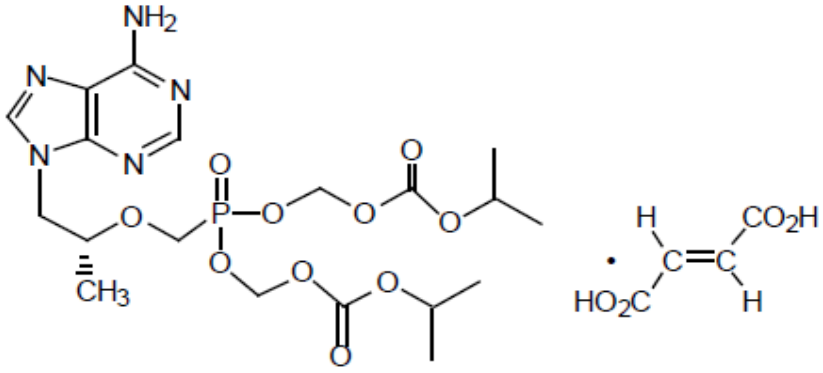
For the use of a Registered Medical Practitioner or a Hospital or a Laboratory

TENOCRUZ
TENOFOVIR DISOPROXIL FUMARATE

COMPOSITION:
Each film coated tablet contains:
Tenofovir Disoproxil Fumarate I.P. 300 mg
Colour: Titanium dioxide I.P.

DESCRIPTION
In vivo tenofovir disoproxil fumarate is converted to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate. Tenofovir exhibits activity against HIV-1 reverse transcriptase.

The chemical name of tenofovir disoproxil fumarate is 9-[(R)-2- [[bis[[(isopropoxycarbonyl) oxy] methoxy] phosphinyl] methoxy] propyl] adenine fumarate (1:1). It has a molecular formula of $C_{19}H_{30}N_5O_{10}P \bullet C_4H_4O_4$ and a molecular weight of 635.52. It has the following structural formula:



CLINICAL PHARMACOLOGY
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, an obligate chain terminator. Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase and HBV reverse transcriptase 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.

Pharmacokinetics
The pharmacokinetics of tenofovir disoproxil fumarate have been reported in healthy volunteers and HIV-1 infected individuals. Tenofovir pharmacokinetics are similar between these populations.

Absorption
Tenofovir is a water soluble diester prodrug of the active ingredient tenofovir. The oral bioavailability of tenofovir from Tenofovir in fasted subjects is approximately 25%.
Following oral administration of a single dose of Tenofovir 300 mg to HIV-1 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 is dose proportional over a Tenofovir dose range of 75 to 600 mg and is not affected by repeated dosing.

Distribution
In vitro binding of tenofovir to human plasma or serum proteins is less than 0.7 and 7.2%, respectively, over the tenofovir 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 1.0 mg/kg and 3.0 mg/kg.

Metabolism and Elimination
In vitro studies reported that neither tenofovir disoproxil nor tenofovir are substrates of CYP enzymes.

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

Tenofovir 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.

Effects of Food on Oral Absorption
Administration of Tenofovir 300 mg tablets following a high-fat meal (~700 to 1000 kcal containing 40 to 50% fat) increases the oral bioavailability, with an increase in tenofovir $AUC_{0-\infty}$ of approximately 40% and an increase in Cmax of approximately 14%. However, administration of Tenofovir with a light meal did not have a significant effect on the pharmacokinetics of tenofovir when compared to fasted administration of the drug.

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

INDICATIONS AND USAGE
Tenocruz is indicated as Anti-HIV and for treatment of chronic Hepatitis B in adults

DOSAGE AND ADMINISTRATION
Recommended Dose in Adults and Pediatric Patients 12 Years of Age and Older (35 kg or more)

For the treatment of HIV-1 or chronic hepatitis B: The dose is one 300 mg Tenofovir tablet once daily taken orally, without regard to food.

Dose Adjustment for Renal Impairment in Adults
Significantly increased drug exposures occurred when Tenofovir was administered to subjects with moderate to severe renal impairment.

Therefore, the dosing interval of Tenofovir tablets 300 mg should be adjusted in patients with baseline creatinine clearance below 50 mL/min using the recommendations in Table.

Table: Dosage adjustment for patients with altered creatinine clearance

	Creatinine Clearance (mL/min)[a]			**Hemodialysis Patients**
	≥50	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 three hemodialysis sessions a week of approximately 4 hours duration. Tenofovir should be administered following completion of dialysis.

These dosing interval recommendations are based on reported single-dose pharmacokinetic data in non-HIV and non-HBV infected subjects 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 reported in patients with moderate or severe renal impairment, therefore clinical response to treatment and renal function should be closely monitored in these patients. There was no data reported to recommend use of Tenofovir tablets in patients with renal impairment.

No dose adjustment of Tenofovir tablets 300 mg 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.

The pharmacokinetics of tenofovir has not been reported in non-hemodialysis patients with creatinine clearance below 10 mL/min; therefore, no dosing recommendation is available for these patients.

USE IN SPECIFIC POPULATIONS
Pregnancy
Pregnancy Category B
There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Tenofovir should be used during pregnancy only if clearly needed.

Animal Data:
Reproduction studies have been reported in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir.

Nursing Mothers
Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV-1. Samples of breast milk obtained from five HIV-1 infected mothers in the first post-partum week show that tenofovir is secreted in human milk.

The impact of this exposure in breastfed infants is unknown. Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving Tenofovir.

CONTRAINDICATIONS
None

WARNINGS AND PRECAUTIONS

WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS AND POST TREATMENT EXACERBATION OF HEPATITIS

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including Tenofovir, in combination with other antiretrovirals.

Severe acute exacerbations of hepatitis have been reported in HBV-infected patients who have discontinued anti-hepatitis B therapy, including Tenofovir. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy, including Tenofovir. If appropriate, resumption of anti-hepatitis B therapy may be warranted.

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, 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 should be suspended in any patient who develop 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).

Exacerbation of Hepatitis after Discontinuation of Treatment
Discontinuation of anti-HBV therapy, including Tenofovir, may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue TENOFOVIR 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.

New Onset or Worsening Renal Impairment
Tenofovir 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.

It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with Tenofovir. Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients at risk for renal impairment, including patients who have previously experienced renal events while receiving adefovir dipivoxil.

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

Tenofovir should be avoided with concurrent or recent use of a nephrotoxic agent.

Co-administration with Other Products
Tenofovir should not be used in combination with the fixed-dose combination products efavirenz/emtricitabine/tenofovir disoproxil fumarate**,** emtricitabine/rilpivirine/tenofovir disoproxil fumarate, elvitegravir, cobicistat, since tenofovir disoproxil fumarate is a component of these products.

Tenofovir should not be administered in combination with adefovir dipivoxil.

Patients Coinfected with HIV-1 and HBV
Due to the risk of development of HIV-1 resistance, Tenofovir 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. It is also recommended that all patients with HIV-1 be tested for the presence of chronic hepatitis B before initiating treatment with Tenofovir.

Decreases in Bone Mineral Density
Assessment of bone mineral density (BMD) should be considered who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained.

Fat Redistribution
In HIV-infected patient’s redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been reported in patients receiving combination antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

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

Early Virologic Failure

In reported Clinical trials in HIV-infected subjects have reported 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.

DRUG INTERACTIONS

Didanosine

Coadministration of Tenofovir and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine associated adverse reactions. Didanosine should be discontinued in patients who develop didanosine-associated adverse reactions.

When administered with Tenofovir, Cmax and AUC of didanosine increased significantly. The mechanism of this interaction is unknown. Higher didanosine concentrations could potentiate didanosine-associated adverse reactions, including pancreatitis and neuropathy. Suppression of CD4+ cell counts has been reported in patients receiving Tenofovir with didanosine 400 mg daily.

In patients weighing greater than 60 kg, the didanosine dose should be reduced to 250 mg when it is coadministered with Tenofovir. Data are not available to recommend a dose adjustment of didanosine for adult or pediatric patients weighing less than 60 kg. When coadministered, Tenofovir and didanosine EC may be taken under fasted conditions or with a light meal (less than 400 kcal, 20% fat).

Atazanavir

Atazanavir has been reported to increase tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving atazanavir and Tenofovir should be monitored for TENOFOVIR-associated adverse reactions. Tenofovir should be discontinued in patients who develop Tenofovir -associated adverse reactions. Tenofovir decreases the AUC and Cmin of atazanavir. When coadministered with Tenofovir, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg. Atazanavir without ritonavir should not be coadministered with Tenofovir.

Lopinavir/Ritonavir

Lopinavir/ritonavir has been reported to increase tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving lopinavir/ritonavir and Tenofovir should be

monitored for Tenofovir -associated adverse reactions. Tenofovir should be discontinued in patients who develop Tenofovir associated adverse reactions.

Drugs Affecting Renal Function

Since tenofovir is primarily eliminated by the kidneys, coadministration of Tenofovir with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir and/or increase the concentrations of other renally eliminated drugs. Some examples include, but are not limited to cidofovir, acyclovir, valacyclovir, ganciclovir, and valganciclovir. Drugs that decrease renal function may also increase serum concentrations of tenofovir. In the treatment of chronic hepatitis B, Tenofovir should not be administered in combination with adefovir dipivoxil.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term oral carcinogenicity studies of tenofovir disoproxil fumarate in mice and rats were reported up to approximately 16 times (mice) and 5 times (rats) those reported 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 human.

In rats, reported study was negative for carcinogenic findings at exposures up to 5 times that reported in humans at the therapeutic dose.

Mutagenesis

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

Impairment of Fertility

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

ADVERSE REACTIONS

Adverse Reactions from Clinical Trials Experience

The most common adverse reactions (incidence greater than or equal to 10%, Grades 2–4) reported from any of the 3 large controlled clinical trials include rash, diarrhea, headache, pain, depression, asthenia, and nausea.

Mild adverse reactions (Grade 1) were common with a similar incidence in both arms, and included dizziness, diarrhea, and nausea. Selected Treatment-Emergent Adverse Reactionsa (Grades 2–4)

Body as a Whole
Headache
Pain
Fever
Abdominal pain
Back pain
Asthenia
Chest pain

Digestive System
Diarrhea
Nausea
Dyspepsia
Anorexia
Flatulence
Vomiting

Respiratory
Pneumonia

Nervous System
Depression
Insomnia
Dizziness
Peripheral neuropathy[a]
Anxiety

Skin and Appendages
Rash event[b]
Sweating
Musculoskeletal
Myalgia

Metabolic Disorders
Weight loss

a. Peripheral neuropathy includes peripheral neuritis and neuropathy.
b. Rash event includes rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, and ustular rash.

Postmarketing Experience
The following adverse reactions have been identified during postapproval use of TENOFOVIR. 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 and Administration Site Conditions
Asthenia
The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia, hypokalemia, muscular weakness, myopathy, hypophosphatemia.

OVERDOSAGE
Limited clinical experience at doses higher than the therapeutic dose of Tenofovir 300 mg is reported. In reported Study 901, 600 mg tenofovir disoproxil fumarate was administered to 8 subjects orally for 28 days. No severe adverse reactions were reported. The effects of higher doses are not known.

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

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

STORAGE:
Store protected from moisture, at a temperature not exceeding 30°C.

EXPIRY:
Do not use later than the date of expiry.

PRESENTATION:
Tenocruz is available as blister strip of 10 tablets

MARKETED BY:

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