

EMTRICITABINE AND TENOFOVIR DISOPROXIL FUMARATE- emtricitabine and tenofovir disoproxil fumarate tablet, film coated
RedPharm Drug, Inc.

EMTRICITABINE and TENOFOVIR DISOPROXIL FUMARATE tablets

BOXED WARNING

WARNING: POSTTREATMENT ACUTE EXACERBATION OF HEPATITIS B and RISK OF DRUG RESISTANCE WITH USE OF EMTRICITABINE AND TENOFOVIR DISOPROXIL FUMARATE TABLETS FOR HIV-1 PRE-EXPOSURE PROPHYLAXIS (PrEP) IN UNDIAGNOSED EARLY HIV-1 INFECTION

Severe acute exacerbations of hepatitis B (HBV) have been reported in HBV-infected individuals who have discontinued emtricitabine and tenofovir disoproxil fumarate tablets. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in individuals who are infected with HBV and discontinue emtricitabine and tenofovir disoproxil fumarate tablets. If appropriate, anti-hepatitis B therapy may be warranted [see Warnings and Precautions (5.1)].

Emtricitabine and tenofovir disoproxil fumarate tablets used for HIV-1 PrEP must only be prescribed to individuals confirmed to be HIV-negative immediately prior to initiating and 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 HIV-1 PrEP following undetected acute HIV-1 infection. Do not initiate emtricitabine and tenofovir disoproxil fumarate tablets for HIV-1 PrEP if signs or symptoms of acute HIV-1 infection are present unless negative infection status is confirmed [see Warnings and Precautions (5.2)].

1 INDICATIONS AND USAGE

1.1 Treatment of HIV-1 Infection

Emtricitabine and tenofovir disoproxil fumarate tablets are 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 *Clinical Studies* (14)] .

1.2 HIV-1 Pre-Exposure Prophylaxis (PrEP)

Emtricitabine and tenofovir disoproxil fumarate tablets are indicated in at-risk adults and adolescents weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection. Individuals must have a negative HIV-1 test immediately prior to initiating emtricitabine and tenofovir disoproxil fumarate tablets for HIV-1 PrEP [see Dosage and Administration (2.2), Warnings and Precautions (5.2)].

3 DOSAGE FORMS AND STRENGTHS

Emtricitabine and tenofovir disoproxil fumarate is available as tablets. Each film-coated tablet contains 200 mg of emtricitabine and 300 mg of tenofovir DF (which is equivalent to 245 mg of tenofovir disoproxil). The tablets are white to off-white, film-coated, modified capsule-shaped, debossed with "TV" on one side of the tablet and with "C75" on the other side.

4 CONTRAINDICATIONS

Emtricitabine and tenofovir disoproxil fumarate tablets for HIV-1 PrEP is contraindicated in individuals with unknown or positive HIV-1 status [see *Warnings and Precautions* (5.2)] .

5 WARNINGS AND PRECAUTIONS

5.1 Severe Acute Exacerbation of Hepatitis B in Individuals with HBV Infection

All individuals should be tested for the presence of chronic hepatitis B virus (HBV) before or when initiating emtricitabine and tenofovir disoproxil fumarate tablets [see *Dosage and Administration* (2.1)] .

Severe acute exacerbations of hepatitis B (e.g., liver decompensation and liver failure) have been reported in HBV-infected individuals who have discontinued emtricitabine and tenofovir disoproxil fumarate tablets. Individuals infected with HBV who discontinue emtricitabine and tenofovir disoproxil fumarate tablets should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, anti-hepatitis B therapy may be warranted, especially in individuals with advanced liver disease or cirrhosis, since posttreatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure. HBV-uninfected individuals should be offered vaccination.

5.2 Comprehensive Management to Reduce the Risk of Sexually Transmitted Infections, Including HIV-1, and Development of HIV-1 Resistance When Emtricitabine and Tenofovir Disoproxil Fumarate Tablets are Used for HIV-1 PrEP

Use emtricitabine and tenofovir disoproxil fumarate tablets for HIV-1 PrEP to reduce the risk of HIV-1 infection as part of a comprehensive prevention strategy that includes other prevention measures, including adherence to daily administration and safer sex practices, including condoms, to reduce the risk of sexually transmitted infections (STIs). The time from initiation of emtricitabine and tenofovir disoproxil fumarate tablets for HIV-1 PrEP to maximal protection against HIV-1 infection is unknown .

Risk for HIV-1 acquisition includes behavioral, biological, or epidemiologic factors including but not limited to condomless sex, past or current STIs, self-identified HIV risk, having sexual partners of unknown HIV-1 viremic status, or sexual activity in a high prevalence area or network.

Counsel individuals on the use of other prevention measures (e.g., consistent and correct condom use, knowledge of partner(s)' HIV-1 status, including viral suppression status, regular testing for STIs that can facilitate HIV-1 transmission). Inform uninfected individuals about and support their efforts in reducing sexual risk behavior.

Use emtricitabine and tenofovir disoproxil fumarate tablets 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 tablets, because emtricitabine and tenofovir disoproxil fumarate tablets alone does not constitute a complete regimen for HIV-1 treatment [see Microbiology (12.4)]; therefore, care should be taken to minimize the risk of initiating or continuing emtricitabine and tenofovir disoproxil fumarate tablets before confirming the individual is HIV-1 negative.

- Some HIV-1 tests only detect anti-HIV antibodies and may not identify HIV-1 during the acute stage of infection. Prior to initiating emtricitabine and tenofovir disoproxil fumarate tablets for HIV-1 PrEP, ask seronegative individuals about recent (in past month) potential exposure events (e.g., condomless sex or condom breaking during sex with a partner of unknown HIV-1 status or unknown viremic status, or a recent STI), and evaluate for current or recent signs or symptoms consistent with acute HIV-1 infection (e.g., fever, fatigue, myalgia, skin rash). Some HIV-1 tests only detect anti-HIV antibodies and may not identify HIV-1 during the acute stage of infection. Prior to initiating emtricitabine and tenofovir disoproxil fumarate tablets for HIV-1 PrEP, ask seronegative individuals about recent (in past month) potential exposure events (e.g., condomless sex or condom breaking during sex with a partner of unknown HIV-1 status or unknown viremic status, or a recent STI), and evaluate for current or recent signs or symptoms consistent with acute HIV-1 infection (e.g., fever, fatigue, myalgia, skin rash).
- If recent (<1 month) exposures to HIV-1 are suspected or clinical symptoms consistent with acute HIV-1 infection are present, use a test approved or cleared by the FDA as an aid in the diagnosis of acute or primary HIV-1 infection.
If recent (<1 month) exposures to HIV-1 are suspected or clinical symptoms consistent with acute HIV-1 infection are present, use a test approved or cleared by the FDA as an aid in the diagnosis of acute or primary HIV-1 infection.

While using emtricitabine and tenofovir disoproxil fumarate tablets for HIV-1 PrEP, HIV-1 testing should be repeated at least every 3 months, and upon diagnosis of any other STIs.

- If an HIV-1 test indicates possible HIV-1 infection, or if symptoms consistent with acute HIV-1 infection develop following a potential exposure event, convert the HIV-1 PrEP regimen to an HIV treatment regimen until negative infection status is confirmed using a test approved or cleared by the FDA as an aid in the diagnosis of acute or primary HIV-1 infection. If an HIV-1 test indicates possible HIV-1 infection, or if symptoms consistent with acute HIV-1 infection develop following a potential exposure event, convert the HIV-1 PrEP regimen to an HIV treatment regimen until negative infection status is confirmed using a test approved or cleared by the FDA as an aid in the diagnosis of acute or primary HIV-1 infection.

Counsel HIV-1 uninfected individuals to strictly adhere to the once daily emtricitabine and tenofovir disoproxil fumarate tablets dosing schedule. The effectiveness of emtricitabine and tenofovir disoproxil fumarate tablets in reducing the risk of acquiring HIV-1 is strongly correlated with adherence, as demonstrated by measurable drug levels in clinical trials of emtricitabine and tenofovir disoproxil fumarate tablets for HIV-1 PrEP. Some individuals, such as adolescents, may benefit from more frequent visits and counseling to support adherence [see *Use in Specific Populations (8.4)*, *Microbiology (12.4)*, and *Clinical Studies (14.3 and 14.4)*] .

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 TDF, a component of emtricitabine and tenofovir disoproxil fumarate tablets [see *Adverse Reactions* (6.2)] .

Prior to initiation and during use of emtricitabine and tenofovir disoproxil fumarate tablets, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all individuals. In individuals with chronic kidney disease, also assess serum phosphorus.

Emtricitabine and tenofovir disoproxil fumarate tablets 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* (7.1)]. 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 TDF. 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 individuals at risk of renal dysfunction.

Treatment of HIV-1 Infection

Dosing interval adjustment of emtricitabine and tenofovir disoproxil fumarate tablets and close monitoring of renal function are recommended in all patients with estimated creatinine clearance 30 to 49 mL/min [see *Dosage and Administration* (2.6)]. No safety or efficacy data are available in patients with renal impairment who received emtricitabine and tenofovir disoproxil fumarate tablets using these dosing guidelines, so the potential benefit of emtricitabine and tenofovir disoproxil fumarate tablets therapy should be assessed against the potential risk of renal toxicity. Emtricitabine and tenofovir disoproxil fumarate tablets are not recommended in patients with estimated creatinine clearance below 30 mL/min or patients requiring hemodialysis.

HIV-1 PrEP

Emtricitabine and tenofovir disoproxil fumarate tablets for HIV-1 PrEP are not recommended in uninfected individuals with estimated creatinine clearance less than 60 mL/min. If a decrease in estimated creatinine clearance is observed while using emtricitabine and tenofovir disoproxil fumarate tablets for HIV-1 PrEP, evaluate potential causes and re-assess potential risks and benefits of continued use [see *Dosage and Administration* (2.6)] .

5.4 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 tablets. During the initial phase of combination antiretroviral treatment, HIV-1 infected patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as infection, cytomegalovirus, pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment. Immune reconstitution syndrome has been reported in HIV-1

infected patients treated with combination antiretroviral therapy, including emtricitabine and tenofovir disoproxil fumarate tablets. During the initial phase of combination antiretroviral treatment, HIV-1 infected patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, Guillain-Barré syndrome, and autoimmune hepatitis) 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.

5.5 Bone Loss and Mineralization Defects

Bone Mineral Density

In clinical trials in HIV-1 infected adults and in a clinical trial of HIV-1 uninfected individuals, TDF (a component of emtricitabine and tenofovir disoproxil fumarate tablets) 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 (6.1)*]. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in subjects receiving TDF.

Clinical trials evaluating TDF 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 TDF-treated HIV-1 infected pediatric subjects as compared to the control groups. Similar trends were observed in adolescent subjects aged 12 years to less than 18 years treated for chronic hepatitis B. In all pediatric trials, skeletal growth (height) appeared to be unaffected.

The effects of TDF-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, 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 TDF use [see *Adverse Reactions (6.1)*]. Arthralgia and muscle pain or weakness have also been reported in cases of proximal renal tubulopathy. Hypophosphatemia and osteomalacia secondary to proximal renal tubulopathy should be considered in patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms while receiving TDF-containing products [see *Warnings and Precautions (5.3)*].

5.6 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 FTC and TDF, components of emtricitabine and tenofovir disoproxil fumarate tablets, alone or in combination with other antiretrovirals. Treatment with emtricitabine and tenofovir disoproxil fumarate tablets should be suspended in any 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).

5.7 Risk of Adverse Reactions Due to Drug Interactions

The concomitant use of emtricitabine and tenofovir disoproxil fumarate tablets and other drugs may result in known or potentially significant drug interactions, some of which may lead to possible clinically significant adverse reactions from greater exposures of concomitant drugs [see *Drug Interactions* (7.2)].

See Table 7 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during therapy with emtricitabine and tenofovir disoproxil fumarate tablets; review concomitant medications during therapy with emtricitabine and tenofovir disoproxil fumarate tablets; and monitor for adverse reactions associated with the concomitant drugs.

6 ADVERSE REACTIONS

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

Severe Acute Exacerbations of Hepatitis B in Patients with HBV Infection [see Warnings and Precautions (5.1)].

New Onset or Worsening Renal Impairment [see Warnings and Precautions (5.3)].

Immune Reconstitution Syndrome [see Warnings and Precautions (5.4)].

Bone Loss and Mineralization Defects [see Warnings and Precautions (5.5)].

Lactic Acidosis/Severe Hepatomegaly with Steatosis [see Warnings and Precautions (5.6)].

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals USA, Inc. at 1-888-838-2872 or FDA at

1-800-FDA-1088 or www.fda.gov/medwatch

6.1 Clinical Trials Experience

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.

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

Clinical Trials in Adult Subjects

In Study 934, 511 antiretroviral-naïve subjects received efavirenz (EFV) administered in combination with either FTC+TDF (N = 257) or zidovudine (AZT)/lamivudine (3TC) (N = 254) for 144 weeks. The most common adverse reactions (incidence greater than or equal to 10%, all grades) included diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash. Table 3 provides the treatment-

emergent adverse reactions (Grades 2 to 4) occurring in greater than or equal to 5% of subjects treated in any treatment group.

Skin discoloration, manifested by hyperpigmentation, occurred in 3% of subjects taking FTC+TDF, and was generally mild and asymptomatic. The mechanism and clinical significance are unknown.

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

	FTC+TDF+EFV ^b	AZT/3TC+EFV
	N = 257	N = 254
Fatigue	9%	8%
Depression	9%	7%
Nausea	9%	7%
Diarrhea	9%	5%
Dizziness	8%	7%
Upper respiratory tract infections	8%	5%
Sinusitis	8%	4%
Rash event ^c	7%	9%
Headache	6%	5%
Insomnia	5%	7%
Nasopharyngitis	5%	3%
Vomiting	2%	5%

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 tablets with efavirenz in place of FTC+TDF 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 TDF and/or FTC (Table 4).

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

	FTC+TDF+EFV ^a	AZT/3TC+EFV
	N = 257	N = 254
Any \geq Grade 3 Laboratory Abnormality	30%	26%
Fasting Cholesterol (> 240 mg/dL)	22%	24%

Creatine Kinase (M: > 990 U/L) (F: > 845 U/L)	9%	7%
Serum Amylase (> 175 U/L)	8%	4%
Alkaline Phosphatase (> 550 U/L)	1%	0%
AST (M: > 180 U/L) (F: > 170 U/L)	3%	3%
ALT (M: > 215 U/L) (F: > 170 U/L)	2%	3%
Hemoglobin (< 8.0 mg/dL)	0%	4%
Hyperglycemia (> 250 mg/dL)	2%	1%
Hematuria (> 75 RBC/HPF)	3%	2%
Glycosuria (≥ 3+)	< 1%	1%
Neutrophils (< 750/mm ³)	3%	5%
Fasting Triglycerides (> 750 mg/dL)	4%	2%

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

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 FTC in the larger of two open-label, uncontrolled pediatric trials (N = 116).

Tenofovir Disoproxil Fumarate: In pediatric clinical trials (Studies 352 and 321) conducted in 184 HIV1 infected subjects 2 to less than 18 years of age, the adverse reactions observed in pediatric subjects who received treatment with TDF were consistent with those observed in clinical trials of TDF in adults.

In Study 352 (2 to less than 12 years of age), 89 pediatric subjects received TDF 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 had decreases in total body or spine BMD Z-score [see *Warnings and Precautions* (5.5)]. Total body BMD gain at Week 48 was less in the TDF group compared to the stavudine (d4T) or zidovudine (AZT) treatment groups. The mean rate of BMD gain in lumbar spine was similar between treatment groups. One TDF-treated subject and none of the d4T- or AZT-treated subjects experienced significant (greater than 4%) lumbar spine BMD loss at Week 48. Changes from baseline in BMD Z-scores were –0.012 for lumbar spine and –0.338 for total body in the 64 subjects who were treated with TDF for 96 weeks.

In Study 321 (12 to less than 18 years of age), the mean rate of BMD gain at Week 48 was less in the TDF compared to the placebo treatment group. Six TDF-treated subjects and one placebo-treated subject had significant (greater than 4%) lumbar spine BMD loss at Week 48. Changes from baseline BMD Z-scores were –0.341 for lumbar spine and –0.458 for total body in the 28 subjects who were treated with TDF for 96 weeks.

In both trials, skeletal growth (height) appeared to be unaffected.

Adverse Reactions from Clinical Trial Experience in Uninfected Subjects Taking Emtricitabine and Tenofovir Disoproxil Fumarate Tablets for HIV-1 PrEP

Clinical Trials in Adult Subjects

The safety profile of emtricitabine and tenofovir disoproxil fumarate tablets for HIV-1 PrEP was comparable to that observed in clinical trials of HIV-infected subjects based on two randomized placebo-controlled clinical trials (iPrEx, Partners PrEP) in which 2,830 HIV-1 uninfected adults received emtricitabine and tenofovir disoproxil fumarate tablets once daily for HIV-1 PrEP. Subjects were followed for a median of 71 weeks and 87 weeks, respectively. Table 5 provides a list of selected adverse events that occurred in 2% or more of subjects in any treatment group in the iPrEx trial, with an incidence greater than placebo.

Table 5 Selected Adverse Events (All Grades) Reported in \geq 2% in Any Treatment Group in the iPrEx Trial and Greater than Placebo

	FTC/TDF (N = 1251)	Placebo (N = 1248)
Headache	7%	6%
Abdominal pain	4%	2%
Weight decreased	3%	2%

In the Partners PrEP trial, the frequency of adverse events in the emtricitabine and tenofovir disoproxil fumarate tablets treatment group was generally either less than or the same as in the placebo group.

Laboratory Abnormalities: Table 6 provides a list of Grade 2 to 4 laboratory abnormalities observed in the iPrEx and Partners PrEP trials. Six subjects in the TDF-containing arms of the Partners PrEP trial discontinued from the trial due to an increase in serum creatinine compared with no discontinuations in the placebo group. One subject in the emtricitabine and tenofovir disoproxil fumarate tablets arm of the iPrEx trial discontinued from the trial due to an increase in serum creatinine and another subject discontinued due to low serum phosphorus. Grades 2–3 proteinuria (2-4+) and/or glycosuria (3+) occurred in less than 1% of subjects treated with emtricitabine and tenofovir disoproxil fumarate tablets in the iPrEx trial and Partners PrEP trial.

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

Grade 2 to 4 ^a	iPrEx Trial		Partners PrEP Trial	
	FTC/TDF (N = 1251)	Placebo (N = 1248)	FTC/TDF (N = 1579)	Placebo (N = 1584)

Creatinine (> 1.4 x ULN)	< 1%	< 1%	< 1%	< 1%
Phosphorus (< 2.0 mg/dL)	10%	8%	9%	9%
AST (> 2.6 x ULN)	5%	5%	< 1%	< 1%
ALT (> 2.6 x ULN)	7%	7%	< 1%	< 1%
Hemoglobin (< 9.4 mg/dL)	1%	2%	2%	2%
Neutrophils (< 750/mm ³)	< 1%	< 1%	5%	3%

a. 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 -1.0% across total hip, spine, femoral neck, and trochanter in the emtricitabine and tenofovir disoproxil fumarate tablets group compared with the placebo group, which returned toward baseline after discontinuation of treatment. Thirteen percent of emtricitabine and tenofovir disoproxil fumarate tablets -treated subjects versus 6% of placebo- treated subjects 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 tablets group compared with 1.4% in the placebo group. No correlation between BMD and fractures was noted [see *Clinical Studies (14.3)*]. The Partners PrEP trial found similar fracture rates between the treatment and placebo groups (0.8% and 0.6%, respectively); no BMD evaluations were performed in this trial [see *Clinical Studies (14.4)*].

Clinical Trials in Adolescent Subjects

In a single-arm, open-label clinical trial (ATN113), in which 67 HIV-1 uninfected adolescent (15 to 18 years of age) men who have sex with men received emtricitabine and tenofovir disoproxil fumarate tablets once daily for HIV-1 PrEP, the safety profile of emtricitabine and tenofovir disoproxil fumarate tablets was similar to that observed in adults. Median duration to exposure of emtricitabine and tenofovir disoproxil fumarate tablets was 47 weeks [see *Use in Specific Populations (8.4)*].

In the ATN113 trial, median BMD increased from baseline to Week 48, +2.58% for lumbar spine and

+0.72% for total body. One subject had significant (greater than or equal to 4%) total body BMD loss at Week 24. Median changes from baseline BMD Z-scores were 0.0 for lumbar spine and -0.2 for total body at Week 48. Three subjects showed a worsening (change from > -2 to ≤ -2) from baseline in their lumbar spine or total body BMD Z-scores at Week 24 or 48. Interpretation of these data, however, may be limited by the low rate of adherence to emtricitabine and tenofovir disoproxil fumarate tablets by Week 48.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of TDF. No additional adverse reactions have been identified during postapproval use of FTC. 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

7.1 Drugs Affecting Renal Function

FTC 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 tablets with drugs that are eliminated by active tubular secretion may increase concentrations of FTC, tenofovir, and/or the coadministered drug. Some examples include, but are not limited to, acyclovir, adefovir dipivoxil, cidofovir, ganciclovir, 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 FTC and/or tenofovir.

7.2 Established and Significant Interactions

Table 7 provides a listing of established or clinically significant drug interactions. The drug interactions described are based on studies conducted with either emtricitabine and tenofovir disoproxil fumarate tablets, the components of emtricitabine and tenofovir disoproxil fumarate tablets (FTC and TDF) as individual agents and/or in combination, or are predicted drug interactions that may occur with emtricitabine and tenofovir disoproxil fumarate tablets [see *Clinical Pharmacology (12.3)*].

Table 7 *Established and Significant^a Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Trials*

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment
<p>NRTI: didanosine^c</p>	<p>↑ didanosine</p>	<p>Patients receiving emtricitabine and tenofovir disoproxil fumarate tablets and didanosine should be monitored closely for didanosine-associated adverse reactions. Discontinue didanosine in patients who develop didanosine-associated adverse reactions. Higher didanosine concentrations could potentiate didanosine-associated adverse reactions, including pancreatitis, and neuropathy. Suppression of CD4+ cell counts has been observed in patients receiving TDF with didanosine 400 mg daily. In patients weighing greater than 60 kg, reduce the didanosine dose to 250 mg when it is coadministered with emtricitabine and tenofovir disoproxil fumarate tablets. 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 tablets and Videx EC may be taken under fasted conditions or with a light meal (less than 400 kcal, 20% fat).</p>
		<p>When coadministered with emtricitabine and tenofovir disoproxil fumarate tablets, atazanavir 300 mg</p>

<p>HIV-1 Protease Inhibitors: atazanavir ^c lopinavir/ritonavir ^c atazanavir/ritonavir ^c darunavir/ritonavir ^c</p>	<p>↓ atazanavir ↑ tenofovir</p>	<p>should be given with ritonavir 100 mg. Monitor patients receiving emtricitabine and tenofovir disoproxil fumarate tablets concomitantly with lopinavir/ritonavir, ritonavir-boosted atazanavir, or ritonavir-boosted darunavir for TDF-associated adverse reactions. Discontinue emtricitabine and tenofovir disoproxil fumarate tablets in patients who develop TDF-associated adverse reactions.</p>
<p>Hepatitis C Antiviral Agents: sofosbuvir/velpatasvir ^c sofosbuvir/velpatasvir/voxilaprevir ^c ledipasvir/sofosbuvir ^c</p>	<p>↑ tenofovir</p>	<p>Monitor patients receiving emtricitabine and tenofovir disoproxil fumarate tablets concomitantly with EPCLUSA® (sofosbuvir/velpatasvir) or VOSEVI® (sofosbuvir/velpatasvir/voxilaprevir) for adverse reactions associated with TDF. Monitor patients receiving emtricitabine and tenofovir disoproxil fumarate tablets concomitantly with HARVONI® (ledipasvir/sofosbuvir) without an HIV-1 protease inhibitor/ritonavir or an HIV-1 protease inhibitor/cobicistat combination for adverse reactions associated with TDF. In patients receiving emtricitabine and tenofovir disoproxil fumarate tablets 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 TDF.</p>

a. This table is not all inclusive.

b. ↑ = Increase, ↓ = Decrease

c. Indicates that a drug-drug interaction trial was conducted.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to emtricitabine and tenofovir disoproxil fumarate tablets during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary

Data on the use of emtricitabine and tenofovir disoproxil fumarate tablets during pregnancy from observational studies have shown no increased risk of major birth defects. Available data from the APR show no significant difference in the overall risk of major birth defects with first trimester exposure for emtricitabine (FTC) (2.3%) or tenofovir disoproxil fumarate (TDF) (2.1%) compared with the background rate for major birth defects of 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) (*see Data*).

The rate of miscarriage for individual drugs is not reported in the APR. In the U.S. general population, the estimated background risk of miscarriage in clinically recognized pregnancies is 15 to 20%.

In animal reproduction studies, no adverse developmental effects were observed when the components of emtricitabine and tenofovir disoproxil fumarate tablets were administered separately at doses/exposures ≥ 60 (FTC), ≥ 14 (TDF) and 2.7 (tenofovir) times those of the recommended daily dose of emtricitabine and tenofovir disoproxil fumarate tablets (*see Data*).

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

HIV-1 PrEP: Published studies indicate an increased risk of HIV-1 infection during pregnancy and an increased risk of mother to child transmission during acute HIV-1 infection. In women at risk of acquiring HIV-1, consideration should be given to methods to prevent acquisition of HIV, including continuing or initiating emtricitabine and tenofovir disoproxil fumarate tablets for HIV-1 PrEP, during pregnancy.

Data

Human Data

Emtricitabine and Tenofovir Disoproxil Fumarate Tablets for HIV-1 PrEP: In an observational study based on prospective reports to the APR, 78 HIV-seronegative women exposed to emtricitabine and tenofovir disoproxil fumarate tablets during pregnancy delivered live-born infants with no major malformations. All but one were first trimester exposures, and the median duration of exposure was 10.5 weeks. There were no new safety findings in the women receiving emtricitabine and tenofovir disoproxil fumarate tablets for HIV-1 PrEP compared with HIV-1 infected women treated with other antiretroviral medications.

Emtricitabine: Based on prospective reports to the APR of exposures to FTC-containing regimens during pregnancy resulting in live births (including over 3,300 exposed in the first trimester and over 1,300 exposed in the second/third trimester), the prevalence of major birth defects in live births was 2.6% (95% CI: 2.1% to 3.2%) and 2.3% (95% CI:

1.6% to 3.3%) following first and second/third trimester exposure, respectively, to FTC-containing regimens.

Tenofovir Disoproxil Fumarate: Based on prospective reports to the APR of exposures to TDF-containing regimens during pregnancy resulting in live births (including over 4,000 exposed in the first trimester and over 1,700 exposed in the second/third trimester), the prevalence of major birth defects in live births was 2.4% (95% CI: 2.0% to 2.9%) and 2.4% (95% CI: 1.7% to 3.2%) following first and second/third trimester exposure, respectively, to TDF-containing regimens.

Methodologic limitations of the APR include the use of MACDP as the external comparator group. The MACDP population is not disease-specific, evaluates women and infants from a limited geographic area, and does not include outcomes for births that occurred at < 20 weeks gestation.

Additionally, published observational studies on emtricitabine and tenofovir exposure in pregnancy have not shown an increased risk for major malformations.

Animal Data

Emtricitabine: FTC was administered orally to pregnant mice (at 0, 250, 500, or 1,000 mg/kg/day), and rabbits (at 0, 100, 300, or 1,000 mg/kg/day) through organogenesis (on gestation days 6 through 15, and 7 through 19, respectively). No significant toxicological effects were observed in embryo-fetal toxicity studies performed with FTC in mice at exposures (AUC) approximately 60 times higher and in rabbits at approximately 120 times higher than human exposures at the recommended daily dose. In a pre/postnatal development study in mice, FTC was administered orally at doses up to 1,000 mg/kg/day; no significant adverse effects directly related to drug were observed in the offspring exposed daily from before birth (in utero) through sexual maturity at daily exposures (AUC) of approximately 60 times higher than human exposures at the recommended daily dose.

Tenofovir Disoproxil Fumarate: TDF was administered orally to pregnant rats (at 0, 50, 150, or 450 mg/kg/day) and rabbits (at 0, 30, 100, or 300 mg/kg/day) through organogenesis (on gestation days 7 through 17, and 6 through 18, respectively). No significant toxicological effects were observed in embryo-fetal toxicity studies performed with TDF in rats at doses up to 14 times the human dose based on body surface area comparisons and in rabbits at doses up to 19 times the human dose based on body surface area comparisons. In a pre/postnatal development study in rats, TDF was administered orally through lactation at doses up to 600 mg/kg/day; no adverse effects were observed in the offspring at tenofovir exposures of approximately 2.7 times higher than human exposures at the recommended daily dose of emtricitabine and tenofovir disoproxil fumarate tablets.

8.2 Lactation

Risk Summary

Based on published data, FTC and tenofovir have been shown to be present in human breast milk (*see Data*). It is not known if the components of emtricitabine and tenofovir disoproxil fumarate tablets affect milk production or have effects on the breastfed child.

Treatment of HIV-1 Infection:

The Centers for Disease Control and Prevention recommend that HIV-1 infected

mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1.

Because of the potential for: (1) HIV transmission (in HIV-negative infants); (2) developing viral resistance (in HIV-positive infants); and (3) adverse reactions in a breastfed infant similar to those seen in adults, instruct mothers not to breastfeed if they are taking emtricitabine and tenofovir disoproxil fumarate tablets for the treatment of HIV-1.

HIV-1 PrEP:

In HIV-uninfected women, the developmental and health benefits of breastfeeding and the mother's clinical need for emtricitabine and tenofovir disoproxil fumarate tablets for HIV-1 PrEP should be considered along with any potential adverse effects on the breastfed child from emtricitabine and tenofovir disoproxil fumarate tablets and the risk of HIV-1 acquisition due to nonadherence and subsequent mother to child transmission.

Women should not breastfeed if acute HIV-1 infection is suspected because of the risk of HIV-1 transmission to the infant.

Data

HIV-1 PrEP: In a study of 50 breastfeeding women who received emtricitabine and tenofovir disoproxil fumarate tablets for HIV-1 PrEP between 1 and 24 weeks postpartum (median 13 weeks), after 7 days of treatment, tenofovir was undetectable but FTC was detectable in the plasma of most infants. In these infants, the average FTC plasma concentration was less than 1% of the FTC C_{max} observed in HIV-infected infants (up to 3 months of age) receiving the therapeutic dose of FTC (3 mg/kg/day). There were no serious adverse events.

Two infants (4%) had an adverse event of mild diarrhea which resolved.

8.4 Pediatric Use

Treatment of HIV-1 Infection

No pediatric clinical trial was conducted to evaluate the safety and efficacy of emtricitabine and tenofovir disoproxil fumarate tablets in patients with HIV-1 infection. Data from previously conducted trials with the individual drug products, FTC and TDF, were relied upon to support dosage recommendations for emtricitabine and tenofovir disoproxil fumarate tablets. For additional information, consult the prescribing information for EMTRIVA and VIREAD.

Emtricitabine and tenofovir disoproxil fumarate tablets 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 tablet. Because it is a fixed-dose combination tablet, emtricitabine and tenofovir disoproxil fumarate tablets 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 tablets are not approved for use in pediatric patients weighing less than 17 kg.

HIV-1 PrEP

The safety and effectiveness of emtricitabine and tenofovir disoproxil fumarate tablets for HIV-1 PrEP in at-risk adolescents weighing at least 35 kg is supported by data from adequate and well-controlled studies of emtricitabine and tenofovir disoproxil fumarate tablets for HIV-1 PrEP in adults with additional data from safety and pharmacokinetic

studies in previously conducted trials with the individual drug products, FTC and TDF, in HIV-1 infected adults and pediatric subjects [see *Dosage and Administration (2.5)*, *Adverse Reactions (6.1)*, *Clinical Pharmacology (12.3 and 12.4)*, and *Clinical Studies (14.3 and 14.4)*].

Safety, adherence, and resistance were evaluated in a single-arm, open-label clinical trial (ATN113) in which 67 HIV-1 uninfected at-risk adolescent men who have sex with men received emtricitabine and tenofovir disoproxil fumarate tablets once daily for HIV-1 PrEP. The mean age of subjects was 17 years (range 15 to 18 years); 46% were Hispanic, 52% Black, and 37% White. The safety profile of emtricitabine and tenofovir disoproxil fumarate tablets in ATN113 was similar to that observed in the adult HIV-1 PrEP trials [see *Adverse Reactions (6.1)*].

In the ATN113 trial, HIV-1 seroconversion occurred in 3 subjects. Tenofovir diphosphate levels in dried blood spot assays indicate that these subjects had poor adherence. No tenofovir- or FTC- associated HIV-1 resistance substitutions were detected in virus isolated from the 3 subjects who seroconverted [see *Microbiology (12.4)*].

Adherence to study drug, as demonstrated by tenofovir diphosphate levels in dried blood spot assays, declined markedly after Week 12 once subjects switched from monthly to quarterly visits, suggesting that adolescents may benefit from more frequent visits and counseling [see *Warnings and Precautions (5.2)*].

Safety and effectiveness of emtricitabine and tenofovir disoproxil fumarate tablets for HIV-1 PrEP in pediatric patients weighing less than 35 kg have not been established.

8.5 Geriatric Use

Clinical trials of FTC, TDF, or emtricitabine and tenofovir disoproxil fumarate tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

8.6 Renal Impairment

Treatment of HIV-1 Infection

The dosing interval for emtricitabine and tenofovir disoproxil fumarate tablets should be modified in HIV-infected adult individuals with estimated creatinine clearance of 30 to 49 mL/min. Emtricitabine and tenofovir disoproxil fumarate tablets are not recommended in individuals with estimated creatinine clearance below 30 mL/min and in individuals with end-stage renal disease requiring dialysis [see *Dosage and Administration (2.6)*].

HIV-1 PrEP

Emtricitabine and tenofovir disoproxil fumarate tablets for HIV-1 PrEP are not recommended 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 tablets for HIV-1 PrEP, evaluate potential causes and reassess potential risks and benefits of continued use [see *Dosage and Administration (2.6)*].

10 OVERDOSAGE

If overdose occurs, the patient must be monitored for evidence of toxicity, and

standard supportive treatment applied as necessary.

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

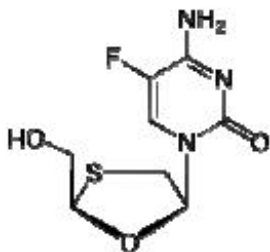
Tenofovir Disoproxil Fumarate: Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of TDF, a four-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

11 DESCRIPTION

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

Emtricitabine: The chemical name of FTC is 5-fluoro-1-(2*R*,5*S*)-[2-(hydroxymethyl)-1,3-oxathiolan-5yl]cytosine. FTC 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.

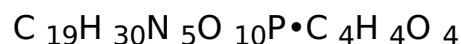
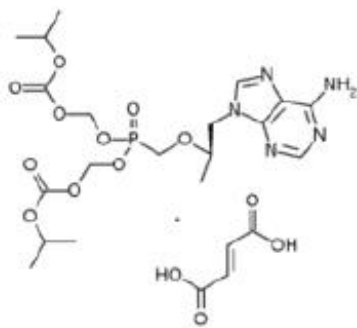
It has the following structural formula:



M.W. 247.25

FTC 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: TDF is a fumaric acid salt of the bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir. The chemical name of tenofovir DF is 9-[(*R*)-2[[bis[[[(isopropoxycarbonyl)oxy]-methoxy]phosphinyl]methoxy]propyl]adenine fumarate. It has the following structural formula:



M.W. 635.52

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 TDF 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 DF (which is equivalent to 245 mg of tenofovir disoproxil), as active ingredients. The tablets also include the following inactive ingredients: crospovidone, lactose monohydrate, magnesium stearate, mannitol, polyethylene glycol, polyvinyl alcohol, povidone, talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Emtricitabine and tenofovir disoproxil fumarate tablets are a fixed-dose combination of antiviral drugs FTC and TDF [see *Microbiology* (12.4)].

12.3 Pharmacokinetics

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

Emtricitabine: The pharmacokinetic properties of FTC are summarized in Table 8. Following oral administration of FTC, FTC is rapidly absorbed with peak plasma concentrations occurring at 1 to 2 hours postdose. Less than 4% of FTC 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 FTC, approximately 86% is recovered in the urine and 13% is recovered as metabolites. The metabolites of FTC 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 FTC, the plasma FTC half-life is approximately 10 hours.

Tenofovir Disoproxil Fumarate: The pharmacokinetic properties of TDF are summarized

in Table 8. Following oral administration of TDF, maximum tenofovir serum concentrations are achieved in 1.0 ± 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 TDF, the terminal elimination half-life of tenofovir is approximately 17 hours.

Table 8 Single Dose Pharmacokinetic Parameters for FTC and Tenofovir in Adults ^a

	FTC	Tenofovir
Fasted Oral Bioavailability ^b (%)	92 (83.1 to 106.4)	25 (NC to 45.0)
Plasma Terminal Elimination Half-Life ^b (hr)	10 (7.4 to 18.0)	17 (12.0 to 25.7)
C _{max} ^c (mcg/mL)	1.8 ± 0.72 ^d	0.30 ± 0.09
AUC ^c (mcg ·hr/mL)	10.0 ± 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 tablets may be administered with or without food. Administration of emtricitabine and tenofovir disoproxil fumarate tablets 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, TDF (tenofovir) was taken under fed conditions. FTC systemic exposures (AUC and C_{max}) were unaffected when emtricitabine and tenofovir disoproxil fumarate tablets were administered with either a high fat or a light meal.

Specific Populations

Race

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

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 TDF.

Gender

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

Pediatric Patients

Treatment of HIV-1 Infection: The pharmacokinetic data for tenofovir and FTC following administration of emtricitabine and tenofovir disoproxil fumarate tablets in pediatric subjects weighing 17 kg and above are not available. The dosage recommendations of emtricitabine and tenofovir disoproxil fumarate tablets in this population are based on the dosage recommendations of FTC and TDF in this population. Refer to the EMTRIVA and VIREAD prescribing information for pharmacokinetic information on the individual products in pediatric patients.

HIV-1 PrEP: The pharmacokinetic data for tenofovir and FTC following administration of emtricitabine and tenofovir disoproxil fumarate tablets in HIV-1 uninfected adolescents weighing 35 kg and above are not available. The dosage recommendations of emtricitabine and tenofovir disoproxil fumarate tablets for HIV-1 PrEP in this population are based on safety and adherence data from the ATN113 trial [see *Use in Specific Populations* (8.4)] and known pharmacokinetic information in HIV-infected adolescents taking TDF and FTC for treatment.

Geriatric Patients

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

Patients with Renal Impairment

The pharmacokinetics of FTC 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 $AUC_{0-\infty}$ of FTC and tenofovir were increased. No data are available to make dosage recommendations in pediatric patients with renal impairment.

Patients with Hepatic Impairment

The pharmacokinetics of tenofovir following a 300 mg dose of TDF 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 tablets or FTC have not been studied in subjects with hepatic impairment; however, FTC 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 FTC and tenofovir were unaffected when FTC and TDF 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 FTC and tenofovir with other

medicinal products is low.

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

No clinically significant drug interactions have been observed between FTC and famciclovir, indinavir, stavudine, TDF, and zidovudine (Tables 9 and 10). Similarly, no clinically significant drug interactions have been observed between TDF and efavirenz, methadone, nelfinavir, oral contraceptives, ribavirin, or sofosbuvir in trials conducted in healthy volunteers (Tables 11 and 12).

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

Coadministered Drug	Dose of Coadministered Drug (mg)	FTC Dose (mg)	N	% Change of FTC Pharmacokinetic Parameters ^b (90% CI)		
				C _{max}	AUC	C _{min}
TDF	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; ↔ = No Effect; NA = Not Applicable

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

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

		days				
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; ↔ = No Effect; NA = Not Applicable

Table 11 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)
Ledipasvir/ Sofosbuvir ^j	90/400 once daily x 10 days	29	↑ 61 (↑ 51 to ↑ 72)	↑ 65 (↑ 59 to ↑ 71)	↑ 115 (↑ 105 to ↑ 126)
Lopinavir/ Ritonavir	400/100 twice daily x 14 days	24	↔	↑ 32 (↑ 25 to ↑ 38)	↑ 51 (↑ 37 to ↑ 66)
	1000/100 twice				↑ 23

Saquinavir/ Ritonavir	1000/100 twice daily x 14 days	35	↔	↔	(↑ 16 to ↑ 30)
Sofosbuvir ^k	400 single dose	16	↑ 25 (↑ 8 to ↑ 45)	↔	↔
Sofosbuvir/ Velpatasvir ^l	400/100 once daily	24	↑ 44 (↑ 33 to ↑ 55)	↑ 40 (↑ 34 to ↑ 46)	↑ 84 (↑ 76 to ↑ 92)
Sofosbuvir/ Velpatasvir ^m	400/100 once daily	30	↑ 46 (↑ 39 to ↑ 54)	↑ 40 (↑ 34 to ↑ 45)	↑ 70 (↑ 61 to ↑ 79)
Sofosbuvir/ Velpatasvir/ Voxilaprevir ⁿ	400/100/100 + Voxilaprevir ^o 100 once daily	29	↑ 48 (↑ 36 to ↑ 61)	↑ 39 (↑ 32 to ↑ 46)	↑ 47 (↑ 38 to ↑ 56)
Tacrolimus	0.05 mg/kg twice daily x 7 days	21	↑ 13 (↑ 1 to ↑ 27)	↔	↔
Tipranavir/ Ritonavir ^p	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 VIREAD 300 mg once daily.

b. Increase = ↑; Decrease = ↓; No Effect = ↔

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 + FTC/TDF.

g. Comparison based on exposures when administered as darunavir/ritonavir + FTC/TDF.

h. Study conducted with ATRIPLA (efavirenz/FTC/TDF) coadministered with HARVONI.

i. Study conducted with COMPLERA (FTC/rilpivirine/TDF) coadministered with HARVONI.

j. Study conducted with emtricitabine and tenofovir disoproxil fumarate tablets (FTC/TDF) + dolutegravir coadministered with HARVONI.

k. Study conducted with ATRIPLA coadministered with SOVALDI [®] (sofosbuvir).

l. Study conducted with COMPLERA coadministered with EPCLUSA; coadministration with EPCLUSA also results in comparable increases in tenofovir exposures when TDF is administered as ATRIPLA, STRIBILD, emtricitabine and tenofovir disoproxil fumarate tablets + atazanavir/ritonavir, or emtricitabine and tenofovir disoproxil fumarate tablets + darunavir/ritonavir.

m. Administered as raltegravir + FTC/TDF.

n. Comparison based on exposures when administered as darunavir + ritonavir + FTC/TDF.

o. Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients

p. Aptivus Prescribing Information.

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

Table 12 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 once daily	12	↑ 16 (↓ 6 to ↑ 42)	↑ 21 (↓ 5 to ↑ 54)	↑ 24 (↓ 10 to ↑ 69)
Didanosine ^e	250 once, simultaneously with TDF 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 ↑ 7)	↔	↔

			12)		
Entecavir	1 once daily x 10 days	28	↔	↑ 13 (↑ 11 to ↑ 15)	↔
Lamivudine	150 twice daily x 7 days	15	↓ 24 (↓ 34 to ↓ 12)	↔	↔
Lopinavir Ritonavir	Lopinavir/Ritonavir 400/100 twice daily x 14 days	24	↔ ↔	↔ ↔	↔ ↔
Saquinavir Ritonavir	Saquinavir/Ritonavir 1000/100 twice daily x 14 days	32	↑ 22 (↑ 6 to ↑ 41) ↔	↑ 29 ^h (↑ 12 to ↑ 48) ↔	↑ 47 ^h (↑ 23 to ↑ 76) ↑ 23 (↑ 3 to ↑ 46)
Tacrolimus	0.05 mg/kg twice daily x 7 days	21	↔	↔	↔
Tipranavir ⁱ	Tipranavir/Ritonavir 500/100 twice daily	22	↓ 17 (↓ 26 to ↓ 6)	↓ 18 (↓ 25 to ↓ 9)	↓ 21 (↓ 30 to ↓ 10)
	Tipranavir/Ritonavir 750/200 twice daily (23 doses)	20	↓ 11 (↓ 16 to ↓ 4)	↓ 9 (↓ 15 to ↓ 3)	↓ 12 (↓ 22 to 0)

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

b. Reyataz Prescribing Information.

c. In HIV-infected subjects, addition of TDF 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. When didanosine 250 mg enteric-coated capsules were administered with TDF, systemic exposures of didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions.

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 TDF and ritonavir-boosted saquinavir are coadministered.

i. Aptivus Prescribing Information.

12.4 Microbiology

Mechanism of Action

Emtricitabine: FTC, a synthetic nucleoside analog of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate (FTC-TP), which 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. FTC-TP is a weak inhibitor of mammalian DNA polymerases α , β , ϵ and mitochondrial DNA polymerase γ .

Tenofovir Disoproxil Fumarate: TDF is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. TDF requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate (TFV-DP), which 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. TFV-DP 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 FTC and tenofovir together.

Emtricitabine: The antiviral activity of FTC 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 (EC₅₀) values for FTC were in the range of 0.0013 to 0.64 μ M (0.0003 to 0.158 mcg/mL). In drug combination studies of FTC with nucleoside RT inhibitors (abacavir, lamivudine, stavudine, zidovudine), non-nucleoside RT 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 (EC₅₀ values ranged from 0.007 to 0.075 μ M) and showed strain-specific activity against HIV-2 (EC₅₀ values ranged from 0.007 to 1.5 μ M).

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 EC₅₀ values for tenofovir were in the range of 0.04 to 8.5 μ M. In drug combination studies of tenofovir with nucleoside RT inhibitors (abacavir, didanosine, lamivudine, stavudine, zidovudine), non-nucleoside RT 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 (EC₅₀ values ranged from 0.5 to 2.2 μ M) and showed strain-specific activity against HIV-2 (EC₅₀ values ranged from 1.6 μ M to 5.5 μ M).

Prophylactic Activity in a Nonhuman Primate Model of HIV-1 Transmission

Emtricitabine and Tenofovir Disoproxil Fumarate: The prophylactic activity of the combination of daily oral FTC and 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 FTC 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 the HIV-1 RT has been selected by tenofovir and results in reduced susceptibility to tenofovir.

In Study 934, a clinical trial of treatment-naïve subjects [see *Clinical Studies (14.2)*] , 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 FTC and lamivudine, was observed in 2/19 analyzed subject isolates in the FTC+TDF 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: FTC-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 FTC 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 TDF 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 TDF 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 the iPrEx trial, a clinical trial of HIV-1 seronegative adult subjects [see *Clinical Studies (14.3)*] , no amino acid substitutions associated with resistance to FTC or TDF were detected at the time of seroconversion among 48 subjects in the emtricitabine and tenofovir disoproxil fumarate tablets 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 FTC were observed in 3 of the 10 subjects (2 of 2 in the emtricitabine and tenofovir disoproxil fumarate tablets group and 1 of 8 in the placebo group). One of the two subjects in the emtricitabine and tenofovir disoproxil fumarate tablets 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 the Partners PrEP trial, a clinical trial of HIV-1 seronegative adult subjects [see *Clinical Studies (14.4)*], no variants expressing amino acid substitutions associated with resistance to FTC or TDF were detected at the time of seroconversion among 12 subjects in the emtricitabine and tenofovir disoproxil fumarate tablets group, 15 subjects in the TDF 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 tablets group, 5 in the TDF group, and 6 in the placebo group). One of the three subjects in the emtricitabine and tenofovir disoproxil fumarate tablets 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 TDF 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 TDF group, 1 in the emtricitabine and tenofovir disoproxil fumarate tablets 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 FTC or TDF and may have been present in the infecting virus.

ATN113 Trial: In ATN113, a clinical trial of HIV-1 seronegative adolescent subjects [see *Use in Specific Populations (8.4)*], no amino acid substitutions associated with resistance to FTC or TDF were detected at the time of seroconversion from any of the 3 subjects who became infected with HIV-1 during the trial. All 3 subjects who seroconverted were nonadherent to the recommended emtricitabine and tenofovir disoproxil fumarate tablets dosage.

Cross Resistance

Emtricitabine and Tenofovir Disoproxil Fumarate: Cross-resistance among certain NRTIs has been recognized. The M184V/I and/or K65R substitutions selected in cell culture by the combination of FTC and tenofovir are also observed in some HIV-1 isolates from subjects failing treatment with tenofovir in combination with either FTC 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: FTC-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 FTC. Viruses harboring substitutions conferring reduced susceptibility to stavudine and zidovudine (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E), or didanosine (L74V) remained sensitive to FTC. HIV-1 containing the K103N substitution associated with resistance to NNRTIs was susceptible to FTC.

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 FTC 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 TDF. 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 FTC, 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).

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

FTC 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 TDF 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.

TDF 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, TDF was negative when administered to male mice.

There were no effects on fertility, mating performance, or early embryonic development when TDF 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 7 of gestation. There was, however, an alteration of the estrous cycle in female rats.

13.2 Animal Toxicology and/or Pharmacology

Tenofovir and TDF 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 four 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

14.1 Overview of Clinical Trials

The efficacy and safety of emtricitabine and tenofovir disoproxil fumarate tablets have been evaluated in the studies summarized in Table 13.

Table 13 Trials Conducted with Emtricitabine and Tenofovir Disoproxil Fumarate Tablets for HIV-1 Treatment and HIV-1 PrEP

Trial	Population	Study Arms (N) ^a	Timepoint
Study 934 ^b (NCT00112047)	HIV-infected, treatment-naïve adults	FTC+TDF + efavirenz (257) zidovudine/lamivudine + efavirenz (254)	48 Weeks
iPrEx ^c (NCT00458393)	HIV-seronegative men or transgender women who have sex with men	Emtricitabine and Tenofovir Disoproxil Fumarate Tablets (1,251) Placebo (1,248)	4,237 person-years
Partners PrEP ^c (NCT00557245)	HIV serodiscordant heterosexual couples	Emtricitabine and Tenofovir Disoproxil Fumarate Tablets (1,583) Placebo (1,586)	7,827 person-years

a. Randomized and dosed.

b. Randomized, open label, active-controlled trial.

c. Randomized, double-blind, placebo-controlled trial.

14.2 Clinical Trial Results for Treatment of HIV-1: Study 934

Data through 144 weeks are reported for Study 934, a randomized, open-label, active-controlled multicenter trial comparing FTC+TDF administered in combination with efavirenz (EFV) versus zidovudine (AZT)/lamivudine (3TC) fixed-dose combination administered in combination with EFV in 511 antiretroviral-naïve adult subjects. From Weeks 96 to 144 of the trial, subjects received emtricitabine and tenofovir disoproxil fumarate tablets with EFV in place of FTC+TDF with EFV. 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 1,191) and median baseline plasma HIV-1 RNA was 5.01 log₁₀ copies/mL (range 3.56 to 6.54). Subjects were stratified by baseline CD4+ cell count (< or ≥ 200 cells/mm³); 41% had CD4+ cell counts < 200 cells/mm³ and 51% of subjects had baseline viral loads > 100,000 copies/mL. Treatment outcomes through 48 and 144 weeks for those subjects who did

not have EFV resistance at baseline are presented in Table 14.

Table 14 Virologic Outcomes of Randomized Treatment at Weeks 48 and 144 (Study 934)

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

a. Subjects who were responders at Week 48 or Week 96 (HIV-1 RNA < 400 copies/mL) but did not consent to continue trial after Week 48 or Week 96 were excluded from analysis.

b. Subjects achieved and maintained confirmed HIV-1 RNA < 400 copies/mL through Weeks 48 and 144.

c. Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Weeks 48 and 144.

d. Includes lost to follow-up, subject withdrawal, noncompliance, protocol violation, and other reasons.

Through Week 48, 84% and 73% of subjects in the FTC+TDF group and the AZT/3TC 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 is largely due to the higher number of discontinuations due to adverse events and other reasons in the AZT/3TC group in this open-label trial. In addition, 80% and 70% of subjects in the FTC+TDF group and the AZT/3TC 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 FTC+TDF group and 158 cells/mm³ in the AZT/3TC group at Week 48 (312 and 271 cells/mm³ at Week 144).

Through 48 weeks, 7 subjects in the FTC+TDF group and 5 subjects in the AZT/3TC group experienced a new CDC Class C event (10 and 6 subjects through 144 weeks).

14.3 Clinical Trial Results for HIV-1 PrEP: iPrEx

The iPrEx trial was a randomized, double-blind, placebo-controlled multinational study evaluating emtricitabine and tenofovir disoproxil fumarate tablets in 2,499 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 2,499 enrolled subjects, 1,251 received emtricitabine and tenofovir disoproxil fumarate tablets and 1,248 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 4,237 person-years. The primary outcome measure 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 tablets 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 tablets 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 greatest in subjects with detectable intracellular tenofovir diphosphate concentrations. Efficacy was therefore strongly correlated with adherence.

14.4 Clinical Trial Results for HIV-1 PrEP: Partners PrEP

The Partners PrEP trial was a randomized, double-blind, placebo-controlled 3-arm trial conducted in 4,758 HIV-1 serodiscordant heterosexual couples in Kenya and Uganda to evaluate the efficacy and safety of TDF (N=1,589) and FTC/TDF (N = 1,583) versus (parallel comparison) placebo (N = 1,586) in preventing HIV-1 acquisition by the uninfected partner.

All uninfected partner 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 7,827 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 tablets and placebo, respectively. Two of the 13 seroconversions in the emtricitabine and tenofovir disoproxil fumarate tablets 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 tablets 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 greatest in subjects with detectable plasma tenofovir concentrations. Efficacy was therefore strongly correlated with adherence.

16 HOW SUPPLIED/STORAGE AND HANDLING

Emtricitabine and tenofovir disoproxil fumarate tablets are available as follows:

200 mg of emtricitabine and 300 mg of tenofovir DF (equivalent to 245 mg of tenofovir disoproxil) - white to off-white, film-coated, modified capsule-shaped tablets, debossed with "TV" on one side of the tablet and with "C75" on the other side. Available in unit of use bottles of 30 (containing a desiccant [silica gel canister] and closed with a child-resistant closure), NDC 0093-7704-56.

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

- Keep container tightly closed
- Dispense only in original container

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Important Information for Uninfected Individuals Taking Emtricitabine and Tenofovir Disoproxil Fumarate Tablets for HIV-1 PrEP

Advise HIV-uninfected individuals about the following [see *Warnings and Precautions (5.2)*]:

- The need to confirm that they are HIV-negative before starting to take emtricitabine and tenofovir disoproxil fumarate tablets to reduce the risk of acquiring HIV-1.
- That HIV-1 resistance substitutions may emerge in individuals with undetected HIV-1 infection who are taking emtricitabine and tenofovir disoproxil fumarate tablets, because emtricitabine and tenofovir disoproxil fumarate tablets alone does not constitute a complete regimen for HIV-1 treatment.
- The importance of taking emtricitabine and tenofovir disoproxil fumarate tablets on a regular dosing schedule and strict adherence 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.
- That emtricitabine and tenofovir disoproxil fumarate tablets do not prevent other sexually acquired infections and should only be used as part of a complete prevention strategy including other prevention measures.
- To use condoms consistently and correctly to lower the chances of sexual contact with any body fluids such as semen, vaginal secretions, or blood.
- The importance of knowing their HIV-1 status and the HIV-1 status of their partner(s).
- The importance of virologic suppression in their partner(s) with HIV-1.
- The need to get tested regularly for HIV-1 (at least every 3 months, or more frequently for some individuals such as adolescents) and to ask their partner(s) to get tested as well.
- To report any symptoms of acute HIV-1 infection (flu-like symptoms) to their healthcare provider immediately.

- That the signs and symptoms of acute infection include fever, headache, fatigue, arthralgia, vomiting, myalgia, diarrhea, pharyngitis, rash, night sweats, and adenopathy (cervical and inguinal).
- To get tested for other sexually transmitted infections, such as syphilis, chlamydia, and gonorrhea, that may facilitate HIV-1 transmission.
- To assess their sexual risk behavior and get support to help reduce sexual risk behavior.

Severe Acute Exacerbation of Hepatitis B in Patients Infected with HBV

Inform individuals that severe acute exacerbations of hepatitis B have been reported in patients who are infected with HBV and have discontinued emtricitabine and tenofovir disoproxil fumarate tablets [see *Warnings and Precautions (5.1)*]. Advise HBV-infected individuals to not discontinue emtricitabine and tenofovir disoproxil fumarate tablets without first informing their healthcare provider.

New Onset or Worsening Renal Impairment

Inform HIV-1 infected patients and uninfected individuals that renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported in association with the use of TDF, a component of emtricitabine and tenofovir disoproxil fumarate tablets. Advise patients to avoid emtricitabine and tenofovir disoproxil fumarate tablets with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple NSAIDs) [see *Warnings and Precautions (5.3)*]. The dosing interval of emtricitabine and tenofovir disoproxil fumarate tablets may need adjustment in HIV-1 infected patients with renal impairment. Emtricitabine and tenofovir disoproxil fumarate tablets for HIV-1 PrEP 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 tablets for HIV-1 PrEP, evaluate potential causes and re-assess potential risks and benefits of continued use [see *Dosage and Administration (2.6)*].

Immune Reconstitution Syndrome

Inform HIV-1 infected patients that in some patients with advanced HIV infection (AIDS), signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. Advise patients to inform their healthcare provider immediately of any symptoms of infection [see *Warnings and Precautions (5.4)*].

Bone Loss and Mineralization Defects

Inform patients that decreases in bone mineral density have been observed with the use of TDF or emtricitabine and tenofovir disoproxil fumarate tablets. 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)*].

Lactic Acidosis and Severe Hepatomegaly

Inform HIV-1 infected patients and uninfected individuals that lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Treatment with emtricitabine and tenofovir disoproxil fumarate tablets should be suspended in any

person who develops clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity [*see Warnings and Precautions (5.6)*] .

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Drug Interactions

Advise individuals that emtricitabine and tenofovir disoproxil fumarate tablets may interact with many drugs; therefore, advise individuals to report to their healthcare provider the use of any other medication, including other HIV drugs and drugs for treatment of hepatitis C virus [*see Warnings and Precautions (5.7) and Drug Interactions (7)*].

Dosage Recommendations for Treatment of HIV-1 Infection

Inform HIV-1 infected patients that it is important to take emtricitabine and tenofovir disoproxil fumarate tablets with other antiretroviral drugs for the treatment of HIV-1 on a regular dosing schedule with or without food and to avoid missing doses as it can result in development of resistance.

Pregnancy Registry

Inform individuals using emtricitabine and tenofovir disoproxil fumarate tablets for HIV-1 treatment or HIV-1 PrEP that there is an antiretroviral pregnancy registry to monitor fetal outcomes of pregnant women exposed to emtricitabine and tenofovir disoproxil fumarate tablets [*see Use in Specific Populations (8.1)*].

Lactation

Instruct mothers not to breastfeed if they are taking emtricitabine and tenofovir disoproxil fumarate tablets for the treatment of HIV-1 infection or if acute HIV-1 infection is suspected in a mother taking emtricitabine and tenofovir disoproxil fumarate tablets for HIV-1 PrEP because of the risk of passing the HIV-1 virus to the baby. In HIV-uninfected women, the benefits and risks of emtricitabine and tenofovir disoproxil fumarate tablets while breastfeeding should be evaluated, including the risk of HIV-1 acquisition due to medication nonadherence and subsequent mother to child transmission [*see Use in Specific Populations (8.2)*].

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Manufactured In Croatia By:

Pliva Hrvatska d.o.o.

Zagreb, Croatia

Manufactured For:

Teva Pharmaceuticals USA, Inc.

Parsippany, NJ 07054

Rev. C 8/2020

Package/Label Display Panel

NDC 0093-7607-56

Emtricitabine and
Tenofovir

Disoproxil Fumarate
Tablets
200 mg/300 mg*

PHARMACIST: Dispense the accompanying
Medication Guide to each patient.

Rx only

30 TABLETS

TEVA

NDC 0093-7607-56

**Emtricitabine and
Tenofovir
Disoproxil Fumarate
Tablets**

200 mg/300 mg*

PHARMACIST: Dispense the accompanying
Medication Guide to each patient.

Rx only

30 TABLETS

TEVA

70063598 Rev. A 12/2019

Serialization Coding Area

N 0093-7607-56 **A**

* Each film-coated tablet contains
200 mg emtricitabine and 300 mg
tenofovir disoproxil fumarate, which
is equivalent to 245 mg tenofovir
disoproxil.

Usual Dosage: See package insert
for full prescribing information.
Store at 20° to 25°C (68° to 77°F)
[See USP Controlled Room
Temperature].
Keep container tightly closed.
Dispense only in original container.
**KEEP THIS AND ALL MEDICATIONS
OUT OF THE REACH OF CHILDREN.**
Manufactured in Croatia By:
Pliva Hrvatska d.o.o.
Zagreb, Croatia
Manufactured For:
Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454

Package/Label Display Panel

New NDC

New Product Appearance

NDC 0093- 7704-56

**Emtricitabine and
Tenofovir
Disoproxil Fumarate
Tablets**
200 mg/300 mg*

PHARMACIST: Dispense the accompanying
Medication Guide to each patient.

Rx only

30 TABLETS

TEVA

New NDC
New Product Appearance

NDC 0093-7704-56

Emtricitabine and Tenofovir Disoproxil Fumarate Tablets

200 mg/300 mg*

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

Rx only
30 Tablets

teva

*Each film-coated tablet contains 200 mg emtricitabine and 300 mg tenofovir disoproxil fumarate, which is equivalent to 245 mg tenofovir disoproxil.

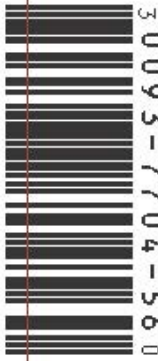
Usual Dosage: See package insert for full prescribing information. Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

Keep container tightly closed. Dispense only in original container. **KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.**

Manufactured in Croatia By: Pliva Hrvatska d.o.o., Zagreb, Croatia
Manufactured For: Teva Pharmaceuticals USA, Inc. Parsippany, NJ 07054

70066252 Rev. B 8/2020

Serialization Coding Area



N 0093-7704-56 0

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

NDC: 67296-1433-3
EMTRICITABINE/TENOFOVIR
200/300MG
3 Tablets

Rx Only

Lot: 440100X1 Exp: 10/22

Usual adult dosage: See package insert
Store at controlled room temperature: 20-25 C (68-77 F)

Mfg: Pliva Hrvatska d.o.o
Zagreb Croatia
0093-7704-56

Dist. by: Redpharm Drug Eden Prairie, MN 55344 SIN 26174




(01)00367296143331
(21)1000000000000033
(17)221031
(10)440100X1

3 67296 14333 1

EMTRICITABINE AND TENOFOVIR DISOPROXIL FUMARATE

emtricitabine and tenofovir disoproxil fumarate tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:67296-1433(NDC:0093-7704)
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
EMTRICITABINE (UNII: G70B4ETF4S) (EMTRICITABINE - UNII:G70B4ETF4S)	EMTRICITABINE	200 mg
TENOFOVIR DISOPROXIL FUMARATE (UNII: OTT9J7900I) (TENOFOVIR ANHYDROUS - UNII:W4HFE001U5)	TENOFOVIR DISOPROXIL FUMARATE	300 mg

Inactive Ingredients

Ingredient Name	Strength
CROSPROVIDONE (15 MPA.S AT 5%) (UNII: 68401960MK)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MANNITOL (UNII: 3OWL53L36A)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WJQ0SDW1A)	
POLYVINYL ALCOHOL, UNSPECIFIED (UNII: 532B59J990)	
POVIDONE K30 (UNII: U725QWY32X)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics

Color	white (white to off-white)	Score	no score
Shape	OVAL (capsule-shaped)	Size	20mm
Flavor		Imprint Code	TV;C75
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:67296-1433-3	3 in 1 BOTTLE; Type 0: Not a Combination Product	04/01/2021	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA090894	04/01/2021	

Labeler - RedPharm Drug, Inc. (828374897)

Establishment

Name	Address	ID/FEI	Business Operations
RedPharm Drug		828374897	repack(67296-1433)

