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Rx

EMTRICITABINE
TENOFOVIR DISOPROXIL FUMARATE
TENOF - EM
200 mg/300 mg Film-coated tablet
Antiretroviral
2078403

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TENOFOVIR DISOPROXIL FUMARATE
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200 mg/300 mg Film-coated tablet
Antiretroviral

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EMTRICITABINE AND TENOFOVIR DISOPROXIL FUMARATE TABLETS safely and effectively. See full prescribing information for EMTRICITABINE AND TENOFOVIR DISOPROXIL FUMARATE TABLETS.

EMTRICITABINE and TENOFOVIR DISOPROXIL FUMARATE tablets, for oral use

Initial U.S. Approval: 2004

WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS, POST-TREATMENT ACUTE EXACERBATION OF HEPATITIS B, and RISK OF DRUG RESISTANCE WITH USE OF EMTRICITABINE AND TENOFOVIR DISOPROXIL FUMARATE TABLET FOR PrEP IN UNDIAGNOSED HIV-1 INFECTION

See full prescribing information for complete boxed warning.

- **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. (5.1)**
- **Emtricitabine and tenofovir disoproxil fumarate is not approved for the treatment of chronic hepatitis B virus (HBV) infection. Severe acute exacerbations of hepatitis B have been reported in patients coinfected with HIV-1 and HBV who have discontinued emtricitabine and tenofovir disoproxil fumarate tablets. Therefore, hepatic function should be monitored closely in HBV-infected patients who discontinue emtricitabine and tenofovir disoproxil fumarate tablets. If appropriate, initiation of anti-hepatitis B therapy may be warranted. (5.2)**
- **Emtricitabine and tenofovir disoproxil fumarate tablets used for a PrEP indication must only be prescribed to individuals confirmed to be HIV-negative immediately prior to initial use and periodically during use. Drug-resistant HIV-1 variants have been identified with the use of emtricitabine and tenofovir disoproxil fumarate tablets for a PrEP indication following undetected acute HIV-1 infection. Do not initiate emtricitabine and tenofovir disoproxil fumarate tablets for a PrEP indication if signs or symptoms of acute HIV infection are present unless negative infection status is confirmed. (5.9)**

RECENT MAJOR CHANGES

Indications and Usage	
Treatment of HIV-1 infection (1.1)	03/2016
Dosage and Administration (2.2)	03/2016
Warnings and Precautions	
Coadministration with Other Products (5.4)	03/2016

INDICATIONS AND USAGE

Emtricitabine and tenofovir disoproxil fumarate tablet is a combination of emtricitabine and tenofovir disoproxil fumarate, both nucleoside analog HIV-1 reverse transcriptase inhibitors.

Emtricitabine and tenofovir disoproxil fumarate tablet 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. (1)

Emtricitabine and tenofovir disoproxil fumarate tablet is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk. (1)

DOSAGE AND ADMINISTRATION

Treatment of HIV-1 Infection (2.1)

- Recommended dose in adults and pediatric patients weighing greater than or equal to 35 kg: One emtricitabine and tenofovir disoproxil fumarate tablet (containing 200 mg/300 mg of emtricitabine and tenofovir disoproxil fumarate) once daily taken orally with or without food. (2.1)
- Recommended dose in pediatric patients weighing greater than or equal to 17 kg and able to swallow a whole tablet: one emtricitabine and tenofovir disoproxil fumarate low strength tablet (100 mg/150 mg, 133 mg/200 mg, or 167 mg/250 mg based on body weight) once daily taken orally with or without food. (2.2)
- Recommended dose in renally impaired HIV-1 infected adult patients: Creatinine clearance 30 to 49 mL/min: 1 tablet every 48 hours. (2.4) CrCl below 30 mL/min or hemodialysis: Do not use emtricitabine and tenofovir disoproxil fumarate tablets. (2.4)

Pre-exposure Prophylaxis (2.3)

- Recommended dose in HIV-1 uninfected adults: One tablet (containing 200 mg/300 mg of emtricitabine and tenofovir disoproxil fumarate) once daily taken orally with or without food. (2.3)
- Recommended dose in renally impaired HIV-uninfected individuals: Do not use emtricitabine and tenofovir disoproxil fumarate tablets in HIV-uninfected individuals if CrCl is below 60 mL/min. If a decrease in CrCl is observed in uninfected individuals while using emtricitabine and tenofovir disoproxil fumarate tablets for PrEP, evaluate potential causes and re-assess potential risks and benefits of continued use. (2.4)

DOSAGE FORMS AND STRENGTHS

Tablets: 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate. (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)

WARNINGS AND PRECAUTIONS

- New onset or worsening renal impairment: Can include acute renal failure and Fanconi syndrome. Assess estimated creatinine clearance before initiating treatment with emtricitabine and tenofovir disoproxil fumarate. In patients at risk for renal dysfunction, assess estimated creatinine clearance, serum phosphorus, urine glucose and urine protein before initiating treatment with emtricitabine and tenofovir disoproxil fumarate and periodically during treatment. Avoid administering emtricitabine and tenofovir disoproxil fumarate with concurrent or recent use of nephrotoxic drugs. (5.3)
- Coadministration with Other Products: Do not use with drugs containing emtricitabine, tenofovir alafenamide or tenofovir disoproxil fumarate including ATRIPLA, COMPLERA, emtricitabine, GENVOYA, ODEFSEY, STRIBILD, tenofovir disoproxil fumarate.; or with drugs containing lamivudine. Do not administer in combination with HEPSERA. (5.4)
- Decreases in bone mineral density (BMD): Consider assessment of BMD in patients with a history of pathologic fracture or other risk factors for osteoporosis or bone loss. (5.5)
- Redistribution/accumulation of body fat: Observed in patients receiving antiretroviral therapy. (5.6)
- Immune reconstitution syndrome: May necessitate further evaluation and treatment. (5.7)
- Triple nucleoside-only regimens: Early virologic failure has been reported in HIV-infected patients. Monitor carefully and consider treatment modification. (5.8)
- Comprehensive management to reduce the risk of acquiring HIV-1: Use as part of a comprehensive prevention strategy including other prevention measures; strictly adhere to dosing schedule. (5.9)
- Management to reduce the risk of acquiring HIV-1 drug resistance:
  Prior to initiating emtricitabine and tenofovir disoproxil fumarate for PrEP -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 negative 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 PrEP - HIV-1 screening tests should be repeated at least every 3 months. (5.9)

ADVERSE REACTIONS

In HIV-1 infected patients, the most common adverse reactions (incidence greater than or equal to 10%) are diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash. (6.1)

In HIV-1 uninfected individuals in PrEP trials, adverse reactions that were reported by more than 2% of emtricitabine and tenofovir disoproxil fumarate subjects and more frequently than by placebo subjects were headache, abdominal pain and weight decreased. (6.2)

DRUG INTERACTIONS

- Didanosine: Tenofovir disoproxil fumarate increases didanosine concentrations. Use with caution and monitor for evidence of didanosine toxicity (e.g., pancreatitis, neuropathy) when coadministered. Consider dose reductions or discontinuations of didanosine if warranted. (7.1)
- HIV-1 protease inhibitors: Coadministration decreases atazanavir concentrations and increases tenofovir concentrations. When coadministered with emtricitabine and tenofovir disoproxil fumarate, use atazanavir given with ritonavir. Coadministration of emtricitabine and tenofovir disoproxil fumarate with atazanavir and ritonavir, darunavir and ritonavir, or lopinavir/ritonavir increases tenofovir concentrations. Monitor for evidence of tenofovir toxicity. (7.2)

USE IN SPECIFIC POPULATIONS

- Nursing mothers: Women infected with HIV-1 should be instructed not to breast feed. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 05/2016

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FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS, POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B, and RISK OF DRUG RESISTANCE WITH USE OF EMTRICITABINE AND TENOFOVIR DISOPROXIL FUMARATE TABLETS FOR PRE-EXPOSURE PROPHYLAXIS (PrEP) IN UNDIAGNOSED EARLY HIV-1 INFECTION

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 tablets, in combination with other antiretrovirals *[See Warnings and Precautions (5.1)]*

Emtricitabine and tenofovir disoproxil fumarate is not approved for the treatment of chronic hepatitis B virus (HBV) infection and the safety and efficacy of emtricitabine and tenofovir disoproxil fumarate tablets have not been established in patients coinfected with HBV and HIV-1. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued emtricitabine and tenofovir disoproxil fumarate tablets. Therefore, hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are infected with HBV and discontinue emtricitabine and tenofovir disoproxil fumarate. If appropriate, initiation of anti-hepatitis B therapy may be warranted *[See Warnings and Precautions (5.2)]*.

Emtricitabine and tenofovir disoproxil fumarate tablets used for a PrEP indication must only be prescribed to individuals confirmed to be HIV-negative immediately prior to initiating and periodically (at least every 3 months) during use. Drug-resistant HIV-1 variants have been identified with use of emtricitabine and tenofovir disoproxil fumarate tablets for a PrEP indication following undetected acute HIV-1 infection. Do not initiate emtricitabine and tenofovir disoproxil fumarate tablets for a PrEP indication if signs or symptoms of acute HIV-1 infection are present unless negative infection status is confirmed *[See Warnings and Precautions (5.9)]*.

1 INDICATIONS AND USAGE

1.1 Treatment of HIV-1 Infection

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. *[See Dosage and Administration (2) and Clinical Studies (14)]*.

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 *[See Warnings and Precautions (5.4)]*.
- In treatment experienced patients, the use of emtricitabine and tenofovir disoproxil fumarate tablet should be guided by laboratory testing and treatment history *[See Microbiology (12.4)]*.

1.2 Pre-Exposure Prophylaxis

Emtricitabine and tenofovir disoproxil fumarate tablet is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk. This indication is based on clinical trials in men who have sex with men (MSM) at high risk for HIV-1 infection and in heterosexual serodiscordant couples *[See Clinical Studies (14.2, 14.3)]*.

When considering emtricitabine and tenofovir disoproxil fumarate tablet for pre-exposure prophylaxis the following factors may help to identify individuals at high risk:

- has partner(s) known to be HIV-1 infected, or
- engages in sexual activity within a high prevalence area or social network and one or more of the following:
  - inconsistent or no condom use
  - diagnosis of sexually transmitted infections
  - exchange of sex for commodities (such as money, food, shelter, or drugs)
  - use of illicit drugs or alcohol dependence
  - incarceration
  - partner(s) of unknown HIV-1 status with any of the factors listed above

When prescribing emtricitabine and tenofovir disoproxil fumarate tablet for pre-exposure prophylaxis, healthcare providers must:

- prescribe emtricitabine and tenofovir disoproxil fumarate tablet as part of a comprehensive prevention strategy because emtricitabine and tenofovir disoproxil fumarate tablet is not always effective in preventing the acquisition of HIV-1 infection *[See Warnings and Precautions (5.9)]*;
- counsel all uninfected individuals to strictly adhere to the recommended emtricitabine and tenofovir disoproxil fumarate tablet dosing schedule because the effectiveness of emtricitabine and tenofovir disoproxil fumarate tablet in reducing the risk of acquiring HIV-1 was strongly correlated with adherence as demonstrated by measurable drug levels in clinical trials *[See Warnings and Precautions (5.9)]*;
- confirm a negative HIV-1 test immediately prior to initiating emtricitabine and tenofovir disoproxil fumarate tablet for a PrEP indication. 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. *[See Warnings and Precautions (5.9)]*; and
- screen for HIV-1 infection at least once every 3 months while taking emtricitabine and tenofovir disoproxil fumarate tablet for PrEP.

2 DOSAGE AND ADMINISTRATION

2.1 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.

2.2 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

2.3 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.

2.4 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 *[see emtricitabine or tenofovir disoproxil fumarate Package Insert]*. 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 *[See Warnings and Precautions (5.3)]*.

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

	Creatinine Clearance (mL/min)[a]		
	≥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.

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 *[See Warnings and Precautions (5.3)]*.

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 *[See Warnings and Precautions (5.3)]*.

Routine monitoring of estimated creatinine clearance, serum phosphorus, urine glucose, and urine protien 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 *[See Warnings and Precautions (5.3)]*.

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 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

5 WARNINGS AND PRECAUTIONS

5.1 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).

5.2 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 coinfected 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.

5.3 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 *[See Adverse Reactions (6.3)]*.

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)) *[See Drug Interactions (7.4)]*. 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 *[See Dosage and Administration (2.4)]*. 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 *[See Dosage and Administration (2.4)]*.

5.4 Coadministration with Other Products

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).

5.5 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 *[See Adverse Reactions (6.2)* and tenofovir disoproxil fumarate prescribing information]. 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 *[See Adverse Reactions (6.3)]*. 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 *[See Warnings and Precautions (5.3)]*.

5.6 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.

5.7 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 systems respond may develop an inflammatory response to indolent or residual opportunistic infections [such as *Mycobacterium avium infection, cytomegalovirus, Pneumocystis jirovecii pneumonia* (PCP), or tuberculosis], which may necessitate further evaluation and treatment.

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

5.8 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.

5.9 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 *[See Clinical Studies (14.2 and 14.3)]*.

- 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 *[See Microbiology: Resistance (12.4)]*; 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 *[See Clinical Studies (14.2 and 14.3)]*.

6 ADVERSE REACTIONS

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

- Lactic Acidosis/Severe Hepatomegaly with Steatosis *[See Boxed Warning, Warnings and Precautions (5.1)]*.
- Severe Acute Exacerbations of hepatitis B *[See Boxed Warning, Warnings and Precautions (5.2)]*.
- New Onset or Worsening Renal Impairment *[See Warnings and Precautions (5.3)]*.
- Bone Effects of Tenofovir DF *[See Warnings and Precautions (5.5)]*.
- Immune Reconstitution Syndrome *[See Warnings and Precautions (5.7)]*.

6.1 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-naive 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-naive 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%

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

b. 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.

c. Rash event includes rash, exfoliative rash, rash generalized, rash macular, rash maculo-papular, 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 ≥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 ≥ 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 (≥ 3+)	<1%	1%
Neutrophils (<750/mm³)	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 x ULN), increased pancreatic amylase (>2 x ULN), increased or decreased serum glucose (<40 or >250 mg/dL), and increased serum lipase (>2 x 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 *[See Warnings and Precautions (5.5)]*. For additional information, please consult the tenofovir disoproxil fumarate prescribing information

6.2 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 ≥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				
Back pain	5%	5%	-	-
Nervous System Disorders			-	-
Headache	7%	6%		
Psychiatric Disorders				
Depression	6%	7%	-	-
Anxiety	3%	3%		
Reproductive System and Breast Disorders				
Genital ulceration	2%	2%	2%	2%
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	(2.5 -<LLN mg/dL)	81 (7%)	110 (9%)	NR[a]	NR[a]
	2-4	(<2 mg/dL)	123 (10%)	101 (8%)	140 (9%)	136 (9%)
AST	1	(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	(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	(8.5 -10 mg/dL)	49 (4%)	62 (5%)	56 (4%)	39 (2%)
	2-4	(<9.4 mg/dL)	13 (1%)	19 (2%)	28 (2%)	39 (2%)
Neutrophils	1	(1000-1300/mm³)	23 (2%)	25 (2%)	208 (13%)	163 (10%)
	2-4	(<750/mm³)	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 *[See Clinical Studies (14.2)]*. 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 *[See Clinical Studies (14.3)]*.

6.3 Postmarketing 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.

7 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 *[See Clinical Pharmacology (12.3)]*.

7.1 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 *[See Clinical Pharmacology (12.3)]*. 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).

7.2 HIV-1 Protease Inhibitors

Tenofovir decreases the AUC and C_{min} of atazanavir *[See Clinical Pharmacology (12.3)]*. 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 *[See Clinical Pharmacology (12.3)]*. 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.

7.3 Hepatitis C Antiviral Agents

Coadministration of tenofovir disoproxil fumarate and HARVONI® (ledipasvir/sofosbuvir) has been shown to increase tenofovir exposure *[See Clinical Pharmacology (12.3)]*.

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.

7.4 Drugs Affecting Renal Function

Emtricitabine and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion *[See Clinical Pharmacology (12.3)]*. 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 *[See Warnings and Precautions (5.3)]*. Drugs that decrease renal function may increase concentrations of emtricitabine and/or tenofovir.

8 USE IN SPECIFIC POPULATIONS

8.1 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.

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.

8.3 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.

8.4 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 *[See Warnings and Precautions (5.5), Adverse Reactions (6.1) and Clinical Pharmacology (12.3)]*. Emtricitabine and tenofovir disoproxil fumarate has not been evaluated for use in pediatric patients weighing less than 17 kg.

8.5 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.

8.6 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. *[See Dosage and Administration (2.4)]*.

Pre-exposure Prophylaxis

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 *[See Dosage and Administration (2.4)]*.

10 OVERDOSAGE

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 a3-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.

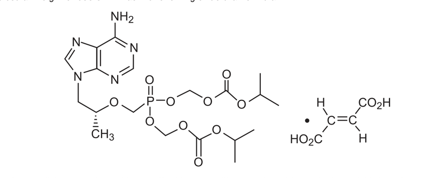
Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of tenofovir disoproxil fumarate, a four-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

11 DESCRIPTION

Emtricitabine and tenofovir disoproxil fumarate tablets are fixed dose combination tablets containing emtricitabine and tenofovir disoproxil fumarate. Emtricitabine, a synthetic nucleoside analog of cytidine. Tenofovir DF is converted *in vivo* to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate. Both emtricitabine and tenofovir exhibit inhibitory activity against HIV-1 reverse transcriptase.

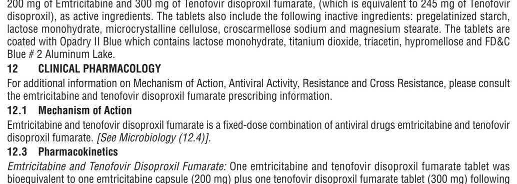
Emtricitabine: The chemical name of emtricitabine is 5-fluoro-1-(2*R*,5*S*)-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl] cytosine. Emtricitabine is the (-) enantiomer of a thio analog of cytidine, which differs from other cytidine analogs in that it has a fluorine in the 5-position.

It has a molecular formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.24. It has the following structural formula:



Emtricitabine is a white to off-white crystalline powder with a solubility of approximately 112 mg/mL in water at 25°C. The partition coefficient (log p) for emtricitabine is -0.43 and the pKa is 2.65.

Tenofovir Disoproxil Fumarate: Tenofovir disoproxil fumarate is a fumaric acid salt of the bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir. 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 $C_{19}H_{30}N_5O_{10}P \cdot C_4H_4O_4$ and a molecular weight of 635.52. It has the following structural formula:



Tenofovir disoproxil fumarate is a white to off-white crystalline powder with a solubility of 13.4 mg/mL in water at 25°C. The partition coefficient (log p) for tenofovir disoproxil is 1.25 and the pKa is 3.75. All dosages are expressed in terms of tenofovir disoproxil fumarate except where otherwise noted.

Emtricitabine and tenofovir disoproxil fumarate tablets are for oral administration. 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), as active ingredients. The tablets also include the following inactive ingredients: pregelatinized starch, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium and magnesium stearate. The tablets are coated with Opadry II Blue which contains lactose monohydrate, titanium dioxide, triacetin, hypromellose and FD&C Blue # 2 Aluminum Lake.

12 CLINICAL PHARMACOLOGY

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

12.1 Mechanism of Action

Emtricitabine and tenofovir disoproxil fumarate is a fixed-dose combination of antiviral drugs emtricitabine and tenofovir disoproxil fumarate. *[See Microbiology (12.4)]*.

12.3 Pharmacokinetics

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 *[See Warnings and Precautions (5.3)]*. 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 *[See Dosage and Administration (2.4)]*.

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 *[See Dosage and Administration (2.4)]*.

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 x 10 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 x 14 days	15	↑ 79 (↑ 56 to ↑ 104)	↑ 98 (↑ 77 to ↑ 123)	↑ 163 (↑ 132 to ↑ 197)
Ledipasvir/ Sofosbuvir[i]	90/400 once daily x 10 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 mg single dose	16	↑ 25 (↑ 8 to ↑ 45)	⇔	⇔
Tacrolimus	0.05 mg/kg twice daily x 7 days	21	↑ 13 (↑ 1 to ↑ 27)	⇔	⇔
Tipranavir/Ritonavir[f]	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)

a. Subjects received tenofovir disoproxil fumarate 300 mg once daily.
b. Increase = ↑; Decrease = ↓; No Effect = ⇔; NC = Not Calculated
c. Reyataz Prescribing Information
d. Prezista Prescribing Information
e. Data generated from simultaneous dosing with HARVONI (ledipasvir/sofosbuvir). Staggered administration (12 hours apart) provided similar results.
f. Comparison based on exposures when administered as atazanavir/ritonavir + emtricitabine/tenofovir DF.
g. Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine/tenofovir DF.
h. Study conducted with ATRIPLA (efavirenz/emtricitabine/tenofovir DF) coadministered with HARVONI.
i. Study conducted with COMPLERA (emtricitabine/rilpivirine/tenofovir DF) coadministered with HARVONI.
j. Study conducted with ATRIPLA coadministered with SOVALDI® (sofosbuvir).
k. 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)	↓ 25[c] (↓ 42 to ↓ 3)	↓ 23[c] (↓ 46 to ↑ 10)
Darunavir[d]	Darunavir/Ritonavir 300/100 mg once daily	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 mg once daily x 10 days	28	⇔	↑ 13 (↑ 11 to ↑ 15)	⇔
Lamivudine	150 twice daily x 7 days	15	↓ 24 (↓ 34 to ↓ 12)	⇔	⇔
Lopinavir	Lopinavir/Ritonavir 400/100 twice daily x 14 days	24	⇔	⇔	⇔
Ritonavir			⇔	⇔	⇔
Saquinavir	Saquinavir/ Ritonavir 1000/100 twice daily x 14 days	32	↑ 22 (↑ 6 to ↑41)	↑ 29[h] (↑ 12 to ↑ 48)	↑ 47[h] (↑ 23 to ↑ 76)
Ritonavir			⇔	⇔	↑ 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.

12.4 Microbiology

Mechanism of Action

Emtricitabine: Emtricitabine, a synthetic nucleoside analog of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of the HIV-1 reverse transcriptase (RT) by competing with the natural substrate deoxycytidine 5'-triphosphate and by being incorporated into nascent viral DNA which results in chain termination. Emtricitabine 5'-triphosphate is a weak inhibitor of mammalian DNA polymerase α, β, ε and mitochondrial DNA polymerase γ.

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

Antiviral Activity

Emtricitabine and Tenofovir Disoproxil Fumarate: No antagonism was observed in combination studies evaluating the cell culture antiviral activity of emtricitabine and tenofovir together.

Emtricitabine: The antiviral activity of emtricitabine against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and peripheral blood mononuclear cells. The 50% effective concentration (EC_{50}) values for emtricitabine were in the range of 0.0013 to 0.64 μM (0.0003 to 0.158 mcg/mL). In drug combination studies of emtricitabine with nucleoside reverse transcriptase inhibitors (abacavir, lamivudine, stavudine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, nelfinavir, ritonavir, saquinavir), no antagonism was observed. Emtricitabine displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, and G (EC_{50} values ranged from 0.007 to 0.075 μM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 0.007 to 1.5 μM).

Tenofovir Disoproxil Fumarate: The antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The EC_{50} values for tenofovir were in the range of 0.04 to 8.5 μM. In drug combination studies of tenofovir with nucleoside reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir), no antagonism was observed. Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G and O (EC_{50} values ranged from 0.5 to 2.2 μM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 1.6 μM to 5.5 μM).

Prophylactic Activity in a Nonhuman Primate Model of HIV Transmission

Emtricitabine and Tenofovir Disoproxil Fumarate: The prophylactic activity of the combination of daily oral emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) was evaluated in a controlled study of macaques inoculated once weekly for 14 weeks with SIV/HIV-1 chimeric virus (SHIV) applied to the rectal surface. Of the 18 control animals, 17 became infected after a median of 2 weeks. In contrast, 4 of the 6 animals treated daily with oral FTC and TDF remained uninfected and the two infections that did occur were significantly delayed until 9 and 12 weeks and exhibited reduced viremia. An M184I-expressing FTC-resistant variant emerged in 1 of the 2 macaques after 3 weeks of continued drug exposure.

Resistance

Emtricitabine and Tenofovir Disoproxil Fumarate: HIV-1 isolates with reduced susceptibility to the combination of emtricitabine and tenofovir have been selected in cell culture. Genotypic analysis of these isolates identified the M184V/I and/or K65R amino acid substitutions in the viral RT. In addition, a K70E substitution in HIV-1 reverse transcriptase has been selected by tenofovir and results in reduced susceptibility to tenofovir.

In a clinical trial of treatment-naïve subjects *[Study 934, see Clinical Studies (14.1)]*, resistance analysis was performed on HIV-1 isolates from all confirmed virologic failure subjects with greater than 400 copies/mL of HIV-1 RNA at Week 144 or early discontinuation. Development of efavirenz resistance-associated substitutions occurred most frequently and was similar between the treatment arms. The M184V amino acid substitution, associated with resistance to emtricitabine and lamivudine, was observed in 2/19 analyzed subject isolates in the emtricitabine + tenofovir disoproxil fumarate group and in 10/29 analyzed subject isolates in the zidovudine/lamivudine group. Through 144 weeks of Study 934, no subjects have developed a detectable K65R or K70E substitution in their HIV-1 as analyzed through standard genotypic analysis.

Emtricitabine: Emtricitabine-resistant isolates of HIV-1 have been selected in cell culture and *in vivo*. Genotypic analysis of these isolates showed that the reduced susceptibility to emtricitabine was associated with a substitution in the HIV-1 RT gene at codon 184 which resulted in an amino acid substitution of methionine by valine or isoleucine (M184V/I).

Tenofovir Disoproxil Fumarate: HIV-1 isolates with reduced susceptibility to tenofovir have been selected in cell culture. These viruses expressed a K65R substitution in RT and showed a 2 to 4 fold reduction in susceptibility to tenofovir.

In treatment-naïve subjects, isolates from 8/47 (17%) analyzed subjects developed the K65R substitution in the tenofovir disoproxil fumarate arm through 144 weeks; 7 occurred in the first 48 weeks of treatment and 1 at Week 96. In treatment-experienced subjects, 14/304 (5%) isolates from subjects failing tenofovir disoproxil fumarate through Week 96 showed greater than 1.4 fold (median 2.7) reduced susceptibility to tenofovir. Genotypic analysis of the resistant isolates showed a K65R amino acid substitution in the HIV-1 RT.

iPrEx Trial: In a clinical study of HIV-1 seronegative subjects *[iPrEx Trial, see Clinical Studies (14.2)]*, no amino acid substitutions associated with resistance to emtricitabine or tenofovir were detected at the time of seroconversion among 48 subjects in the emtricitabine and tenofovir disoproxil fumarate group and 83 subjects in the placebo group who became infected with HIV-1 during the trial. Ten subjects were observed to be HIV-1 infected at time of enrollment. The M184V/I substitutions associated with resistance to emtricitabine were observed in 3 of the 10 subjects (2 of 2 in the emtricitabine and tenofovir disoproxil fumarate group and 1 of 8 in the placebo group). One of the two subjects in the emtricitabine and tenofovir disoproxil fumarate group harbored wild type virus at enrollment and developed the M184V substitution 4 weeks after enrollment. The other subject had indeterminate resistance at enrollment but was found to have the M184I substitution 4 weeks after enrollment.

Partners PrEP Trial: In a clinical study of HIV-1 seronegative subjects *[Partners PrEP Trial, see Clinical Studies (14.3)]*, no variants expressing amino acid substitutions associated with resistance to emtricitabine or tenofovir were detected at the time of seroconversion among 12 subjects in the emtricitabine and tenofovir disoproxil fumarate group, 15 subjects in the tenofovir disoproxil fumarate group, and 51 subjects in the placebo group. Fourteen subjects were observed to be HIV-1 infected at the time of enrollment (3 in the emtricitabine and tenofovir disoproxil fumarate group, 5 in the tenofovir disoproxil fumarate group, and 6 in the placebo group). One of the three subjects in the emtricitabine and tenofovir disoproxil fumarate group who was infected with wild type virus at enrollment selected an M184V expressing virus by week 12. Two of the five subjects in the tenofovir disoproxil fumarate group had tenofovir-resistant viruses at the time of seroconversion; one subject infected with wild type virus at enrollment developed a K65R substitution by week 16, while the second subject had virus expressing the combination of D67N and K70R substitutions upon seroconversion at week 60, although baseline virus was not genotyped and it is unclear if the resistance emerged or was transmitted. Following enrollment, 4 subjects (2 in the tenofovir disoproxil fumarate group, 1 in the emtricitabine and tenofovir disoproxil fumarate group, and 1 in the placebo group) had virus expressing K103N or V106A substitutions, which confer high-level resistance to NNRTIs but have not been associated with tenofovir or emtricitabine and may have been present in the infecting virus.

Cross Resistance

Emtricitabine and Tenofovir Disoproxil Fumarate: Cross-resistance among certain nucleoside reverse transcriptase inhibitors (NRTIs) has been recognized. The M184V/I and/or K65R substitutions selected in cell culture by the combination of emtricitabine and tenofovir are also observed in some HIV-1 isolates from subjects failing treatment with tenofovir in combination with either emtricitabine or lamivudine, and either abacavir or didanosine. Therefore, cross-resistance among these drugs may occur in patients whose virus harbors either or both of these amino acid substitutions.

Emtricitabine: Emtricitabine-resistant isolates (M184V/I) were cross-resistant to lamivudine but retained susceptibility in cell culture to the NRTIs didanosine, stavudine, tenofovir, and zidovudine, and to NNRTIs (delavirdine, efavirenz, and nevirapine). HIV-1 isolates containing the K65R substitution, selected *in vivo* by abacavir, didanosine, and tenofovir, demonstrated reduced susceptibility to inhibition by emtricitabine. Viruses harboring substitutions conferring reduced susceptibility to stavudine and zidovudine (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E), or didanosine (L74V) remained sensitive to emtricitabine. HIV-1 containing the K103N substitution associated with resistance to NNRTIs was susceptible to emtricitabine.

Tenofovir Disoproxil Fumarate: The K65R and K70E substitutions selected by tenofovir are also selected in some HIV-1-infected patients treated with abacavir or didanosine. HIV-1 isolates with the K65R and K70E substitutions also showed reduced susceptibility to emtricitabine and lamivudine. Therefore, cross-resistance among these NRTIs may occur in patients whose virus harbors the K65R or K70E substitutions. HIV-1 isolates from subjects (N=20) whose HIV-1 expressed a mean of 3 zidovudine-associated RT amino acid substitutions (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N) showed a 3.1-fold decrease in the susceptibility to tenofovir. Subjects whose virus expressed an L74V substitution without zidovudine resistance-associated substitutions (N=8) had reduced response to tenofovir disoproxil fumarate. Limited data are available for patients whose virus expressed a Y115F substitution (N=3), Q151M substitution (N=2), or T69 insertion (N=4), all of whom had a reduced response.

13 NONCLINICAL TOXICOLOGY

13.1 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.

13.2 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.

14 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.

14.1 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 log_{10} 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 FTC + TDF + EFV (N=244)	At Week 48 AZT/3TC + EFV (N=243)	At Week 144 FTC + TDF + EFV (N=227)[a]	At Week 144 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).

14.2 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.

14.3 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

The blue, capsule shaped, film coated tablets contain 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate (which is equivalent to 245 mg of tenofovir disoproxil), are debossed with 'H' on one side and with '124' on the other side, and are available in unit of use bottles [containing a dessicant (silica gel sachet) and closed with a child-resistant closure] of:

- 30 tablets
- Storage condition: Store below 30°C and protect from moisture.
- Keep container tightly closed
- Dispense only in original container
- Do not use if seal over bottle opening is broken or missing.

17 PATIENT COUNSELING INFORMATION

As a part of patient counseling, healthcare providers must review the emtricitabine and tenofovir disoproxil fumarate Medication Guide with every uninfected individual taking emtricitabine and tenofovir disoproxil fumarate to reduce the risk of acquiring HIV.

Important Information for All Patients and Uninfected Individuals

Advise patients and uninfected individuals that:

- The long term effects of emtricitabine and tenofovir disoproxil fumarate are unknown.
- Emtricitabine and Tenofovir disoproxil fumarate Tablets are for oral ingestion only.
- Patients and uninfected individuals should not discontinue emtricitabine and tenofovir disoproxil fumarate without first informing their physicians.
- Patients and uninfected individuals should remain under the care of a physician when using emtricitabine and tenofovir disoproxil fumarate.
- It is important to take emtricitabine and tenofovir disoproxil fumarate on a regular dosing schedule to avoid missing doses.
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Treatment with emtricitabine and tenofovir disoproxil fumarate should be suspended in patients or uninfected individuals who develop clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity (including nausea, vomiting, unusual or unexpected stomach discomfort, and weakness) *[See Warnings and Precautions (5.1)]*.
- Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with hepatitis B virus (HBV) and HIV-1 and have discontinued emtricitabine and tenofovir disoproxil fumarate. Before initiating emtricitabine and tenofovir disoproxil fumarate, test all patients and uninfected individuals for HBV. All patients who are infected with HBV need close medical follow-up for several months after stopping emtricitabine and tenofovir disoproxil fumarate to monitor for exacerbations of hepatitis *[See Warnings and Precautions (5.2)]*.
- Renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported in association with the use of tenofovir disoproxil fumarate. Emtricitabine and Tenofovir disoproxil fumarate should be avoided with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple NSAIDs) *[See Warnings and Precautions (5.3)]*. Dosing interval of emtricitabine and tenofovir disoproxil fumarate may need adjustment in HIV-1 infected patients with renal impairment. Emtricitabine and tenofovir disoproxil fumarate for a PrEP indication should not be used in HIV-1 uninfected individuals 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 *[See Dosage and Administration (2.4)]*.
- Do not administer emtricitabine and tenofovir disoproxil fumarate with ATRIPLA, COMPLERA, emtricitabine, GENVOYA, ODEFSEY, STRIBILD, or tenofovir disoproxil fumarate; or with 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) *[See Warnings and Precautions (5.4)]*.
- Do not administer emtricitabine and tenofovir disoproxil fumarate with HEPSERA *[See Warnings and Precautions (5.4)]*.
- Decreases in bone mineral density have been observed with the use of tenofovir disoproxil fumarate or emtricitabine and tenofovir disoproxil fumarate. Consider bone monitoring in patients and uninfected individuals who have a history of pathologic bone fracture or at risk for osteopenia *[See Warnings and Precautions (5.5)]*.
- Patients and uninfected individuals should avoid doing things that can spread HIV-1 or HBV infection.
  - Do not share needles or other injection equipment.
  - Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.
  - Do not have any kind of sex without protection. Always practice safer sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.
  - Patients and uninfected individuals should not breastfeed because the drugs in emtricitabine and tenofovir disoproxil fumarate can be passed to the baby in breast milk, and it is not known whether they can harm the baby. HIV-positive women should also not breastfeed because of the risk of passing the HIV-1 virus to the baby.

Treatment of HIV-1 Infection

When emtricitabine and tenofovir disoproxil fumarate is used in the treatment of HIV-infection, advise patients that:

- Emtricitabine and Tenofovir disoproxil fumarate is not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections.
- It is important to take emtricitabine and tenofovir disoproxil fumarate in a regular dosing schedule with combination therapy to avoid missing doses.
- All patients with HIV-1 should be tested for hepatitis B virus (HBV) before initiating and monitored after discontinuing taking emtricitabine and tenofovir disoproxil fumarate.

Pre-Exposure Prophylaxis

When emtricitabine and tenofovir disoproxil fumarate is used to reduce the risk of acquiring HIV-1, advise uninfected individuals about the importance of the following:

- Confirming that they are HIV-negative before starting to take emtricitabine and tenofovir disoproxil fumarate to reduce the risk of acquiring HIV-1.
- Emtricitabine and Tenofovir disoproxil fumarate should only be used as part of a complete prevention strategy including other prevention measures. In clinical trials, emtricitabine and tenofovir disoproxil fumarate only protected some subjects from acquiring HIV-1.
- Using condoms consistently and correctly to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions, or blood.
- Knowing their HIV status and the status of their partner(s).
- Getting tested regularly (at least every 3 months) for HIV-1 and ask their partner(s) to get tested as well.
- HIV-1 resistance substitutions may emerge in individuals with undetected HIV-1 infection who are taking emtricitabine and tenofovir disoproxil fumarate, because emtricitabine and tenofovir disoproxil fumarate alone does not constitute a complete regimen for HIV-1 treatment *[See Warnings and Precautions (5.9)]*
- Reporting any symptoms of acute HIV-1 infection (flu-like symptoms) to their healthcare provider immediately.
- Signs and symptoms of acute infection include: fever, headache, fatigue, arthralgia, vomiting, myalgia, diarrhea, pharyngitis, rash, night sweats, and adenopathy (cervical and inguinal).
- Getting tested for other sexually transmitted infections such as syphilis and gonorrhea that may facilitate HIV-1 transmission.
- Learning about sexual risk behavior and getting support to help reduce sexual risk behavior.
- Taking emtricitabine and tenofovir disoproxil fumarate on a regular dosing schedule and strictly adhere to the recommended dosing schedule to reduce the risk of acquiring HIV-1. Uninfected individuals who miss doses are at greater risk of acquiring HIV-1 than those who do not miss doses. *[See Warnings and Precautions (5.9)]*.
- Women who are pregnant should learn about the risks and benefits of emtricitabine and tenofovir disoproxil fumarate to reduce the risk of acquiring HIV-1 during their pregnancy.
- Encourage use of the Agreement Form for Initiating emtricitabine and tenofovir disoproxil fumarate for PrEP of Sexually Acquired HIV-1 Infection.

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Caution:

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription

ADR REPORTING STATEMENT:

For suspected adverse drug reaction. report to the FDA: www.fda.gov.ph

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Medication Guide

EMTRICITABINE
TENOFOVIR DISOPROXIL FUMARATE
TENOF - EM
200 mg/300 mg Film-coated tablet
Antiretroviral

Read this Medication Guide before you start taking emtricitabine and tenofovir disoproxil fumarate tablets and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

This Medication Guide provides information about two different ways that emtricitabine and tenofovir disoproxil fumarate tablets may be used (See the Medication Guide section "**What is emtricitabine and tenofovir disoproxil fumarate tablets?**" for important information about how emtricitabine and tenofovir disoproxil fumarate tablets may be used:

- to treat Human Immunodeficiency Virus-1 (HIV-1) infection, and
- to reduce the risk of getting HIV-1 infection in adults who are HIV-negative. HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).

What is the most important information I should know about emtricitabine and tenofovir disoproxil fumarate Tablets?

Emtricitabine and Tenofovir disoproxil fumarate Tablets can cause serious side effects, including:

1. Too much lactic acid in your blood (lactic acidosis). Your body normally makes lactic acid, but too much lactic acid is a serious medical emergency. It can be treated, but it can also lead to death. **Call your healthcare provider right away if you get these symptoms:**

- weakness or being more tired than usual
- unusual muscle pain
- being short of breath or fast breathing
- nausea, vomiting, and stomach-area pain
- cold or blue hands and feet
- feel dizzy or lightheaded
- fast or abnormal heartbeats

2. Severe liver problems. Severe liver problems can happen in people who take emtricitabine and tenofovir disoproxil fumarate tablets. In some cases these liver problems can lead to death. Your liver may become large and tender. You may develop fat in your liver when you take emtricitabine and tenofovir disoproxil fumarate tablets. **Call your healthcare provider right away if you get the following symptoms:**

- your skin or the white part of your eyes turns yellow
- dark "tea-colored" urine
- light-colored stools
- loss of appetite for several days or longer
- nausea
- stomach-area pain

You may be more likely to get lactic acidosis or severe liver problems if you are female, if you are very overweight (obese), or if you have been taking emtricitabine and tenofovir disoproxil fumarate tablets for a long time.

3. If you also have hepatitis B virus (HBV) infection and take emtricitabine and tenofovir disoproxil fumarate tablets, your hepatitis B may become worse if you stop taking emtricitabine and tenofovir disoproxil fumarate tablets.

- Do not stop taking emtricitabine and tenofovir disoproxil fumarate tablets without first talking to your healthcare provider.
- Do not run out of emtricitabine and tenofovir disoproxil fumarate tablets. Refill your prescription or talk to your healthcare provider before your emtricitabine and tenofovir disoproxil fumarate tablets are all gone.
- If your healthcare provider stops emtricitabine and tenofovir disoproxil fumarate tablets, your healthcare provider will need to watch you closely for several months to check your hepatitis B infection, or give you a medication to treat hepatitis B.

Tell your healthcare provider about any new or unusual symptoms you may have after you stop taking emtricitabine and tenofovir disoproxil fumarate tablets.

For more information about side effects, see the section **"What are the possible side effects of emtricitabine and tenofovir disoproxil fumarate tablets?"** in this Medication Guide.

Other important information for people who take emtricitabine and tenofovir disoproxil fumarate tablets to help reduce their risk of getting HIV-1 infection:

Before taking emtricitabine and tenofovir disoproxil fumarate tablets to reduce your risk of getting HIV-1 infection:

- **You must be HIV-negative to start emtricitabine and tenofovir disoproxil fumarate tablets. You must get tested to make sure that you do not already have HIV-1 infection.**
- **Do not take emtricitabine and tenofovir disoproxil fumarate tablets to reduce the risk of getting HIV unless you are confirmed to be HIV-negative.**
- Many HIV-1 tests can miss HIV-1 infection in a person who has recently become infected. If you have flu-like symptoms, you could have recently become infected with HIV-1. Tell your healthcare provider if you had a flu-like illness within the last month before starting emtricitabine and tenofovir disoproxil fumarate tablets or at any time while taking emtricitabine and tenofovir disoproxil fumarate tablets. Symptoms of new HIV-1 infection include:

• tiredness	• vomiting or diarrhea
• fever	• rash
• joint or muscle aches	• night sweats
• headache	• enlarged lymph nodes in the neck or groin
• sore throat	

While you are taking Emtricitabine and tenofovir disoproxil fumarate tablets to reduce your risk of getting HIV-1:

- **Just taking emtricitabine and tenofovir disoproxil fumarate tablets may not keep you from getting HIV-1.**
- **You must continue using safer sex practices** while you are taking emtricitabine and tenofovir disoproxil fumarate tablets to reduce your risk of getting HIV-1.
- **You must stay HIV-negative to keep taking emtricitabine and tenofovir disoproxil fumarate tablets to reduce your risk of infection.**
  - Know your HIV-1 status and the HIV-1 status of your partners.
  - Get tested for HIV-1 at least every 3 months or when your healthcare provider tells you.
  - Get tested for other sexually transmitted infections such as syphilis and gonorrhea. These infections make it easier for HIV-1 to infect you.
  - If you think you were exposed to HIV-1, tell your healthcare provider right away. They may want to do more tests to be sure you are still HIV-negative.
  - Get information and support to help reduce risky sexual behavior.
  - Have fewer sex partners.
  - Do not miss any doses of emtricitabine and tenofovir disoproxil fumarate tablets. Missing doses may increase your risk of getting HIV-1 infection.
- If you do become HIV-positive, you need more medicine than emtricitabine and tenofovir disoproxil fumarate tablets alone to treat HIV-1. Emtricitabine and tenofovir disoproxil fumarate tablets by itself is not a complete treatment for HIV-1.
  - If you have HIV-1 and take only emtricitabine and tenofovir disoproxil fumarate tablets, over time your HIV-1 may become harder to treat.

See the section **"What should I avoid while taking emtricitabine and tenofovir disoproxil fumarate tablets?"** and talk to your healthcare provider for more information about how to prevent HIV-1 infection.

What are emtricitabine and tenofovir disoproxil fumarate tablets?

Emtricitabine and Tenofovir disoproxil fumarate Tablets contains the prescription medicines emtricitabine and tenofovir disoproxil fumarate. Emtricitabine and Tenofovir disoproxil fumarate Tablets are used:

- **to treat HIV-1 infection** when used with other HIV-1 medicines in adults and children who weigh at least 37 pounds (at least 17 kg).
- **to help reduce the risk of getting HIV-1 infection** when used with safer sex practices in:
  - HIV-negative men who have sex with men, who are at high risk of getting infected with HIV-1 through sex.
  - Male-female sex partners when one partner has HIV-1 infection and the other does not.

Use of emtricitabine and tenofovir disoproxil fumarate tablets to treat HIV-1 infection:

- When used with other HIV-1 medicines to treat HIV-1 infection, emtricitabine and tenofovir disoproxil fumarate tablets may help:
  - Reduce the amount of HIV in your blood. This is called "viral load."
  - Increase the number of CD4+ (T) cells in your blood that help fight off other infections.

Reducing the amount of HIV-1 and increasing the CD4+ (T) cells in your blood may help improve your immune system. This may reduce your risk of death or infections that can happen when your immune system is weak (opportunistic infections).

- **Emtricitabine and Tenofovir disoproxil fumarate tablets does not cure HIV-1 or AIDS.** If you have HIV-1 infection, you must keep taking HIV-1 medicines to control HIV-1 infection and decrease HIV-related illnesses.
- It is not known if emtricitabine and tenofovir disoproxil fumarate tablets are safe and effective in children with HIV-1 infection who weigh less than 37 pounds (less than 17 kg).

Use of emtricitabine and tenofovir disoproxil fumarate tablets to reduce the risk of HIV-1 infection:

- **When used with safer sex practices, emtricitabine and tenofovir disoproxil fumarate tablets may help** to reduce the risk of getting HIV-1 infection:
  - Emtricitabine and Tenofovir disoproxil fumarate Tablets works better to reduce the risk of getting HIV-1 when the medicines are in your bloodstream before you are exposed to HIV-1.

Who should not take emtricitabine and tenofovir disoproxil fumarate tablets?

For people using emtricitabine and tenofovir disoproxil fumarate tablets to reduce the risk of getting HIV-1 infection:

Emtricitabine and tenofovir disoproxil fumarate tablets can only help reduce your risk of getting HIV-1 before you are infected. **Do not take emtricitabine and tenofovir disoproxil fumarate tablets to help reduce your risk of getting HIV-1 if**:

- you already have HIV-1 infection. If you are HIV-positive, you need to take other medicines with emtricitabine and tenofovir disoproxil fumarate tablets to treat HIV-1.
- you do not know your HIV-1 infection status. You may already be HIV-positive. You need to take other HIV-1 medicines with emtricitabine and tenofovir disoproxil fumarate tablets to treat HIV-1.

What should I tell my healthcare provider before taking emtricitabine and tenofovir disoproxil fumarate tablets?

Tell your healthcare provider if you:

- have liver problems including hepatitis B virus infection
- have kidney problems or receive kidney dialysis treatment
- have bone problems
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if emtricitabine and tenofovir disoproxil fumarate tablets can harm your unborn baby.

If you are a female who is taking emtricitabine and tenofovir disoproxil fumarate tablets to reduce the risk of getting HIV-1 infection and you become pregnant while taking emtricitabine and tenofovir disoproxil fumarate tablets, talk to your healthcare provider to decide if you should keep taking emtricitabine and tenofovir disoproxil fumarate tablets.

Pregnancy Registry: A pregnancy registry collects information about your health and the health of your baby. There is a pregnancy registry for women who take medicines to treat or prevent HIV-1 during pregnancy. For more information about the registry and how it works, talk to your healthcare provider.

- are breastfeeding or plan to breastfeed.
  - You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.
  - Do not breastfeed if you take emtricitabine and tenofovir disoproxil fumarate tablets. Emtricitabine and Tenofovir disoproxil fumarate Tablets can pass to your baby in your breast milk.
  - Talk with your healthcare provider about the best way to feed your baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Do not take emtricitabine and tenofovir disoproxil fumarate tablets if you also take any of the medicines listed below:

- medicines which also contain emtricitabine or tenofovir disoproxil fumarate (ATRIPLA®, COMPLERA®, emtricitabine, GENVOYA®, ODEFSEY®, STRIBILD®, or tenofovir disoproxil fumarate). These medicines contain one or more of the same active ingredients as emtricitabine and tenofovir disoproxil fumarate tablets.
- medicines which contain tenofovir alafenamide (GENVOYA® or ODEFSEY®)
- medicines which contain lamivudine (Combivir, Dutrebis, Epivir or Epivir-HBV, Epzicom, Triumeq, or Trizivir)
- adefovir (HEPSERA®)

Emtricitabine and tenofovir disoproxil fumarate tablets may interact with other medicines. Especially tell your healthcare provider if you take:

- didanosine (Videx EC)
- atazanavir (Reyataz)
- ledipasvir with sofosbuvir (HARVONI®)
- darunavir (Prezista)
- lopinavir with ritonavir (Kaletra)

Your healthcare provider may need to check you more often or change your dose if you take any of these medicines and emtricitabine and tenofovir disoproxil fumarate tablets.

Know the medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get a new medicine.

How should I take emtricitabine and tenofovir disoproxil fumarate tablets?

- Take emtricitabine and tenofovir disoproxil fumarate tablets exactly as prescribed.
- Take emtricitabine and tenofovir disoproxil fumarate tablets by mouth, with or without food.
- Children who take emtricitabine and tenofovir disoproxil fumarate tablets are prescribed a lower strength tablet than adults.
  - **Children should swallow the tablet whole.** Tell your healthcare provider if your child cannot swallow the tablet whole, because they may need a different HIV-1 medicine.
  - Your healthcare provider will change the dose of emtricitabine and tenofovir disoproxil fumarate tablets as needed based on your child's weight.
- Emtricitabine and tenofovir disoproxil fumarate tablets are usually taken 1 time each day. Take emtricitabine and tenofovir disoproxil fumarate tablets at the same time each day to keep emtricitabine and tenofovir disoproxil fumarate tablets blood levels constant.
  - If you have any kidney problems, your healthcare provider may tell you to take emtricitabine and tenofovir disoproxil fumarate tablets less often.
- Do not miss any doses of emtricitabine and tenofovir disoproxil fumarate tablets. Missing a dose lowers the amount of medicine in your blood.
- If you miss a dose of emtricitabine and tenofovir disoproxil fumarate tablets, take it as soon as you remember that day. Do not take more than 1 dose of emtricitabine and tenofovir disoproxil fumarate tablets in a day. Do not take 2 doses at the same time to make up for a missed dose. Call your healthcare provider or pharmacist if you are not sure what to do.
- Do not change your dose or stop taking emtricitabine and tenofovir disoproxil fumarate tablets without first talking with your healthcare provider. Stay under a healthcare provider's care when taking emtricitabine and tenofovir disoproxil fumarate tablets.
- Refill your emtricitabine and tenofovir disoproxil fumarate tablets prescription before you run out of medicine.
- If you take too much emtricitabine and tenofovir disoproxil fumarate tablets, call your healthcare provider or go to the nearest hospital emergency room right away.
- If you take emtricitabine and tenofovir disoproxil fumarate tablets to treat HIV-1 infection, you need to take other HIV-1 medicines. Your healthcare provider will tell you what medicines to take and how to take them.
- If you take emtricitabine and tenofovir disoproxil fumarate tablets to reduce your risk of getting HIV-1:
- you must also use other methods to reduce your risk of getting HIV-1. See the section "**What should I avoid while taking emtricitabine and tenofovir disoproxil fumarate tablets?"** in this Medication Guide.
- **Take emtricitabine and tenofovir disoproxil fumarate tablets every day,** not just when you think you have been exposed to HIV-1.

What should I avoid while taking emtricitabine and tenofovir disoproxil fumarate tablets?

While taking emtricitabine and tenofovir disoproxil fumarate tablets, avoid doing things that increase your risk of getting HIV-1 or spreading HIV-1 to other people.

- See the section "**What is the most important information I should know about emtricitabine and tenofovir disoproxil fumarate tablets?"** at the beginning of this Medication Guide.
- Do not have any kind of sex without protection. Always practice safer sex by using a latex or polyurethane condom, tolower the chance of sexual contact with semen,veginal fluids, or blood.
- Do not share personal items that can have blood or body fluids on them, such as toothbrushes and razor blades.
- Do not share or re-use needles or other injection equipment. Ask your healthcare provider if you have any questions about how to prevent getting HIV-1 or spreading HIV-1 to other people.

What are the possible side effects of emtricitabine and tenofovir disoproxil fumarate tablets?

Emtricitabine and Tenofovir disoproxil fumarate Tablets may cause serious side effects, including:

- **See "What is the most important information I should know about emtricitabine and tenofovir disoproxil fumarate tablets?"**
- **New or worse kidney problems, including kidney failure.** If you had kidney problems in the past or take another medicine that can cause kidney problems, your healthcare provider may do blood tests to check your kidneys before you start and while you are taking emtricitabine and tenofovir disoproxil fumarate tablets. Your healthcare provider may tell you to take emtricitabine and tenofovir disoproxil fumarate tablets less often, or to stop taking emtricitabine and tenofovir disoproxil fumarate tablets if you have kidney problems.
- **Bone problems** can happen in some people who take emtricitabine and tenofovir disoproxil fumarate tablets. Bone problems include bone pain, or softening or thinning of bones, which may lead to fractures. Your healthcare provider may need to do tests to check your bones.
- **Changes in body fat can happen in people who take HIV-1 medicines.** The exact cause and long-term health effects of these problems are not known. The changes may include:
  - increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the middle of your body (trunk)
  - loss of fat from the legs, arms, and face
- **Changes in your immune system (Immune Reconstitution Syndrome) can happen when an HIV-1-infected person starts taking HIV-1 medicines.** Your immune system may get stronger, and can then cause you to develop inflammation in areas of your body where infections may have been hiding for a long time. This inflammation may cause you to have minor symptoms, such as fever, but inflammation can also lead to serious problems. Tell your healthcare provider right away if you start having any new symptoms after starting emtricitabine and tenofovir disoproxil fumarate tablets for treatment of HIV-1 infection.

The most common side effects of emtricitabine and tenofovir disoproxil fumarate tablets in people with HIV-1 infection include:

The most common side effects of emtricitabine and tenofovir disoproxil fumarate tablets in people taking emtricitabine and tenofovir disoproxil fumarate tablets to treat HIV-1 infection include:

• diarrhea	• dizziness
• nausea	• depression
• tiredness	• problems sleeping
• headache	• abnormal dreams
	• rash

Common side effects in people who take emtricitabine and tenofovir disoproxil fumarate tablets to reduce the risk of getting HIV-1 infection include:

- stomach-area (abdomen) pain
- headache
- decreased weight

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of emtricitabine and tenofovir disoproxil fumarate tablets. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects.

How should I store emtricitabine and tenofovir disoproxil fumarate tablets?

- Store below 30°C and protect from moisture.
- Keep emtricitabine and tenofovir disoproxil fumarate tablets in its original container and keep the container tightly closed.
- Do not use emtricitabine and tenofovir disoproxil fumarate tablets if seal over bottle opening is broken or missing.

Keep emtricitabine and tenofovir disoproxil fumarate tablets and all other medicines out of reach of children.

General information about emtricitabine and tenofovir disoproxil fumarate tablets.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use emtricitabine and tenofovir disoproxil fumarate tablets for a condition for which it was not prescribed. Do not give emtricitabine and tenofovir disoproxil fumarate tablets to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about emtricitabine and tenofovir disoproxil fumarate tablets. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about emtricitabine and tenofovir disoproxil fumarate tablets that is written for health professionals.

What are the ingredients in emtricitabine and tenofovir disoproxil fumarate tablets?

Active Ingredients: emtricitabine and tenofovir disoproxil fumarate

Inactive Ingredients: pregelatinized starch, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium and magnesium stearate. The tablets are coated with Opadry II Blue containing lactose monohydrate, titanium dioxide, triacetin, hypromellose and FD&C Blue # 2 Aluminum Lake.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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