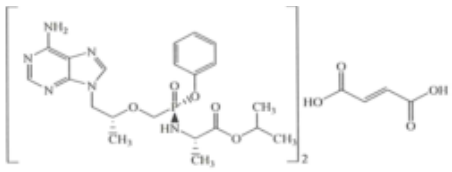
TENOFOVIR ALAFENAMIDE
TAFNEXT
25 mg Film-Coated Tablet
Antiviral

FORMULATION:
Each film-coated tablet contains
Tenofovir Alafenamide 25mg equivalent to .....28.043 mg
(as Tenofovir Alafenamide Hemifumarate)

DRUG DESCRIPTION
Tenofovir alafenamide Tablets 25 mg:
Pink, round, biconvex, film - coated tablets de-bossed with 'H' on one side and 'T25' on other side.
Tenofovir alafenamide hemifumarate is described chemically as Isopropyl N-{(S)-({[(2R)1-(6amino-9H-purin-9-yl}-2-propanyl]oxy}methyl)(phenoxy)phosphoryl]-Lalanfnate(2E)-2-butenedioate(2:1) The molecular formula is C46H62N12O14P12 and the molecular weight is 1068.39. The chemical structure of Tenofovir alafenamide hemifumarate is:



Tenofovir alafenamide hemifumarate is a white to off-white powder, and a pKa of 3.86. Soluble in dimethyl formamide and slightly soluble in methanol, Sample was not hygroscopic
(Sample weight increased up to 0.07% to the original weight)
Tenofovir alafenamide Tablets contain the following inactive ingredients: Lactose monohydrate, Microcrystalline Cellulose, Croscarmellose sodium, Magnesium Stearate, Opadry II Pink 85F94172, Purified Water.

THERAPEUTIC INDICATIONS
Tenofovir alafenamide tablets are indicated for the treatment of chronic hepatitis B virus (HBV) infection in adults with compensated liver disease

POSOLOGY AND METHOD OF ADMINISTRATION
Testing Prior to Initiation of Tenofovir Alafenamide
Prior to initiation of Tenofovir Alafenamide, patients should be tested for HIV-1 infection. Tenofovir Alafenamide alone should not be used in patients with HIV-1 infection *(see Warnings and Precautions)*.
Prior to or when initiating Tenofovir Alafenamide, and during treatment with Tenofovir Alafenamide on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus *(see Warnings and Precautions)*.

Recommended Dosage in Adults
The recommended dosage of Tenofovir Alafenamide is 25 mg (one tablet) taken orally once daily with food *(see Clinical Pharmacology)*.

Dosage in Patients with Renal Impairment
No dosage adjustment of Tenofovir Alafenamide is required in patients with estimated creatinine clearance greater than or equal to 15 mL per minute, or in patients with end stage renal disease (ESRD; estimated creatinine clearance below 15 mL per minute) who are receiving chronic hemodialysis. On days of hemodialysis, administer Tenofovir Alafenamide after completion of hemodialysis treatment.
Tenofovir Alafenamide is not recommended in patients with ESRD who are not receiving chronic hemodialysis *(see Use in Specific Populations and Clinical Pharmacology)*.
Dosage in Patients with Hepatic Impairment
No dosage adjustment of Tenofovir Alafenamide is required in patients with mild hepatic impairment (Child-Pugh A). Tenofovir Alafenamide is not recommended in patients with decompensated (Child-Pugh B or C) hepatic impairment *(see Use in Specific Populations and Clinical Pharmacology)*.

CONTRAINDICATIONS
None.

DRUG INTERACTIONS
Potential for Other Drugs to Affect Tenofovir Alafenamide
Tenofovir Alafenamide is a substrate of P-glycoprotein (P-gp) and BCRP. Drugs that strongly affect P-gp and BCRP activity may lead to changes in tenofovir alafenamide absorption (see Table 4). Drugs that induce P-gp activity are expected to decrease the absorption of tenofovir alafenamide, resulting in decreased plasma concentrations of tenofovir alafenamide, which may lead to loss of therapeutic effect of Tenofovir Alafenamide. Coadministration of Tenofovir Alafenamide with other drugs that inhibit P-gp and BCRP may increase the absorption and plasma concentration of tenofovir alafenamide.

Drugs Affecting Renal Function
Because tenofovir is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion, coadministration of Tenofovir Alafenamide with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of tenofovir and other renally eliminated drugs and this may increase the risk of adverse reactions. Some examples of drugs that are eliminated by active tubular secretion include, but are not limited to, acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs *(see Warnings and Precautions)*.

Established and Other Potentially Significant Interactions
Table 4 provides a listing of established or potentially clinically significant drug interactions. The drug interactions described are based on studies conducted with tenofovir alafenamide or are predicted drug interactions that may occur with Tenofovir Alafenamide *(For magnitude of interaction, see Clinical Pharmacology)*. Information regarding potential drug-drug interactions with HIV antiretrovirals is not provided (see the prescribing information for emtricitabine/tenofovir alafenamide for interactions with HIV antiretrovirals). The table includes potentially significant interactions but is not all inclusive.

Table 4 Established and Other Potentially Significant Drug Interactions[a]

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Anticonvulsants: Carbamazepine[c]* Oxcarbazepine* Phenobarbital* Phenytoin*	↓ tenofovir alafenamide	When coadministered[d] with carbamazepine, the tenofovir alafenamide dose should be increased to two tablets once daily. Coadministration of Tenofovir Alafenamide with oxcarbazepine, phenobarbital, or phenytoin is not recommended.
Antimycobacterials: Rifabutin* Rifampin* Rifapentine*	↓ tenofovir alafenamide	Coadministration of Tenofovir Alafenamide with rifabutin, rifampin or rifapentine is not recommended.
Herbal Products: St. John's wort* *(Hypericum perforatum)*	↓ tenofovir alafenamide	Coadministration of Tenofovir Alafenamide with St. John's wort is not recommended.

a. This table is not all inclusive.
b. ↓ = decrease.
c. Indicates that a drug interaction study was conducted.
* P-gp inducer

Drugs without Clinically Significant Interactions withTenofovir Alafenamide
Based on drug interaction studies conducted withTenofovir Alafenamide, no clinically significant drug interactions have been observed with: ethinyl estradiol, ledipasvir/sofosbuvir, midazolam, norgestimate, sertraline, sofosbuvir, sofosbuvir/velpatasvir, and sofosbuvir/velpatasvir/voxilaprevir.

WARNINGS AND PRECAUTIONS
Severe Acute Exacerbation of Hepatitis B after Discontinuation of Treatment
Discontinuation of anti-hepatitis B therapy, includingTenofovir Alafenamide, may result in severe acute exacerbations of hepatitis B. Patients who discontinueTenofovir Alafenamide should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, resumption of anti-hepatitis B therapy may be warranted.

Risk of Development of HIV-1 Resistance in Patients Coinfected with HBVand HIV-1
Due to the risk of development of HIV-1 resistance, Tenofovir Alafenamide alone is not recommended for the treatment of HIV-1 infection. The safety and efficacy of Tenofovir Alafenamidehav[e] not been established in patients coinfected with HBV and HIV-1. HIV antibody testing should be offered to all HBV-infected patients before initiating therapy with Tenofovir Alafenamide, and, if positive, an appropriate antiretroviral combination regimen that is recommended for patients coinfected with HIV-1 should be used.

New Onset or Worsening Renal Impairment
Post marketing cases of renal impairment, including acute renal failure, proximal renal tubulopathy (PRT), and Fanconi syndrome have been reported with TAF-containing products; while most of these cases were characterized by potential confounders that may have contributed to the reported renal events, it is also possible these factors may have predisposed patients to tenofovir-related adverse events *(see Adverse Reactions (6.2))*.
Patients taking tenofovir prodrugs who have impaired renal function and those taking nephrotoxic agents, including non-steroidal anti-inflammatory drugs, are at increased risk of developing renal-related adverse reactions *(see Drug Interactions (7.2))*.
Prior to or when initiating Tenofovir Alafenamide, and during treatment with Tenofovir Alafenamide on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus. Discontinue Tenofovir Alafenamide in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome *(see Adverse Reactions (6.1) and Use in Specific Populations (8.6))*.

Lactic Acidosis/Severe Hepatomegaly with Steatosis
Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including tenofovir disoproxil fumarate (TDF), another prodrug of tenofovir, alone or in combination with other antiretrovirals. Treatment withTenofovir Alafenamide should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Pregnancy:
USE IN SPECIFIC POPULATIONS
Risk Summary
Available data from the APR show no statistically 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%.
In animal studies, no adverse developmental effects were observed when tenofovir alafenamide was administered during the period of organogenesis at exposure equal to or 51 times (rats and rabbits, respectively) the tenofovir alafenamide exposure at the recommended daily dose of Tenofovir Alafenamide*(see Data)*. No adverse effects were observed in the offspring when TDF was administered through lactation at tenofovir exposures of approximately 12 times the exposure at the recommended daily dosage of Tenofovir Alafenamide.

Data
Human Data
Based on prospective reports to the APR of over 660 exposures to TAF-containing regimens during pregnancy resulting in live births (including over 520 exposed in the first trimester and over 130 exposed in the second/third trimester), the prevalence of birth defects in live births was 4.2% (95% CI: 2.6% to 6.3%) and 3.0% (95% CI: 0.8% to 7.5%) 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 less than 20 weeks gestation.

Animal Data
Embryonic fetal development studies performed in rats and rabbits revealed no evidence of impaired fertility or harm to the fetus. The embryo-fetal NOAELs (no observed adverse effect level) in rats and rabbits occurred at tenofovir alafenamide exposures similar to and 51 times higher than, respectively, the exposure in humans at the recommended daily dose. Tenofovir alafenamide is rapidly converted to tenofovir; the observed tenofovir exposure in rats and rabbits were 54 (rats) and 85 (rabbits) times higher than human tenofovir exposures at the recommended daily dose.
Tenofovir alafenamide was administered orally to pregnant rats (25, 100, or 250 mg/kg/day) and rabbits (10, 30, or 100 mg/kg/day) through organogenesis (on gestation days 6 through 17, and 7 through 20, respectively). No adverse embryo-fetal effects were observed in rats and rabbits at tenofovir alafenamide exposures approximately similar to (rats) and 51 (rabbits) times higher than the exposure in humans at the recommended daily dose of Tenofovir Alafenamide. Tenofovir alafenamide is rapidly converted to tenofovir; the observed tenofovir exposures in rats and rabbits were 54 (rats) and 85 (rabbits) times higher than human tenofovir exposures at the recommended daily dose. Since tenofovir alafenamide is rapidly converted to tenofovir and a lower tenofovir exposure in rats and mice was observed after tenofovir alafenamide administration compared to TDF, another prodrug for tenofovir administration, a pre/postnatal development study in rats was conducted only with TDF. Doses up to 600 mg/kg/day were administered through lactation; no adverse effects were observed in the offspring on gestation day 7 [and lactation day 20] at tenofovir exposures of approximately 12
[18] times higher than the exposures in humans at the recommended daily dose of Tenofovir Alafenamide.

Lactation
Risk Summary
It is not known whether Tenofovir Alafenamide and its metabolites are present in human breast milk, affect human milk production, or have effects on the breastfed infant. Tenofovir has been shown to be present in the milk of lactating rats and rhesus monkeys after administration of TDF *(see Data)*. It is not known if tenofovir alafenamide can be present in animal milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Tenofovir Alafenamide and any potential adverse effects on the breastfed infant from Tenofovir Alafenamide or from the underlying maternal condition.

Data
Animal Data
Studies in rats and monkeys have demonstrated that tenofovir is secreted in milk. Tenofovir was excreted into the milk of lactating rats following oral administration of TDF (up to 600 mg/kg/day) at up to approximately 24% of the median plasma concentration in the highest dosed animals at lactation day 11 *(see Data 8.1)*. Tenofovir was excreted into the milk of lactating monkeys following a single subcutaneous (30 mg/kg) dose of tenofovir at concentrations up to approximately 4% of plasma concentration, resulting in exposure (AUC) of approximately 20% of plasma exposure.

Pediatric Use
Safety and effectiveness of Tenofovir Alafenamide in Pediatric patients less than 18 years of age have not been established.

Geriatric Use
In clinical trials, Tenofovir Alafenamide was administered to 89 subjects aged 65 and over. No clinically significant differences in safety or efficacy have been observed between elderly subjects and subjects between 18 and less than 65 years of age.

Renal Impairment
No dosage adjustment of Tenofovir Alafenamide is required in patients with mild, moderate, or severe renal impairment, or in patients with ESRD (estimated creatinine clearance below 15 mL per minute) who are receiving chronic hemodialysis. On days of hemodialysis, administer Tenofovir Alafenamide after completion of hemodialysis treatment *(see Dosage and Administration (2.3))*.
The safety and efficacy of Tenofovir Alafenamide in HBV-infected adult subjects with moderate to severe renal impairment (estimated creatinine clearance between 15 and 59 mL per minute by Cockcroft-Gault method) and ESRD (estimated creatinine clearance of less than 15 mL per minute by Cockcroft-Gault method) receiving chronic hemodialysis were evaluated in 78 and 15 subjects, respectively, in an open-label trial (Trial 4035, Part A). Overall, 98% of subjects achieved HBV DNA < 20 IU/mL at Week 24 (Cohort 1, 97%; Cohort 2, 100%) and the safety of Tenofovir Alafenamide was similar to that observed in clinical trials of Tenofovir Alafenamide in subjects with compensated liver disease but without renal impairment *(see Adverse Reactions)*.
The safety and efficacy of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide 150/150/200/10 mg was previously evaluated in 55 virologically suppressed HIV-1 infected subjects with ESRD receiving chronic hemodialysis in an open-label study (Trial 1825). Tenofovir alafenamide exposures are similar when comparing tenofovir alafenamide 25 mg and tenofovir alafenamide 10 mg as part of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide.
Among subjects with ESRD receiving chronic hemodialysis and administered tenofovir alafenamide, higher exposures of tenofovir were observed in HBV-infected subjects (Trial 4035 Part A) compared to HIV-infected subjects (Trial 1825). The clinical significance of these higher exposures is not established *(see Clinical Pharmacology (12.3))*.
Tenofovir Alafenamide is not recommended in patients with ESRD (estimated creatinine clearance below 15 mL per minute by Cockcroft-Gault method) who are not receiving chronic hemodialysis as the safety of Tenofovir Alafenamide has not been established in this population *(see Dosage and Administration (2.3) and Clinical Pharmacology (12.3))*.

Hepatic Impairment
No dosage adjustment of Tenofovir Alafenamide is required in patients with mild hepatic impairment (Child-Pugh A). The safety and efficacy of Tenofovir Alafenamide in patients with decompensated cirrhosis (Child-Pugh B or C) have not been established; therefore, Tenofovir Alafenamide is not recommended in patients with decompensated (Child-Pugh B or C) hepatic impairment *(see Dosage and Administration (2.4) and Clinical Pharmacology (12.3))*.

ADVERSE DRUG REACTIONS;
The following adverse reactions are discussed in other sections of the labeling:

- Severe Acute Exacerbation of Hepatitis B *(see Warnings and Precautions (5.1))*
- New Onset or Worsening of Renal Impairment *(see Warnings and Precautions (5.3))*
- Lactic Acidosis/Severe Hepatomegaly with Steatosis *(see Warnings and Precautions (5.4))*

Adverse Reactions in Adult Subjects with Chronic Hepatitis B and Compensated Liver Disease
The safety assessment of Tenofovir Alafenamide was based on pooled data through the Week 96 data analysis from 1298 subjects in two randomized, double-blind, active-controlled trials, Trial 108 and Trial 110, in adult subjects with chronic hepatitis B and compensated liver disease. A total of 866 subjects received Tenofovir Alafenamide 25 mg once daily *(see Clinical Studies (14.2))*. Further safety assessment was based on pooled data from Trials 108 and 110 from subjects who continued to receive their original blinded treatment through Week 120 and additionally from subjects who received open-label
Tenofovir Alafenamide was from Week 96 through Week 120 (n = 361 remained on Tenofovir Alafenamide; n = 180 switched from TDF toTenofovir Alafenamide at Week 96).
Based on the Week 96 analysis, the most common adverse reaction (all Grades) reported in at least 10% of subjects in theTenofovir Alafenamide group was headache. The proportion of subjects who discontinued treatment withTenofovir Alafenamide or TDF due to adverse reactions of any severity was 1.5% and 0.9%, respectively. Table 1 displays the frequency of the adverse reactions (all Grades) greater than or equal to 5% in theTenofovir Alafenamide group.

Table 1 Adverse Reactions[a](All Grades) Reported in 5% of Subjects with Chronic HBV Infection and Compensated Liver Disease in Trials 108 and 110 (Week 96 analysis[b])

	Tenofovir Alafenamide (N=866)	TDF (N=432)
Headache	12%	10%
Abdominal painc	9%	6%
Cough	8%	8%
Back pain	6%	6%
Fatigue	6%	5%
Nausea	6%	6%
Arthralgia	5%	6%
Diarrhea	5%	5%
Dyspepsia	5%	5%

a. Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.
b. Double-blind phase.
c. Grouped term including abdominal pain upper, abdominal pain, abdominal pain lower, and abdominal tenderness.
Additional adverse reactions occurring in less than 5% of subjects in Trials 108 and 110 included vomiting, rash, and flatulence.
The safety profile of Tenofovir Alafenamide in subjects who continued to receive blinded treatment through Week 120 was similar to that at Week 96. The safety profile of Tenofovir Alafenamide in subjects who remained on Tenofovir Alafenamide in the open-label phase through Week 120 was similar to that in subjects who switched from TDF to Tenofovir Alafenamide at Week 96.

Renal Laboratory Tests
In a pooled analysis of Trials 108 and 110 in adult subjects with chronic hepatitis B and a median baseline estimated creatinine clearance between 106 and 105 mL per minute (for the Tenofovir Alafenamide and TDF groups, respectively), mean serum creatinine increased by less than 0.1 mg/dL and median serum phosphorus decreased by 0.1 mg/dL in both treatment groups at Week 96. Median change from baseline to Week 96 in estimated creatinine clearance was -1.2 mL per minute in the Tenofovir Alafenamide group and -4.8 mL per minute in those receiving TDF.
In subjects who remained on blinded treatment beyond Week 96 in Trials 108 and 110, change from baseline in renal laboratory parameter values in each group at Week 120 were similar to those at Week 96. In the open-label phase, median change in estimated creatinine clearance by Cockcroft-Gault method from Week 96 to Week 120 was -0.6 mL per minute in subjects who remained on Tenofovir Alafenamide and + 1.8 mL per minute in those who switched from TDF to Tenofovir Alafenamide at Week 96. Mean serum creatinine and median serum phosphorus values at Week 120 were similar to those at Week 96 in subjects who remained on Tenofovir Alafenamide and in subjects who switched from TDF to Tenofovir Alafenamide.
The long-term clinical significance of these renal laboratory changes on adverse reaction frequencies between Tenofovir Alafenamide and TDF is not known.

Bone Mineral Density Effects
In a pooled analysis of Trials 108 and 110, the mean percentage change in bone mineral density (BMD) from baseline to Week 96 as assessed by dual-energy X-ray absorptiometry (DXA) was -0.7% with Tenofovir Alafenamide compared to -2.6% with TDF at the lumbar spine and -0.3% compared to -2.5% at the total hip. BMD declines of 5% or greater at the lumbar spine were experienced by 11% of Tenofovir Alafenamide subjects and 25% of TDF subjects at Week 96. BMD declines of 7% or greater at the femoral neck were experienced by 5% of Tenofovir Alafenamide subjects and 13% of TDF subjects at Week 96.
In subjects who remained on blinded treatment beyond Week 96 in Trials 108 and 110, mean percentage change in BMD in each group at Week 120 was similar to that at Week 96. In the open-label phase, mean percentage change in BMD from Week 96 to Week 120 in subjects who remained on Tenofovir Alafenamide was 0.6% at the lumbar spine and 0% at the total hip, compared to 1.7% at the lumbar spine and 0.6% at the total hip in those who switched from TDF to Tenofovir Alafenamide.
The long-term clinical significance of these BMD changes is not known.

Laboratory Abnormalities
The frequency of laboratory abnormalities (Grades 3–4) occurring in at least 2% of subjects receiving Tenofovir Alafenamide in Trials 108 and 110 are presented in Table 2.

Table 2 Laboratory Abnormalities (Grades 3–4) Reported in 2% of Subjects with Chronic HBV Infection and Compensated Liver Disease in Trials108 and 110 (Week 96 analysis[a])

Laboratory Parameter Abnormality[b]	TENOFOVIR ALAFENAMIDE (N=866)	TDF (N=432)
ALT (> 5 × ULN)	8%	10%
LDL-cholesterol (fasted) (> 190 mg/dL)	6%	1%
Glycosuria (> 3+)	5%	2%
AST (> 5 × ULN)	3%	5%
Creatine Kinase (= 10 × ULN)	3%	3%
Serum Amylase (> 2.0 × ULN)	3%	3%

ULN = Upper Limit of Normal
a. Double-blind phase.
b. Frequencies are based on treatment-emergent laboratory abnormalities.
The overall incidence of blinded treatment ALT flares (defined as confirmed serum ALT greater than 2 × baseline and greater than 10 × ULN at 2 consecutive postbaseline visits, with or without associated symptoms) was similar between Tenofovir Alafenamide (0.6%) and TDF (0.9%) through Week 96. ALT flares generally were not associated with coincident elevations in bilirubin, occurred within the first 12 weeks of treatment, and resolved without recurrence.
Based on the Week 120 analysis, the frequencies of lab abnormalities in subjects who remained on Tenofovir Alafenamide in the open-label phase were similar to those in subjects who switched from TDF to Tenofovir Alafenamide at Week 96.
Amylase and Lipase Elevations and Pancreatitis
At Week 96, in Trials 108 and 110, eight subjects treated with Tenofovir Alafenamide with elevated amylase levels had associated symptoms, such as nausea, low back pain; abdominal tenderness, pain, and distension; and biliary pancreatitis and pancreatitis. Of these eight, two subjects discontinued Tenofovir Alafenamide due to elevated amylase and/or lipase; one subject experienced recurrence of adverse events when Tenofovir Alafenamide was restarted. No subject treated with TDF had associated symptoms or discontinued treatment.
From Week 96 to Week 120, one additional subject who continued open-label Tenofovir Alafenamide and none of the subjects who switched from TDF to Tenofovir Alafenamide had elevated amylase levels and associated symptoms.
Serum Lipids
Changes from baseline in total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, and total cholesterol to HDL ratio among subjects treated with Tenofovir Alafenamide and TDF in Trials 108 and 110 are presented in Table 3.

Table 3 Lipid Abnormalities: Mean Change from Baseline in Lipid Parameters in Patients with Chronic HBV Infection and Compensated Liver Disease in Trials 108 and 110 (Week 96 analysis)

	Tenofovir Alafenamide (N=866)		TDF (N=432)	
	Baseline	Week 96	Baseline	Week 96
	mg/dL	Change[a]	mg/dL	Change[a]
Total Cholesterol (fasted)	188 [n=835]	-1 [n=742]	193 [n=423]	-25 [n=368]
HDL-Cholesterol (fasted)	60 [n=835]	-5 [n=740]	61 [n=423]	-12 [n=368]
LDL-Cholesterol (fasted)	116 [n=835]	+ 7 [n=741]	120 [n=423]	-10 [n=368]
Triglycerides (fasted)	102 [n=836]	+ 13 [n=743]	102 [n=423]	-7 [n=368]
Total Cholesterol to HDL ratio	3 [n=835]	0 [n=740]	3 [n=423]	0 [n=368]

a. The change from baseline is the mean of within-subject changes from baseline for subjects with both baseline and Week 96 values.
In the open-label phase, lipid parameters at Week 120 in subjects who remained on Tenofovir Alafenamide were similar to those at Week 96. In subjects who switched from TDF to Tenofovir Alafenamide, mean change from Week 96 to Week 120 in total cholesterol was 23 mg/dL, HDL-cholesterol was 5 mg/dL, LDL-cholesterol was 16 mg/dL, triglycerides was 30 mg/dL, and total cholesterol to HDL ratio was 0 mg/dL.

Adverse Reactions in Virologically Suppressed Adult Subjects with Chronic Hepatitis B
The safety of Tenofovir Alafenamide 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 Tenofovir Alafenamide (N = 243) or to continue their TDF treatment (N = 245). Adverse reactions observed with Tenofovir Alafenamide in Trial 4018 were similar to those in Trials 108 and 110 *(see Clinical Studies (14.3))*.
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 Tenofovir Alafenamide and TDF groups at Week 48 were similar to those observed in Trials 108 and 110 at Week 96.

Adverse Reactions in Adult Subjects with Chronic Hepatitis B and Renal Impairment
In an open-label trial (Trial 4035) in virologically suppressed adult subjects with chronic hepatitis B switching to Tenofovir Alafenamide 25 mg, the safety of Tenofovir Alafenamide was assessed in 78 subjects with moderate to severe renal impairment (estimated creatinine clearance between 15 and 59 mL per minute by Cockcroft-Gault method; Part A, Cohort 1) and 15 subjects with ESRD (estimated creatinine clearance below 15 mL per minute) receiving chronic hemodialysis (Part A, Cohort 2). The safety of Tenofovir Alafenamide, including changes from baseline in renal function, BMD, and lipid parameters, was similar to that observed in clinical trials of Tenofovir Alafenamide in subjects with compensated liver disease but without renal impairment *(see Use in Specific Populations)*.

Post marketing Experience
The following adverse reactions have been identified during post approval use of Tenofovir Alafenamide or other products containing tenofovir alafenamide. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Skin and Subcutaneous Tissue Disorders
Angioedema, urticaria
Renal and Urinary Disorders
Acute renal failure, acute tubular necrosis, proximal renal tubulopathy, and Fanconi syndrome

Leaflet size: 280 x 380 mm
Printing colour: **BLACK**
Die cut:

OVERDOSE
If overdose occurs, monitor patient for evidence of toxicity. Treatment of overdosage with Tenofovir Alafenamide consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient. Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%.

PHARMACOLOGICAL PROPERTIES

CLINICAL PHARMACOLOGY

Mechanism of Action
Tenofovir alafenamide is an antiviral drug against the hepatitis B virus *(see Microbiology (12.4))*.

Pharmacodynamics
Cardiac Electrophysiology
In a thorough QT/QTc study in 48 healthy subjects, tenofovir alafenamide at the recommended dose or at a dose 5 times the recommended dose did not affect the QT/QTc interval and did not prolong the PR interval.

Pharmacokinetics
The pharmacokinetic properties of Tenofovir Alafenamide are provided in Table 5. The multiple dose PK parameters of tenofovir alafenamide and its metabolite tenofovir are provided in Table 6.

Table 5 Pharmacokinetic Properties of Tenofovir Alafenamide

	Tenofovir Alafenamide
Absorption	
Tmax (h)	**0.48**
Effect of high fat meal (relative to fasting): AUClast Ratio[a]	1.65 (1.51, 1.81)
Distribution	
% Bound to human plasma proteins	80%
Source of protein binding data	*Ex vivo*
Blood-to-plasma ratio	1.0
Metabolism	
Metabolism[b]	CES1 (hepatocytes) Cathepsin A (PBMCs) CYP3A (minimal)
Elimination	
Major route of elimination	Metabolism (> 80% of oral dose)
t1/2 (h)c	0.51
% Of dose excreted in urine[d]	< 1
% Of dose excreted in feces[d]	31.7

CES1 = carboxylesterase 1; PBMCs = peripheral blood mononuclear cells.

a. Values refer to geometric mean ratio in AUC_{last} [fed/fasted] and (90% confidence interval). High fat meal = ~ 800 kcal, 50% fat.

b. In vivo, TAF is hydrolyzed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite, tenofovir diphosphate. In vitro studies have shown that TAF is metabolized to tenofovir by CES1 in hepatocytes, and by cathepsin A in PBMCs and macrophages.

c. t1/2 values refer to median terminal plasma half-life.

d. Dosing in mass balance study: TAF 25 mg (single dose administration of [^{14}C] TAF).

Table 6 Multiple Dose PK Parameters of Tenofovir Alafenamide and its Metabolite Tenofovir Following Oral Administration in Adults with Chronic Hepatitis B

Parameter Mean (CV%)	Tenofovir Alafenamide[a]	Tenofovir[a]
C_{max} (microgram per mL)	0.27 (63.3)	0.03 (24.6)
AUC_{tau} (microgram•hour per mL)	0.27 (47.8)	0.40 (35.2)
C_{trough} (microgram per mL)	NA	0.01 39.6)

CV = coefficient of variation; NA = not applicable
a. From Intensive PK analyses in Trial 108 and Trial 110; N = 8.

Specific Populations
Geriatric Patients, Race, and Gender
Limited data in subjects aged 65 years and over suggest a lack of clinically relevant differences in tenofovir alafenamide or tenofovir pharmacokinetics. No clinically relevant differences in tenofovir alafenamide or tenofovir pharmacokinetics due to race or gender have been identified *(see Use in Specific Populations (8.5))*.
Patients with Renal Impairment
In a Phase 1, open-label study, tenofovir alafenamide and tenofovir systemic exposures (AUCinf) were evaluated in subjects with severe renal impairment and in subjects with normal renal function (Table 7). In an open-label trial of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide 150/150/200/10 mg, tenofovir alafenamide and tenofovir AUC were evaluated in a subset of virologically suppressed HIV-1 infected subjects with ESRD receiving chronic hemodialysis (Table 7). In a Phase 2, open-label trial, tenofovir alafenamide and tenofovir AUC were evaluated in a subset of virologically suppressed HBV-infected subjects with ESRD receiving chronic hemodialysis (Table 7) *[see Use in Specific Populations (8.6)]*. The pharmacokinetics of tenofovir alafenamide were similar among subjects with normal renal function, subjects with severe renal impairment, and subjects with ESRD receiving chronic hemodialysis. Relative to those with normal renal function, increased tenofovir exposures were observed in subjects with severe renal impairment and subjects with ESRD receiving chronic hemodialysis. Within the chronic hemodialysis population, increased tenofovir exposures were observed in subjects with HBV relative to those with HIV.

Table 7 Pharmacokinetics of Tenofovir Alafenamide and its Metabolite Tenofovir in Subjects with Renal Impairment as Compared to Subjects with Normal Renal Function.

Estimated Creatinine Clearancea Mean (CV%)	= 90 mL per minute 25 mg TAF (N = 13)[b]	15–29 mL per minute 25 mg TAF (N = 14)[b]	< 15 mL per minute 25 mg TAF[c] (N = 5)	< 15 mL per minute 10 mg TAFd (N = 12)
Tenofovir alafenamide				
AUC (mcg•hour per mL)	0.27 (49.2)[e]	0.51 (47.3)[e]	0.30 (26.7)[f]	0.23 (53.2)[f]
Cmax (mcg per mL)	0.20 (62.1)	0.36 (65.7)	0.23 (48.4)	0.25 (75.4)
Tenofovir				
AUC (mcg•hour per mL)	0.34 (27.2)[e]	2.07 (47.1)[e]	18.8 (30.4)[g]	8.72 (39.4)[g,h]
C_{max} (mcg per mL)	0.01 (36.5)	0.03 (32.4)	0.89 (26.4)	0.44 (40.9)
C_{24h} (mcg per mL)	0.004 (25.6)	0.02 (41.9)	0.89 (26.4)	0.26 (73.2)[h]

CV = coefficient of variation

a. By Cockcroft-Gault method.

b. PK assessed on a single dose of TAF 25 mg in subjects with normal renal function and in subjects with severe renal impairment.

c. PK assessed on the day prior to hemodialysis of TAF 25 mg. These subjects from Study 4035 had a median baseline eGFR by Cockcroft-Gault of 7.2 mL/min (range, 4.8 to 12.0).

d. Exposures from TAF 25 mg = exposures from TAF 10 mg as part of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide. PK assessed on the day prior to hemodialysis following 3 consecutive daily doses of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide. These subjects from Study 1825 had a median baseline eGFR by Cockcroft-Gault of 10.2 mL/min (range, 6.8 to 19.2) .

e. AUCinf.

f. AUClast.

g. AUCtau.

h. N = 10.

Patients with Hepatic Impairment
Tenofovir alafenamide and tenofovir pharmacokinetics are similar in subjects with mild (Child-Pugh Class A) hepatic impairment and in subjects with normal hepatic function.
HIV and/or Hepatitis C Virus Coinfection
The pharmacokinetics of tenofovir alafenamide have not been fully evaluated in subjects coinfected with HIV and/or hepatitis C virus.

Drug Interaction Studies
(see Drug Interactions (7))
The effects of coadministered drugs on the exposure of tenofovir alafenamide are shown in Table 8. The effects of tenofovir alafenamide on the exposure of coadministered drugs are shown in Table 9 *(For information regarding clinical recommendations, see Drug Interactions (7))*. Information regarding potential drug-drug interactions with HIV antiretrovirals is not provided (see the prescribing information for emtricitabine/tenofovir alafenamide for interactions with HIV antiretrovirals).

Table 8 Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir Alafenamide in the Presence of the Coadministere[a]Drug[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	Tenofovir Alafenamide (mg)	N	Geometric Mean Ratio of TAF Pharmacokinetic Parameters (90% CI)b; No effect = 1.00		
				C_{max}	AUC	C_{min}
Carbamazepine	300 twice daily	25 once daily[c]	26	0.43 (0.36, 0.51)	0.45 (0.40, 0.51)	NC
Cobicistat[d]	150 once daily	8 once daily	12	2.83 (2.20, 3.65)	2.65 (2.29, 3.07)	NC
Ledipasvir/ Sofosbuvir	90/400 once daily	25 once daily[e]	42	1.03 (0.94, 1.14)	1.32 (1.25, 1.40)	NC
Sertraline	50 single dose	10 once daily[f]	19	1.00 (0.86, 1.16)	0.96 (0.89, 1.03)	NC
Sofosbuvir/ Velpatasvir/ Voxilaprevir	400/100/100 + 100 oxilaprevirg once daily	25 once daily[e]	30	1.32 (1.17, 1.48)	1.52 (1.43, 1.61)	NC

NC = not calculated

a. All interaction studies conducted in healthy subjects.

b. All no effect boundaries are 70%–143%.

c. Study conducted with emtricitabine/tenofovir alafenamide.

d. A representative inhibitor of P-glycoprotein.

e. Study conducted with emtricitabine/rilpivirine/tenofovir alafenamide.

f. Study conducted with elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide.

g. Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

Table 9 Drug Interactions: Changes in Pharmacokinetic Parameters forCoadministered Drug in the Presence of Tenofovir Alafenamide[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	Tenofovir Alafenamide (mg)	N	Geometric Mean Ratio of Coadministered Drug PharmacokineticParameters (90% CI)b; No effect = 1.00		
				C_{max}	AUC	C_{min}
Ledipasvir	90 ledipasvir / 400 sofosbuvir once daily	25 once dailyd	41	1.01 (0.97, 1.05)	1.02 (0.97, 1.06)	1.02 (0.98, 1.07)
Sofosbuvir				0.96 (0.89, 1.04)	1.05 (1.01, 1.09)	NC
GS-331007[c]				1.08 (1.05, 1.11)	1.08 (1.06, 1.10)	1.10 (1.07, 1.12)
Midazolam[e]	90 ledipasvir / 400 sofosbuvir once daily	25 once daily[d]	18	1.02 (0.92, 1.13)	1.13 (1.04, 1.23)	NC
	1 single dose IV			0.99 (0.89, 1.11)	1.08 (1.04, 1.14)	NC
Norelgestromin	norgestimate 0.180/0.215/0.250 once daily / ethinyl estradiol 0.025 once daily	25 once daily	29	1.17 (1.07, 1.26)	1.12 (1.07, 1.17)	1.16 (1.08, 1.24)
Norgestrel				1.10 (1.02, 1.18)	1.09 (1.01, 1.18)	1.11 (1.03, 1.20)
Ethinyl estradiol				1.22 (1.15, 1.29)	1.11 (1.07, 1.16)	1.02 (0.93, 1.12)
Sertraline	50 single dose	10 once daily[g]	19	1.14 (0.94, 1.38)	0.93 (0.77, 1.13)	NC
Sofosbuvir	400 once daily	25 once daily[h]	30	0.95 (0.86, 1.05)	1.01 (0.97, 1.06)	NC
GS-331007c				1.02 (0.98, 1.06)	1.04 (1.01, 1.06)	NC
Velpatasvir	100 once daily			1.05 (0.96, 1.16)	1.01 (0.94, 1.07)	1.01 (0.95, 1.09)
Voxilaprevir	100 + 100i once daily			0.96 (0.84, 1.11)	0.94 (0.84, 1.05)	1.02 (0.92, 1.12)

NC = not calculated

a. All interaction studies conducted in healthy subjects.

b. All no effect boundaries are 70%–143%.

c. The predominant circulating nucleoside metabolite of sofosbuvir.

d. Study conducted with emtricitabine/rilpivirine/tenofovir alafenamide.

e. A sensitive CYP3A4 substrate.

f. Study conducted with emtricitabine/tenofovir alafenamide.

g. Study conducted with elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide.

h. Study conducted with emtricitabine/rilpivirine/tenofovir alafenamide.

i. Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

Microbiology
Mechanism of Action
Tenofovir alafenamide is a phosphonamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analog). Tenofovir alafenamide as a lipophilic cell-permeant compound enters primary hepatocytes by passive diffusion and by the hepatic uptake transporters OATP1B1 and OATP1B3. Tenofovir alafenamide is then converted to tenofovir through hydrolysis primarily by carboxylesterase 1 (CES1) in primary hepatocytes. Intracellular tenofovir is subsequently phosphorylated by cellular kinases to the pharmacologically active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HBV replication through incorporation into viral DNA by the HBV reverse transcriptase, which results in DNA chain-termination.
Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there is no evidence of toxicity to mitochondria in cell culture.

Antiviral Activity in Cell Culture
The antiviral activity of tenofovir alafenamide was assessed in a transient transfection assay using HepG2 cells against a panel of HBV clinical isolates representing genotypes A-H. The EC50 (50% effective concentration) values for tenofovir alafenamide ranged from 34.7 to 134.4 nM, with an overall mean EC50 value of 86.6 nM. The CC50 (50% cytotoxicity concentration) values in HepG2 cells were greater than 44,400 nM. In cell culture combination antiviral activity studies of tenofovir with the HBV nucleoside reverse transcriptase inhibitors entecavir, lamivudine, and telbivudine, no antagonistic activity was observed.

Resistance in Clinical Trials
Genotypic resistance analysis was performed on paired baseline and on-treatment HBV isolates for subjects who either experienced virologic breakthrough (2 consecutive visits with HBV DNA greater than or equal to 69 IU/mL [400 copies/mL] after having been less than 69 IU/mL, or 1.0-log10 or greater increase in HBV DNA from nadir) through Week 48, or had HBV DNA greater than or equal to 69 IU/mL at early discontinuation at or after Week 24.
In a pooled analysis of treatment-naïve and treatment-experienced subjects receivingTenofovir Alafenamide in Trials 108 and 110 *(see Clinical Studies (14.2))*, treatment-emergent amino acid substitutions in the HBV reverse transcriptase domain, all occurring at polymorphic positions, were observed in some HBV isolates evaluated (5/20); however, no specific substitutions occurred at a sufficient frequency to be associated with resistance toTenofovir Alafenamide.
In virologically suppressed subjects receiving Tenofovir Alafenamide in Trial 4018 *(see Clinical Studies (14.3))*, no subjects qualified for resistance analysis through 48 weeks of Tenofovir Alafenamide treatment.

Cross-Resistance
The antiviral activity of tenofovir alafenamide was evaluated against a panel of isolates containing substitutions associated with HBV nucleoside reverse transcriptase inhibitor resistance in a transient transfection assay using HepG2 cells. HBV isolates expressing the lamivudine resistance-associated substitutions rtM204V/I (±rtL180M±rtV173L) and expressing the entecavir resistance-associated substitutions rtT184G, rtS202G, or rtM250V in the presence of rtL180M and rtM204V showed less than 2-fold reduced susceptibility (within the inter-assay variability) to tenofovir alafenamide. HBV isolates expressing the rtA181T, rtA181V, or rtN236T single substitutions associated with resistance to adefovir also had less than 2-fold changes in EC50 values; however, the HBV isolate expressing the rtA181V plus rtN236T double substitutions exhibited reduced susceptibility (3.7-fold) to tenofovir alafenamide. The clinical relevance of these substitutions is not known.

AVAILABILITY:
30's HDPE container

STORAGE CONDITION
Store at temperatures not exceeding 30°C.

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

ADR REPORTING STATEMENT:
For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph
Please seek medical attention immediately at the first sign of any adverse drug reaction

Tenofovir Alafenamide is manufactured under a license from Gilead Sciences, Inc.

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