EMTRICITABINE AND TENOFOVIR DISOPROXIL FUMARATE- emtricitabine and tenofovir disoproxil fumarate tablet, film coated
DirectRx

EMTRICITABINE AND TENOFOVIR DISOPROXIL FUMARATE

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)].

2.1 Testing Prior to Initiation of Emtricitabine and Tenofovir Disoproxil Fumarate Tablets for Treatment of HIV-1 Infection or for HIV-1 PrEP

Prior to or when initiating emtricitabine and tenofovir disoproxil fumarate tablets, test individuals for hepatitis B virus infection [see Warnings and Precautions (5.1)].

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 [see Warnings and Precautions (5.3)].

2.2 HIV-1 Screening for Individuals Receiving Emtricitabine and Tenofovir Disoproxil Fumarate Tablets for HIV-1 PrEP

Screen all individual for HIV-1 infection immediately prior to initiating emtricitabine and tenofovir disoproxil fumarate tablets for HIV-1 PrEP and at least once every 3 months while taking emtricitabine and tenofovir disoproxil fumarate tablets, and upon diagnosis of any other sexually transmitted infections (STIs) [see Indications and Usage (1.2), Contraindications (4) and Warnings and Precautions (5.2)].

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 [see Warnings and Precautions (5.2), Use in Specific Populations (8.4), and Clinical Studies (14.3 and 14.4)].

2.3 Recommended Dosage for Treatment of HIV-1 Infection in Adults and Pediatric Patients Weighing at Least 35 kg

Emtricitabine and tenofovir disoproxil fumarate tablet is a two-drug fixed dose combination product containing emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF). The recommended dosage of emtricitabine and tenofovir disoproxil fumarate tablets in adults and in pediatric patients weighing at least 35 kg is one tablet (containing 200 mg of FTC and 300 mg of TDF) once daily taken orally with or without food [see

Clinical Pharmacology (12.3)].

2.5 Recommended Dosage for HIV-1 PrEP in Adults and Adolescents Weighing at Least 35 kg

The dosage of emtricitabine and tenofovir disoproxil fumarate tablets for HIV-1 PrEP is one tablet (containing 200 mg of FTC and 300 mg of TDF) once daily taken orally with or without food in HIV-1 uninfected adults and adolescents weighing at least 35 kg [see Clinical Pharmacology (12.3)].

2.6 Dosage Adjustment in Individuals with Renal Impairment

Treatment of HIV-1 Infection

Table 2 provides dosage interval adjustment for patients with renal impairment. No dosage adjustment is necessary for HIV-1 infected patients with mild renal impairment (creatinine clearance 50 to 80 mL/min). The safety and effectiveness of the dosing interval adjustment recommendations in patients with moderate renal impairment (creatinine clearance 30 to 49 mL/min) have not been clinically evaluated; therefore, clinical response to treatment and renal function should be closely monitored in these patients [see Warnings and Precautions (5.3)].

No data are available to make dosage recommendations in pediatric patients with renal impairment.

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

a.Calculated using ideal (lean) body weight

Creatinine Clearance (mL/min)a
50
30 to 49
<30
(Including Patients Requiring Hemodialysis)
Recommended Dosing Interval
Every 24 hours
Every 48 hours
Emtricitabine and tenofovir disoproxil fumarate tablets are not recommended.

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 [see Warnings and Precautions (5.3)].

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 Warnings and Precautions (5.3)]

Emtricitabine and tenofovir disoproxil fumarate tablets are available in one dose strength.

200 mg/300 mg Tablets: 200 mg of FTC and 300 mg of TDF (equivalent to 245 mg of tenofovir disoproxil): white, capsule shaped, biconvex film-coated, debossed with "LU" on one side and "Q31" on the other side.

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

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 of 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).
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.

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 individuals 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 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 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-Barr¡SR 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.

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)] .

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 Reactionsa (Grades 2 to 4) Reported in 5% in Any Treatment Group in Study 934 (0 to 144 Weeks)

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.

FTC+TDF+EFVb
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 eventc
7%

9%
Headache
6%
5%
Insomnia
5%
7%
Nasopharyngitis
5%
3%
Vomiting
2%
5%

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 1% of Subjects in Any Treatment Group in Study 934 (0 to 144 Weeks)

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.

FTC+TDF+EFVa
AZT/3TC+EFV
N=257
N=254
Any Grade 3 Laboratory Abnormality
30%
26%
Fasting Cholesterol (>240 mg/dL)
22%
24%
Creatine Kinase
(M: >990 U/L)
(F: >845 U/L)

9%

7%
Serum Amylase (>175 U/L)
8%
4%
Alkaline Phosphatase (>550 U/L)
1%
0%
AST
(M: >180 U/L)
(F: >170 U/L)

3%

3%
ALT
(M: >215 U/L)
(F: >170 U/L)

2%

3%
Hemoglobin (<8.0 mg/dL)
0%
4%
Hyperglycemia (>250 mg/dL)
2%
1%
Hematuria (>75 RBC/HPF)
3%
2%
Glycosuria (3+)
<1%
1%
Neutrophils (<750/mm3)
3%
5%
Fasting Triglycerides (>750 mg/dL)
4%
2%

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 HIV 1 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 2 % in Any Treatment Group in the iPrEx Trial and Greater than Placebo

	FTC/TDF	Placebo
	(N=1251)	(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 to 3 proteinuria (2 to 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

a.Grading is per DAIDS criteria.

	iPrEx Trial		Partners PrEP Trial	
Grade 2 to 4a	FTC/TDF (N=1251)	Placebo (N=1248)	FTC/TDF (N=1579)	Placebo (N=1584)
Creatinine (>1.4 ULN)	<1%	<1%	<1%	<1%
Phosphorus (<2.0 mg/dL)	10%	8%	9%	9%
AST (>2.6 ULN)	5%	5%	<1%	<1%
ALT (>2.6 ULN)	7%	7%	<1%	<1%
Hemoglobin (<9.4 mg/dL)	1%	2%	2%	2%
Neutrophils (<750/mm3)	<1%	<1%	5%	3%

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.

7.1 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, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs [see Warnings and Precautions (5.3)]. Drugs that decrease renal function may increase concentrations of 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, 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 Significanta Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Trials

a.This table is not all inclusive.

b.↑=Increase, ↓=Decrease

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

8.1 Pregnancy

Teratogenic Effects

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 Cmax 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 re-assess potential risks and benefits of continued use [see Dosage and Administration (2.6)].

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-(2R,5S)-[2-(hydroxymethyl)-1,3-oxathiolan-5

yl]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 a molecular formula of C8H10FN3O3S and a molecular weight of 247.24. It has the following structural formula:

[Image]

FTC is a white to off-white colored 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 (1:1). It has a molecular formula of C19H30N5O10P • C4H4O4 and a molecular weight of 635.51. It has the following structural formula:

[Image]

Tenofovir disoproxil fumarate is a white to off-white crystalline powder with a solubility of 9.78 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, and are available in the following strengths:

Film-coated tablet containing 200 mg of FTC and 300 mg of TDF (which is equivalent to 245 mg of tenofovir disoproxil) as active ingredients

Emtricitabine and tenofovir disoproxil fumarate tablets also include the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, mannitol and microcrystalline cellulose. The tablets are coated with Opadry II White 32K180001, which contains hypromellose 2910, lactose monohydrate, titanium dioxide and triacetin.

Emtricitabine and tenofovir disoproxil fumarate tablets are available in bottles containing 30 and 100 tablets with child-resistant closure as follows:

200 mg of FTC and 300 mg of TDF (equivalent to 245 mg of tenofovir disoproxil) tablets are white, capsule shaped, biconvex, film-coated, debossed with "LU" on one side and "Q31" on the other side.

Bottles of 30
68180-287-06
Bottles of 100
68180-287-01

Store at 25 C (77 F); excursions permitted to 15º to 30 C (59 to 86 F) [See USP Controlled Room Temperature].

Keep container tightly closed
Dispense only in original container

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 does 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)].

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)].

Manufactured for:

Lupin Pharmaceuticals, Inc.

Baltimore, Maryland 21202

United States

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Medication Guide

Emtricitabine and Tenofovir Disoproxil Fumarate

(EM-trye-SYE-ta-been and ten-OF-oh-vir DYE-soe-PROX-il FUE-ma-rate)

Tablets

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

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

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

Emtricitabine and tenofovir disoproxil fumarate tablets can cause serious side effects, including:

Worsening of hepatitis B virus infection (HBV). Your healthcare provider will test you for HBV before start or when you start treatment with emtricitabine and tenofovir disoproxil fumarate tablets. If you have HBV infection and take emtricitabine and tenofovir disoproxil fumarate tablets, your HBV may get worse (flare-up) if you stop taking emtricitabine and tenofovir disoproxil fumarate tablets. A "flare-up" is when your HBV infection suddenly returns in a worse way than before.

Do not run out of emtricitabine and tenofovir disoproxil fumarate tablets. Refill your prescription or talk to your healthcare provider before your emtricitabine and tenofovir disoproxil fumarate tablets are all gone.

Do not stop taking emtricitabine and tenofovir disoproxil fumarate tablets without first talking to your healthcare provider.
If you stop taking emtricitabine and tenofovir disoproxil fumarate tablets, your healthcare provider will need to check your health often and do blood tests regularly for several months to check your HBV infection, or give you a medicine to treat hepatitis B. Tell your healthcare provider about any new or unusual symptoms you may have after you stop taking emtricitabine and tenofovir disoproxil fumarate tablets.

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

Other important information for people who take emtricitabine and tenofovir disoproxil fumarate tablets to help reduce their risk of getting human immunodeficiency virus-1 (HIV-1) infection, also called pre-exposure prophylaxis or "PrEP":

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

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

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

While you are taking emtricitabine and tenofovir disoproxil fumarate tablets for HIV-1 PrEP:

Emtricitabine and tenofovir disoproxil fumarate tablets does not prevent other sexually transmitted infections (STIs). Practice safer sex by using a latex or polyurethane condom to reduce the risk of getting STIs.
You must stay HIV-negative to keep taking emtricitabine and tenofovir disoproxil fumarate tablets for HIV-1 PrEP.

Know your HIV-1 status and the HIV-1 status of your partners.
Ask your partners with HIV-1 if they are taking anti-HIV-1 medicines and have an undetectable viral load. An undetectable viral load is when the amount of virus in the blood is too low to be measured in a lab test. To maintain an undetectable viral load, your partners must keep taking HIV-1 medicines every day. Your risk of getting HIV-1 is lower if your partners with HIV-1 are taking effective treatment.

Get tested for HIV-1 at least every 3 months or when your healthcare provider tells you.
Get tested for other STIs such as syphilis, chlamydia, and gonorrhea. These infections make it easier for HIV-1 to infect you.
If you think you were exposed to HIV-1, tell your healthcare provider right away. They may want to do more tests to be sure you are still HIV-1 negative.
Get information and support to help reduce sexual risk rbehaviors.
Do not miss any doses of emtricitabine and tenofovir disoproxil fumarate tablets. Missing doses increases your risk of getting HIV-1 infection.

If you do become HIV-1 positive, you need more medicine than emtricitabine and tenofovir disoproxil fumarate tablets alone to treat HIV-1. Emtricitabine and tenofovir disoproxil fumarate tablets by itself is not a complete treatment for HIV-1.

If you have HIV-1 and take only emtricitabine and tenofovir disoproxil fumarate tablets, over time your HIV-1 may become harder to treat.

What are emtricitabine and tenofovir disoproxil fumarate tablets?

Emtricitabine and tenofovir disoproxil fumarate tablet is a prescription medicine that may be used in two different ways. Emtricitabine and tenofovir disoproxil fumarate tablet is used:

to treat HIV-1 infection when used with other anti-HIV-1 medicines in adults and children who weigh at least 37 pounds (at least 17 kg).
for HIV-1 PrEP to reduce the risk of getting HIV-1 infection in adults and adolescents who weigh at least 77 pounds (at least 35 kg).

HIV-1 is the virus that causes Acquired Immune Deficiency Syndrome(AIDS).

Emtricitabine and tenofovir disoproxil fumarate tablets contains the medicines emtricitabine and tenofovir disoproxil fumarate.

It is not known if emtricitabine and tenofovir disoproxil fumarate tablets for treatment of HIV-1 infection are safe and effective in children who weigh less than 37 pounds (17 kg).

It is not known if emtricitabine and tenofovir disoproxil fumarate tablets are safe and effective in reducing the risk of HIV-1 infection in people who weigh less than 77 pounds (35 kg)

For people taking emtricitabine and tenofovir disoproxil fumarate tablets for HIV-1 PrEP:

Do not take emtricitabine and tenofovir disoproxil fumarate tablets for HIV-1 PrEP if:

you already have HIV-1 infection . If you are HIV-1 positive, you need to take other medicines with emtricitabine and tenofovir disoproxil fumarate tablets to treat HIV-1. Emtricitabine and tenofovir disoproxil fumarate tablet by itself is not a complete treatment for HIV-1.
you do not know your HIV-1 infection status . You may already be HIV-1 positive. You need to take other HIV-1 medicines with emtricitabine and tenofovir disoproxil fumarate tablets to treat HIV-1.

Emtricitabine and tenofovir disoproxil fumarate tablets can only help reduce your risk of getting HIV-1 before you are infected.

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

Before taking emtricitabine and tenofovir disoproxil fumarate tablets, tell your healthcare provider about all of your medical conditions, including if you:

have liver problems, including HBV infection
have kidney problems or receive kidney dialysis treatment
have bone problems
are pregnant or plan to become pregnant. It is not known if emtricitabine and tenofovir disoproxil fumarate tablets can harm your unborn baby. Tell your healthcare provider if you become pregnant during treatment with emtricitabine and tenofovir disoproxil fumarate tablets.

Pregnancy Registry: There is a pregnancy registry for people who take emtricitabine and tenofovir disoproxil fumarate tablets during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk with your healthcare provider about how you can take part in this registry.

are breastfeeding or plan to breastfeed. Emtricitabine and tenofovir disoproxil fumarate can pass to your baby in your breast milk.

Do not breastfeed if you have HIV-1 or if you think you have recently become infected with HIV-1 because of the risk of passing HIV-1 to your baby.
If you take emtricitabine and tenofovir disoproxil fumarate tablets for HIV-1 PrEP, talk with your healthcare provider about the best way to feed your baby.

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

Some medicines may interact with emtricitabine and tenofovir disoproxil fumarate tablets. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

You can ask your healthcare provider or pharmacist for a list of medicines that interact with emtricitabine and tenofovir disoproxil fumarate tablets.
Do not start a new medicine without telling your healthcare provider. Your healthcare provider can tell you if it is safe to take emtricitabine and tenofovir disoproxil fumarate tablets with other medicines.

How should I take emtricitabine and tenofovir disoproxil fumarate tablets?

Take emtricitabine and tenofovir disoproxil fumarate tablets exactly as your healthcare provider tells you to take it.
If you take emtricitabine and tenofovir disoproxil fumarate tablets to treat HIV-1 infection, you need to take other HIV-1 medicines. Your healthcare provider will tell you what medicines to take and how to take them.
Take emtricitabine and tenofovir disoproxil fumarate tablets 1 time each day with or without food.
Do not change your dose or stop taking emtricitabine and tenofovir disoproxil fumarate tablets without first talking with your healthcare provider. Stay under a healthcare provider's care when taking emtricitabine and tenofovir disoproxil fumarate tablets. Do not miss a dose of emtricitabine and tenofovir disoproxil fumarate tablets.
If you take too much emtricitabine and tenofovir disoproxil fumarate tablets, call your healthcare provider or go to the nearest hospital emergency room right away.
When your emtricitabine and tenofovir disoproxil fumarate tablets supply starts to run low, get more from your healthcare provider or pharmacy.

If you are taking emtricitabine and tenofovir disoproxil fumarate tablets for treatment of HIV-1, the amount of virus in your blood may increase if the medicine is stopped for even a short time. The virus may develop resistance to emtricitabine and tenofovir disoproxil fumarate tablets and become harder to treat.
If you are taking emtricitabine and tenofovir disoproxil fumarate tablets for HIV-1 PrEP, missing doses increases your risk of getting HIV-1 infection.

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

Emtricitabine and tenofovir disoproxil fumarate tablets may cause serious side effects, including:

See "What is the most important information I should know about emtricitabine and tenofovir disoproxil fumarate tablets?"
New or worse kidney problems, including kidney failure . Your healthcare provider should do blood and urine tests to check your kidneys before you start and during treatment with emtricitabine and tenofovir disoproxil fumarate tablets. Your healthcare provider may tell you to take emtricitabine and tenofovir disoproxil fumarate tablets less often, or to stop taking emtricitabine and tenofovir disoproxil fumarate tablets if you get new or worse kidney problems.
Changes in your immune system (Immune Reconstitution Syndrome) can happen when taking medicines to treat HIV-1 infection. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider right away if you start having any new symptoms after starting your HIV-1 medicine.
Bone problems can happen in some people who take emtricitabine and tenofovir disoproxil fumarate tablets. Bone problems include bone pain, or softening or thinning of bones, which may lead to fractures. Your healthcare provider may need to do tests to check your bones.
Too much lactic acid in your blood (lactic acidosis). Too much lactic acid is a serious but rare medical emergency that can lead to death. Tell your healthcare provider right away if you get these symptoms: weakness or being more tired than usual, unusual muscle pain, being short of breath or fast breathing, stomach pain with nausea and vomiting, cold or blue hands and feet, feel dizzy or lightheaded, or a fast or abnormal heartbeat.
Severe liver problems . In rare cases, severe liver problems can happen that can lead to death. Tell your healthcare provider right away if you get these symptoms : skin or the white part of your eyes turns yellow, dark "tea-colored" urine, light-colored stools, loss of appetite for several days or longer, nausea, or stomach-area pain.

The most common side effects of emtricitabine and tenofovir disoproxil fumarate tablets for treatment of HIV-1 include:

Diarrhea
depression
nausea
problems sleeping
tiredness
abnormal dreams
headache
rash
dizziness

Common side effects in people who take emtricitabine and tenofovir disoproxil fumarate tablets for HIV-1 PrEP include:

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

These are not all the possible side effects of emtricitabine and tenofovir disoproxil fumarate tablets.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store emtricitabine and tenofovir disoproxil fumarate tablets?

Store emtricitabine and tenofovir disoproxil fumarate tablets at room temperature between 68 F to 77 F (20 C to 25 C).
Keep emtricitabine and tenofovir disoproxil fumarate tablets in its original container.
Keep the container tightly closed.
Do not use emtricitabine and tenofovir disoproxil fumarate tablets if seal over bottle opening is broken or missing.

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

General information about emtricitabine and tenofovir disoproxil fumarate tablets.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use emtricitabine and tenofovir disoproxil fumarate tablets for a condition for which it was not prescribed. Do not give emtricitabine and tenofovir disoproxil fumarate tablets to other people, even if they have the same symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for information about emtricitabine and tenofovir disoproxil fumarate tablets that is written for health professionals.

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

Active ingredients: emtricitabine and tenofovir disoproxil fumarate.

Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, mannitol and microcrystalline cellulose. The tablets are coated with Opadry II White 32K180001, which contains hypromellose 2910, lactose monohydrate, titanium dioxide and triacetin.

The brands listed are trademarks of their respective owners and are not trademarks of Lupin Pharmaceuticals, Inc. The makers of these brands are not affiliated with and do not endorse Lupin Pharmaceuticals, Inc. or its products.

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

Manufactured for:

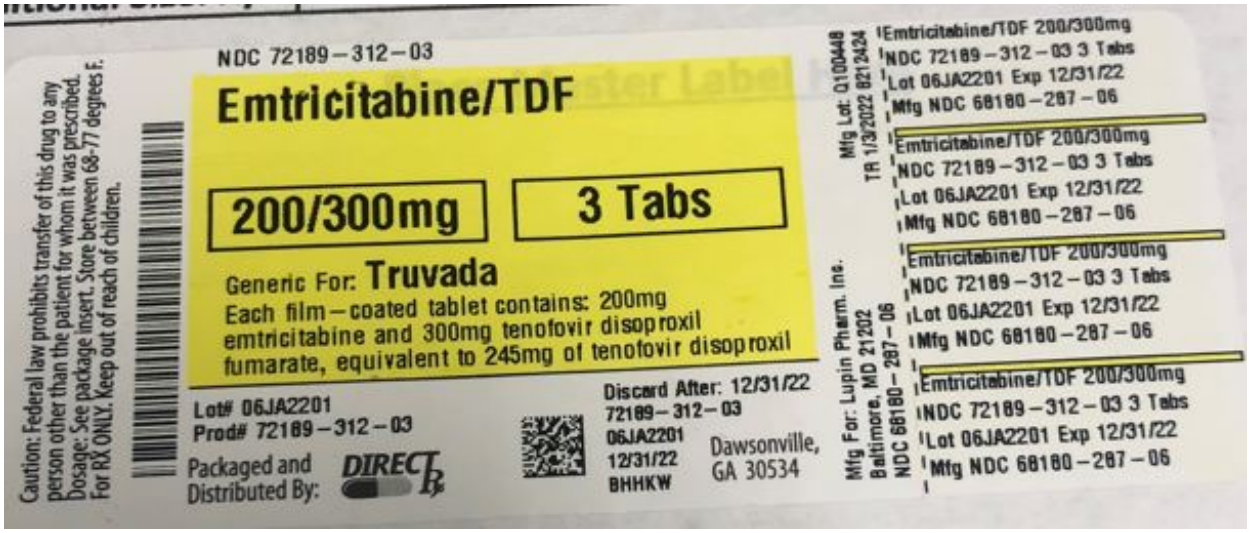
Lupin Pharmaceuticals, Inc.

Baltimore, Maryland 21202

United States

MADE IN INDIA

Revised: December 2020



EMTRICITABINE AND TENOFOVIR DISOPROXIL FUMARATE

emtricitabine and tenofovir disoproxil fumarate tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:72189-312(NDC:68180-287)
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
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
HYPROMELLOSE 2910 (6 MPA.S) (UNII: 0WZ8WG20P6)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
TRIACETIN (UNII: XHX3C3X673)	
MANNITOL (UNII: 3OWL53L36A)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics

Color	white	**Score**	no score
Shape	CAPSULE ((Biconvex film-coated))	**Size**	19mm
Flavor		**Imprint Code**	LU;Q31

Contains	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:72189-312-03	3 in 1 BOTTLE; Type 0: Not a Combination Product	01/26/2022	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA204131	01/26/2022	

Labeler - DirectRx (079254320)

Registrant - DirectRx (079254320)

Establishment

Name	Address	ID/FEI	Business Operations
DirectRx		079254320	relabel(72189-312)

Revised: 1/2025 DirectRx