

1. Name of the medicinal product

Emtricitabine and Tenofovir Disoproxil Fumarate Tablets
200mg/300mg

2. Qualitative and quantitative composition

Each film-coated tablet contains 200 mg of Emtricitabine and 300 mg of Tenofovir disoproxil fumarate, which is equivalent to 245 mg of Tenofovir disoproxil.
For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Film coated Tablet

Blue, Capsule shaped, film coated tablets, debossed with 'H' on one side and '124' on the other side.

4. Clinical particulars

4.1 Therapeutic indications

Emtricitabine and tenofovir disoproxil fumarate tablet, a combination of emtricitabine and tenofovir disoproxil fumarate, is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 17 kg.

The following points should be considered when initiating therapy with emtricitabine and tenofovir disoproxil fumarate tablets for the treatment of HIV-1 infection:

- It is not recommended that emtricitabine and tenofovir disoproxil fumarate tablet be used as a component of a triple nucleoside regimen.
- Emtricitabine and tenofovir disoproxil fumarate tablet should not be coadministered with ATRIPLA®, COMPLERA®, emtricitabine, GENVOYA®, ODEFSEY®, STRIBILD®, tenofovir disoproxil fumarate or lamivudine-containing products.
- In treatment experienced patients, the use of emtricitabine and tenofovir disoproxil fumarate tablet should be guided by laboratory testing and treatment history.

4.2 Posology and method of administration

Recommended Dose for Treatment of HIV-1 Infection in Adults and Pediatric Patients Weighing 35 Kg or More

The recommended dose of emtricitabine and tenofovir disoproxil fumarate tablets in adults and in pediatric patients with body weight greater than or equal to 35 kg is one tablet (containing 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate) once daily taken orally with or without food.

Recommended Dose for Treatment of HIV-1 Infection in Pediatric Patients Weighing at Least 17kg or More and Able to Swallow a Whole Tablet

The recommended oral dose for pediatric patients weighing greater than or equal to 17 kg and who are able to swallow a whole tablet, is one emtricitabine and

tenofovir disoproxil fumarate low strength tablet (emtricitabine [FTC]/tenofovir disoproxil fumarate [TDF]) (167 mg/250 mg, 133 mg/200 mg, or 100 mg/150 mg based on body weight) taken orally once daily with or without food.

The recommended oral dosage of emtricitabine and tenofovir disoproxil fumarate low strength tablets is presented in Table 1. Weight should be monitored periodically and the emtricitabine and tenofovir disoproxil fumarate tablet dose adjusted accordingly.

Table 1 Dosing for Pediatric Patients Weighing 17 kg to less than 35 kg using Emtricitabine and Tenofovir disoproxil fumarate Low Strength Tablets

Body Weight (kg)	Dosing of FTC (mg)/TDF (mg) 17 to less than
22	one 100/150 tablet once daily
22 to less than 28	one 133/200 tablet once daily
28 to less than 35	one 167/250 tablet once daily

Recommended Dose for Pre-exposure Prophylaxis

The dose of emtricitabine and tenofovir disoproxil fumarate tablet in HIV-1 uninfected adults is one tablet (containing 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate) once daily taken orally with or without food.

Dose Adjustment for Renal Impairment

Treatment of HIV-1 infection

Significantly increased drug exposures occurred when emtricitabine or tenofovir disoproxil fumarate tablets were administered to subjects with moderate to severe renal impairment. Therefore, adjust the dosing interval of emtricitabine and tenofovir disoproxil fumarate tablet in HIV-1 infected adult patients with baseline creatinine clearance 30 to 49 mL/min using the recommendations in Table 2. These dosing interval recommendations are based on modeling of single-dose pharmacokinetic data in non-HIV infected subjects. The safety and effectiveness of these dosing interval adjustment recommendations have not been clinically evaluated in patients with moderate renal impairment, therefore clinical response to treatment and renal function should be closely monitored in these patients.

No dose adjustment is necessary for HIV-1 infected patients with mild renal impairment (creatinine clearance 50 to 80 mL/min). No data are available to make dose recommendations in pediatric patients with renal impairment.

Table 2 Dosage Adjustment for HIV-1 Infected Adult Patients with Altered Creatinine Clearance

	^a Creatinine Clearance (mL/min)		
	≥50	30–49	<30 (Including Patients Requiring Hemodialysis)

Recommended Dosing Interval	Every 24 hours	Every 48 hours	Emtricitabine and Tenofovir disoproxil fumarate should not be administered.
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a. Calculated using ideal (lean) body weight

Routine monitoring of estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein should be performed in all individuals with mild renal impairment.

Pre-exposure Prophylaxis

Do not use emtricitabine and tenofovir disoproxil fumarate tablet for a PrEP indication in HIV-1 uninfected individuals with estimated creatinine clearance below 60 mL/min.

Routine monitoring of estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein should be performed in all individuals with mild renal impairment. If a decrease in estimated creatinine clearance is observed in uninfected individuals while using emtricitabine and tenofovir disoproxil fumarate tablet for PrEP, evaluate potential causes and re-assess potential risks and benefits of continued use.

4.3 Dosage Forms and Strengths

Emtricitabine and Tenofovir disoproxil fumarate is available as tablets. Each tablet contains 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate (which is equivalent to 245 mg of tenofovir disoproxil). The tablets are blue, capsule shaped, film coated tablets, debossed with 'H' on one side and with '124' on the other side.

4.3 Contraindications

Do not use emtricitabine and tenofovir disoproxil fumarate tablets for pre-exposure prophylaxis in individuals with unknown or positive HIV-1 status. Emtricitabine and tenofovir disoproxil fumarate tablets should be used in HIV-infected patients only in combination with other antiretroviral agents.

4.4 Special warnings and precautions for 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, a component of emtricitabine and tenofovir disoproxil fumarate tablet, 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 or uninfected individual with known risk factors for liver disease; however, cases have also been reported in HIV-1 infected patients with no known risk factors. Treatment with emtricitabine and tenofovir

disoproxil fumarate should be suspended in any patient or uninfected individual 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).

HBV Infection

It is recommended that all individuals be tested for the presence of chronic hepatitis B virus

(HBV) before initiating emtricitabine and tenofovir disoproxil fumarate. Emtricitabine and Tenofovir disoproxil fumarate is not approved for the treatment of chronic HBV infection and the safety and efficacy of emtricitabine and tenofovir disoproxil fumarate have not been established in patients infected with HBV. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfecting with HBV and HIV-1 and have discontinued emtricitabine and tenofovir disoproxil fumarate. In some patients infected with HBV and treated with emtricitabine, the exacerbations of hepatitis B were associated with liver decompensation and liver failure. Patients who are infected with HBV should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment with emtricitabine and tenofovir disoproxil fumarate. If appropriate, initiation of anti-hepatitis B therapy may be warranted. HBV-uninfected individuals should be offered vaccination.

New Onset or Worsening Renal Impairment

Emtricitabine and tenofovir are 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 fumarate.

It is recommended that estimated creatinine clearance be assessed in all individuals prior to initiating therapy and as clinically appropriate during therapy with emtricitabine and tenofovir disoproxil fumarate. In patients at risk of renal dysfunction, including patients who have previously experienced renal events while receiving HEPSERA[®], it is recommended that estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein be assessed prior to initiation of emtricitabine and tenofovir disoproxil fumarate, and periodically during emtricitabine and tenofovir disoproxil fumarate therapy.

Emtricitabine and tenofovir disoproxil fumarate should be avoided with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs)). 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 fumarate (tenofovir DF). 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 at-risk patients.

Treatment of HIV-1 Infection

Dosing interval adjustment of emtricitabine and tenofovir disoproxil fumarate and close monitoring of renal function are recommended in all patients with estimated creatinine clearance 30 to 49 mL/min. No safety or efficacy data are available in patients with renal impairment who received emtricitabine and tenofovir disoproxil fumarate using these dosing guidelines, so the potential benefit of emtricitabine and tenofovir disoproxil fumarate therapy should be assessed against the potential risk of renal toxicity. Emtricitabine and Tenofovir disoproxil fumarate should not be administered to patients with estimated creatinine clearance below 30 mL/min or patients requiring hemodialysis.

Pre-exposure Prophylaxis

Emtricitabine and Tenofovir disoproxil fumarate for a PrEP indication should not be used if estimated creatinine clearance is less than 60 mL/min. If a decrease in estimated creatinine clearance is observed in uninfected individuals while using emtricitabine and tenofovir disoproxil fumarate for PrEP, evaluate potential causes and re-assess potential risks and benefits of continued use.

Emtricitabine and tenofovir disoproxil fumarate is a fixed-dose combination of emtricitabine and tenofovir disoproxil fumarate. Do not coadminister emtricitabine and tenofovir disoproxil fumarate with other drugs containing emtricitabine or tenofovir disoproxil fumarate, or containing tenofovir alafenamide, including ATRIPLA, COMPLERA, emtricitabine, GENVOYA, ODEFSEY, STRIBILD, or tenofovir disoproxil fumarate. Due to similarities between emtricitabine and lamivudine, do not coadminister emtricitabine and tenofovir disoproxil fumarate with other drugs containing lamivudine, including Combivir (lamivudine/zidovudine), Dutrebis (lamivudine/raltegravir), Epivir or Epivir-HBV (lamivudine), Epzicom (abacavir sulfate/lamivudine), Triumeq (abacavir sulfate/dolutegravir/lamivudine), or Trizivir (abacavir sulfate/lamivudine/zidovudine).

Do not coadminister emtricitabine and tenofovir disoproxil fumarate with HEPSERA (adefovir dipivoxil).

Bone Effects of Tenofovir DF

Bone Mineral Density:

In clinical trials in HIV-1 infected adults and in a clinical trial of HIV-1 uninfected individuals, tenofovir DF 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. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in subjects receiving tenofovir DF.

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

in chronic hepatitis B infected adolescent subjects aged 12 years to less than 18 years. In all pediatric trials, skeletal growth (height) appeared to be unaffected. For more information, please consult the tenofovir disoproxil fumarate prescribing information.

The effects of tenofovir DF-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. 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. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial. If bone abnormalities are suspected then 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 the use of tenofovir DF. Arthralgias 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 products containing tenofovir DF.

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in HIV-1 infected patients receiving 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-1 infected patients treated with combination antiretroviral therapy, including emtricitabine and tenofovir disoproxil fumarate. 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.

Early Virologic Failure

Clinical trials in HIV-1 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.

Comprehensive Management to Reduce the Risk of Acquiring HIV-1

Use emtricitabine and tenofovir disoproxil fumarate for pre-exposure prophylaxis only as part of a comprehensive prevention strategy that includes other prevention measures, such as safer sex practices, because emtricitabine and tenofovir disoproxil fumarate is not always effective in preventing the acquisition of HIV-1.

- Counsel uninfected individuals about safer sex practices that include consistent and correct use of condoms, knowledge of their HIV-1 status and that of their partner(s), and regular testing for other sexually transmitted infections that can facilitate HIV-1 transmission (such as syphilis and gonorrhea).
- Inform uninfected individuals about and support their efforts in reducing sexual risk behavior.

Use emtricitabine and tenofovir disoproxil fumarate to reduce the risk of acquiring HIV-1 only in individuals confirmed to be HIV-negative. HIV-1 resistance substitutions may emerge in individuals with undetected HIV-1 infection who are taking only emtricitabine and tenofovir disoproxil fumarate, because emtricitabine and tenofovir disoproxil fumarate alone does not constitute a complete treatment regimen for HIV-1 treatment; therefore, care should be taken to minimize drug exposure in HIV-infected individuals.

- Many HIV-1 tests, such as rapid tests, detect anti-HIV antibodies and may not identify HIV-1 during the acute stage of infection. Prior to initiating emtricitabine and tenofovir disoproxil fumarate for a PrEP indication, evaluate seronegative individuals for current or recent signs or symptoms consistent with acute viral infections (e.g., fever, fatigue, myalgia, skin rash, etc.) and ask about potential exposure events (e.g., unprotected, or condom broke during sex with an HIV-1 infected partner) that may have occurred within the last month.
- If clinical symptoms consistent with acute viral infection are present and recent (<1 month) exposures are suspected, delay starting PrEP for at least one month and reconfirm HIV-1 status or use a test approved by the FDA as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection.

- While using emtricitabine and tenofovir disoproxil fumarate for a PrEP indication, HIV-1 screening tests should be repeated at least every 3 months. If symptoms consistent with acute HIV-1 infection develop following a potential exposure event, PrEP should be discontinued until negative infection status is confirmed using a test approved by the FDA as an aid in the diagnosis of HIV-1, including acute or primary HIV-1 infection.

Counsel uninfected individuals to strictly adhere to the recommended emtricitabine and tenofovir disoproxil fumarate dosing schedule. The effectiveness of emtricitabine and tenofovir disoproxil fumarate in reducing the risk of acquiring HIV-1 is strongly correlated with adherence as demonstrated by measurable drug levels in clinical trials.

4.5 Drug Interactions

No drug interaction trials have been conducted using emtricitabine and tenofovir disoproxil fumarate tablets. Drug interaction trials have been conducted with emtricitabine and tenofovir disoproxil fumarate, the components of emtricitabine and tenofovir disoproxil fumarate tablet. This section describes clinically relevant drug interactions observed with emtricitabine and tenofovir disoproxil fumarate.

Didanosine

Coadministration of emtricitabine and tenofovir disoproxil fumarate 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 tenofovir disoproxil fumarate was administered with didanosine the C_{max} 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 observed in patients receiving tenofovir DF 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 emtricitabine and tenofovir disoproxil fumarate. Data are not available to recommend a dose adjustment of didanosine for adult or pediatric patients weighing less than 60 kg. When coadministered, emtricitabine and tenofovir disoproxil fumarate and Videx EC may be taken under fasted conditions or with a light meal (less than 400 kcal, 20% fat).

HIV-1 Protease Inhibitors

Tenofovir decreases the AUC and C_{min} of atazanavir. When coadministered with emtricitabine and tenofovir disoproxil fumarate, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg. Emtricitabine and tenofovir

disoproxil fumarate should not be coadministered with atazanavir without ritonavir.

Lopinavir/ritonavir, atazanavir coadministered with ritonavir, and darunavir coadministered with ritonavir have been shown to increase tenofovir concentrations. Tenofovir disoproxil fumarate is a substrate of P-glycoprotein (Pgp) and breast cancer resistance protein (BCRP) transporters. When tenofovir disoproxil fumarate is co-administered with an inhibitor of these transporters, an increase in absorption may be observed. Patients receiving emtricitabine and tenofovir disoproxil fumarate concomitantly with lopinavir/ritonavir, ritonavir-boosted atazanavir, or ritonavir-boosted darunavir should be monitored for tenofovir disoproxil fumarate-associated adverse reactions. Emtricitabine and tenofovir disoproxil fumarate should be discontinued in patients who develop tenofovir disoproxil fumarate -associated adverse reactions.

Hepatitis C Antiviral Agents

Coadministration of tenofovir disoproxil fumarate and HARVONI[®] (ledipasvir/sofosbuvir) has been shown to increase tenofovir exposure.

In patients receiving emtricitabine and tenofovir disoproxil fumarate concomitantly with HARVONI without an HIV-1 protease inhibitor/ritonavir or an HIV-1 protease inhibitor/cobicistat combination, monitor for adverse reactions associated with tenofovir disoproxil fumarate.

In patients receiving emtricitabine and tenofovir disoproxil fumarate concomitantly with HARVONI 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 concentrations in this setting has not been established. If coadministration is necessary, monitor for adverse reactions associated with tenofovir disoproxil fumarate.

Drugs Affecting Renal Function

Emtricitabine and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. No drug-drug interactions due to competition for renal excretion have been observed; however, coadministration of emtricitabine and tenofovir disoproxil fumarate with drugs that are eliminated by active tubular secretion may increase concentrations of emtricitabine, tenofovir, and/or the coadministered drug. Some examples include, but are not limited to acyclovir, adefovir dipivoxil, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs. Drugs that decrease renal function may increase concentrations of emtricitabine and/or tenofovir.

4.6 Fertility, pregnancy and lactation

Pregnancy: Teratogenic Effects:

Pregnancy Category B

Antiretroviral Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to emtricitabine and tenofovir disoproxil fumarate, an Antiretroviral

Pregnancy Registry (APR) has been established. Healthcare providers are encouraged to register patients by calling 1-800-2584263.

Risk Summary

Emtricitabine and Tenofovir disoproxil fumarate has been evaluated in a limited number of women during pregnancy and postpartum. Available human and animal data suggest that emtricitabine and tenofovir disoproxil fumarate does not increase the risk of major birth defects overall compared to the background rate. There are, however, no adequate and well-controlled trials in pregnant women. Because the studies in humans cannot rule out the possibility of harm, emtricitabine and tenofovir disoproxil fumarate should be used during pregnancy only if clearly needed. If an uninfected individual becomes pregnant while taking emtricitabine and tenofovir disoproxil fumarate for a PrEP indication, careful consideration should be given to whether use of emtricitabine and tenofovir disoproxil fumarate should be continued, taking into account the potential increased risk of HIV-1 infection during pregnancy.

Clinical Considerations

As of July 2011, the APR has received prospective reports of 764 and 1219 exposures to emtricitabine- and tenofovir- containing regimens, respectively in the first trimester, 321 and 455 exposures, respectively, in second trimester, and 140 and 257 exposures, respectively, in the third trimester. Birth defects occurred in 18 of 764 (2.4%) live births for emtricitabine-containing regimens and 27 of 1219 (2.2%) live births for tenofovir-containing regimens (first trimester exposure) and 10 of 461 (2.2%) live births for emtricitabine-containing regimens and 15 of 714 (2.1%) live births for tenofovir- containing regimens (second/third trimester exposure). Among pregnant women in the U.S. reference population, the background rate of birth defects is 2.7%. There was no association between emtricitabine or tenofovir and overall birth defects observed in the APR.

Animal Data

Emtricitabine:

The incidence of fetal variations and malformations was not increased in embryofetal toxicity studies performed with emtricitabine in mice at exposures (AUC) approximately 60-fold higher and in rabbits at approximately 120-fold higher than human exposures at the recommended daily dose.

Tenofovir Disoproxil Fumarate:

Reproduction studies have been performed 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.

Studies in humans have shown that both tenofovir and emtricitabine are excreted in human milk. Because the risks of low level exposure to emtricitabine and tenofovir to infants are unknown, **mothers should be instructed not to breast-feed if they are receiving emtricitabine and tenofovir disoproxil fumarate**, whether they are taking emtricitabine and tenofovir disoproxil fumarate for treatment or to reduce the risk of acquiring HIV-1.

Emtricitabine

Samples of breast milk obtained from five HIV-1 infected mothers show that emtricitabine is secreted in human milk. Breastfeeding infants whose mothers are being treated with emtricitabine may be at risk for developing viral resistance to emtricitabine. Other emtricitabine-associated risks in infants breastfed by mothers being treated with emtricitabine are unknown.

Tenofovir Disoproxil Fumarate

Samples of breast milk obtained from five HIV-1 infected mothers show that tenofovir is secreted in human milk. Tenofovir-associated risks, including the risk of viral resistance to tenofovir, in infants breastfed by mothers being treated with tenofovir disoproxil fumarate are unknown.

Pediatric Use

No pediatric clinical trial was conducted to evaluate the safety and efficacy of emtricitabine and tenofovir disoproxil fumarate tablets. Data from previously conducted trials with the individual drug products, emtricitabine and tenofovir disoproxil fumarate, were relied upon to support dosing recommendations for emtricitabine and tenofovir disoproxil fumarate. For additional information, please consult the prescribing information for emtricitabine and tenofovir disoproxil fumarate.

Emtricitabine and tenofovir disoproxil fumarate should only be administered to HIV-1 infected pediatric patients with body weight greater than or equal to 17 kg and who are able to swallow a whole tablet. Because it is a fixed-dose combination tablet, emtricitabine and tenofovir disoproxil fumarate cannot be adjusted for patients of lower weight. Emtricitabine and tenofovir disoproxil fumarate has not been evaluated for use in pediatric patients weighing less than 17 kg.

Geriatric Use

Clinical trials of emtricitabine or tenofovir disoproxil fumarate 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 patients should be cautious, keeping in mind the greater frequency of

decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Patients with Impaired Renal Function

Treatment of HIV-1 infection

The dosing interval for emtricitabine and tenofovir disoproxil fumarate should be modified in HIV-infected adult patients with estimated creatinine clearance of 30 to 49 mL/min. Emtricitabine and tenofovir disoproxil fumarate should not be used in patients with estimated creatinine clearance below 30 mL/min and in patients with end-stage renal disease requiring dialysis.

Pre-exposure Prophylaxis

Emtricitabine and tenofovir disoproxil fumarate for a PrEP indication should not be used in HIV1 uninfected individuals with estimated creatinine clearance below 60 mL/min. If a decrease in estimated creatinine clearance is observed in uninfected individuals while using emtricitabine and tenofovir disoproxil fumarate for PrEP, evaluate potential causes and re-assess potential risks and benefits of continued use.

4.7 Undesirable effects

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

- Lactic Acidosis/Severe Hepatomegaly with Steatosis

- Severe Acute Exacerbations of hepatitis B.
- New Onset or Worsening Renal Impairment.
- Bone Effects of Tenofovir DF.
- Immune Reconstitution Syndrome.

Adverse Reactions from Clinical Trials Experience in HIV-1 Infected Subjects

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

Clinical Trials in Adult Subjects

The most common adverse reactions (incidence greater than or equal to 10%, any severity) occurring in Study 934, an active-controlled clinical trial of efavirenz, emtricitabine, and tenofovir disoproxil fumarate, include diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash. See also Table 3 for the frequency of treatment-emergent adverse reactions (Grades 2 to 4) occurring in greater than or equal to 5% of subjects treated in any treatment group in this trial.

Skin discoloration, manifested by hyperpigmentation on the palms and/or soles, was generally mild and asymptomatic. The mechanism and clinical significance are unknown.

Study 934 - Treatment Emergent Adverse Reactions: In Study 934, 511 antiretroviral- naïve subjects received either tenofovir disoproxil fumarate + emtricitabine administered in combination with efavirenz (N=257) or zidovudine/lamivudine administered in combination with efavirenz (N=254) for 144 weeks. Subjects had a mean age of 40 years (range 20 to 73 years) and were predominantly male (88%). Overall, 65% were White, 17% were Black, and 13% were Hispanic. Adverse reactions observed in this trial were generally consistent with those seen in other trials in treatment-experienced or treatment- naïve subjects receiving tenofovir disoproxil fumarate and/or emtricitabine (Table 3).

Table 3 Selected Treatment-Emergent Adverse-Reactions^a (Grades 2 to 4) Reported in ≥5% in Any Treatment Group in Study 934 (0 to 144 Weeks)

	FTC + TDF + EFV ^b	AZT/3TC + EFV
	N=257	N=254
Gastrointestinal Disorder		
Diarrhea	9%	5%
Nausea	9%	7%
Vomiting	2%	5%
General Disorders and Administration Site Condition		
Fatigue	9%	8%
Infections and Infestations		
Sinusitis	8%	4%
Upper respiratory tract infections	8%	5%
Nasopharyngitis	5%	3%
Nervous System Disorders		
Headache	6%	5%
Dizziness	8%	7%
Psychiatric Disorders		
Depression	9%	7%
Insomnia	5%	7%
Skin and Subcutaneous Tissue Disorders Rash event ^c	7%	9%

- Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.
- From Weeks 96 to 144 of the trial, subjects received emtricitabine and tenofovir disoproxil fumarate with efavirenz in place of tenofovir disoproxil fumarate + emtricitabine with efavirenz.
- Rash event includes rash, exfoliative rash, rash generalized, rash macular, rash maculopapular, rash pruritic, and rash vesicular

Laboratory Abnormalities: Laboratory abnormalities observed in this trial were generally consistent with those seen in other trials of tenofovir disoproxil fumarate and/or emtricitabine (Table 4).

Table 4 Significant Laboratory Abnormalities Reported in $\geq 1\%$ of Subjects in Any Treatment Group in Study 934 (0 to 144 Weeks)

	FTC + TDF + EFV ^a	AZT/3TC + EFV
	N=257	N=254
Any $\geq$ Grade 3 Laboratory Abnormality	30%	26%
Fasting Cholesterol (>240 mg/dL)	22%	24%
Creatine Kinase (M: >990 U/L) (F: >845 U/L)	9%	7%
Serum Amylase (>175 U/L)	8%	4%
Alkaline Phosphatase (>550 U/L)	1%	0%
AST (M: >180 U/L) (F: >170 U/L)	3%	3%
ALT (M: >215 U/L) (F: >170 U/L)	2%	3%
Hemoglobin (<8 mg/dL)	0%	4%
Hyperglycemia (>250 mg/dL)	2%	1%
Hematuria (>75 RBC/HPF)	3%	2%
Glycosuria ($\geq 3+$)	$<1\%$	1%
Neutrophils ($<750/\text{mm}^3$)	3%	5%
Fasting Triglycerides (>750 mg/dL)	4%	2%

- a. From Weeks 96 to 144 of the trial, subjects received emtricitabine and tenofovir disoproxil fumarate with efavirenz in place of tenofovir disoproxil fumarate + emtricitabine with efavirenz.

In addition to the events described above for Study 934, other adverse reactions that occurred in at least 5% of subjects receiving emtricitabine or tenofovir disoproxil fumarate with other antiretroviral agents in clinical trials include anxiety, arthralgia, increased cough, dyspepsia, fever, myalgia, pain, abdominal pain, back pain, paresthesia, peripheral neuropathy (including peripheral neuritis and neuropathy), pneumonia, and rhinitis.

In addition to the laboratory abnormalities described above for Study 934, Grade 3 to 4 laboratory abnormalities of increased bilirubin ($>2.5 \times \text{ULN}$), increased pancreatic amylase ($>2 \times \text{ULN}$), increased or decreased serum glucose (<40 or $>250 \text{ mg/dL}$), and increased serum lipase ($>2 \times \text{ULN}$) occurred in up to 3% of subjects treated with emtricitabine or tenofovir disoproxil fumarate with other antiretroviral agents in clinical trials.

Clinical Trials in Pediatric Subjects

Emtricitabine: In addition to the adverse reactions reported in adults, anemia and hyperpigmentation were observed in 7% and 32%, respectively, of pediatric subjects (3 months to less than 18 years of age) who received treatment with emtricitabine in the larger of two open-label, uncontrolled pediatric trials (N=116). For additional information, please consult the emtricitabine prescribing information.

Tenofovir Disoproxil Fumarate: In pediatric clinical trials (Studies 352 and 321) conducted in 184 HIV-1 infected subjects 2 to less than 18 years of age, the adverse reactions observed in pediatric subjects who received treatment with tenofovir disoproxil fumarate were consistent with those observed in clinical trials of tenofovir disoproxil fumarate in adults.

Eighty-nine pediatric subjects (2 to less than 12 years of age) received tenofovir disoproxil fumarate in Study 352 for a median exposure of 104 weeks. Of these, 4 subjects discontinued from the trial due to adverse reactions consistent with proximal renal tubulopathy. Three of these 4 subjects presented with hypophosphatemia and also had decreases in total body or spine BMD Z score. For additional information, please consult the tenofovir disoproxil fumarate prescribing information.

Adverse Reactions from Clinical Trial Experience in HIV-1 Uninfected Adult Subjects

No new adverse reactions to emtricitabine and tenofovir disoproxil fumarate were identified from two randomized placebo-controlled clinical trials (iPrEx, Partners PrEP) in which 2830 HIV-1 uninfected adults received emtricitabine and tenofovir disoproxil fumarate once daily for pre-exposure prophylaxis. Subjects were followed for a median of 71 weeks and 87 weeks, respectively. These trials enrolled HIV-negative individuals ranging in age from 18 to 67 years. The iPrEx trial enrolled only males or transgender females of Hispanic/Latino (72%), White (18%), Black (9%) and Asian (5%) race. The Partners PrEP trial enrolled both males (61 to 64% across treatment groups) and females in Kenya and Uganda. Table 5 provides a list of all adverse events that occurred $\geq 2\%$ of subjects in any treatment group in the iPrEx and Partners PrEP trials.

Laboratory Abnormalities: Table 6 provides a list of laboratory abnormalities observed in both trials. Six subjects in the TDF-containing arms of the Partners PrEP trial discontinued participation in the study due to an increase in blood creatinine compared with no discontinuations in the placebo group. One subject in the emtricitabine and tenofovir disoproxil fumarate arm of the iPrEx trial

discontinued from the study due to an increase in blood creatinine and another due to low phosphorous.

In addition to the laboratory abnormalities described above, Grade 1 proteinuria (1+) occurred in

6% of subjects receiving emtricitabine and tenofovir disoproxil fumarate in the iPrEx trial. Grade 2 to 3 proteinuria (2 to 4+) and glycosuria (3+) occurred in less than 1% of subjects treated with emtricitabine and tenofovir disoproxil fumarate in the iPrEx trial and Partners PrEP trial.

Table 5 Selected Adverse-Events (All Grades) Reported in ≥2% in Any Treatment Group in the iPrEx Trial and Partners PrEP Trial

	iPrEx Trial		Partners PrEP Trial	
	FTC/TDF (N=1251)	Placebo (N=1248)	FTC/TDF (N=1579)	Placebo (N=1584)
Gastrointestinal Disorders				
Diarrhea	7%	8%	2%	3%
Abdominal pain	4%	2%	- ^a	-
Infections and Infestations				
Pharyngitis	13%	16%	-	-
Urethritis	5%	7%	-	-
Urinary tract infection	2%	2%	5%	7%
Syphilis	6%	5%	-	-
Secondary syphilis	6%	4%	-	-
Anogenital warts	2%	3%	-	-
Musculoskeletal and Connective Tissue Disorders	5%	5%	-	-
Back pain				
Nervous System Disorders				
Headache	7%	6%	-	-
Psychiatric Disorders				
Depression	6%	7%	-	-
Anxiety	3%	3%	-	-
Reproductive System and Breast Disorders	2%	2%	2%	2%
Genital ulceration				
Investigations				
Weight decreased	3%	2%	-	-

^a. Not reported or reported below 2%.

Table 6 Laboratory Abnormalities (Highest Toxicity Grade) Reported for Each Subject in the iPrEx Trial and Partners PrEP Trial

	Grade ^b	iPrEx Trial		Partners PrEP Trial	
		FTC/TDF N= 1251	Placebo N= 1248	FTC/TDF N=1579	Placebo N=1584
Creatinine	1 (1.1-1.3 X ULN)	27 (2%)	21 (2%)	18 (1%)	12 (<1%)
	2-4 (> 1.4 x ULN)	5 (<1%)	3 (<1%)	2 (<1%)	1 (<1%)

Phosphorus	1 mg/dL	(2.5 - <LLN)	81 (7%)	110 (9%)	NR ^a	NR ^a
	2-4	(<2 mg/dL)	123 (10%)	101 (8%)	140 (9%)	136 (9%)
AST	1 ULN	(1.25-<2.5 x ULN)	175 (14%)	175 (14%)	20 (1%)	25 (2%)
	2-4	(> 2.6 x ULN)	57 (5%)	61 (5%)	10 (<1%)	4 (<1%)
ALT	1 ULN	(1.25-<2.5 x ULN)	178 (14%)	194 (16%)	21 (1%)	13 (<1%)
	2-4	(> 2.6 x ULN)	84 (7%)	82 (7%)	4 (<1%)	6 (<1%)
Hemoglobin	1 mg/dL	(8.5 -10)	49 (4%)	62 (5%)	56 (4%)	39 (2%)
	2-4	(<9.4 mg/dL)	13 (1%)	19 (2%)	28 (2%)	39 (2%)
Neutrophils	1 1300/mm ³)	(1000-)	23 (2%)	25 (2%)	208 (13%)	163 (10%)
	2-4	(<750/mm ³)	7 (<1%)	7 (<1%)	73 (5%)	56 (3%)

a. Grade 1 phosphorus was not reported for the Partners PrEP trial.

b. Grading is per DAIDS criteria.

Changes in Bone Mineral Density:

In clinical trials of HIV-1 uninfected individuals, decreases in BMD were observed. In the iPrEx trial, a substudy of 503 subjects found mean changes from baseline in BMD ranging from -0.4% to 1% across total hip, spine, femoral neck, and trochanter in the emtricitabine and tenofovir disoproxil fumarate group compared with the placebo group, which returned toward baseline after discontinuation of treatment. Thirteen percent of subjects receiving emtricitabine and tenofovir disoproxil fumarate vs. 6% of subjects receiving placebo lost at least 5% of BMD at the spine during treatment. Bone fractures were reported in 1.7% of the emtricitabine and tenofovir disoproxil fumarate group compared with 1.4% in the placebo group. No correlation between BMD and fractures was noted. The Partners PrEP trial found similar fracture rates between treatment and placebo groups (0.8% and 0.6%, respectively). No BMD evaluations were conducted during this trial.

Post marketing Experience

The following adverse reactions have been identified during postapproval use of tenofovir disoproxil fumarate. No additional adverse reactions have been identified during postapproval use of emtricitabine. 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 ADR reporting tool of health authority; search for Adverse Reactions Reporting Tool in the Google Play Store

4.8 Overdose

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

Emtricitabine: Limited clinical experience is available at doses higher than the therapeutic dose of emtricitabine. In one clinical pharmacology trial, single doses of emtricitabine 1200 mg were administered to 11 subjects. No severe adverse reactions were reported.

Hemodialysis treatment removes approximately 30% of the emtricitabine dose over a 3-hour dialysis period starting within 1.5 hours of emtricitabine dosing (blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min). It is not known whether emtricitabine can be removed by peritoneal dialysis.

Tenofovir Disoproxil Fumarate: Limited clinical experience at doses higher than the therapeutic dose of tenofovir disoproxil fumarate 300 mg is available. In one trial, 600 mg tenofovir disoproxil fumarate was administered to 8 subjects orally for 28 days, and no severe adverse reactions were reported. The effects of higher doses are not known.

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

5. Pharmacological properties

For additional information on Mechanism of Action, Antiviral Activity, Resistance and Cross Resistance, please consult the emtricitabine and tenofovir disoproxil fumarate prescribing information.

Mechanism of Action

Emtricitabine and tenofovir disoproxil fumarate is a fixed-dose combination of antiviral drugs emtricitabine and tenofovir disoproxil fumarate.

5.1 Pharmacokinetic properties

Pharmacotherapeutic group: Antiretroviral

ATC-code: Emtricitabine: J05AF09, Tenofovir Disoproxil Fumarate: J05AF07

Emtricitabine and Tenofovir Disoproxil Fumarate: One emtricitabine and tenofovir disoproxil fumarate tablet was bioequivalent to one emtricitabine capsule (200 mg) plus one tenofovir disoproxil fumarate tablet (300 mg) following single-dose administration to fasting healthy subjects (N=39).

Emtricitabine: The pharmacokinetic properties of emtricitabine are summarized in Table 7. Following oral administration of emtricitabine, emtricitabine is rapidly absorbed with peak plasma concentrations occurring at 1 to 2 hours post-dose. Less than 4% of emtricitabine binds to human plasma proteins *in vitro* and the binding is independent of concentration over the range of 0.02 to 200 mcg/mL. Following administration of radiolabelled emtricitabine, approximately 86% is recovered in the urine and 13% is recovered as metabolites. The metabolites of emtricitabine include 3'-sulfoxide diastereomers and their glucuronic acid conjugate. Emtricitabine is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of emtricitabine, the plasma emtricitabine half-life is approximately 10 hours.

Tenofovir Disoproxil Fumarate: The pharmacokinetic properties of tenofovir disoproxil fumarate are summarized in Table 7. Following oral administration of tenofovir disoproxil fumarate, maximum tenofovir serum concentrations are achieved in 1 ± 0.4 hour. Less than 0.7% of tenofovir binds to human plasma proteins *in vitro* and the binding is independent of concentration over the range of 0.01 to 25 mcg/mL. Approximately 70 to 80% of the intravenous dose of tenofovir is recovered as unchanged drug in the urine. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. Following a

single oral dose of tenofovir disoproxil fumarate, the terminal elimination half-life of tenofovir is approximately 17 hours.

Table 7 Single Dose Pharmacokinetic Parameters for Emtricitabine and Tenofovir in Adults^a

	Emtricitabine	Tenofovir
Fasted Oral Bioavailability ^b (%)	92 (83.1–106.4)	25 (NC–45)
Plasma Terminal Elimination Half-Life ^b (hr)	10 (7.4–18)	17 (12–25.7)
C _{max} ^c (mcg/mL)	1.8 ± 0.72 ^d	0.30±0.09
AUC ^c (mcg·hr/mL)	10 ± 3.12 ^d	2.29±0.69
CL/F ^c (mL/min)	302 ± 94	1043±115
CL _{renal} ^c (mL/min)	213 ± 89	243±33

a. NC = Not calculated

b. Median (range)

c. Mean (± SD)

d. Data presented as steady state values.

Effects of Food on Oral Absorption

Emtricitabine and Tenofovir disoproxil fumarate may be administered with or without food. Administration of emtricitabine and tenofovir disoproxil fumarate following a high fat meal (784 kcal; 49 grams of fat) or a light meal (373 kcal; 8 grams of fat) delayed the time of tenofovir C_{max} by approximately 0.75 hour. The mean increases in tenofovir AUC and C_{max} were approximately 35% and 15%, respectively, when administered with a high fat or light meal, compared to administration in the fasted state. In previous safety and efficacy trials, tenofovir disoproxil fumarate was taken under fed conditions. Emtricitabine systemic exposures (AUC and C_{max}) were unaffected when emtricitabine and tenofovir disoproxil fumarate was administered with either a high fat or a light meal.

Special Populations

Race

Emtricitabine: No pharmacokinetic differences due to race have been identified following the administration of emtricitabine.

Tenofovir Disoproxil Fumarate: There were insufficient numbers from racial and ethnic groups other than Caucasian to adequately determine potential pharmacokinetic differences among these populations following the administration of tenofovir disoproxil fumarate.

Gender

Emtricitabine and Tenofovir Disoproxil Fumarate: Emtricitabine and tenofovir pharmacokinetics are similar in male and female subjects.

Pediatric Patients

The pharmacokinetic data for tenofovir and emtricitabine following administration of emtricitabine and tenofovir disoproxil fumarate in pediatric subjects weighing 17 kg and above are not available. The dosing recommendations of emtricitabine and tenofovir disoproxil fumarate in this population are based on the dosing recommendations of emtricitabine and tenofovir disoproxil fumarate in this population. Refer to the emtricitabine and tenofovir disoproxil fumarate prescribing information for pharmacokinetic information on the individual products in pediatric patients.

Emtricitabine and tenofovir disoproxil fumarate should not be administered to HIV-1 infected pediatric patients weighing less than 17 kg.

Geriatric Patients

Pharmacokinetics of emtricitabine and tenofovir have not been fully evaluated in the elderly (65 years of age and older).

Patients with Impaired Renal Function

The pharmacokinetics of emtricitabine and tenofovir are altered in subjects with renal impairment. In adult subjects with creatinine clearance below 50 mL/min, C_{max} , and $AUC_{0 \text{ to } \infty}$ of emtricitabine and tenofovir were increased. It is recommended that the dosing interval for emtricitabine and tenofovir disoproxil fumarate be modified in HIV-infected adult patients with estimated creatinine clearance 30 to 49 mL/min. No data are available to make dose recommendations in pediatric patients with renal impairment. Emtricitabine and Tenofovir disoproxil fumarate should not be used in patients with estimated creatinine clearance below 30 mL/min and in patients with end-stage renal disease requiring dialysis.

Emtricitabine and Tenofovir disoproxil fumarate for a PrEP indication should not be used in HIV-1 uninfected individuals with estimated creatinine clearance below 60 mL/min. If a decrease in estimated creatinine clearance is observed in uninfected individuals while using emtricitabine and tenofovir disoproxil fumarate for PrEP, evaluate potential causes and re-assess potential risks and benefits of continued use.

Patients with Hepatic Impairment

The pharmacokinetics of tenofovir following a 300 mg dose of tenofovir disoproxil fumarate have been studied in non-HIV infected subjects with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in subjects with hepatic impairment compared with unimpaired subjects. The pharmacokinetics of emtricitabine and tenofovir disoproxil fumarate or emtricitabine have not been studied in subjects with

hepatic impairment; however, emtricitabine is not significantly metabolized by liver enzymes, so the impact of liver impairment should be limited.

Assessment of Drug Interactions

The steady state pharmacokinetics of emtricitabine and tenofovir were unaffected when emtricitabine and tenofovir disoproxil fumarate were administered together versus each agent dosed alone.

In vitro studies and clinical pharmacokinetic drug-drug interaction trials have shown that the potential for CYP mediated interactions involving emtricitabine and tenofovir with other medicinal products is low.

No clinically significant drug interactions have been observed between emtricitabine and famciclovir, indinavir, stavudine, tenofovir disoproxil fumarate, and zidovudine (see Tables 8 and 9). Similarly, no clinically significant drug interactions have been observed between tenofovir disoproxil fumarate and efavirenz, methadone, nelfinavir, oral contraceptives, ribavirin, or sofosbuvir in trials conducted in healthy volunteers (see Tables 10 and 11). **Table 8 Drug Interactions: Changes in Pharmacokinetic Parameters for**

Emtricitabine in the Presence of the Coadministered Drug^a

Coadministered Drug	Dose of Coadministered Drug (mg)	Emtricitabine Dose (mg)	N	% Change of Emtricitabine Pharmacokinetic Parameters ^b (90% CI)		
				C _{max}	AUC	C _{min}
Tenofovir DF	300 once daily x 7 days	200 once daily x 7 days	17	↔	↔	↑ 20 (↑ 12 to ↑ 29)
Zidovudine	300 twice daily x 7 days	200 once daily x 7 days	27	↔	↔	↔
Indinavir	800 x 1	200 x 1	12	↔	↔	NA
Famciclovir	500 x 1	200 x 1	12	↔	↔	NA
Stavudine	40 x 1	200 x 1	6	↔	↔	NA

a. All interaction trials conducted in healthy volunteers

b. ↑ = Increase; ↓ = Decrease; ↔ = No Effect; NA = Not Applicable

Table 9 Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Emtricitabine^a

Coadministered Drug	Dose of Coadministered Drug (mg)	Emtricitabine Dose (mg)	N	% Change of Coadministered Drug Pharmacokinetic Parameters ^b (90% CI)		
				C _{max}	AUC	C _{min}

Tenofovir DF	300 once daily x 7 days	200 once daily x 7 days	17	⇔	⇔	⇔
Zidovudine	300 twice daily x 7 days	200 once daily x 7 days	27	↑ 17 (↑ 0 to ↑ 38)	↑ 13 (↑ 5 to ↑ 20)	⇔
Indinavir	800 x 1	200 x 1	12	⇔	⇔	NA
Famciclovir	500 x 1	200 x 1	12	⇔	⇔	NA
Stavudine	40 x 1	200 x 1	6	⇔	⇔	NA

a. All interaction trials conducted in healthy volunteers

b. ↑ = Increase; ↓ = Decrease; ⇔ = No Effect; NA = Not Applicable

Table 10 Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir^a in the Presence of the Coadministered Drug

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Tenofovir Pharmacokinetic Parameters ^b (90% CI)		
			C _{max}	AUC	C _{min}
Atazanavir ^c	400 once daily x 14 days	33	↑ 14 (↑ 8 to ↑ 20)	↑ 24 (↑ 21 to ↑ 28)	↑ 22 (↑ 15 to ↑ 30)
Atazanavir/ Ritonavir ^c	300/100 once daily	12	↑ 34 (↑ 20 to ↑ 51)	↑ 37 (↑ 30 to ↑ 45)	↑ 29 (↑ 21 to ↑ 36)
Darunavir/ Ritonavir ^d	300/100 twice daily	12	↑ 24 (↑ 8 to ↑ 42)	↑ 22 (↑ 10 to ↑ 35)	↑ 37 (↑ 19 to ↑ 57)
Indinavir	800 three times daily x 7 days	13	↑ 14 (↓ 3 to ↑ 33)	⇔	⇔
Ledipasvir/ Sofosbuvir ^{e, f}	90/400 once daily x10 days	24	↑ 47 (↑ 37 to ↑ 58)	↑ 35 (↑ 29 to ↑ 42)	↑ 47 (↑ 38 to ↑ 57)
Ledipasvir/ Sofosbuvir ^{e, g}		23	↑ 64 (↑ 54 to ↑ 74)	↑ 50 (↑ 42 to ↑ 59)	↑ 59 (↑ 49 to ↑ 70)
Ledipasvir/ Sofosbuvir ^h	90/400 once daily x14 days	15	↑ 79 (↑ 56 to ↑ 104)	↑ 98 (↑ 77 to ↑ 123)	↑ 163 (↑ 132 to ↑ 197)
Ledipasvir/ Sofosbuvir ⁱ	90/400 once daily x10 days	14	↑ 32 (↑ 25 to ↑ 39)	↑ 40 (↑ 31 to ↑ 50)	↑ 91 (↑ 74 to ↑ 110)
Lopinavir/ Ritonavir	400/100 twice daily x 14 days	24	⇔	↑ 32 (↑ 25 to ↑ 38)	↑ 51 (↑ 37 to ↑ 66)
Saquinavir/ Ritonavir	1000/100 twice daily x 14 days	35	⇔	⇔	↑ 23 (↑ 16 to ↑ 30)
Sofosbuvir ^j	400 single dose	16	↑ 25 (↑ 8 to ↑ 45)	⇔	⇔
Tacrolimus	0.05 mg/kg twice daily x 7 days	21	↑ 13 (↑ 1 to ↑ 27)	⇔	⇔

Tipranavir/ Ritonavir ^k	500/100 twice daily	22	↓ 23 (↓ 32 to ↓ 13)	↓ 2 (↓ 9 to ↑ 5)	↑ 7 (↓ 2 to ↑ 17)
	750/200 twice daily (23 doses)	20	↓ 38 (↓ 46 to ↓ 29)	↑ 2 (↓ 6 to ↑ 10)	↑ 14 (↑ 1 to ↑ 27)

- Subjects received tenofovir disoproxil fumarate 300 mg once daily
- Increase = ↑; Decrease = ↓; No Effect = ⇔; NC = Not Calculated
- Reyataz Prescribing Information
- Prezista Prescribing Information
- Data generated from simultaneous dosing with HARVONI (ledipasvir/sofosbuvir). Staggered administration (12 hours apart) provided similar results.
- Comparison based on exposures when administered as atazanavir/ritonavir + emtricitabine/tenofovir DF.
- Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine/tenofovir DF.
- Study conducted with ATRIPLA (efavirenz/emtricitabine/tenofovir DF) coadministered with HARVONI.
- Study conducted with COMPLERA (emtricitabine/rilpivirine/tenofovir DF) coadministered with HARVONI.
- Study conducted with ATRIPLA coadministered with SOVALDI® (sofosbuvir).
- Aptivus Prescribing Information.

No effect on the pharmacokinetic parameters of the following coadministered drugs was observed with emtricitabine and tenofovir disoproxil fumarate: abacavir, didanosine (buffered tablets), emtricitabine, entecavir and lamivudine.

Table 11 Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Tenofovir

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Coadministered Drug Pharmacokinetic Parameters ^a (90% CI)		
			C _{max}	AUC	C _{min}
Abacavir	300 once	8	↑ 12 (↓ 1 to ↑ 26)	⇔	NA
Atazanavir ^b	400 once daily x 14 days	34	↓ 21 (↓ 27 to ↓ 14)	↓ 25 (↓ 30 to ↓ 19)	↓ 40 (↓ 48 to ↓ 32)
Atazanavir ^b	Atazanavir/ Ritonavir 300/100 once daily x 42 days	10	↓ 28 (↓ 50 to ↑ 5)	^c ↓ 25 (↓ 42 to ↓ 3)	↓ 23 ^c (↓ 46 to ↑ 10)
Darunavir ^d	Darunavir/Ritona	12	↑ 16 (↓ 6 to ↑ 42)	↑ 21 (↓ 5 to ↑ 54)	↑ 24 (↓ 10 to ↑ 69)

Didanosine ^e	250 once, simultaneously with tenofovir DF and a light meal ^f	33	↓ 20 ^g (↓ 32 to ↓ 7)	⇔ ^g	NA
Emtricitabine	200 once daily x 7 days	17	⇔	⇔	↑ 20 (↑ 12 to ↑ 29)
Indinavir	800 three times daily x 7 days	12	↓ 11 (↓ 30 to ↑ 12)	⇔	⇔
Entecavir	1 once daily x 10 days	28	⇔	↑ 13 (↑ 11 to ↑ 15)	⇔
Lamivudine	150 twice daily x 7 days	15	↓ 24 (↓ 34 to ↓ 12)	⇔	⇔
Lopinavir Ritonavir	Lopinavir/ Ritonavir 400/100 twice daily x 14 days	24	⇔ ⇔	⇔ ⇔	⇔ ⇔
Saquinavir Ritonavir	 Saquinavir/ Ritonavir 1000/100 twice daily x 14 days	32	↑ 22 (↑ 6 to ↑ 41) ⇔	↑ 29 ^h (↑ 12 to ↑ 48) ⇔	↑ 47 ^h (↑ 23 to ↑ 76) ↑ 23 (↑ 3 to ↑ 46)
Tacrolimus	0.05 mg/kg twice daily x 7 days	21	⇔	⇔	⇔
Tipranavir ⁱ	Tipranavir/Ritonavir 500/100 twice daily	22	↓ 17 (↓ 26 to ↓ 6)	↓ 18 (↓ 25 to ↓ 9)	↓ 21 (↓ 30 to ↓ 10)
	Tipranavir/Ritonavir 750/200 twice daily (23 doses)	20	↓ 11 (↓ 16 to ↓ 4)	↓ 9 (↓ 15 to ↓ 3)	↓ 12 (↓ 22 to 0)

a. Increase = ↑; Decrease = ↓; No Effect = ⇔; NA = Not Applicable

b. Reyataz Prescribing Information

c. In HIV-infected subjects, addition of tenofovir DF to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and C_{min} values of atazanavir that were 2.3 and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone. d Prezista Prescribing Information. e Videx EC Prescribing Information. Subjects received didanosine enteric-coated capsules. f 373 kcal, 8.2 g fat

g. Compared with didanosine (enteric-coated) 400 mg administered alone under fasting conditions.

- h. Increases in AUC and C_{min} are not expected to be clinically relevant; hence no dose adjustments are required when tenofovir DF and ritonavir-boosted saquinavir are coadministered. i. Aptivus Prescribing Information.

Coadministration of tenofovir disoproxil fumarate with didanosine results in changes in the pharmacokinetics of didanosine that may be of clinical significance. Concomitant dosing of tenofovir disoproxil fumarate with didanosine enteric-coated capsules significantly increases the C_{max} and AUC of didanosine. When didanosine 250 mg enteric-coated capsules were administered with tenofovir disoproxil fumarate, systemic exposures of didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions. The mechanism of this interaction is unknown. See *Drug Interactions* (7.1) regarding use of didanosine with tenofovir disoproxil fumarate.

5.2 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

Emtricitabine: In long-term oral carcinogenicity studies of emtricitabine, no drug-related increases in tumor incidence were found in mice at doses up to 750 mg/kg/day (26 times the human systemic exposure at the therapeutic dose of 200 mg/day) or in rats at doses up to 600 mg/kg/day (31 times the human systemic exposure at the therapeutic dose).

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

Emtricitabine did not affect fertility in male rats at approximately 140-fold or in male and female mice at approximately 60-fold higher exposures (AUC) than in humans given the recommended 200 mg daily dose. Fertility was normal in the offspring of mice exposed daily from before birth (*in utero*) through sexual maturity at daily exposures (AUC) of approximately 60-fold higher than human exposures at the recommended 200 mg daily dose.

Tenofovir Disoproxil Fumarate: 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.

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.

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 to 20 times higher than those observed in humans. The relationship of the renal abnormalities, particularly the phosphaturia, to the bone toxicity is not known.

5.3 Clinical Studies

Clinical Study 934 supports the use of emtricitabine and tenofovir disoproxil fumarate tablets for the treatment of HIV-1 infection. Additional data in support of the use of emtricitabine and tenofovir disoproxil fumarate are derived from clinical Study 903, in which lamivudine and tenofovir disoproxil fumarate (tenofovir DF) were used in combination in treatment-naïve adults, and clinical Study 303 in which emtricitabine and lamivudine demonstrated comparable efficacy, safety and resistance patterns as part of multidrug regimens. For additional information about these trials, please consult the prescribing information for tenofovir DF and emtricitabine. The iPrEx study and Partners PrEP study support the use of emtricitabine and tenofovir disoproxil fumarate to help reduce the risk of acquiring HIV-1.

Study 934

Data through 144 weeks are reported for Study 934, a randomized, open-label, active-controlled multicenter trial comparing emtricitabine + tenofovir DF 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 emtricitabine and tenofovir disoproxil fumarate with efavirenz in place of emtricitabine + tenofovir DF with efavirenz. Subjects had a mean age of 38 years (range 18 to 80), 86% were

male, 59% were

Caucasian and 23% were Black. The mean baseline CD4+ cell count was 245 cells/mm³ (range 2 to 1191) and median baseline plasma HIV-1 RNA was 5.01 log₁₀ copies/mL

(range 3.56 to 6.54). Subjects were stratified by baseline CD4 + cell count (< or ≥200

cells/mm³); 41% had CD4+ cell counts <200 cells/mm³ 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 12. **Table 12 Outcomes of Randomized Treatment at Week 48 and 144 (Study 934)**

Outcomes	At Week 48		At Week 144	
	FTC + TDF + EFV (N=244)	AZT/3TC + EFV (N=243)	FTC + TDF + 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%
Change in antiretroviral regimen	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 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 DF 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 DF 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/mm³ in the emtricitabine

+ tenofovir DF group and 158 cells/mm³ in the zidovudine/lamivudine group at Week 48 (312

and 271 cells/mm³ at Week 144).

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

The iPrEx trial was a randomized double-blind placebo-controlled multinational study evaluating emtricitabine and tenofovir disoproxil fumarate in 2499 HIV-seronegative men or transgender women who have sex with men and with evidence of high risk behavior for HIV-1 infection. Evidence of high risk behavior included any one of the following reported to have occurred up to six months prior to study screening: no condom use during anal intercourse with an HIV-1 positive partner or a partner of unknown HIV status; anal intercourse with more than 3 sex partners; exchange of money, gifts, shelter or drugs for anal sex; sex with male partner and diagnosis of sexually transmitted infection; no consistent use of condoms with sex partner known to be HIV-1 positive.

All subjects received monthly HIV-1 testing, risk-reduction counseling, condoms and management of sexually transmitted infections. Of the 2499 enrolled, 1251 received emtricitabine and tenofovir disoproxil fumarate and 1248 received placebo. The mean age of subjects was 27 years, 5% were Asian, 9% Black, 18% White, and 72% Hispanic/Latino.

Subjects were followed for 4237 person-years. The primary outcome measure for the study was the incidence of documented HIV seroconversion. At the end of treatment, emergent HIV-1 seroconversion was observed in 131 subjects, of which 48 occurred in the emtricitabine and tenofovir disoproxil fumarate group and 83 occurred in the placebo group, indicating a 42% (95% CI: 18 to 60%) reduction in risk. Risk reduction was found to be higher (53%; 95% CI: 34 to 72%) among subjects who reported previous unprotected anal intercourse (URAI) at screening (732 and 753 subjects reported URAI within the last 12 weeks at screening in the emtricitabine and tenofovir disoproxil fumarate and placebo groups, respectively). In a post-hoc case control study of plasma and intracellular

drug levels in about 10% of study subjects, risk reduction appeared to be the greatest in subjects with detectable intracellular tenofovir. Efficacy was therefore strongly correlated with adherence.

Partners PrEP Trial

The Partners PrEP trial was a randomized, double-blind, placebo-controlled 3 arm trial conducted in 4758 serodiscordant heterosexual couples in Kenya and Uganda to evaluate the efficacy and safety of TDF (N=1589) and FTC/TDF (N=1583) versus (parallel comparison) placebo (N=1586), in preventing HIV-1 acquisition by the uninfected partner.

All subjects received monthly HIV-1 testing, evaluation of adherence, assessment of sexual behavior, and safety evaluations. Women were also tested monthly for pregnancy. Women who became pregnant during the trial had study drug interrupted for the duration of the pregnancy and while breastfeeding. The uninfected partner subjects were predominantly male (61 to 64% across study drug groups), and had a mean age of 33 to 34 years.

Following 7827 person-years of follow up, 82 emergent HIV-1 seroconversions were reported, with an overall observed seroincidence rate of 1.05 per 100 person-years. Of the 82 seroconversions, 13 and 52 occurred in partner subjects randomized to emtricitabine and tenofovir disoproxil fumarate and placebo, respectively. Two of the 13 seroconversions in the emtricitabine and tenofovir disoproxil fumarate arm and 3 of the 52 seroconversions in the placebo arm occurred in women during treatment interruptions for pregnancy. The risk reduction for emtricitabine and tenofovir disoproxil fumarate relative to placebo was 75% (95% CI: 55 to 87%). In a post-hoc case control study of plasma drug levels in about 10% of study subjects, risk reduction appeared to be the greatest in subjects with detectable plasma tenofovir. Efficacy was therefore strongly correlated with adherence.

6. Pharmaceutical

particulars 6.1 List of excipients

Core Tablet:

-Pregelatinized Starch (starch 1500), Lactose Monohydrate, (Pharmatose 200M), Microcrystalline Cellulose (Avicel PH 102), Croscarmellose sodium, (Primellose), Magnesium Stearate, (LIGAMED MF-2-V),

Film Coating:

Opadry II Blue (32K505037)

6.2

Incompatibilities

Not applicable.

6.3 Shelf

life 2 years.

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of container Container pack:

30's HDPE Container.

6.6 Special precautions for disposal and other handling

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

7. Marketing Authorisation Holder and Manufacturing Site Addresses

Marketing Authorisation Holder:

M/s. Hetero Labs Limited,
7-2-A2, Hetero Corporate,
Industrial Estates, Sanath Nagar,
Hyderabad-500 018,
Telangana ,India

8. MARKETING AUTHORIZATION NUMBER

H2011/CTD221/369.

9. DATE OF FIRST <REGISTRATION> / RENEWAL OF THE <REGISTRATION

14-Oct-2011

10. DATE OF REVISION OF THE TEXT

14-Oct-2011