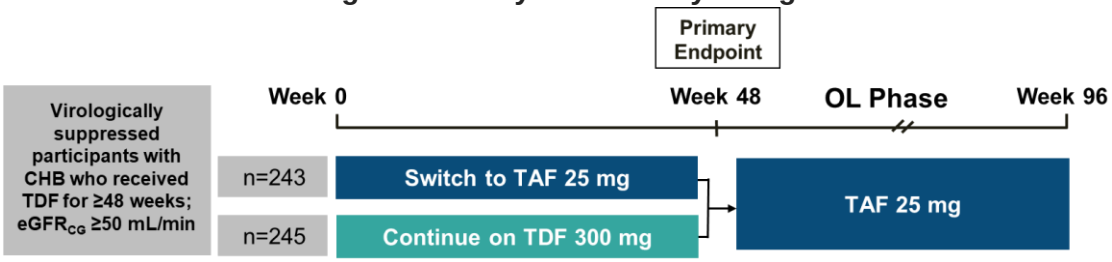


Table 10. Study 4018: Baseline Demographics and Disease Characteristics[5]

Key Demographics and Characteristics		TAF (n=243)	TDF (n=245)
Age, median ± SD, years		51±10.5	51±10.8
Age ≥60 years, n (%)		51 (21)	57 (23)
Male, n (%)		179 (74)	166 (68)
Asian, n (%)		195 (80)	205 (84)
HBeAg-, n (%)		165 (68)	166 (68)
ALT, mean ± SD, U/L		28±15.6	26±12
History of cirrhosis, n/N (%)		32/233 (14)	45/235 (19)
$eGFR_{CG}$, median (Q1, Q3), mL/min		91 (77, 110)	90 (76, 109)
Normal bone mineral density status (T-score ≥-1), n (%)	Hip	143 (59)	124 (51)
	Spine	125 (51)	120 (49)

Week 48 and Week 96 serology results

At Week 48, a higher rate of HBsAg loss was observed in participants receiving TDF. By Week 96, similar rates of HBsAg loss and seroconversion were observed between the TAF→TAF and TDF→TAF groups. Additionally, at Weeks 48 and 96, similar rates of HBeAg loss/seroconversion and similar rates of quantitative HBsAg decline were observed between the treatment groups (Table 11).

Table 11. Study 4018: Serology at Week 48 and Week 96[5,6]

Parameter		Week 48			Week 96		
		TAF	TDF	*P*-Value	TAF → TAF	TDF → TAF	*P*-Value
HBeAg	Loss, n/N (%)	6/78 (8)	5/78 (6)	0.73	14/78 (18)	7/78 (9)	0.1
	Seroconversion, n/N (%)	2/78 (3)	0	0.13	4/78 (5)	2/78 (3)	0.42
HBsAg	Loss, n/N (%)	0	5/245 (2)	0.03	4/243 (2)	6/245 (2)	0.54
	Seroconversion, n/N (%)	0	0	-	2/243 (<1)	1/245 (<1)	0.58
	Mean change ± SD, log_{10} IU/mL	-0.07±0.14	-0.1±0.29	0.15	-0.12±0.28	-0.13±0.35	0.81

Safety

Overall, switching to TAF from TDF was safe and well tolerated, with similar treatment-emergent AEs between treatment groups through Week 96 (Table 12 and Table 13).

Table 12. Study 4018: Safety Through Week 48[5]

Safety Outcomes, n (%)	TAF (n=243)	TDF (n=245)
AE	126 (52)	118 (48)
Grade 3–4 AE	8 (3)	4 (2)
SAE	11 (5)	3 (1)
Related to study drug	0	0
Discontinued due to AE	2 (<1)	0
HCC	1 (<1)	1 (<1)
Death	0	0

Table 13. Study 4018: Safety From Week 48 Through Week 96[6]

Safety Outcomes, n (%)	TAF→TAF (n=235)	TDF→TAF (n=237)
AE	81 (34)	84 (35)
Grade 3–4 AE	8 (3)	7 (3)
SAE	8 (3)	5 (2)
Related to study drug	0	0
Discontinued due to AE	1 (<1)	0
HCC	2 (<1)	1 (<1)
Death	0	0

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Abbreviations

AASLD=American Association for the Study of Liver Diseases
AE=adverse event
CHB=chronic hepatitis B
CG=Cockcroft-Gault
GT=genotype
HBeAg=hepatitis B envelope antigen
HBsAg=hepatitis B surface antigen
HCC=hepatocellular carcinoma
M=E=missing=excluded
METAVIR=meta-analysis of histological data in viral hepatitis
OL=open-label
PK=pharmacokinetic(s)
Q=quartile
SAE=serious adverse event
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil fumarate
TRAE=treatment-related adverse event

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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