FRONT

hovid

Hovid Tenofovir Disoproxil Fumarate Tablets 300 mg

VITENxx-07 (SIN)

DESCRIPTION
A film-coated tablet which the white core appears when coating removed.

COMPOSITION
Each film-coated tablet contains:
Tenofovir disoproxil fumarate 300 mg equivalent to tenofovir disoproxil 245 mg
Excipient: Lactose, Pregelatinized Starch, Croscarmellose Sodium, Magnesium Stearate , Gastric-soluble Film-Coating Premix, Purified Water

PHARMACOKINETICS
Tenofovir disoproxil is a water-soluble ester prodrug which is rapidly converted *in vivo* to Tenofovir disoproxil and formaldehyde. Tenofovir disoproxil is converted intracellularly to Tenofovir disoproxil monophosphate and to the active component, Tenofovir disoproxil diphosphate.

Absorption
Following oral administration of Tenofovir disoproxil to HIV infected patients, Tenofovir disoproxil is rapidly absorbed and converted to Tenofovir disoproxil. Administration of Tenofovir disoproxil with a light meal did not have a significant effect on the pharmacokinetics of Tenofovir disoproxil

Following oral administration of a single dose of Tenofovir disoproxil 300 mg to HIV infected subjects in the fasted state, maximum serum concentrations (Cmax) are achieved in 1.0 ± 0.4 hrs. Cmax and AUC values are 0.30 ± 0.09 µg/mL and 2.29 ± 0.69 ± µg·hr/mL, respectively.

The pharmacokinetics of Tenofovir disoproxil are dose proportional over a Tenofovir disoproxil dose range of 75 to 600 mg and are not affected by repeated dosing.

Distribution
After oral administration of Tenofovir disoproxil, Tenofovir disoproxil is distributed to most tissues with the highest concentrations occurring in the kidney, liver and the intestinal contents.

In vitro binding of Tenofovir disoproxil to human plasma or serum proteins is less than 0.7 and 7.2%, respectively, over the Tenofovir disoproxil concentration range 0.01 to 25 µg/mL. The volume of distribution at steady-state is 1.3 ± 0.6 L/kg and 1.2 ± 0.4 L/kg, following intravenous administration of Tenofovir disoproxil 1.0 mg/kg and 3.0 mg/kg.

Metabolism
It is unlikely that clinically significant interactions involving Tenofovir disoproxil and medicinal products metabolised by CYP450 would occur.

In vitro studies indicate that neither Tenofovir disoproxil nor Tenofovir are substrates of CYP enzymes.

Elimination
Tenofovir disoproxil is eliminated by a combination of glomerular filtration and active tubular secretion. There may be competition for elimination with other compounds that are also renally eliminated.

Within 72 hours, approximately 70-80% of the Tenofovir disoproxil dose is excreted unchanged in urine following intravenous administration. Following single dose, oral administration of Tenofovir disoproxil, the terminal elimination half-life of Tenofovir disoproxil is approximately 17 hours. After multiple oral doses of Tenofovir disoproxil 300 mg once daily (under fed conditions), 32 ± 10% of the administered dose is recovered in urine over 24 hours.

Effects of Food on Oral Absorption
Administration of Tenofovir disoproxil following a high-fat meal increases the oral bioavailability, with an increase in Tenofovir disoproxil AUC0-∞ of approximately 40% and an increase in Cmax of approximately 14%.

However, administration of Tenofovir disoproxil with a light meal did not have a significant effect on the pharmacokinetics of Tenofovir disoproxil when compared to fasted administration of the drug.

Food delays the time to Tenofovir disoproxil Cmax by approximately 1 hour. Cmax and AUC of Tenofovir disoproxil are 0.33 ± 0.12 µg/mL and 3.32 ± 1.37 µg·hr/mL following multiple doses of Tenofovir disoproxil 300 mg once daily in the fed state, when meal content was not controlled.

Specific Populations
Race: There were insufficient numbers from racial and ethnic groups other than Caucasian to adequately determine potential pharmacokinetic differences among these populations.

Gender: Tenofovir disoproxil pharmacokinetics are similar in male and female subjects.

Pediatric Patients 12 Years of Age and Older: Tenofovir disoproxil exposure achieved in pediatric subjects receiving oral daily doses of Tenofovir disoproxil 300 mg was similar to exposures achieved in adults receiving once-daily doses of Tenofovir disoproxil 300 mg.

Geriatric Patients: Pharmacokinetic trials have not been performed in the elderly (65 years and older).

Patients with Renal Impairment: The pharmacokinetics of Tenofovir disoproxil are altered in subjects with renal impairment [see Warnings and Precautions]. In subjects with creatinine clearance below 50 mL/min or with end-stage renal disease (ESRD) requiring dialysis, Cmax, and AUC0-∞ of Tenofovir disoproxil were increased.

Patients with Hepatic Impairment: There were no substantial alterations in Tenofovir disoproxil pharmacokinetics in subjects with hepatic impairment compared with unimpaired subjects. No change in Tenofovir disoproxil dosing is required in patients with hepatic impairment.

Assessment of Drug Interactions
At concentrations substantially higher (~300-fold) than those observed *in vivo*, Tenofovir disoproxil did not inhibit *in vitro* drug metabolism mediated by any of the following human CYP isoforms: CYP3A4, CYP2D6, CYP2C9, or CYP2E1.

However, a small (6%) but statistically significant reduction in metabolism of CYP1A substrate was observed. Based on the results of in vitro experiments and the known elimination pathway of Tenofovir disoproxil, the potential for CYP mediated interactions involving Tenofovir disoproxil with other medicinal products is low.

Tenofovir disoproxil is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) transporters. When Tenofovir disoproxil is co administered with an inhibitor of these transporters, an increase in absorption may be observed.

No clinically significant drug interactions have been observed between Tenofovir disoproxil and efavirenz, methadone, nelfinavir, oral contraceptives, ribavirin, or sofosbuvir.

INDICATION
HIV-1 infection
Hovid Tenofovir Disoproxil Fumarate Tablets is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and paediatric patients 12 years of age and older.

The following points should be considered when initiating therapy with Hovid Tenofovir Disoproxil Fumarate Tablets for the treatment of HIV-1 infection.

Hovid Tenofovir Disoproxil Fumarate Tablets should not be used in combination with other products containing Tenofovir disoproxil fumarate OR Tenofovir alafenamide (see Warnings and Precautions).

Chronic Hepatitis B
Hovid Tenofovir Disoproxil Fumarate Tablets is indicated for the treatment of chronic hepatitis B in adults.

The following points should be considered when initiating therapy with Hovid Tenofovir Disoproxil Fumarate Tablets for the treatment of HBV infection:
- This indication is based primary on data from treatment of subjects who were nucleoside-treatment-naïve and subjects who were treatment-experienced with documented resistance to lamivudine Subjects were adults with HBeAg-positive and HBeAg negative chronic hepatitis B with compensated liver disease.
- Tenofovir disoproxil was evaluated in a limited number of patients with chronic hepatitis B and decompensated liver disease.
- The numbers of patients who had adefovir resistance-associated substitutions at baseline were too small to reach conclusions of efficacy

CONTRAINDICATIONS
Hypersensitivity to the active substance or to any of the excipients in Hovid Tenofovir Disoproxil Fumarate.

WARNING AND PRECAUTIONS
Severe Acute Exacerbation of Hepatitis B in Patients with HBV Infection
All patients should be tested for the presence of chronic hepatitis B virus (HBV) before or when initiating Tenofovir disoproxil *[see Dosage and Administration].*

Discontinuation of anti-HBV therapy, including Tenofovir disoproxil , may be associated with severe acute exacerbations of hepatitis B. Patients infected with HBV who discontinue Tenofovir disoproxil should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, resumption of antihepatitis B therapy may be warranted, especially in patients with advanced liver disease or cirrhosis, since posttreatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure.

New Onset or Worsening Renal Impairment
Tenofovir disoproxil is principally eliminated by the kidney. 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 disoproxil *[see Adverse Reactions].*

Prior to initiation and during use of Tenofovir disoproxil, 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.

Dosing interval adjustment of Tenofovir disoproxil and close monitoring of renal function are recommended in all patients with creatinine clearance below 50 mL/min [see Dosage and Administration]. No safety or efficacy data are available in patients with renal impairment who received Tenofovir disoproxil using these dosing guidelines, so the potential benefit of Tenofovir disoproxil therapy should be assessed against the potential risk of renal toxicity.

Tenofovir disoproxil should be avoided with concurrent or recent use of a nephrotoxic agent (e.g.,high-dose or multiple non-steroidal anti-inflammatory drugs [NSAIDs]) [see Drug Interactions]. Cases of acute renal failure after initiation of high dose or multiple NSAIDs have been reported in HIV-infected patients with risk factors for renal dysfunction who appeared stable on Tenofovir disoproxil. Some patients required hospitalization and renal replacement therapy. Alternatives to NSAIDs should be considered, if needed, in patients at risk for renal dysfunction.

Persistent or worsening bone pain, pain in extremities, fractures and/or muscular pain or weakness may be manifestations of proximal renal tubulopathy and should prompt an evaluation of renal function in patients at risk of renal dysfunction.

Patients Coinfected with HIV-1 and HBV
Due to the risk of development of HIV-1 resistance, Tenofovir disoproxil should only be used in HIV-1 and HBV coinfected patients as part of an appropriate antiretroviral combination regimen.

HIV-1 antibody testing should be offered to all HBV-infected patients before initiating therapy with Tenofovir disoproxil. It is also recommended that all patients with HIV-1 be tested for the presence of chronic hepatitis B before initiating treatment with Tenofovir disoproxil.

Immune Reconstitution Syndrome
Immune reconstitution syndrome has been reported in HIV-1 infected patients treated with combination antiretroviral therapy, including Tenofovir disoproxil. During the initial phase of combination antiretroviral treatment, HIV-1 infected patients whose immune system responds 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.

Bone Loss and Mineralization Defects
Bone Mineral Density
In clinical trials in HIV-1 infected adults, Tenofovir disoproxil was associated with slightly greater decreases in bone mineral density (BMD) and increases in biochemical markers of bone metabolism, suggesting increased bone turnover relative to comparators [see Adverse Reactions]. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in subjects receiving Tenofovir disoproxil.

Clinical trials evaluating Tenofovir disoproxil in pediatric subjects were conducted. Under normal circumstances, BMD increases rapidly in pediatric patients. In HIV-1 infected subjects 2 years to less than 18 years of age, bone effects were similar to those observed in adult subjects and suggest increased bone turnover. Total body BMD gain was less in the Tenofovir disoproxil -treated HIV-1 infected pediatric subjects as compared to the control groups.

Similar trends were observed in chronic HBV-infected pediatric subjects 2 years to less than 18 years of age. In all pediatric trials, normal skeletal growth (height) was not affected for the duration of the clinical trials *[see Adverse Reactions].*

The effects of Tenofovir disoproxil-associated changes in BMD and biochemical markers on longterm bone health and future fracture risk in adults and pediatric subjects are unknown.

The long-term effect of lower spine and total body BMD on skeletal growth in pediatric patients, and in particular, the effects of long-duration exposure in younger children is unknown.

Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial. Assessment of BMD should be considered for adult and pediatric patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. If bone abnormalities are suspected, appropriate consultation should be obtained.

Mineralization Defects
Cases of osteomalacia associated with proximal renal tubulopathy, manifested as bone pain or pain in extremities and which may contribute to fractures, have been reported in association with Tenofovir disoproxil use [see Adverse Reactions]. Arthralgia and muscle pain or weakness have also been reported in cases of proximal renal tubulopathy.

Hypophosphatemia and osteomalacia secondary to proximal renal tubulopathy should be considered in patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms while receiving Tenofovir disoproxil -containing products *[see Warnings and Precautions].*

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, alone or in combination with other antiretrovirals. Treatment with Tenofovir disoproxil 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).

Risk of Adverse Reactions Due to Drug Interactions
The concomitant use of Tenofovir disoproxil and other drugs may result in known or potentially significant drug interactions, some of which may lead to possible clinically significant adverse reactions from greater exposures of concomitant drugs *[see Drug Interactions].*

Consider the potential for drug interactions prior to and during therapy with Tenofovir disoproxil; review concomitant medications during therapy with Tenofovir disoproxil ; and monitor for adverse reactions associated with the concomitant drugs.

Early Virologic Failure
Clinical trials in HIV-infected subjects have demonstrated that certain regimens that only contain three nucleoside reverse transcriptase inhibitors (NRTI) are generally less effective than triple drug regimens containing two NRTIs in combination with either a non-nucleoside reverse transcriptase inhibitor or a HIV-1 protease inhibitor. In particular, early virological failure and high rates of resistance substitutions have been reported. Triple nucleoside regimens should therefore be used with caution. Patients on a therapy utilizing a triple nucleoside-only regimen should be carefully monitored and considered for treatment modification.

HBV Patients with Decompensated Liver Disease
There are limited data on the safety and efficacy of Tenofovir disoproxil in HBV infected patients with decompensated liver disease and who have a Child-Pugh-Turcotte (CPT) score > 9. These patients may be at higher risk of experiencing serious hepatic or renal adverse reactions. Therefore, hepatobiliary and renal parameters should be closely monitored in this patient population.

UNDESIRABLE EFFECTS
The following adverse reactions, listed under the body system headings, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia, hypokalemia, muscular weakness, myopathy, hypophosphatemia.

The following adverse reactions have been identified during postapproval use of Tenofovir disoproxil. Because postmarketing 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.

Immune System Disorders	Allergic reaction, including angioedema
Metabolism and Nutrition Disorders	Lactic acidosis, hypokalemia, hypophosphatemia
Respiratory, Thoracic, and Mediastinal Disorders	Dyspnea
Gastrointestinal Disorders	Pancreatitis, increased amylase, abdominal pain
Hepatobiliary Disorders	Hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT gamma GT)
Skin and Subcutaneous Tissue Disorders	Rash
Musculoskeletal and Connective Tissue Disorders	Rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy
Renal and Urinary Disorders	Acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria
General Disorders	Asthenia

DRUG INTERACTIONS
Concomitant use not recommended
Tenofovir disoproxil 300mg should not be administered concomitantly with other medicinal products containing Tenofovir disoproxil or Tenofovir alafenamide.

Concomitant Drug	Effect on Concentration	Recommendation
NRTI: didanosine	Increases didanosine	Patients receiving Tenofovir disoproxil and didanosine should be monitored closely for didanosine associated adverse reactions. Discontinue didanosine in patients who develop didanosine-associated adverse reactions. Higher didanosine concentrations could potentiate didanosine-associated adverse reactions, including pancreatitis, and neuropathy. Suppression of CD4+ cell counts has been observed in patients receiving Tenofovir disoproxil with didanosine 400 mg daily. In patients weighing greater than 60 kg, reduce the didanosine dose to 250 mg when it is coadministered with Tenofovir disoproxil. In patients weighing less than 60 kg, reduce the didanosine dose to 200 mg when it is coadministered with Tenofovir disoproxil. When coadministered, Tenofovir disoproxil.and didanosine (enteric coated) may be taken under fasted conditions or with a light meal (less than 400 kcal, 20% fat).
HIV-1 Protease Inhibitors: atazanavir lopinavir/ritonavir atazanavir/ritonavir darunavir/ritonavir	Reduces atazanavir Increases Tenofovir disoproxil	When coadministered with Tenofovir disoproxil, atazanavir 300 mg should be given with ritonavir 100 mg. Monitor patients receiving Tenofovir disoproxil concomitantly with lopinavir/ritonavir, ritonavir-boosted atazanavir, or ritonavir boosted darunavir for Tenofovir disoproxil -associated adverse reactions.
Hepatitis C Antiviral Agents: sofosbuvir/ velpatasvir sofosbuvir/ velpatasvir/ voxilaprevir ledipasvir/sofosbuvir	Increases Tenofovir disoproxil	Monitor patients receiving Tenofovir disoproxil concomitantly with sofosbuvir/velpatasvir for adverse reactions associated with Tenofovir disoproxil. Monitor patients receiving Tenofovir disoproxil concomitantly with ledipasvir/sofosbuvir without an HIV-1 protease inhibitor/ritonavir or an HIV-1 protease inhibitor/cobicistat combination for adverse reactions associated with Tenofovir disoproxil. In patients receiving Tenofovir disoproxil concomitantly with ledipasvir/sofosbuvir and an HIV-1 protease inhibitor/ritonavir or an HIV-1 protease inhibitor/cobicistat combination, consider an alternative HCV or antiretroviral therapy, as the safety of increased Tenofovir disoproxil concentrations in this setting has not been established. If coadministration is necessary, monitor for adverse reactions associated with Tenofovir disoproxil.
Hepatitis B Antiviral Agents Adefovir dipivoxil	Increases Tenofovir disoproxil	Tenofovir disoproxil should not be administered concurrently with adefovir dipivoxil (see 'WARNING AND PRECAUTIONS').

Note : This table is not all inclusive.

Drugs Affecting Renal Function
Tenofovir disoproxil is primarily eliminated by the kidneys. Coadministration of Tenofovir disoproxil with drugs that are eliminated by active tubular secretion may increase concentrations of Tenofovir disoproxil and/or the co administered drug. Some examples include, but are not limited to acyclovir, cidofovir, ganciclovir,v alacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs [see Warnings and Precautions (5.2)]. Drugs that decrease renal function may increase concentrations of Tenofovir disoproxil.

Interaction with other medicinal products and other forms of interaction
The potential for CYP450-mediated interactions involving Tenofovir disoproxil with other medicinal products is low.

There were no clinically significant pharmacokinetic interactions when tenofovir disoproxil was co-administered with emtricitabine, lamivudine, indinavir, efavirenz, nelfinavir, saquinavir (ritonavir boosted), methadone, ribavirin, rifampicin, tacrolimus, or the hormonal contraceptive norgestimate/ethinyl oestradiol.

OVERDOSAGE
If overdose occurs the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary.

Tenofovir disoproxil is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of Tenofovir disoproxil, a four-hour hemodialysis session removed approximately 10% of the administered Tenofovir disoproxil dose.

DOSAGE & ADMINISTRATION
Testing Prior to Initiation of Tenofovir disoproxil for Treatment of HIV-1 Infection or Chronic Hepatitis B
Prior to or when initiating Tenofovir disoproxil, test patients for HBV infection and HIV-1 infection. Tenofovir disoproxil alone should not be used in patients with HIV-1 infection *[see Warnings and Precautions].* Prior to initiation and during use of Tenofovir disoproxil, 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 Tablet Dosage in Adults and Pediatric Patients 12 Years of Age and Older (35 kg or more)
The recommended dosage of Tenofovir disoproxil in adults and pediatric patients weighing at least 35 kg is one 300 mg tablet taken orally, once daily without regard to food. The dosage for Tenofovir disoproxil is the same for both HIV and HBV indications. In the treatment of chronic hepatitis B, the optimal duration of treatment is unknown. Safety and efficacy in pediatric patients with chronic hepatitis B weighing less than 35 kg have not been established.

Dosage Adjustment in Patients with Renal Impairment
Significantly increased drug exposures occurred when Tenofovir Disoproxil was administered to patients with moderate to severe renal impairment. Therefore, the dosing interval of Tenofovir Disoproxil should be adjusted in patients with baseline creatinine clearance <50mL/min using the recommendations provided in the table below:

	Creatinine Clearance (mL/min)[a]			Hemodialysis Patients
	50 or greater	30 – 49	10 – 29	
Recommended 300 mg Dosing Interval	Every 24 hours	Every 48 hours	Every 72 to 96 hours	Every 7 days or after a total of approximately 12 hours of dialysis[b]

a. Calculated using ideal (lean) body weight.
b. Generally, once weekly assuming 3 hemodialysis sessions a week of approximately 4 hours' duration. Tenofovir disoproxil should be administered following completion of dialysis.

These dosing interval recommendations are based on modelling of single-dose pharmacokinetic data in non-HIV and non- HBV infected patients with varying degrees of renal impairment, including end-stage renal disease requiring hemodialysis. The safety and effectiveness of these dosing interval adjustment recommendations have not been clinically evaluated in patients with moderate or severe renal impairment, therefore clinical response to treatment and renal function should be closely monitored in these patients.

No dosage adjustment is necessary for patients with mild renal impairment (creatinine clearance 50–80 mL/min) Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients with mild renal impairment.

No data are available to make dosage recommendations in patients with creatinine clearance below 10 mL/min who are not on hemodialysis.

No data are available to make dosage recommendations in pediatric patients 12 years of age and older with renal impairment.

Geriatric Patients
Clinical trials of Tenofovir disoproxil did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for the elderly patient should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

PREGNANCY AND LACTATION
Pregnancy
A large amount of data on pregnant women (more than 1,000 pregnancy outcomes) indicate no malformations or foetal/neonatal toxicity associated with Tenofovir disoproxil. The use of Tenofovir disoproxil may be considered during pregnancy, if necessary.

Lactation
Tenofovir has been shown to be excreted in human milk. There is insufficient information on the effects of tenofovir in newborns/infants. Therefore, Tenofovir disoproxil should not be used during breast-feeding. As a general rule, it is recommended that HIV and HBV infected women do not breast-feed their infants in order to avoid transmission of HIV and HBV to the infant.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Patients should be informed that dizziness has been reported during treatment with Tenofovir disoproxil.

MICROBIOLOGY
Mechanism of Action
Tenofovir Disoproxil Fumarate is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir Disoproxil Fumarate requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate (TFV-DP), an obligate chain terminator.

Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase (RT) and HBV RT by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Activity against HIV
Antiviral Activity
The antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The EC50 (50% effective concentration) values for tenofovir were in the range of 0.04 µM to 8.5 µM. In drug combination studies, tenofovir was not antagonistic with HIV-1 NRTIs (abacavir, didanosine, lamivudine, stavudine, zalcitabine, zidovudine), NNRTIs (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir). Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC50 values ranged from 0.5 µM to 2.2 µM) and strain specific activity against HIV-2 (EC50 values ranged from 1.6 µM to 5.5 µM).

Resistance
HIV-1 isolates with reduced susceptibility to tenofovir have been selected in cell culture. These viruses expressed a K65R substitution in RT and showed a 2–4 fold reduction in susceptibility to tenofovir. In addition, a K70E substitution in HIV-1 RT has been selected by tenofovir and results in low-level reduced susceptibility to tenofovir.

Cross-Resistance
Cross-resistance among certain HIV-1 NRTIs has been recognized.

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Activity against HBV
Antiviral Activity
The antiviral activity of tenofovir against HBV was assessed in the HepG2 2.2.15 cell line. The EC50 values for tenofovir ranged from 0.14 to 1.5 μM, with CC50 (50% cytotoxicity concentration) values > 100 μM. In cell culture combination antiviral activity studies of tenofovir with HBV NRTIs entecavir, lamivudine, and telbivudine, and with the HIV-1 NRTI emtricitabine, no antagonistic activity was observed.

Resistance
HBV isolates from trial subjects who remained viremic showed treatment-emergent substitutions; however, no specific substitutions occurred at a sufficient frequency to be associated with resistance to Tenofovir disoproxil (genotypic and phenotypic analyses).

Cross-Resistance
Cross-resistance has been observed between HBV NRTIs.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis
Long-term oral carcinogenicity studies of Tenofovir Disoproxil Fumarate in mice and rats were carried out at exposures up to approximately 16 times (mice) and 5 times (rats) those observed in humans at the therapeutic dose for HIV-1 infection. At the high dose in female mice, liver adenomas were increased at exposures 16 times that in humans. In rats, the study was negative for carcinogenic findings at exposures up to 5 times that observed in humans at the therapeutic dose.

Mutagenesis
Tenofovir Disoproxil Fumarate was mutagenic in the in vitro mouse lymphoma assay and negative in an in vitro bacterial mutagenicity test (Ames test). In an in vivo mouse micronucleus assay, Tenofovir Disoproxil Fumarate was negative when administered to male mice.

Impairment of Fertility
There were no effects on fertility, mating performance or early embryonic development when Tenofovir Disoproxil Fumarate was administered to male rats at a dose equivalent to 10 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 15 days prior to mating through day seven of gestation. There was however, an alteration of the estrous cycle in female rats.

Animal Toxicology and/or Pharmacology
Tenofovir and Tenofovir Disoproxil Fumarate administered in toxicology studies to rats, dogs, and monkeys at exposures (based on AUCs) greater than or equal to 6 fold those observed in humans caused bone toxicity. In monkeys the bone toxicity was diagnosed as osteomalacia.

Osteomalacia observed in monkeys appeared to be reversible upon dose reduction or discontinuation of tenofovir. In rats and dogs, the bone toxicity manifested as reduced bone mineral density. The mechanism(s) underlying bone toxicity is unknown.

Evidence of renal toxicity was noted in 4 animal species. Increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia, and/or calciuria and decreases in serum phosphate were observed to varying degrees in these animals. These toxicities were noted at exposures (based on AUCs) 2–20 times higher than those observed in humans. The relationship of the renal abnormalities, particularly the phosphaturia, to the bone toxicity is not known.

PATIENT COUNSELING INFORMATION

Severe Acute Exacerbation of Hepatitis B in Patients Infected with HBV
Inform patients that severe acute exacerbations of hepatitis B have been reported in patients infected with hepatitis B virus (HBV) and have discontinued Tenofovir Disoproxil. Advise patients not to discontinue Tenofovir Disoproxil without first informing their healthcare provider. All patients should be tested for HBV infection before or when starting TENOFOVIR DISOPROXIL and those who are infected with HBV need close medical follow-up for several months after stopping Tenofovir Disoproxil to monitor for exacerbations of hepatitis *[see Warnings and Precautions]*.

New Onset or Worsening Renal Impairment
Inform patients that renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported in association with the use of Tenofovir Disoproxil. Advise patients to avoid Tenofovir Disoproxil with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple NSAIDs) [see Warnings and Precautions]. The dosing interval of Tenofovir Disoproxil may need adjustment in HIV-1 infected patients with renal impairment.

Immune Reconstitution Syndrome
Inform patients that in some patients with advanced HIV infection (AIDS) signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. Advise patients to inform their healthcare provider immediately of any symptoms of infection *[see Warnings and Precautions]*.

Bone Loss and Mineralization Defects
Inform patients that decreases in bone mineral density have been observed with the use of Tenofovir Disoproxil. Consider bone monitoring in patients who have a history of pathologic bone fracture or at risk for osteopenia *[see Warnings and Precautions]*.

Lactic Acidosis and Severe Hepatomegaly
Inform patients that lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Treatment with Tenofovir Disoproxil should be suspended in any patient who develops clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity *[see Warnings and Precautions]*.

Drug Interactions
Advise patients that Tenofovir Disoproxil may interact with many drugs; therefore, advise patients to report to their healthcare provider the use of any other medication, including other HIV drugs and drugs for treatment of hepatitis C virus *[see Warnings and Precautions and Drug Interactions]*.

Dosing Recommendations
Inform patients that it is important to take Tenofovir Disoproxil on a regular dosing schedule with or without food and to avoid missing doses as it can result in development of resistance [see Dosage and Administration].

Lactation
Instruct mothers not to breastfeed if they are taking Tenofovir Disoproxil for the treatment of HIV-1 infection because of the risk of passing the HIV-1 virus to the baby *[see Use in Specific Populations]*.

Treatment Duration
Advise patients that in the treatment of chronic hepatitis B, the optimal duration of treatment is unknown. The relationship between response and long-term prevention of outcomes such as hepatocellular carcinoma is not known.

CLINICAL STUDIES

Clinical Efficacy in Adults with HIV-1 Infection
Treatment-Naïve Adult Patients

Study 903
Data through 144 weeks are reported for Study 903, a double-blind, active-controlled multicenter trial comparing Tenofovir Disoproxil Fumarate (300 mg once daily) administered in combination with lamivudine and efavirenz versus stavudine (d4T), lamivudine, and efavirenz in 600 antiretroviral-naïve subjects. Subjects had a mean age of 36 years (range 18–64); 74% were male, 64% were Caucasian, and 20% were Black. The mean baseline CD4 + cell count was 279 cells/mm^3 (range 3–956) and median baseline plasma HIV-1 RNA was 77,600 copies/mL (range 417–5,130,000). Subjects were stratified by baseline HIV-1 RNA and CD4 + cell count. Forty-three percent of subjects had baseline viral loads >100,000 copies/mL and 39% had CD4 + cell counts <200 cells/mm^3. Treatment outcomes through 48 and 144 weeks are presented in Table 1.

Table 1 Outcomes of Randomized Treatment at Week 48 and 144 (Study 903)

Outcomes	At Week 48		At Week 144	
	Tenofovir Disoproxil Fumarate +3TC +EFV (N=299)	d4T+3TC +EFV (N=301)	Tenofovir Disoproxil Fumarate +3TC +EFV (N=299)	d4T+3TC +EFV (N=301)
Responder[a]	79%	82%	68%	62%
Virologic failure[b]	6%	4%	10%	8%
Rebound	5%	3%	8%	7%
Never suppressed	0%	1%	0%	0%
Added an antiretroviral	1%	1%	2%	1%
Death	<1%	1%	<1%	2%
Discontinued due to adverse event	6%	6%	8%	13%
Discontinued for other reasons[c]	8%	7%	14%	15%

a. Subjects achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Week 48 and 144.
b. Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Week 48 and 144.
c. Includes lost to follow-up, subject's withdrawal, noncompliance, protocol violation and other reasons.

Achievement of plasma HIV-1 RNA concentrations of less than 400 copies/mL at Week 144 was similar between the two treatment groups for the population stratified at baseline on the basis of HIV-1 RNA concentration (> or ≤100,000 copies/mL) and CD4 + cell count (< or ≥200 cells/mm^3). Through 144 weeks of therapy, 62% and 58% of subjects in the Tenofovir Disoproxil Fumarate and stavudine arms, respectively achieved and maintained confirmed HIV-1 RNA <50 copies/mL. The mean increase from baseline in CD4 + cell count was 263 cells/mm^3 for the Tenofovir Disoproxil Fumarate arm and 283 cells/mm^3 for the stavudine arm.

Through 144 weeks, 11 subjects in the Tenofovir Disoproxil Fumarate group and 9 subjects in the stavudine group experienced a new CDC Class C event.

Study 934
Data through 144 weeks are reported for Study 934, a randomized, open-label, active-controlled multicenter trial comparing emtricitabine + Tenofovir Disoproxil Fumarate administered in combination with efavirenz versus zidovudine/lamivudine fixed-dose combination administered in combination with efavirenz in 511 antiretroviral-naïve subjects. From Weeks 96 to 144 of the trial, subjects received a fixed-dose combination of emtricitabine and Tenofovir Disoproxil Fumarate with efavirenz in place of emtricitabine + Tenofovir Disoproxil Fumarate with efavirenz. Subjects had a mean age of 38 years (range 18–80); 86% were male, 59% were Caucasian, and 23% were Black. The mean baseline CD4 + cell count was 245 cells/mm^3 (range 2–1191) and median baseline plasma HIV-1 RNA was 5.01 log 10 copies/mL (range 3.56–6.54). Subjects were stratified by baseline CD4 + cell count (< or ≥200 cells/mm^3); 41% had CD4 + cell counts <200 cells/mm^3 and 51% of subjects had baseline viral loads >100,000 copies/mL. Treatment outcomes through 48 and 144 weeks for those subjects who did not have efavirenz resistance at baseline are presented in Table 2.

Table 2 Outcomes of Randomized Treatment at Week 48 and 144 (Study 934)

Outcomes	At Week 48		At Week 144	
	FTC + Tenofovir Disoproxil Fumarate + EFV (N=244)	AZT/3TC + EFV (N=243)	FTC + Tenofovir Disoproxil Fumarate +EFV (N=227)[a]	AZT/3TC + EFV (N=229)[a]
Responder[b]	84%	73%	71%	58%
Virologic failure[c]	2%	4%	3%	6%
Rebound	1%	3%	2%	5%
Never suppressed	0%	0%	0%	0%
Added an antiretroviral	1%	1%	1%	1%
Death	<1%	1%	<1%	1%
Discontinued due to adverse event	4%	9%	5%	12%
Discontinued for other reasons[d]	10%	14%	20%	22%

a. Subjects who were responders at Week 48 or Week 96 (HIV-1 RNA <400 copies/mL) but did not consent to continue the trial after Week 48 or Week 96 were excluded from analysis.
b. Subjects achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Weeks 48 and 144.
c. Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Weeks 48 and 144.
d. Includes lost to follow-up, subject withdrawal, noncompliance, protocol violation and other reasons.

Through Week 48, 84% and 73% of subjects in the emtricitabine + Tenofovir Disoproxil Fumarate group and the zidovudine/lamivudine group, respectively, achieved and maintained HIV-1 RNA <400 copies/mL (71% and 58% through Week 144). The difference in the proportion of subjects who achieved and maintained HIV-1 RNA <400 copies/mL through 48 weeks largely results from the higher number of discontinuations due to adverse events and other reasons in the zidovudine/lamivudine group in this open-label trial. In addition, 80% and 70% of subjects in the emtricitabine + Tenofovir Disoproxil Fumarate group and the zidovudine/lamivudine group, respectively, achieved and maintained HIV-1 RNA <50 copies/mL through Week 48 (64% and 56% through Week 144). The mean increase from baseline in CD4 + cell count was 190 cells/mm^3 in the emtricitabine + Tenofovir Disoproxil Fumarate group and 158 cells/mm^3 in the zidovudine/lamivudine group at Week 48 (312 and 271 cells/mm^3 at Week 144).

Through 48 weeks, 7 subjects in the emtricitabine + Tenofovir Disoproxil Fumarate group and 5 subjects in the zidovudine/lamivudine group experienced a new CDC Class C event (10 and 6 subjects through 144 weeks).

Treatment-Experienced Adult Patients

Study 907
Study 907 was a 24-week, double-blind placebo-controlled multicenter trial of Tenofovir Disoproxil Fumarate added to a stable background regimen of antiretroviral agents in 550 treatment-experienced subjects. After 24 weeks of blinded trial treatment, all subjects continuing on trial were offered open-label Tenofovir Disoproxil Fumarate for an additional 24 weeks. Subjects had a mean baseline CD4 + cell count of 427 cells/mm^3 (range 23–1385), median baseline plasma HIV-1 RNA of 2340 (range 50–75,000) copies/mL, and mean duration of prior HIV-1 treatment was 5.4 years. Mean age of the subjects was 42 years; 85% were male , 69% Caucasian, 17% Black and 12% Hispanic.

The percent of subjects with HIV-1 RNA <400 copies/mL and outcomes of subjects through 48 weeks are summarized in Table 3.

Table 3 Outcomes of Randomized Treatment (Study 907)

Outcomes	0 - 24 weeks		0 - 48 weeks	24 - 48 weeks
	Tenofovir Disoproxil Fumarate (N=368)	Placebo (N=182)	Tenofovir Disoproxil Fumarate (N=368)	Placebo Crossover to Tenofovir Disoproxil Fumarate (N=170)
HIV-1 RNA <400 copies/ml[a]	40%	11%	28%	30%
Virologic failure[b]	53%	84%	61%	64%
Discontinued due to adverse event	3%	3%	5%	5%
Discontinued for other reasons[c]	3%	3%	5%	1%

a. Subjects with HIV-1 RNA <400 copies/mL and no prior study drug discontinuation at Week 24 and 48 respectively.
b. Subjects with HIV-1 RNA ≥400 copies/mL efficacy failure or missing HIV-1 RNA at Week 24 and 48 respectively.
c. Includes lost to follow-up, subject withdrawal, noncompliance, protocol violation and other reasons.

At 24 weeks of therapy, there was a higher proportion of subjects in the Tenofovir Disoproxil Fumarate arm compared to the placebo arm with HIV-1 RNA <50 copies/mL (19% and 1%, respectively). Mean change in absolute CD4 + cell counts by Week 24 was +11 cells/mm^3 for the Tenofovir Disoproxil Fumarate group and -5 cells/mm^3 for the placebo group. Mean change in absolute CD4 + cell counts by Week 48 was +4 cells/mm^3 for the Tenofovir Disoproxil Fumarate group. Through Week 24, one subject in the Tenofovir Disoproxil Fumarate group and no subjects in the placebo arm experienced a new CDC Class C event.

Clinical Efficacy in Adults with Chronic Hepatitis B
HBeAg-Negative Chronic Hepatitis B
Study 0102 was a Phase 3, randomized, double-blind, active-controlled trial of Tenofovir Disoproxil Fumarate 300 mg compared to HEPSERA 10 mg in 375 HBeAg- (anti-HBe+) subjects with compensated liver function, the majority of whom were nucleoside-naïve. The mean age of subjects was 44 years; 77% were male, 25% were Asian, 65% were Caucasian, 17% had previously received alpha-interferon therapy and 18% were nucleoside-experienced (16% had prior lamivudine experience). At baseline, subjects had a mean Knodell necroinflammatory score of 7.8; mean plasma HBV DNA was 6.9 log 10 copies/mL; and mean serum ALT was 140 U/L.

HBeAg-Positive Chronic Hepatitis B
Study 0103 was a Phase 3, randomized, double-blind, active-controlled trial of Tenofovir Disoproxil Fumarate 300 mg compared to HEPSERA 10 mg in 266 HBeAg+ nucleoside-naïve subjects with compensated liver function. The mean age of subjects was 34 years; 69% were male, 36% were Asian, 52% were Caucasian, 16% had previously received alpha-interferon therapy, and <5% were nucleoside experienced. At baseline, subjects had a mean Knodell necroinflammatory score of 8.4; mean plasma HBV DNA was 8.7 log 10 copies /mL; and mean serum ALT was 147 U/L.

The primary data analysis was conducted after all subjects reached 48 weeks of treatment and results are summarized below.
The primary efficacy endpoint in both trials was complete response to treatment defined as HBV DNA <400 copies/mL (69 IU/mL) and Knodell necroinflammatory score improvement of at least 2 points, without worsening in Knodell fibrosis at Week 48 (Table 4).

Table 4 Histological, Virological, Biochemical, and Serological Response at Week 48

	0102 (HBeAg-)		0103 (HBeAg+)	
	Tenofovir Disoproxil Fumarate (N=250)	HEPSERA (N=125)	Tenofovir Disoproxil Fumarate (N=176)	HEPSERA (N=90)
Complete Response	71%	49%	67%	12%
Histology Histological Response[a]	72%	69%	74%	68%
HBV DNA <400 copies/mL (<69 IU/mL)	93%	63%	76%	13%
ALT Normalized ALT[b]	76%	77%	68%	54%
Serology HBeAg Loss/ Seroconversion	NA[c]	NA[c]	20% / 19%	16% / 16%
HBsAg Loss/ Seroconversion	0 / 0	0 / 0	3% / 1%	0 / 0

a. Knodell necroinflammatory score improvement of at least 2 points without worsening in Knodell fibrosis.
b. The population used for analysis of ALT normalization included only subjects with ALT above ULN at baseline.
c. NA = Not Applicable

Treatment Beyond 48 Weeks
In Studies 0102 (HBeAg-negative) and 0103 (HBeAg-positive), subjects who completed double-blind treatment (389 and 196 subjects who were originally randomized to Tenofovir Disoproxil Fumarate and HEPSERA, respectively) were eligible to roll over to open-label Tenofovir Disoproxil Fumarate with no interruption in treatment.

In Study 0102, 266 of 347 subjects who entered the open-label period (77%) continued in the study through Week 384. Among subjects randomized to Tenofovir Disoproxil Fumarate followed by open-label treatment with Tenofovir Disoproxil Fumarate, 73% had HBV DNA < 400 copies/ml ((69 IU/ml), and 63% had ALT normalization at Week 384. Among subjects randomized to HEPSERA followed by open-label treatment with Tenofovir Disoproxil Fumarate, 80% had HBV DNA < 400 copies/mL (69 IU/mL) and 70% had ALT normalization through Week 384. At Week 384, both HBsAg loss and seroconversion were approximately 1% in both treatment groups.

In Study 0103, 146 of 238 subjects who entered the open-label period (61%) continued in the study through Week 384. Among subjects randomized to Tenofovir Disoproxil Fumarate, 49% had HBV DNA <400 copies/mL, (69 IU/mL), 42% had ALT normalization, and 20% had HBeAg loss (13% seroconversion to anti-HBe antibody) through Week 384. Among subjects randomized to HEPSERA followed by open-label treatment with Tenofovir Disoproxil Fumarate, 56% had HBV DNA < 400 copies/mL, (69 IU/mL), 50% had ALT normalization, and 28% had HBeAg loss (19% seroconversion to anti-HBe antibody) through Week 384. At Week 384, HBsAg loss and seroconversion were 11% and 8% respectively, in subjects initially randomized to Tenofovir Disoproxil Fumarate and 12% and 10%, respectively, in subjects initially randomized to HEPSERA.

Of the originally randomized and treated 641 subjects in the two studies, liver biopsy data from 328 subjects who received continuing open-label treatment with Tenofovir Disoproxil Fumarate monotherapy were available for analysis at baseline, Week 48 and Week 240. There were no apparent differences between the subset of subjects who had liver biopsy data at Week 240 and those subjects remaining on open-label Tenofovir Disoproxil Fumarate without biopsy data that would be expected to affect histological outcomes at Week 240. Among the 328 subjects evaluated, the observed histological response rates were 80% and 88% at Week 48 and Week 240, respectively. In the subjects without cirrhosis at baseline (Ishak fibrosis score 0-4), 92% (216/235) and 95% (223/235) had either improvement or no change in Ishak fibrosis score at Week 48 and Week 240, respectively. In subjects with cirrhosis at baseline (Ishak fibrosis score 5-6), 97% (90/93) and 99% (92/93) had either improvement or no change in Ishak fibrosis score at Week 48 and Week 240, respectively. Twenty-nine percent (27/93) and 72% (67/93) of subjects with cirrhosis at baseline experienced regression of cirrhosis by Week 48 and Week 240, respectively, with a reduction in Ishak fibrosis score of at least 2 points. No definitive conclusions can be established about the remaining study population who were not part of this subset analysis.

Patients with Lamivudine-Resistant Chronic Hepatitis B
Study 121 was a randomized, double-blind, active-controlled trial evaluating the safety and efficacy of Tenofovir Disoproxil Fumarate compared to an unapproved antiviral regimen in subjects with chronic hepatitis B, persistent viremia (HBV DNA ≥ 1,000 IU/mL), and genotypic evidence of lamivudine resistance (rtM204I/V +/- rtL180M). One hundred forty-one adult subjects were randomized to the Tenofovir Disoproxil Fumarate treatment arm. The mean age of subjects randomized to Tenofovir Disoproxil Fumarate was 47 years (range 18-73); 74% were male, 59% were Caucasian, and 37% were Asian. At baseline, 54% of subjects were HBeAg-negative, 46% were HBeAg-positive, and 56% had abnormal ALT. Subjects had a mean HBV DNA of 6.4 log 10 copies/mL and mean serum ALT of 71 U/L at baseline.

After 96 weeks of treatment, 126 of 141 subjects (89%) randomized to Tenofovir Disoproxil Fumarate had HBV DNA < 400 copies/mL (69 IU/mL), and 49 of 79 subjects (62%) with abnormal ALT at baseline had ALT normalization. Among the HBeAg-positive subjects randomized to Tenofovir Disoproxil Fumarate, 10 of 65 subjects (15%) experienced HBeAg loss, and 7 of 65 subjects (11%) experienced anti-HBe seroconversion through Week 96. The proportion of subjects with HBV DNA concentrations below 400 copies/mL (69 IU/mL) at Week 96 was similar between the Tenofovir Disoproxil Fumarate monotherapy and the comparator arms.

Across the combined chronic hepatitis B treatment trials, the number of subjects with adefovir-resistance associated substitutions at baseline was too small to establish efficacy in this subgroup.

Patients with Chronic Hepatitis B and Decompensated Liver Disease
Tenofovir Disoproxil Fumarate was studied in a small randomized, double-blind, active-controlled trial evaluating the safety of Tenofovir Disoproxil Fumarate compared to other antiviral drugs in subjects with chronic hepatitis B and decompensated liver disease through 48 weeks (Study 0108).

Forty-five adult subjects (37 males and 8 females) were randomized to the Tenofovir Disoproxil Fumarate treatment arm. At baseline, 69% subjects were HBeAg-negative, and 31% were HBeAg-positive. Subjects had a mean Child-Pugh score of 7, a mean MELD score of 12, mean HBV DNA of 5.8 log 10 copies/mL and mean serum ALT of 61 U/L at baseline. Trial endpoints were discontinuation due to an adverse event and confirmed increase in serum creatinine ≥ 0.5 mg/dL or confirmed serum phosphorus of < 2 mg/dL [See Adverse Reactions (6.1)].

At 48 weeks, 31/44 (70%) and 12/26 (46%) Tenofovir Disoproxil Fumarate -treated subjects achieved an HBV DNA < 400 copies/mL, and normalized ALT, respectively. The trial was not designed to evaluate treatment impact on clinical endpoints such as progression of liver disease, need for liver transplantation, or death.

Clinical Trial Results in Pediatric Subjects 12 Years to less than 18 Years of Age with Chronic Hepatitis B
In Trial 115, 106 HBeAg negative (9%) and positive (91%) subjects aged 12 to less than 18 years with chronic HBV infection were randomized to receive blinded treatment with Tenofovir Disoproxil Fumarate 300 mg (N=52) or placebo (N=54) for 72 weeks. At trial entry, the mean HBV DNA was 8.1 log 10 copies/mL and mean ALT was 101 U/L. Of 52 subjects treated with Tenofovir Disoproxil Fumarate, 20 subjects were nucleos(t)ide-naïve and 32 subjects were nucleos(t)ide-experienced. Thirty-one of the 32 nucleos(t)ide-experienced subjects had prior lamivudine experience. At Week 72, 88% (46/52) of subjects in the Tenofovir Disoproxil Fumarate group and 0% (0/54) of subjects in the placebo group had HBV DNA <400 copies/mL (69 IU/mL). Among subjects with abnormal ALT at baseline, 74% (26/35) of subjects receiving Tenofovir Disoproxil Fumarate had normalized ALT at Week 72 compared to 31% (13/42) in the placebo group. One Tenofovir Disoproxil Fumarate-treated subject experienced sustained HBsAg-loss and seroconversion to anti-HBs during the first 72 weeks of trial participation.

Storage	: Store below 30°C.
Presentation/ Packing	: 30 tablets per plastic bottle.
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