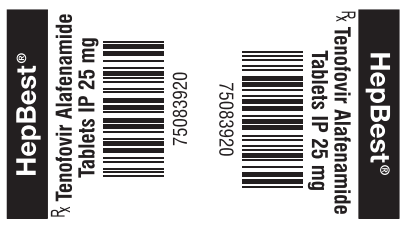

For the use of Gastroenterologist / Hepatologist only

HepBest®

℞ Tenofovir Alafenamide Tablets IP 25 mg

1. Name of the medicinal product

HepBest®

Tenofovir Alafenamide Tablets IP 25 mg

2. Qualitative and quantitative composition

Each film coated tablet contains

Tenofovir Alafenamide Fumarate IP

equivalent to Tenofovir Alafenamide 25 mg

Colours: Titanium di oxide IP

3. Pharmaceutical form

Film coated Tablets.

A white to off white, film coated round, biconvex tablet debossed with M on one side of the tablets and TF1 on the other side.

4. Clinical particulars

4.1 Therapeutic indications

Tenofovir Alafenamide is indicated for the treatment of chronic hepatitis B virus infection in adults with compensated liver disease

4.2 Posology and method of administration

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 infection.

It is recommended that serum creatinine, serum phosphorous, estimated creatinine clearance, urine glucose, and urine protein be assessed before initiating Tenofovir Alafenamide and during therapy in all patients as clinically appropriate.

Posology

The recommended dosage of Tenofovir Alafenamide is 25 mg (one tablet) taken orally once daily with or without food.

Elderly

Tenofovir Alafenamide dose adjustment is not required in patients aged 65 years and older. In clinical trials, 89 HBV-infected patients aged 65 years and over received TAF 25mg. No differences in safety or efficacy have been observed between elderly patients and those 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. Tenofovir Alafenamide is not recommended in patients with end stage renal disease (estimated creatinine clearance below 15 mL per minute). For patients on hemodialysis, on days of hemodialysis, TAF 25mg should be administered after completion of hemodialysis treatment.

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.

Paediatric population

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

Method of administration

For oral use.

Patients should be instructed to swallow the tablet whole with food

4.3 Contraindications

None

4.4 Special warnings and precautions of use

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 in combination with other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. 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).

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

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 Alafenamide have 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

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 [see Drug Interactions (4.5)].

It is recommended that renal function is assessed in all patients prior to, or when, initiating therapy with Tenofovir Alafenamide Tablets 25 mg and that it is also monitored during therapy in all patients as clinically appropriate. In patients who develop clinically significant decreases in renal function or evidence of proximal renal tubulopathy discontinuation of Tenofovir Alafenamide Tablets 25 mg should be considered.

Talk to your doctor or pharmacist if you have kidney disease or if tests have shown problems with your kidneys, before or during treatment. Before starting treatment and during treatment with Tenofovir Alafenamide Tablets 25 mg, your doctor may order blood tests to monitor how your kidneys work.

It is recommended that serum creatinine, serum phosphorous, estimated creatinine clearance, urine glucose, and urine protein be assessed before initiating Tenofovir Alafenamide and during therapy in all patients as clinically appropriate. Discontinue Tenofovir Alafenamide in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

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) and BCRP. Drugs that strongly affect P-gp and BCRP activity may lead to changes in tenofovir alafenamide absorption (see Table 1). 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 Special Warnings and Precautions (4.4)].

Established and Other Potentially Significant Interactions

Table 1 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. 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 1 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 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, itraconazole, ketoconazole, ledipasvir/sofosbuvir, midazolam, norgestimate, sertraline, sofosbuvir, and Sofosbuvir/Velpatasvir/Voxilaprevir.

Use with Related Products

TAF 25mg should not be administered with products containing tenofovir alafenamide, tenofovir disoproxil fumarate, or adefovir dipivoxil.

Fertility, pregnancy and lactation

Pregnancy

Risk Summary

There are no human data on the use of Tenofovir Alafenamide in pregnant women to inform a drug associated risks 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. 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.

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 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. 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.

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. 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.

4.6 Undesirable effects

Experience from Clinical Studies

NERVOUS SYSTEM DISORDERS Very Common: Headache

GASTROINTESTINAL DISORDER Common: Nausea, Diarrhea, Abdominal Pain, vomiting, Flatulence.

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS Common: Fatigue

SKIN AND SUBCUTANEOUS TISSUE DISORDERS Common: Rash

Summary of Safety profile

The safety assessment of Tenofovir Alafenamide was based on pooled data through the Week 48 data ***(96-week data based on their study)*** 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 (5.1)]*.

The proportion of subjects who discontinued treatment with Tenofovir Alafenamide or tenofovir disoproxil fumarate due to adverse reactions of any severity was 1.0% and 1.2%, respectively. Table 1 displays the frequency of the adverse reaction (all Grades) greater than or equal to 5% in the Tenofovir Alafenamide group.

Table 2 Adverse Reactions[a] (All Grades) Reported in ≥5% of Subjects with Chronic HBV Infection and Compensated Liver Disease in Studies 108 and 110 (Week 48 analysis)

	Tenofovir Alafenamide (N=866)	Tenofovir Disoproxil Fumarate (N=432)
Headache	9%	8%
Abdominal pain	7%	6%
Fatigue	6%	5%
Cough	6%	6%
Nausea	5%	5%
Back pain	5%	4%

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

Renal Laboratory Tests

In a pooled analysis of Studies 108 and 110 in adult subjects with chronic hepatitis B and a median baseline eGFR of 106 and 105 mL per minute (for the Tenofovir Alafenamide and tenofovir disoproxil fumarate [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. Median change from baseline in eGFR was -1.2 mL per minute in the Tenofovir Alafenamide group and -5.4 mL per minute in those receiving TDF. The long-term clinical significance of these renal laboratory changes on adverse reaction frequencies between Tenofovir Alafenamide and TDF is not known.

Decrease in Bone Mineral Density

In a pooled analysis of Studies 108 and 110, the mean percentage change in bone mineral density (BMD) from baseline to Week 48 as assessed by dual-energy X-ray absorptiometry (DXA) was -0.6% with Tenofovir Alafenamide compared to -2.4% with TDF at the lumbar spine and -0.2% compared to -1.9% at the total hip. BMD declines of 5% or greater at the lumbar spine were experienced by 6% of Tenofovir Alafenamide subjects and 20% of TDF subjects. BMD declines of 7% or greater at the femoral neck were experienced by 3% of Tenofovir Alafenamide subjects and 6% of TDF subjects. 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 3 Laboratory Abnormalities (Grades 3–4) Reported in ≥2% of Subjects with Chronic HBV Infection and Compensated Liver Disease in Studies 108 and 110 (Week 48 analysis)

Laboratory Parameter Abnormality[a]	Tenofovir Alafenamide (N=866)	Tenofovir Disoproxil Fumarate (N=432)
ALT (>5 x ULN)	8%	9%
Glycosuria (≥3+)	5%	1%
LDL-cholesterol (fasted) (>190 mg/dL)	4%	<1%
AST (>5 x ULN)	3%	5%
Creatine Kinase (≥10 x ULN)	3%	3%
Serum Amylase (>2.0 x ULN)	3%	2%

a. Frequencies are based on treatment-emergent laboratory abnormalities.

Amylase and Lipase Elevations and Pancreatitis

In Studies 108 and 110, seven subjects treated with Tenofovir Alafenamide with elevated amylase levels had associated symptoms, such as nausea, low back pain, abdominal tenderness, biliary pancreatitis and pancreatitis. Of these seven, 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.

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 4 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 48 Analysis)

	Tenofovir Alafenamide (N=866)		Tenofovir Disoproxil Fumarate (N=432)	
	Baseline	Week 48	Baseline	Week 48
	mg/dL	Change[a]	mg/dL	Change[a]
Total Cholesterol (fasted)	188 [n=835]	0 [n=772]	193 [n=423]	-25 [n=394]
HDL-Cholesterol (fasted)	60 [n=835]	-4 [n=771]	61 [n=423]	-10 [n=394]
LDL-Cholesterol (fasted)	116 [n=835]	+6 [n=772]	120 [n=423]	-11 [n=394]
Triglycerides (fasted)	102 [n=836]	+11 [n=773]	102 [n=423]	-10 [n=394]
Total Cholesterol to HDL ratio	3 [n=835]	0 [n=771]	3 [n=423]	0 [n=394]

a. The change from baseline is the mean of within-subject changes from baseline for subjects with both baseline and Week 48 values.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:

Address:
Mylan Pharmaceuticals Private Limited
10th Floor, Prestige Platina, Block 3,
Kadubeesanahalli Village,
Varthur Hobli, Outer Ring Road,
Bangalore East Taluk,
Bangalore 560 087, India
Email: ProductSafety@mylan.com

4.7 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: Antiviral, ATC code: not yet assigned

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

In a pooled analysis of treatment-naïve and treatment-experienced subjects receiving Tenofovir alafenamide in Studies 108 and 110, 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. 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 to Tenofovir alafenamide.

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.

Clinical efficacy

The efficacy and safety of Tenofovir alafenamide in the treatment of adults with chronic hepatitis B virus infection with compensated liver disease are based on 48-week data from two randomized, double-blind, active-controlled studies, Study 108 (N=425) and Study 110 (N=873). In both studies, besides study treatment, patients were not allowed to receive other nucleosides, nucleotides, or interferon.

In Study 108, HBeAg-negative treatment-naïve and treatment-experienced subjects with compensated liver disease (no evidence of ascites, hepatic encephalopathy, variceal bleeding, INR <1.5x ULN, total bilirubin <2.5x ULN, and albumin >3.0 mg/dL) were randomized in a 2:1 ratio to receive Tenofovir alafenamide 25 mg (N=285) once daily or tenofovir disoproxil fumarate 300 mg (N=140) once daily for 48 weeks. The mean age

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Barcodes Should be readable in both the side of the folded leaflet. It should be scannable. Position of barcode can be changed by vendor to meet the above requirement.

Mylan				Date of Final	dd / mm / yy	Date of Issue	dd / mm / yy	Page Count	1 of 2
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Vendor Job No.	NA	Affiliate New Code	NA	Product Description	LIT HEPBEST (TAF) TABS 25MG INDIA V4				
Artwork Proof No.	NA	Aff. Superseded Code	NA						
Pharma Code	NA	Barcode Information	NA	New Material Code	75083920	Actual A/w Size	Flat - 306 x 400 mm		
Product Render ID No.	NA	MA Number	....	ITF Barcode		Other Sizes (if any)	Folded - 34 x 50 mm		
Main Font Type - 1	Swis721 Cn BT	SAP or SPC Code	....	Superseded Code	75080056	Pitch After Every	NA		
Main Font Type - 2	.....	Packaging Site	Mylan Laboratories Ltd. , FDF 3 (Pithampur, Dhar Dist., M.P. - IN)	Component Type	Printed Literature	Eye / Sensor Mark	NA		
Min. Font Size	6.5pt	Mfg. Lic. No. / Code No.	NA	No. of Printed Colors	1	ITF Barcode Size	NA		
Reason for Revision / Issuance	Updation of IP & Size Change			Printed Colors CMYK / PMS Coated / PMS Color Bridge Coated	BLACK 100%	NA	NA	NA	NA	NA
	.....			Non Printed Colors	Die Line				
	.....								
Artwork Implementation Schedule, (✓) whichever is applicable	New Component			Equivalent with CMYK (Pantones Ref. Code)	NA				
	Immediately (Stock of supperseded component to be destroyed, if applicable)			Material of Construction	60gsm century maplitho paper				
	After Consumption of Existing (supperseded) stock								
	Others (specify)			Design & Style	Supply in folded form as proposed size with tape				

LABEL CONTROL / BUSINESS DEVELOPMENT / REGULATORY / MARKETING				Prepared By	Checked By	Approved By		
Sign Offs	Digital Signature	Digital Signature	Digital Signature	Digital Signature	Packaging Technical Services		Production	Regulatory Affairs	Quality Assurance

Revision History	Date / Remarks	Date / Remarks
08.12.2021 - Artwork Revised 12.12.2021 - Updation	Date / Remarks Date / Remarks Date / Remarks	Date / Remarks Date / Remarks Date / Remarks

was 46 years, 61% were male, 72% were Asian, 25% were White, 2% were Black, and 1% were other races. 24%, 38%, and 31% had HBV genotype B, C, and D, respectively. 21% were treatment experienced [previous treatment with oral antivirals, including entecavir (N=41), lamivudine (N=42), tenofovir disoproxil fumarate (N=21), or other (N=18)]. At baseline, mean plasma HBV DNA was 5.8 $\log_{10}$ IU/mL, mean serum ALT was 94 U/L, and 9% of subjects had a history of cirrhosis.

In Study 110, HBeAg-positive treatment-naïve and treatment-experienced subjects with compensated liver disease were randomized in a 2:1 ratio to receive Tenofovir alafenamide 25 mg (N=581) once daily or tenofovir disoproxil fumarate 300 mg (N=292) once daily for 48 weeks. The mean age was 38 years, 64% were male, 82% were Asian, 17% were White, and 1% were Black or other races. 17%, 52%, and 23% had HBV genotype B, C, and D, respectively. 26% were treatment experienced [previous treatment with oral antivirals, including adefovir (N=42), entecavir (N=117), lamivudine (N=84), telbivudine (N=25), tenofovir disoproxil fumarate (N=70), or other (n=17)]. At baseline, mean plasma HBV DNA was 7.6 $\log_{10}$ IU/mL, mean serum ALT was 120 U/L, and 7% of subjects had a history of cirrhosis.

In both studies, randomization was stratified on prior treatment history (nucleoside naïve or experienced) and baseline HBV DNA (<7, ≥7 to <8, and ≥8 $\log_{10}$ IU/mL in Study 108; and <8 and ≥8 $\log_{10}$ IU/mL in Study 110). The efficacy endpoint in both trials was the proportion of subjects with plasma HBV DNA levels below 29 IU/mL at Week 48. Additional efficacy endpoints include the proportion of subjects with ALT normalization, HBsAg loss and seroconversion, and HBeAg loss and seroconversion in Study 110. Treatment outcomes of Studies 108 and 110 at Week 48 are presented in Table 5 and Table 6.

Table 5 Studies 108 and 110: HBV DNA Virologic Outcome at Week 48[a] in Patients with Chronic HBV Infection and Compensated Liver Disease

	Study 108 (HBeAg-Negative)		Study 110 (HBeAg-Positive)	
	Tenofovir alafenamide (N=285)	**Tenofovir Disoproxil Fumarate** (N=140)	**Tenofovir alafenamide (N=581)**	**Tenofovir Disoproxil Fumarate** (N=292)
HBV DNA <29 IU/mL	94%	93%	64%	67%
Treatment Difference[b]	1.8% (95% CI = -3.6% to 7.2%)		-3.6% (95% CI = -9.8% to 2.6%)	
HBV DNA ≥ 29 IU/mL	2%	3%	31%	30%
Baseline HBV DNA <7 $\log_{10}$ IU/mL ≥7 $\log_{10}$ IU/mL	 96% (221/230) 85% (47/55)	 92% (107/116) 96% (23/24)	N/A	N/A
Baseline HBV DNA <8 $\log_{10}$ IU/mL ≥8 $\log_{10}$ IU/mL	N/A	N/A	82% (254/309) 43% (117/272)	82% (123/150) 51% (72/142)
Nucleoside Naïve[c] Nucleoside Experienced	94% (212/225) 93% (56/60)	93% (102/110) 93% (28/30)	68% (302/444) 50% (69/137)	70% (156/223) 57% (39/69)
No Virologic Data at Week 48[d]	4%	4%	5%	3%

a. Missing= Failure analysis
b. Adjusted by baseline plasma HBV DNA categories and oral antiviral treatment status strata.
c. Treatment-naïve subjects received <12 weeks of oral antiviral treatment with any nucleoside or nucleotide analog including TDF or Tenofovir alafenamide.
d. Includes subjects who discontinued due to lack of efficacy, adverse event or death, for reasons other than an AE, death or lack or loss of efficacy, e.g., withdrew consent, loss to follow-up, etc., or missing data during Week 48 window but still on study drug.

In Study 108, the proportion of subjects with cirrhosis who achieved HBV DNA <29 IU/mL at Week 48 was 92% (22/24) in the Tenofovir alafenamide group and 93% (13/14) in the TDF group. The corresponding proportions in Study 110 were 63% (26/41) and 67% (16/24) in the Tenofovir alafenamide and TDF groups, respectively.

Table 6 Additional Efficacy Parameters at Week 48[a]

	Study 108 (HBeAg-Negative)		Study 110 (HBeAg-Positive)	
	Tenofovir alafenamide (N=285)	**Tenofovir Disoproxil Fumarate** (N=140)	**Tenofovir alafenamide** (N=581)	**Tenofovir Disoproxil Fumarate** (N=292)
ALT Normalized ALT (Central Lab)[b]	 83%	 75%	 72%	 67%
Normalized ALT (AASLD)[c]	50%	32%	45%	36%
Serology HBeAg Loss / Seroconversion[d]	 N/A	 N/A	 14% / 10%	 12% / 8%
HBsAg Loss / Seroconversion	0 / 0	0 / 0	1% / 1%	<1% / 0

N/A = not applicable
a. Missing = failure analysis
b. The population used for analysis of ALT normalization included only subjects with ALT above upper limit of normal (ULN) of the central laboratory range (>43 U/L for males aged 18 to <69 years and >35 U/L for males ≥69 years; >34 U/L for females 18 to <69 years and >32 U/L for females ≥69 years) at baseline.
c. The population used for analysis of ALT normalization included only subjects with ALT above ULN of the American Association of the Study of Liver Diseases (AASLD) criteria (>30 U/L males and >19 U/L females) at baseline.
d. The population used for serology analysis included only subjects with antigen (HBeAg) positive and antibody (HBeAb) negative or missing at baseline.

Pharmacokinetic properties

The pharmacokinetic properties of Tenofovir alafenamide are provided in Table 7. The multiple dose PK parameters of tenofovir alafenamide and its metabolite tenofovir are provided in Table 8.

Table 7 Pharmacokinetic Properties of Tenofovir alafenamide

	Tenofovir Alafenamide
Absorption	
T_{max} (h)	0.48
Effect of high fat meal (relative to fasting): AUC_{last} 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. $t_{1/2}$ 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 8 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 Study 108 and Study 110; N = 8.

Pharmacokinetics in special 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

Relative to subjects with normal renal function (estimated creatinine clearance ≥90 mL/min), the tenofovir alafenamide and tenofovir systemic exposures in subjects with severe renal impairment were 1.9-fold and 5.7-fold higher, respectively. The pharmacokinetics of tenofovir alafenamide have not been evaluated in patients with creatinine clearance less than 15 mL per minute.

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.

5.2 Preclinical safety data

Tenofovir alafenamide

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.

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
- Microcrystalline Cellulose
- Croscarmellose sodium
- Magnesium Stearate

6.2 Incompatibilities

No incompatibility with any drug

6.3 Special precautions for storage

Do not Store above 30°C. Store in the original container. Protect from Moisture.

6.4 Nature and contents of container

HDPE bottle

6.5 Special precautions for disposal and other handling

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

For further information write to

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	After Consumption of Existing (supperseded) stock								
	Others (specify)			Design & Style	Supply in folded form as proposed size with tape				

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