SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the finished pharmaceutical product

INN Name: Tenofovir alafenamide hemifumarate

Trade Name: Not Applicable

Strength: 25 mg

Pharmaceutical form: Tablets

2. Qualitative and quantitative composition

Each film coated tablet contains 25 mg of Tenofovir alafenamide equivalent to 28.043 mg of Tenofovir alafenamide hemifumarate.

3. Pharmaceutical form

Dosage form: Film coated tablet

Description: Pink, round, biconvex, film-coated tablets de-bossed with "H" on one side and "T25" on the other side.

4. Clinical particulars

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Testing Prior to Initiation of Treatment

- 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.
- 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.

Recommended Dosage in Adults

The recommended dosage of Tenofovir alafenamide is 25 mg (one tablet) taken orally once daily with food.

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

4.3 Contraindications

None

4.4 Special warnings and precautions for use

Severe Acute Exacerbation of Hepatitis B after Discontinuation of Treatment

Discontinuation of anti-hepatitis B therapy, including tenofovir alafenamide, may result in severe acute exacerbations of hepatitis B. Patients who discontinue tenofovir 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 HBV and HIV-1

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir prodrugs in both animal toxicology studies and human trials. In clinical trials of tenofovir alafenamide, there have been no cases of Fanconi syndrome or Proximal Renal Tubulopathy (PRT).

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

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.

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 DF, another prodrug of tenofovir, alone or in combination with other antiretrovirals. Treatment with tenofovir 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).

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy. During the initial phase of combination antiretroviral treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections (such as Mycobacterium avium infection, cytomegalovirus, Pneumocystis jirovecii pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable and can occur many months after initiation of treatment.

Lactic Acidosis and Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues, including emtricitabine alone or in combination with other antiretrovirals. Treatment with dolutegravir, emtricitabine, and tenofovir alafenamide tablets 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).

4.5 Interaction with other medicinal products and other forms of interaction

Potential for Other Drugs to Affect Tenofovir Alafenamide

Tenofovir alafenamide is a substrate of P-glycoprotein (P-gp), BCRP, OATP1B1, and OATP1B3. 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. Tenofovir alafenamide is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or UGT1A1. TAF is a weak inhibitor of CYP3A *in vitro*. TAF is not an inhibitor or inducer of CYP3A *in vivo*.

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.

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 (12.3)]*. 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**
Antiretroviral Agents: Protease Inhibitors (PI)		
Anticonvulsants: carbamazepine**c*** oxcarbazepine* phenobarbital* phenytoin*	↓ tenofovir alafenamide	When coadministered 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.
Antimycobacterial: 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 with Tenofovir alafenamide

Based on drug interaction studies conducted with tenofovir alafenamide, no clinically significant drug interactions have been observed with: ethinyl estradiol, ledipasvir/sofosbuvir, midazolam,norgestimate,sertraline,sofosbuvir,sofosbuvir/velpatasvir,andsofosbuvir/velpatasvir/ voxilaprevr

4.6 Fertility, pregnancy and lactation

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to tenofovir alafenamide during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-2584263.

Risk Summary

There are no human data on the use of tenofovir alafenamide in pregnant women to inform a drug associated risk of adverse fetal developmental outcome. 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 (tenofovir disoproxil fumarate) was administered through lactation at tenofovir exposures of approximately 12 times the exposure at the recommended daily dosage of tenofovir alafenamide.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

Data

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

Clinical trials of Tenofovir alafenamide did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

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

The pharmacokinetics and safety of tenofovir alafenamide were studied in HIV-1 infected adults with ESRD (estimated creatinine clearance below 15 mL per minute by Cockcroft-Gault method) receiving chronic hemodialysis in an open-label trial of 55 subjects who received elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide 150/150/200/10 mg. Tenofovir alafenamide 10 mg, given in this combination, achieves similar exposures as tenofovir alafenamide 25 mg alone [see Clinical Pharmacology (12.3)]. The safety profile of subjects in this trial was consistent with that expected in patients with ESRD on chronic hemodialysis and HIV-1 infection.

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

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

4.7 Effects on ability to drive and use machines

Not Applicable

4.8 Undesirable effects

The following adverse reactions are discussed in other sections of the labeling:

- Severe Acute Exacerbation of Hepatitis B [see Boxed Warning and 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)]

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

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, Study 108 and Study 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 (14.1)]. Further safety assessment was based on pooled data from Studies 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 from Week 96 through Week 120 (n = 361 remained on Tenofovir alafenamide; n = 180 switched from TDF to Tenofovir 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 the Tenofovir alafenamide group was headache. The proportion of subjects who discontinued treatment with Tenofovir 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 the Tenofovir alafenamide group.

Table 1 Adverse Reactions* (All Grades) Reported in ≥5% of Subjects with Chronic HBV Infection and Compensated Liver Disease in Studies 108 and 110 (Week 96 analysis†)

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

* Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.

† Double-blind phase

‡ 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 Studies 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 Studies 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 Studies 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 eGFR 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 Studies 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 Studies 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 lumber 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 Studies 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 Studies 108 and 110 (Week 96 analysis*)

Laboratory Parameter Abnormality†	**Tenofovir Alafenamide (N=866)**	**Tenofovir Disoproxil Fumarate (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

***** Double-blind phase

† 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 Studies 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 tenofovir disoproxil fumarate 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 tenofovir disoproxil fumarate 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 Studies 108 and 110 (Week 96 Analysis)

	Tenofovir Alafenamide (N=866)		**Tenofovir Disoproxil Fumarate (N=432)**	
	Baseline	**Week 96**	**Baseline**	**Week 96**
	mg/dL	**Change***	**mg/dL**	**Change***
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]

* 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.

4.9 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%.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

Pharmacotherapeutic group: Anti-viral drug

ATC code: J05AF13- Tenofovir Alafenamide

Mechanism of action

Tenofovir alafenamide is an antiviral drug against the hepatitis B virus 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.

5.2 Pharmacokinetics properties

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): AUC last Ratio*	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†	CES1 (hepatocytes) Cathepsin A (PBMCs) CYP3A (minimal)
Elimination	
Major route of elimination	Metabolism (>80% of oral dose)
t1/2 (h)‡	0.51
% Of dose excreted in urine§	<1
% Of dose excreted in feces§	31.7

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

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

† 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.

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

§ Dosing in mass balance study: TAF 25 mg (single dose administration of [14C] 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*	Tenofovir*
Cmax (microgram per mL)	0.27 (63.3)	0.03 (24.6)
AUCtau (microgram·hour per mL)	0.27 (47.8)	0.40 (35.2)
Ctrough (microgram per mL)	NA	0.01 (39.6)

CV = coefficient of variation; NA = not applicable

* From Intensive PK analyses in Study 108 and Study 110; N = 8.

Specific Populations

Geriatric Patients, Race, and Gender

No clinically relevant differences in tenofovir alafenamide or tenofovir pharmacokinetics due to race or gender have been identified. Limited data in subjects aged 65 and over suggest a lack of clinically relevant differences in tenofovir alafenamide or tenofovir pharmacokinetics

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 was evaluated in a

subset of virologically suppressed HIV-1 infected subjects with ESRD receiving chronic hemodialysis (Table 7)

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

	AUC (mcg·hour per mL) Mean (CV%)		
Estimated Creatinine Clearance*	**≥90 mL per minute 25 mg TAF (N=13)†**	**15–29 mL per minute 25 mg TAF (N=14)†**	**<15 mL per minute 10 mg TAF‡ (N=12)§**
Tenofovir alafenamide	0.27 (49.2)¶	0.51 (47.3)¶	0.23 (53.2)#
Tenofovir	0.34 (27.2)¶	2.07 (47.1)¶	8.72 (39.4)Þ,ß

* By Cockcroft-Gault method.

† PK assessed on a single dose of TAF 25 mg in subjects with severe renal impairment and healthy subjects.

‡ Exposures from TAF 25 mg = exposures from TAF 10 mg as part of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide.

§ PK assessed prior to hemodialysis following 3 consecutive daily doses of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide in HIV-infected subjects.

¶ AUC_{inf}.

AUC_{last}.

Þ AUC_{tau}.

ß N=10.

Patients with Hepatic Impairment

Relative to subjects with normal hepatic function, tenofovir alafenamide and tenofovir systemic exposures were 7.5% and 11% lower in subjects with mild hepatic impairment, respectively.

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

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 Coadministered Drug*

Coadministered Drug	**Dose of Coadministered Drug (mg)**	**Tenofovir Alafenamide (mg)**	**N**	**Geometric Mean Ratio of TAF Pharmacokinetic Parameters (90% CI)†; No effect = 1.00**		
				C_{max}	**AUC**	**C_{min}**
Carbamazepine	300 twice daily	25 once daily‡	26	0.43 (0.36, 0.51)	0.45 (0.40, 0.51)	NC
Cobicistat§	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¶	42	1.03 (0.94, 1.14)	1.32 (1.25, 1.40)	NC
Sertraline	50 single dose	10 once daily#	19	1.00 (0.86, 1.16)	0.96 (0.89, 1.03)	NC
Sofosbuvir/ Velpatasvir/ Voxilaprevir	400/100/100+ 100 voxilaprevirÞ once daily	25 once daily¶	30	1.32 (1.17, 1.48)	1.52 (1.43, 1.61)	NC

NC = not calculated

* All interaction studies conducted in healthy subjects.

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

‡ Study conducted with emtricitabine/tenofovir alafenamide.

§ A representative inhibitor of P-glycoprotein.

¶ Study conducted with emtricitabine/rilpivirine/tenofovir alafenamide.

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

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

Table 9 Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Tenofovir Alafenamide*

Drug	**Dose of Coadministered Drug (mg)**	**Tenofovir Alafenamide (mg)**	**N**	**Geometric Mean Ratio of Coadministered Drug Pharmacokinetic Parameters (90% CI)†; No effect = 1.00**		
				C_{max}	**AUC**	**C_{min}**
Ledipasvir	90 ledipasvir / 400 sofosbuvir once daily	25 once daily‡	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§				1.08 (1.05, 1.11)	1.08 (1.06, 1.10)	1.10 (1.07, 1.12)
Midazolam¶	2.5 single dose orally	25 once daily	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.	25 once	29	1.17 (1.07, 1.26)	1.12 (1.07, 1.17)	1.16 (1.08, 1.24)

Norgestrel	250 once daily / ethinyl estradiol 0.025 once daily	daily#		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[Þ]	19	1.14 (0.94, 1.38)	0.93 (0.77, 1.13)	NC
Sofosbuvir	400 once daily	25 once daily[ß]	30	0.95 (0.86, 1.05)	1.01 (0.97, 1.06)	NC
GS-331007[§]				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+100[à] once daily			0.96 (0.84, 1.11)	0.94 (0.84, 1.05)	1.02 (0.92, 1.12)

NC = not calculated

* All interaction studies conducted in healthy subjects.

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

‡ Study conducted with emtricitabine/rilpivirine/tenofovir alafenamide.

§ The predominant circulating nucleoside metabolite of sofosbuvir.

¶ A sensitive CYP3A4 substrate.

Study conducted with emtricitabine/tenofovir alafenamide.

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

ß Study conducted with emtricitabine/rilpivirine/tenofovir alafenamide.

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

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

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 tenofovir disoproxil fumarate administration, carcinogenicity studies were conducted only with tenofovir disoproxil fumarate. Long-term oral carcinogenicity studies of tenofovir disoproxil fumarate in mice and rats were carried out at exposures up to approximately 10 times (mice) and 4 times (rats) those observed in humans at the 300 mg therapeutic dose of tenofovir disoproxil fumarate for chronic hepatitis B. The tenofovir exposure in these studies was approximately 151 times (mice) and 50 times (rat) those observed in humans after administration of Tenofovir alafenamide treatment. At the high dose in female mice, liver adenomas were increased at tenofovir exposures approximately 151 times those observed after Tenofovir alafenamide administration in humans. In rats, the study was negative for carcinogenic findings.

Tenofovir alafenamide was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or rat micronucleus assays.

There were no effects on fertility, mating performance or early embryonic development when tenofovir alafenamide was administered to male rats at a dose equivalent to 155 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 14 days prior to mating through Day 7 of gestation.

Animal Toxicology and/or Pharmacology

Minimal to slight infiltration of mononuclear cells in the posterior uvea was observed in dogs with similar severity after three- and nine-month administration of tenofovir alafenamide; reversibility was seen after a three month recovery period. At the NOAEL for eye toxicity, the systemic exposure in dogs was 5 (tenofovir alafenamide) and 14 (tenofovir) times the exposure seen in humans at the recommended daily Tenofovir alafenamide dosage.

6. Pharmaceutical particulars

6.1 List of excipients

Lactose Monohydrate,(Supertab 11SD), Microcrystalline Cellulose (Avicel PH 102), Croscarmellose sodium (Ac-di-sol), Magnesium stearate (Ligamed MF-2-V-VEG), Magnesium stearate (Ligamed MF-2-V-VEG), Opadry II Pink 85F94172, HIS, Purified Water,

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

<2 Years>

6.4 Special precautions for storage

Store below 30˚C

6.5 Nature and contents of container

Container pack: 30's HDPE container and 100's HDPE container

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorisation Holder and Manufacturing Site Addresses

7.1 Name and Address of Manufacturer

Name: Hetero Labs Limited (Unit-V)

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7.2 Name and Address of Principal

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Hyderabad-500 018
Telangana.

Country : INDIA

Telephone : 0091-040-23704923/24

8. Registration Number

Not Applicable

9. Category for Distribution

Prescription only medicine – List I

10. Date of Publication of This Package Insert