EMTRICITABINE AND TENOFOVIR ALAFENAMIDE

Rx TAFNEXT-EM

200 mg / 25 mg film-coated tablet

Antiretroviral

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EMTRICITABINE AND TENOFOVIR ALAFENAMIDE TABLETS safely and effectively.

See full prescribing information for EMTRICITABINE AND TENOFOVIR ALAFENAMIDE TABLETS.

EMTRICITABINE AND TENOFOVIR ALAFENAMIDE TABLETS for oral use

Initial U.S. Approval: 2015

WARNING: POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

See full prescribing information for complete boxed warning.

- **Emtricitabine and Tenofovir alafenamide tablets is not approved for the treatment of chronic hepatitis B virus (HBV) infection. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing emtricitabine (FTC) and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of emtricitabine and tenofovir alafenamide tablets. Hepatic function should be monitored closely in these patients. If appropriate, initiation of anti-hepatitis B therapy may be warranted. (5.1)**

RECENT MAJOR CHANGES

Indications and Usage (1)	09/2017
Dosage and Administration, Recommended Dosage (2.2)	09/2017
Warnings and Precautions, Bone Loss and Mineralization Defects [removed]	09/2017
Boxed Warning, Lactic Acidosis/Severe Hepatomegaly with Steatosis [removed]	04/2017
Warnings and Precautions, Lactic Acidosis/Severe Hepatomegaly With Steatosis (5.4)	04/2017
Warnings and Precautions, Fat Redistribution [removed]	04/2017

INDICATIONS AND USAGE

Emtricitabine and Tenofovir alafenamide tablet is a two-drug combination of emtricitabine (FTC) and tenofovir alafenamide (TAF), both HIV nucleoside analog reverse transcriptase inhibitors (NRTIs), and is indicated:

- in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 35kg.
- in combination with other antiretroviral agents other than protease inhibitors that require a CYP3A inhibitor for the treatment of HIV-1 infection in pediatric patients weighing at least 25 kg and less than 35 kg. (1)

Limitations of Use:

Emtricitabine and tenofovir alafenamide tablet is not indicated for use as pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk.

DOSAGE AND ADMINISTRATION

- Testing: Prior to initiation of Emtricitabine and Tenofovir alafenamide tablets, patients should be tested for hepatitis B virus infection, and estimated creatinine clearance, urine glucose and urine protein should be obtained. (2.1)
- Recommended dosage: One tablet taken once daily with or without food in patients with body weight at least 25 kg and a creatinine clearance greater than or equal to 30 mL per minute. (2.2)
- Renal impairment: Emtricitabine and Tenofovir alafenamide tablet is not recommended in patients with estimated creatinine clearance below 30 mL per minute. (2.3)

DOSAGE FORMS AND STRENGTHS

Tablets: 200 mg of emtricitabine and 25 mg of tenofovir alafenamide (3)

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

- Immune reconstitution syndrome: May necessitate further evaluation and treatment.(5.2)
- New onset or worsening renal impairment: Assess creatinine clearance, urine glucose, and urine protein in all patients before initiating Emtricitabine and Tenofovir alafenamide tablet therapy and monitor during therapy. Monitor serum phosphorus in patients with chronic kidney disease. (5.3)
- Lactic acidosis/severe hepatomegaly with steatosis: Discontinue treatment in patients who develop symptoms or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity. (5.4)

ADVERSE REACTIONS

Most common adverse reaction (incidence greater than or equal to 10%, all grades) is nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact hetero Labs Limited at 1-866-495-1995 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

DRUG INTERACTIONS

Consult the Full Prescribing Information prior to and during treatment for potential drug interactions. (7, 12.3)

USE IN SPECIFIC POPULATIONS

- Lactation: Women infected with HIV should be instructed not to breastfeed, due to the potential for HIV transmission. (8.2)
- Pediatrics: Not recommended for patients weighing less than 25 kg. (8.4)
- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**

Revised: 09/2018

FULL PRESCRIBING INFORMATION: CONTENTS*WARNING: POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

Emtricitabine and Tenofovir alafenamide tablets is not approved for the treatment of chronic hepatitis B virus (HBV) infection, and the safety and efficacy of Emtricitabine and Tenofovir alafenamide tablets have not been established in patients coinfected with human immunodeficiency virus-1 (HIV-1) and HBV. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing emtricitabine (FTC) and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of Emtricitabine and Tenofovir alafenamide tablets.

Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are coinfected with HIV-1 and HBV and discontinue Emtricitabine and Tenofovir alafenamide tablets. If appropriate, initiation of anti-hepatitis B therapy may be warranted *[see Warnings and Precautions (5.1)]*.

1. INDICATIONS AND USAGE

Emtricitabine and Tenofovir alafenamide tablets is indicated, in combination with other antiretroviral agents, for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 35 kg.

Emtricitabine and tenofovir alafenamide tablet is also indicated, in combination with other antiretroviral agents other than protease inhibitors that require a CYP3A inhibitor, for the treatment of HIV-1 infection in pediatric patients weighing at least 25 kg and less than 35 kg.

Limitations of Use:

Emtricitabine and tenofovir alafenamide tablet is not indicated for use as pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk.

2. DOSAGE AND ADMINISTRATION

2.1 Testing Prior to Initiation of emtricitabine and tenofovir alafenamide

Prior to initiation of emtricitabine and tenofovir alafenamide tablets, patients should be tested for hepatitis B virus infection *[see Warnings and Precautions (5.1)]*.

Estimated creatinine clearance, urine glucose, and urine protein should be assessed before initiating emtricitabine and tenofovir alafenamide tablet therapy and should be monitored during therapy in all patients *[see Warnings and Precautions (5.3)]*.

2.2 Recommended Dosage

Emtricitabine and tenofovir alafenamide tablets is a two-drug fixed dose combination product containing 200 mg of emtricitabine (FTC) and 25 mg of tenofovir alafenamide (TAF). The recommended dosage of emtricitabine and tenofovir alafenamide tablets is one tablet taken orally once daily with or without food in adults and pediatric patients with body weight at least 25 kg and creatinine clearance greater than or equal to 30 mL per minute *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

For specific dosing recommendations for coadministered third agents, refer to their respective prescribing information *[see Drug Interactions (7)]*. The safety and effectiveness of emtricitabine and tenofovir alafenamide tablets coadminstered with an HIV-1 protease inhibitor that is administered with either ritonavir or cobicistat have not been established in pediatric subjects weighing less than 35 kg.

2.3 Not Recommended in Patients with Severe Renal Impairment

Emtricitabine and tenofovir alafenamide tablet is not recommended in patients with estimated creatinine clearance below 30 mL per minute *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.6)]*.

3 DOSAGE FORMS AND STRENGTHS

Each film-coated tablet contains 200mg of Emtricitabine and 25 mg Tenofovir alafenamide equivalent to 28.043 mg of Tenofovir alafenamide hemi fumarate.The tablets Pink, oval shaped, biconvex film coated tablets debossed with 'V' on one side and '21' on other side. *[see Description (11)]*.

4 CONTRAINDICATIONS

None.

5. WARNINGS AND PRECAUTIONS

5.1 Severe Acute Exacerbation of Hepatitis B in Patients Coinfected with HIV-1 and HBV

Patients with HIV-1 should be tested for the presence of chronic hepatitis B virus (HBV) before initiating antiretroviral therapy *[see Dosage and Administration (2.1)]*. Emtricitabine and tenofovir alafenamide tablet is not approved for the treatment of chronic HBV infection, and the safety and efficacy of emtricitabine and tenofovir alafenamide tablets have not been established in patients coinfected with HIV-1 and HBV.

Severe acute exacerbations of hepatitis B (e.g., liver decompensation and liver failure) have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing FTC and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of emtricitabine and tenofovir alafenamide tablets. Patients coinfected with HIV-1 and HBV who discontinue emtricitabine and tenofovir alafenamide tablets should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, initiation of anti-hepatitis B therapy may be warranted, especially in patients with advanced liver disease or cirrhosis, since post-treatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure.

5.2 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including FTC, a component of emtricitabine and tenofovir alafenamide tablets. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections [*such as Mycobacterium avium infection, cytomegalovirus, Pneumocystis jirovecii* pneumonia (PCP), or tuberculosis], which may necessitate further evaluation and treatment.

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

5.3 New Onset or Worsening Renal Impairment

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir prodrugs in both animal toxicology studies and human trials. In clinical trials of FTC + TAF with cobicistat (COBI) plus elvitegravir (EVG), there have been no cases of Fanconi syndrome or Proximal Renal Tubulopathy (PRT). In clinical trials of FTC + TAF with EVG + COBI in treatment-naïve subjects and in virally suppressed subjects switched to FTC + TAF with EVG + COBI with eGFRs greater than 50 mL per minute, renal serious adverse events or discontinuations due to renal adverse reactions were encountered in less than 1% of participants treated with FTC + TAF with EVG + COBI. In a study of virally suppressed subjects with baseline eGFRs between 30 and 69 mL per minute treated with FTC + TAF with EVG + COBI for a median duration of 43 weeks, FTC + TAF with EVG + COBI was permanently discontinued due to worsening renal function in two of 80 (3%) subjects with a baseline eGFR between 30 and 50 mL per minute *[see Adverse Reactions (6.1)]*. Emtricitabine and tenofovir alafenamide tablet is not recommended in patients with estimated creatinine clearance below 30 mL per minute because data in this population are insufficient.

Patients taking tenofovir prodrugs who have impaired renal function and those taking nephrotoxic agents including non-steroidal anti-inflammatory drugs are at increased risk of developing renal-related adverse reactions.

Estimated creatinine clearance, urine glucose, and urine protein should be assessed before initiating emtricitabine and tenofovir alafenamide tablets therapy and should be monitored during therapy in all patients. Serum phosphorus should be monitored in patients with chronic kidney disease because these patients are at greater risk of developing Fanconi syndrome on tenofovir prodrugs. Discontinue emtricitabine and tenofovir alafenamide tablets in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

5.4 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 emtricitabine, a component of emtricitabine and tenofovir alafenamide tablets, and tenofovir DF, another prodrug of tenofovir, alone or in combination with other antiretrovirals. Treatment with emtricitabine and tenofovir alafenamide tablets should be suspended in any patient 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).

6 ADVERSE REACTIONS

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

- Severe Acute Exacerbations of Hepatitis B *[see Boxed Warning and Warnings and Precautions (5.1)]*.
- Immune Reconstitution Syndrome *[see Warnings and Precautions (5.2)]*.
- New Onset or Worsening Renal Impairment *[see Warnings and Precautions (5.3)]*.
- Lactic Acidosis/Severe Hepatomegaly with Steatosis *[see Warnings and Precautions (5.4)]*

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 (or a drug given in various combinations with other concomitant therapy) cannot be directly compared to rates in the clinical trials of another drug (or drug given in the same or different combination therapy) and may not reflect the rates observed in practice.

Adverse Reactions in Clinical Trials of FTC + TAF with EVG + COBI in Treatment-Naïve Adults with HIV-1 Infection

In pooled 48-week trials of antiretroviral treatment-naïve HIV-1 infected adult subjects, the most common adverse reaction in subjects treated with FTC + TAF with EVG + COBI (N = 866) (incidence greater than or equal to 10%, all grades) was nausea (10%). In this treatment group, 0.9% of subjects discontinued FTC + TAF with EVG + COBI due to adverse events during the 48-week treatment period *[see Clinical Studies (14)]*. The safety profile was similar in virologically-suppressed adults with HIV-1 infection who were switched to FTC + TAF with EVG + COBI (N = 799). Antiretroviral treatment-naïve adult subjects treated with FTC + TAF with EVG + COBI experienced mean increases of 30 mg/dL of total cholesterol, 15 mg/dL of LDL cholesterol, 7 mg/dL of HDL cholesterol and 29 mg/dL of triglycerides after 48 weeks of use.

Renal Laboratory Tests

In two 48-week trials in antiretroviral treatment-naïve HIV-1 infected adults treated with FTC + TAF with EVG + COBI (N = 866) with a median baseline eGFR of 115 mL per minute, mean serum creatinine increased by 0.1 mg per dL from baseline to Week 48. Median urine protein-to-creatinine ratio (UPCR) was 44 mg per gram at baseline and at Week 48. In a 48-week trial in virologically-suppressed TDF-treated adults who switched to FTC + TAF with EVG + COBI (N = 959) with a mean baseline eGFR of 112 mL per minute, mean serum creatinine was similar to baseline and median UPCR was 61 mg per gram at baseline and 46 mg per gram at Week 48. In a 24-week trial in adults with renal impairment (baseline eGFR 30 to 69 mL per minute) who received FTC + TAF with EVG + COBI (N = 248), mean serum creatinine was 1.5 mg per dL at both baseline and Week 24. Median UPCR was 161 mg per gram at baseline and 93 mg per gram at Week 24.

Bone Mineral Density Effects

In the pooled analysis of two 48-week trials of antiretroviral treatment-naïve HIV-1 infected adult subjects, bone mineral density (BMD) from baseline to Week 48 was assessed by dual-energy X-ray absorptiometry (DXA). Mean BMD decreased from baseline to Week 48 −1.30% with FTC + TAF with EVG + COBI at the lumbar spine and −0.66% at the total hip. BMD declines of 5% or greater at the lumbar spine were experienced by 10% of FTC + TAF with EVG + COBI subjects. BMD declines of 7% or greater at the femoral neck were experienced by 7% of FTC + TAF with EVG + COBI subjects. The long-term clinical significance of these BMD changes is not known. Fractures (excluding fingers and toes) were reported in 7 (0.8%) subjects in the FTC + TAF with EVG + COBI group.

In 799 virologically-suppressed TDF-treated adult subjects that switched to FTC + TAF with EVG + COBI, at Week 48 mean BMD increased (1.86% lumbar spine, 1.95% total hip). BMD declines of 5% or greater at the lumbar spine were experienced by 1% of FTC + TAF with EVG + COBI subjects. BMD declines of 7% or greater at the femoral neck were experienced by 1% of FTC + TAF with EVG + COBI subjects.

Adverse Reactions in Clinical Trials in Pediatric Subjects with HIV-1 Infection

In an open-label trial of antiretroviral treatment-naïve HIV-1 infected pediatric subjects between the ages of 12 to less than 18 years weighing at least 35 kg through 48 weeks (N = 50; cohort 1) and virologically-suppressed subjects between the ages of 6 to less than 12 years weighing at least 25 kg (N = 23; cohort 2) who received FTC + TAF with EVG + COBI through 24 weeks, with the exception of a decrease in the mean CD4 + cell count observed in cohort 2, the safety of this combination was similar to that of adults.

Cohort 1: Treatment-naïve adolescents (12 to less than 18 years; at least 35 kg)

Among the subjects in cohort 1 receiving FTC + TAF with EVG + COBI, mean BMD increased from baseline to Week 48, +4.2% at the lumbar spine and +1.3% for the total body less head (TBLH). Mean changes from baseline BMD Z-scores were −0.07 for lumbar spine and −0.20 for TBLH at Week 48. One subject had significant (at least 4%) lumbar spine BMD loss at Week 48.

Cohort 2: Virologically-suppressed children (6 to less than 12 years; at least 25 kg)

Among the subjects in cohort 2 receiving FTC + TAF with EVG + COBI, mean BMD increased from baseline to Week 24, +2.9% at the lumbar spine and +1.7% for TBLH. Mean changes from baseline BMD Z-scores were -0.06 for lumbar spine and -0.18 for TBLH at Week 24. Two subjects had significant (at least 4%) lumbar spine BMD loss at Week 24.

Change from Baseline in CD4+ cell counts

Cohort 2: Virologically-suppressed children (6 to less than 12 years; at least 25 kg)

Cohort 2 evaluated pediatric subjects (N = 23) who were virologically-suppressed and who switched from their antiretroviral regimen to FTC + TAF with EVG + COBI. Although all subjects had HIV-1 RNA < 50 copies/mL, there was a decrease from baseline in CD4 + cell count at Week 24. The mean baseline and mean change from baseline in CD4 + cell count and in CD4% from Week 2 to Week 24 are presented in Table 1. All subjects maintained their CD4 + cell counts above 400 cells/mm^3 *[see Use in Specific Populations (8.4)]*.

Table 1 Mean Change in CD4$^+$ Count and Percentage from Baseline to Week 24 in Virologically-Suppressed Pediatric Patients from 6 to < 12 Years Who Switched to FTC+TAF with EVG+COBI

	Baseline	Mean Change from Baseline			
CD4+ Cell Count (cells/mm^3)	966(201.7)[a]	Week 2	Week 4	Week 12	Week 24
		-162	-125	-162	-150
CD4%	40(5.3)[a]	+0.5%	-0.1%	-0.8%	-1.5%

a. Mean (SD)

7 DRUG INTERACTIONS

7.1 Potential for Other Drugs to Affect One or More Components of emtricitabine and tenofovir alafenamide tablets

TAF, a component of emtricitabine and tenofovir alafenamide tablets, is a substrate of P-gp, BCRP, OATP1B1, and OATP1B3. Drugs that strongly affect P-gp and BCRP activity may lead to changes in TAF absorption *(see Table 2)*. Drugs that induce P-gp activity are expected to decrease the absorption of TAF, resulting in decreased plasma concentration of TAF, which may lead to loss of therapeutic effect of emtricitabine and tenofovir alafenamide tablets and development of resistance. Coadministration of emtricitabine and tenofovir alafenamide tablets with other drugs that inhibit P-gp and BCRP may increase the absorption and plasma concentration of TAF. TAF is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or UGT1A1. TAF is a weak inhibitor of CYP3A in vitro. TAF is not an inhibitor or inducer of CYP3A in vivo.

7.2 Drugs Affecting Renal Function

Because FTC and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion, coadministration of emtricitabine and tenofovir alafenamide tablets with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of FTC, tenofovir, and other renally eliminated drugs and this may increase the risk of adverse reactions. Some examples of drugs that are eliminated by active tubular secretion include, but are not limited to, acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs *[see Warnings and Precautions (5.3)]*.

7.3 Established and Other Potentially Significant Interactions

Table 2 provides a listing of established or potentially clinically significant drug interactions with recommended steps to prevent or manage the drug interaction (the table is not all inclusive). The drug interactions described are based on studies conducted with either emtricitabine and tenofovir alafenamide tablets, the components of emtricitabine and tenofovir alafenamide as individual agents, or are predicted drug interactions that may occur with emtricitabine and tenofovir alafenamide tablets. For magnitude of interaction, *see Clinical Pharmacology (12.3).*

Table 2 Established and Other Potentially Significant a Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Antiretroviral Agents: Protease Inhibitors (PI)		
tipranavir/ritonavir	↓TAF	Coadministration with emtricitabine and tenofovir alafenamide tabletsis not recommended.
Other Agents		
Anticonvulsants: carbamazepine oxcarbazepine phenobarbital phenytoin	↓TAF	Consider alternative anticonvulsant.
Antimycobacterials: Rifabutin, rifampin rifapentine	↓TAF	Coadministration of emtricitabine and tenofovir alafenamide tabletswith rifabutin, rifampin, or rifapentine is not recommended.
Herbal Products: St. John's wort *(Hypericum perforatum)*	↓TAF	Coadministration of emtricitabine and tenofovir alafenamide tabletswith St. John's wort is not recommended.

a. This table is not all inclusive.

b. ↓ = Decrease

7.4 Drugs without Clinically Significant Interactions with emtricitabine and tenofovir alafenamide tablets

Based on drug interaction studies conducted with the components of emtricitabine and tenofovir alafenamide tablets, no clinically significant drug interactions have been either observed or are expected when emtricitabine and tenofovir alafenamide tablets is combined with the following antiretroviral agents: atazanavir with ritonavir or cobicistat, darunavir with ritonavir or cobicistat, dolutegravir, efavirenz, ledipasvir, lopinavir/ritonavir, maraviroc, nevirapine, raltegravir, rilpivirine, and sofosbuvir. No clinically significant drug interactions have been either observed or are expected when emtricitabine and tenofovir alafenamide tablets is combined with the following drugs: buprenorphine, itraconazole, ketoconazole, lorazepam, methadone, midazolam, naloxone, norbuprenorphine, norgestimate/ethinyl estradiol, and sertraline.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are insufficient human data on the use of emtricitabine and tenofovir alafenamide tablets during pregnancy to inform a drug-associated risk of birth defects and miscarriage. Tenofovir alafenamide (TAF) use in women during pregnancy has not been evaluated; however, emtricitabine (FTC) use during pregnancy has been evaluated in a limited number of women reported to the APR. Available data from the APR show no difference in the risk of overall major birth defects for FTC (2.4%) 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). The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in the clinically recognized pregnancies in the U.S. general population is 15 – 20%. In animal studies, no adverse developmental effects were observed when the components of emtricitabine and tenofovir alafenamide tablets were administered separately during the period of organogenesis at exposures 60 and 108 times (mice and rabbits, respectively) the FTC exposure and at exposure equal to or 53 times (rats and rabbits, respectively) the TAF exposure at the recommended daily dose of emtricitabine and tenofovir alafenamide tablets *[see Data (8.1)]*. Likewise, no adverse developmental effects were seen when FTC was administered to mice through lactation at exposures up to approximately 60 times the exposure at the recommended daily dose of emtricitabine and tenofovir alafenamide tablets. No adverse effects were observed in the offspring when TDF was administered through lactation at tenofovir exposures of approximately 14 times the exposure at the recommended daily dosage of emtricitabine and tenofovir alafenamide tablets.

Data

Human Data

Emtricitabine: Based on prospective reports to the APR through July 2015 of 2933 exposures to FTC-containing regimens during pregnancy (including 1984 exposed in the first trimester and 949 exposed in the second/third trimester), there was no difference between FTC and overall birth defects compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The prevalence of birth defects in live births was 2.4% (95% CI: 1.7% to 3.1%) with first trimester exposure to FTC-containing regimens and 2.1% (95% CI: 1.3% to 3.2%) with the second/third trimester exposure to FTC-containing regimens.

Animal Data

Emtricitabine: FTC was administered orally to pregnant mice (250, 500, or 1000 mg/kg/day) and rabbits (100, 300, or 1000 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 (area under the curve [AUC]) approximately 60 times higher and in rabbits at approximately 108 times higher than human exposures at the recommended daily dose. In a pre/postnatal development study with FTC, mice were administered doses up to 1000 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-fold higher than human exposures at the recommended daily dose.

Tenofovir Alafenamide: TAF was administered orally to pregnant rats (25, 100, or 250 mg/kg/day) and rabbits (10, 30, or 100 mg/kg/day) through organogenesis (on gestation days 6 through 17, and 7 through 20, respectively). No adverse embryo-fetal effects were observed in rats and rabbits at TAF exposures approximately similar to (rats) and 53 (rabbits) times higher than the exposure in humans at the recommended daily dose of emtricitabine and tenofovir alafenamide tablets. TAF is rapidly converted to tenofovir; the observed tenofovir exposures in rats and rabbits were 59 (rats) and 93 (rabbits) times higher than human tenofovir exposures at the recommended daily dose. Since TAF is rapidly converted to tenofovir and a lower tenofovir exposure in rats and mice was observed after TAF administration compared to tenofovir disoproxil fumarate (TDF, another prodrug for tenofovir) administration, a pre/postnatal development study in rats was conducted only with TDF. Doses up to 600 mg/kg/day were administered through lactation; no adverse effects were observed in the offspring on gestation day 7 [and lactation day 20] at tenofovir exposures of approximately 14 [21] times higher than the exposures in humans at the recommended daily dose of emtricitabine and tenofovir alafenamide tablets.

8.2 Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants, to avoid risking postnatal transmission of HIV.

FTC has been shown to be present in human breast milk; it is not known if TAF is present in human breast milk *[see Data (8.2)]*. Tenofovir has been shown to be present in the milk of lactating rats and rhesus monkeys after administration of TDF *[see Data (8.2)]*. It is not known if TAF is present in animal milk.

It is not known if emtricitabine and tenofovir alafenamide tablet affects milk production or has effects on the breastfed child. 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 receiving emtricitabine and tenofovir alafenamide tablets *[see Data (8.2)]*.

Data

Human Data

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

Animal Data

Tenofovir Alafenamide: Studies in rats and monkeys have demonstrated that tenofovir is secreted in milk. Tenofovir was excreted into the milk of lactating rats following oral administration of TDF (up to 600 mg/kg/day) at up to approximately 24% of the median plasma concentration in the highest dosed animals at lactation day 11 *[see Data (8.1)]*. Tenofovir was excreted into the milk of lactating monkeys following a single subcutaneous (30 mg/kg) dose of tenofovir at concentrations up to approximately 4% of plasma concentration, resulting in exposure (AUC) of approximately 20% of plasma exposure.

8.4 Pediatric Use

The safety and effectiveness of emtricitabine and tenofovir alafenamide tablets, in combination with other antiretroviral agents, for the treatment of HIV-1 infection was established in pediatric patients with body weight greater than or equal to 25 kg *[see Indication and Usage (1) and Dosage and Administration (2.2)]*.

Use of emtricitabine and tenofovir alafenamide tablets in pediatric patients between the ages of 12 to less than 18 years weighing at least 35 kg is supported by adequate and well controlled studies of FTC + TAF with EVG + COBI in adults and by an open-label trial in antiretroviral treatment-naïve HIV-1 infected pediatric subjects ages 12 to less than 18 years and weighing at least 35 kg (N = 50; cohort 1). The safety and efficacy of FTC + TAF with EVG + COBI in these pediatric subjects was similar to that of HIV-1 infected adults on this regimen *[see Clinical Pharmacology (12.3) and Clinical Studies (14)]*.

Use of emtricitabine and tenofovir alafenamide tablets in pediatric patients weighing at least 25 kg is supported by adequate and well controlled studies of FTC + TAF with EVG + COBI in adults and by an open-label trial in virologically-suppressed pediatric subjects between the ages of 6 to less than 12 years weighing at least 25 kg, in which subjects were switched from their antiretroviral regimen to FTC + TAF with EVG + COBI (N = 23; cohort 2). The safety in these subjects through 24 weeks of FTC + TAF with EVG + COBI was similar to that of HIV-1 infected adults on this regimen, with the exception of a decrease in mean change from baseline in CD4 + cell count *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies (14)]*.

Safety and effectiveness of emtricitabine and tenofovir alafenamide tablets coadminstered with an HIV-1 protease inhibitor that is administered with either ritonavir or cobicistat have not been established in pediatric subjects weighing less than 35 kg *[see Dosage and Administration (2.2)]*.

Safety and effectiveness of emtricitabine and tenofovir alafenamide tablets in pediatric patients less than 25 kg have not been established.

8.5 Geriatric Use

In clinical trials, 80 of the 97 subjects enrolled aged 65 years and over received FTC + TAF and EVG + COBI. No differences in safety or efficacy have been observed between elderly subjects and adults between 18 and less than 65 years of age.

8.6 Renal Impairment

Emtricitabine and tenofovir alafenamide tablet is not recommended in patients with severe renal impairment (estimated creatinine clearance below 30 mL per minute). No dosage adjustment of emtricitabine and tenofovir alafenamide tablet is recommended in patients with estimated creatinine clearance greater than or equal to 30 mL per minute *[see Dosage and Administration (2.3) and Clinical Studies (14)]*.

8.7 Hepatic Impairment

No dosage adjustment of emtricitabine and tenofovir alafenamide tablets is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. Emtricitabine and tenofovir alafenamide tablets has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

No data are available on overdose of emtricitabine and tenofovir alafenamide tablet in patients. If overdose occurs, monitor the patient for evidence of toxicity. Treatment of overdose with emtricitabine and tenofovir alafenamide tablets consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient.

Emtricitabine (FTC): Limited clinical experience is available at doses higher than the recommended dose of FTC in emtricitabine and tenofovir alafenamide tablets. In one clinical pharmacology study, single doses of FTC 1200 mg (6 times the FTC dose in emtricitabine and tenofovir alafenamide tablets) were administered to 11 subjects. No severe adverse reactions were reported. The effects of higher doses are not known.

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 per minute and a dialysate flow rate of 600 mL per minute). It is not known whether FTC can be removed by peritoneal dialysis.

Tenofovir alafenamide (TAF): Limited clinical experience is available at doses higher than the recommended dose of TAF. A single dose of 125 mg TAF (5 times the TAF dose in 200/25 mg emtricitabine and tenofovir alafenamide tablets) was administered to 48 healthy subjects; no serious adverse reactions were reported. The effects of higher doses are unknown. Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%.

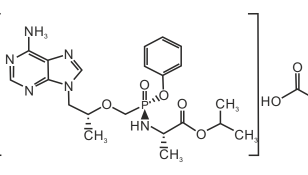
11 DESCRIPTION

Emtricitabine and Tenofovir alafenamide tablets are fixed dose combination tablets containing emtricitabine and tenofovir alafenamide. Emtricitabine, a synthetic nucleoside analog of cytidine, Tenofovir alafenamide, an HIV NRTI, is converted in vivo to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate both emtricitabine and tenofovir alafenamide are HIV nucleoside analog reverse transcriptase inhibitors (NRTIs).

Emtricitabine and tenofovir alafenamide tablets are for oral administration. Each film-coated tablet contains 200mg of Emtricitabine and 25 mg Tenofovir alafenamide equivalent to 28.043 mg of Tenofovir alafenamide hemi fumarate. Emtricitabine and Tenofovir alafenamide tablets Pink, oval shaped, biconvex film coated tablets debossed with 'V' on one side and '21' on other side. In addition, each tablet contains the following inactive ingredients: croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The tablets are film-coated with a coating material containing indigo carmine aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Emtricitabine: The chemical name of Emtricitabine 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.

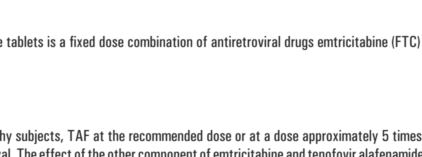
Its empirical formula is $C_8H_{10}FN_3O_3S$ and its molecular weight is 247.24. Emtricitabine has the following structural formula:



Emtricitabine is a white to off-white powder with a solubility of approximately 112 mg per mL in water at 25°C

Tenofovir Alafenamide Hemifumarate

Tenofovir Alafenamide Hemifumarate is chemically designated as Isopropyl N-{(S)-({[(2R)1-(6amino-9H-purin-9-yl}-2-propanyl]oxy}methyl)(phenoxy)phosphoryl]-L-alanfnate(2E)-2-butenedioate(2:1). Its molecular formula is $C_{46}H_{62}N_{12}O_{14}P_{12}$, and its molecular weight is 1068.39. Ritonavir has the following structural formula:



Tenofovir Alafenamide Hemifumarate is a A white to off-white powder and is Soluble in dimethyl formamide and slightly soluble in methanol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Emtricitabine and tenofovir alafenamide tablets is a fixed dose combination of antiretroviral drugs emtricitabine (FTC) and tenofovir alafenamide (TAF) *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

Cardiac Electrophysiology

In a thorough QT/QTc study in 48 healthy subjects, TAF at the recommended dose or at a dose approximately 5 times the recommended dose, did not affect the QT/QTc interval and did not prolong the PR interval. The effect of the other component of emtricitabine and tenofovir alafenamide tablets, FTC, or the combination of FTC and TAF on the QT interval is not known.

12.3 Pharmacokinetics

Absorption, Distribution, Metabolism, and Excretion

The pharmacokinetic (PK) properties of the components of emtricitabine and tenofovir alafenamide are provided in Table 3. The multiple dose PK parameters of FTC and TAF and its metabolite tenofovir are provided in Table 4.

Table 3 Pharmacokinetic Properties of the Components of emtricitabine and tenofovir alafenamide tablets

	Emtricitabine	Tenofovir Alafenamide
Absorption		
T_{max} (h)	3	1
Effect of high fat meal (relative to fasting)[a]	AUC Ratio = 0.91 (0.89, 0.93) C_{max} Ratio = 0.74 (0.69, 0.78)	AUC Ratio = 1.75 (1.64, 1.88) C_{max} Ratio = 0.85 (0.75, 0.95)
Distribution		
% Bound to human plasma proteins	< 4	~ 80
Source of protein binding data	*In vitro*	*Ex vivo*
Blood-to-plasma ratio	0.6	1.0
Metabolism		
Metabolism	Not significantly metabolized	Cathepsin A[b] (PBMCs) CES1(hepatocytes) CYP3A (minimal)

	Emtricitabine	Tenofovir Alafenamide
Elimination		
Major route of elimination	Glomerular filtration and active tubular secretion	Metabolism (> 80% of oral dose)
$t_{1/2}$ (h)[a]	10	0.51
% Of dose excreted in urine[a]	70	< 1
% Of dose excreted in feces[a]	13.7	31.7

PBMCs = peripheral blood mononuclear cells; CES1 = carboxylesterase 1

a. Values refer to geometric mean ratio (High-fat meal/ fasting) in PK parameters and (90% confidence interval). High-calorie/high-fat meal ~ ~ 800 kcal, 50% fat.

b. In vivo, TAF is hydrolyzed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite, tenofovir diphosphate. In vitro studies have shown that TAF is metabolized to tenofovir by cathepsin A in PBMCs and macrophages; and by CES1 in hepatocytes. Upon coadministration with the moderate CYP3A inducer probe efavirenz, TAF exposure was unaffected.

c. $t_{1/2}$ values refer to median terminal plasma half-life. Note that the pharmacologically active metabolite, tenofovir diphosphate, has a half-life of 150-180 hours within PBMCs.

d. Dosing in mass balance studies: FTC (single dose administration of ^{14}C-emtricitabine after multiple dosing of emtricitabine for ten days); TAF (single dose administration of ^{14}C-tenofovir alafenamide).

Table 4 Multiple Dose PK Parameters of Emtricitabine, Tenofovir Alafenamide and its Metabolite Tenofovir Following Oral Administration with Food in HIV-Infected Adults

Parameter Mean (CV%)	Emtricitabine[a]	Tenofovir Alafenamide[a]	Tenofovir[a]
C_{max} (microgram per mL)	2.1 (20.2)	0.16 (51.1)	0.02 (26.1)
AUC_{tau} (microgram•hour per mL)	11.7 (16.6)	0.21 (71.8)	0.29 (27.4)
C_{trough} (microgram per mL)	0.10 (46.7)	NA	0.01 (28.5)

CV = Coefficient of Variation; NA = Not Applicable

a. From Intensive PK analysis in a phase 2 trial in HIV infected adults treated with FTC + TAF and EVG + COBI.

b. From Population PK analysis in two trials of treatment-naïve adults with HIV-1 infection treated with FTC + TAF with EVG + COBI (N = 539).

c. From Population PK analysis in two trials of treatment-naïve adults with HIV-1 infection treated with FTC + TAF with EVG + COBI (N = 841).

Specific Populations

Patients with Renal Impairment

The pharmacokinetics of FTC + TAF combined with EVG + COBI in HIV infected subjects with renal impairment (eGFR 30 to 69 mL per minute by Cockcroft-Gault method) were evaluated in a subset of virologically-suppressed subjects in an open-label trial (Table 5).

Table 5 Pharmacokinetics of the Components of emtricitabine and tenofovir alafenamide and a Metabolite of TAF (Tenofovir) in HIV-Infected Adults with Renal Impairment Compared to Subjects with Normal Renal Function[a]

	AUC_{24h} (microgram•hour per mL) Mean (CV%)		
CreatinineClearance	**≥ 90 mL per minute (N = 18)**	**60–89 mL per minute (N = 11)[b]**	**30–59 mL per minute (N = 18)**
Emtricitabine	11.4 (11.8)[c]	17.6 (18.2)	23.0 (23.8)
Tenofovir Alafenamide[d]	0.23 (47.2)	0.24 (45.6)	0.26 (58.8)
Tenofovir	0.32 (14.9)	0.46 (21.5)	0.61 (28.4)

* AUC last

a. Trial in HIV infected adults with renal impairment treated with FTC + TAF with EVG + COBI.

b. From a phase 2 trial in HIV infected adults with normal renal function treated with FTC + TAF with EVG + COBI.

c. These subjects had an eGFR ranging from 60 to 69 mL per minute.

Patients with Hepatic Impairment

Emtricitabine: The pharmacokinetics of FTC has not been studied in subjects with hepatic impairment; however, FTC is not significantly metabolized by liver enzymes, so the impact of hepatic impairment should be limited.

Tenofovir Alafenamide: Clinically relevant changes in tenofovir pharmacokinetics in subjects with hepatic impairment were not observed in subjects with mild to moderate (Child-Pugh Class A and B) hepatic impairment.*(see Use in Specific Populations (8.7))*.

Hepatitis B and/or Hepatitis C Virus Coinfection

The pharmacokinetics of FTC and TAF have not been fully evaluated in subjects coinfected with hepatitis B and/or C virus.

Pediatric Patients

Mean exposures of TAF in 24 pediatric subjects aged 12 to less than 18 years who received FTC + TAF with EVG + COBI were decreased (23% for AUC) and FTC exposures were similar compared to exposures achieved in treatment-naïve adults following administration of this dosage regimen. The TAF exposure differences are not thought to be clinically significant based on exposure-response relationships (Table 6).

Table 6 Multiple Dose PK Parameters of Emtricitabine, Tenofovir Alafenamide and its Metabolite Tenofovir Following Oral Administration of FTC + TAF with EVG + COBI in HIV-Infected Pediatric Subjects Aged 12 to less than 18 Years[a]

Parameter Mean (CV%)	Emtricitabine	Tenofovir Alafenamide	Tenofovir
C_{max} (microgram per mL)	2.3 (22.5)	0.17 (64.4)	0.02 (23.7)
AUC_{24h} (microgram•hour per mL)	14.4 (23.9)	0.20[b] (50.0)	0.29[b] (18.8)
C_{trough} (microgram per mL)	0.10[b] (38.8)	NA	0.01 (21.4)

CV = Coefficient of Variation; NA = Not Applicable

a. From Intensive PK analysis in a trial in treatment naïve pediatric subjects with HIV-1 infection (N = 24).

b. N = 23

Exposures of FTC and TAF achieved in 23 pediatric subjects between the ages of 6 to less than 12 years and weighing at least 25 kg (55 lbs) who received FTC + TAF with EVG + COBI were higher (20 to 80% for AUC) than exposures achieved in adults following the administration of this dosage regimen; however, the increase was not considered clinically significant (Table 7).*(see Use in Specific Populations (8.4))*.

Table 7 Multiple Dose PK Parameters of Emtricitabine, Tenofovir Alafenamide and its Metabolite Tenofovir Following Oral Administration of FTC + TAF with EVG + COBI in HIV-Infected Pediatric Subjects Aged 6 to less than 12 Years[a]

Parameter Mean (CV%)	Emtricitabine	Tenofovir Alafenamide	Tenofovir
C_{max} (microgram per mL)	3.4 (27.0)	0.31 (61.2)	0.03 (20.8)
AUC_{24h} (microgram•hour per mL)	20.8[b] (18.9)	0.33 (44.8)	0.44 (20.9)
C_{trough} (microgram per mL)	0.11 (24.1)	NA	0.02 (24.9)

CV = Coefficient of Variation; NA = Not Applicable

a. From Intensive PK analysis in a trial in virologically-suppressed pediatric subjects with HIV-1 infection (N = 23).

b. N = 22

Geriatric Patients

Pharmacokinetics of FTC and TAF have not been fully evaluated in the elderly (65 years of age and older). Population pharmacokinetics analysis of HIV infected subjects in Phase 2 and Phase 3 trials of FTC + TAF and EVG + COBI showed that age did not have a clinically relevant effect on exposures of TAF up to 75 years of age *(see Use in Specific Populations (8.5))*.

Race

Based on population pharmacokinetic analyses, no dosage adjustment is recommended based on race.

Gender

Based on population pharmacokinetic analyses, no dosage adjustment is recommended based on gender.

Drug Interaction Studies

The effects of coadministered drugs on the exposure of TAF are shown in Table 8 and the effects of emtricitabine and tenofovir alafenamide tablets or its components on the exposure of coadministered drugs are shown in Table 9 (these studies were conducted with emtricitabine and tenofovir alafenamide tablets or the components of emtricitabine and tenofovir alafenamide tablets (FTC or TAF) administered alone). For information regarding clinical recommendations, *see Drug Interactions (7)*.

Table 8 Drug Interactions: Changes in TAF Pharmacokinetic Parameters in the Presence of Coadministered Drugs[a]

Coadministered Drug	Coadministered Drug(a) Dosage (once daily) (mg)	Tenofovir Alafenamide Dosage (once daily) (mg)	N	Mean Ratio of TAF PK Parameters (90% CI); No effect = 1.00		
				C_{max}	AUC	C_{min}
Atazanavir	300 (+ 100 ritonavir)	10	10	1.77 (1.28, 2.44)	1.91 (1.55, 2.35)	NC
Cobicistat	150	8	12	2.93 (2.20, 3.85)	2.65 (2.29, 3.07)	NC
Darunavir	800 (+ 150 cobicistat)	25[b]	11	0.93 (0.72, 1.21)	0.98 (0.80, 1.19)	NC
Darunavir	800 (+ 100 ritonavir)	10	10	1.42 (0.96, 2.09)	1.06 (0.84, 1.35)	NC
Dolutegravir	50	10	10	1.24 (0.88, 1.74)	1.19 (0.96, 1.48)	NC
Efavirenz	600	8[b] 40	11	0.79 (0.58, 1.05)	0.86 (0.72, 1.02)	NC
Lopinavir	800 (+ 200 ritonavir)	10	10	2.19 (1.72, 2.79)	1.47 (1.17, 1.85)	NC
Rilpivirine	25	25	17	1.01 (0.84, 1.22)	1.01 (0.94, 1.09)	NC
Sertraline	50 (dosed as a single dose)	10[c]	19	1.00 (0.86, 1.16)	0.96 (0.89, 1.03)	NC

NC = Not Calculated

a. All interaction studies conducted in healthy volunteers.

b. Study conducted with emtricitabine and tenofovir alafenamide tablet (FTC/TAF).

c. Study conducted with FTC + TAF with EVG + COBI.

Table 9 Drug Interactions: Changes in PK Parameters for Coadministered Drug in the Presence of emtricitabine and tenofovir alafenamide tablets or the Individual Components[a]

Coadministered Drug	Coadministered Drug Dosage (once daily): (mg)	Tenofovir Alafenamide Dosage (once daily) (mg)	N	Mean Ratio of Coadministered Drug PK Parameter(90% CI); No effect = 1.00		
				C_{max}	AUC	C_{min}
Atazanavir	300 + 100 ritonavir	10	10	0.99 (0.89, 1.07)	0.99 (0.90, 1.01)	1.00 (0.96, 1.04)
Darunavir	800 + 150 cobicistat	25[b]	11	1.02 (0.96, 1.09)	0.99 (0.92, 1.07)	0.97 (0.92, 1.15)
Darunavir	800 + 100 ritonavir	10	10	0.99 (0.91, 1.08)	1.01 (0.96, 1.06)	1.13 (0.95, 1.34)
Dolutegravir	50 mg	10	10	1.15 (1.04, 1.27)	1.02 (0.97, 1.08)	1.05 (0.97, 1.13)
Lopinavir	800 + 200 ritonavir	10	10	1.00 (0.95, 1.06)	1.00 (0.92, 1.08)	0.98 (0.85, 1.12)
Midazolam[c]	2.5 (single dose, oral)/ 1 (single dose, intravenous)	25	18	1.02 (0.87, 1.19) 0.98 (0.89, 1.11)	1.13 (1.04, 1.23) 1.08 (1.04, 1.14)	NC NC
Rilpivirine	25	25	16	0.93 (0.83,0.99)	1.01 (0.96, 1.06)	1.13 (1.04, 1.23)
Sertraline	50 (single dose)	10[c]	19	1.14 (0.94, 1.38)	0.93 (0.77, 1.13)	NC

NC = Not Calculated

a. All interaction studies conducted in healthy volunteers.

b. Study conducted with emtricitabine and tenofovir alafenamide tablets (FTC/TAF).

c. A sensitive CYP3A4 substrate.

d. Study conducted with FTC + TAF with EVG + COBI.

12.4 Microbiology

Mechanism of Action

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

Tenofovir Alafenamide: TAF is a phosphonoamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analog). Plasma exposure to TAF allows for permeation into cells and then TAF is intracellularly converted to tenofovir through hydrolysis by cathepsin A. Tenofovir is subsequently phosphorylated by cellular kinases to the active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HIV-1 replication through incorporation into viral DNA by the HIV reverse transcriptase, which results in DNA chain termination.

Tenofovir has activity against HIV-1. Cell culture studies have shown that both tenofovir and FTC can be fully phosphorylated when combined in cells. diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase (and there is no evidence of toxicity to mitochondria in cell cultures.

Antiviral Activity in Cell Culture

Emtricitabine: The antiviral activity of FTC against laboratory and clinical isolates of HIV-1 was assessed in T lymphoblastoid cell lines, the MAGI-CCR5 cell line, and primary peripheral blood mononuclear cells. The EC_{50} values for FTC were in the range of 0.001-0.4 micromolar. FTC displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, and G (EC_{50} values ranged from 0.007–0.075 micromolar) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 0.007–1.5 micromolar).

In a study of FTC with a broad panel of representatives from the major classes of approved anti-HIV agents (NRTIs, non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase strand transfer inhibitors (INSTIs), and PIs) no antagonism was observed for these combinations.

Tenofovir Alafenamide: The antiviral activity of TAF against laboratory and clinical isolates of HIV-1 subtype B was assessed in lymphoblastoid cell lines, PBMCs, primary monocytes/macrophages and CD4-T lymphocytes. The EC_{50} values for TAF ranged from 2.0 to 14.7 nM.

TAF displayed antiviral activity in cell culture against all HIV-1 groups (M, N, O), including sub-types A, B, C, D, E, F, and G (EC_{50} values ranged from 0.10 to 12.0 nM) and strain specific activity against HIV-2 (EC_{50} values ranged from 0.91 to 2.63 nM).

In a study of TAF with a broad panel of representatives from the major classes of approved anti-HIV agents (NRTIs, NNRTIs, INSTIs, and PIs) no antagonism was observed for these combinations.

Resistance

In Cell Culture

Emtricitabine: HIV-1 isolates with reduced susceptibility to FTC were selected in cell culture and in subjects treated with FTC. Reduced susceptibility to FTC was associated with M184V or I substitutions in HIV-1 RT.

Tenofovir Alafenamide: HIV-1 isolates with reduced susceptibility to TAF were selected in cell culture. HIV-1 isolates selected by TAF expressed a K65R substitution in HIV-1 RT, sometimes in the presence of S68N or L429R substitutions; in addition, a K70E substitution in HIV-1 RT was observed.

In Clinical Trials

The resistance profile of emtricitabine and tenofovir alafenamide tablets in combination with other antiretroviral agents for the treatment of HIV-1 infection is based on studies of FTC + TAF with EVG + COBI in the treatment of HIV-1 infection. In pooled analysis of antiretroviral-naïve subjects, genotyping was performed on plasma HIV-1 isolates from all subjects with HIV-1 RNA greater than 400 copies per mL at confirmed virologic failure, at Week 48, or at time of early study drug discontinuation. Genotypic resistance developed in 7 of 14 evaluable subjects. The resistance-associated substitutions that emerged were M184V/I (N = 7) and K65R (N = 1). Three subjects had virus with emergent R, H, or E at the polymorphic Q237 residue in reverse transcriptase.

One subject was identified with emergent resistance to FTC (M184M/I) out of 4 virologic failure subjects in a clinical study of virologically-suppressed subjects who switched from a regimen containing FTC + TDF to FTC + TAF with EVG + COBI (N = 799).

Cross-Resistance

Emtricitabine: FTC-resistant viruses with the M184V or I substitution were cross-resistant to lamivudine, but retained sensitivity to didanosine, stavudine, tenofovir, and zidovudine.

Viruses harboring substitutions conferring reduced susceptibility to stavudine and zidovudine-thymidine analog substitutions (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) or didanosine (L74V) remained sensitive to FTC. HIV-1 containing the K103N substitution or other substitutions associated with resistance to NNRTIs was susceptible to FTC.

Tenofovir Alafenamide: Tenofovir resistance substitutions K65R and K70E result in reduced susceptibility to abacavir, didanosine, emtricitabine, lamivudine, and tenofovir.

HIV-1 with multiple thymidine analog substitutions (M41L, D67N, K70R, L210W, T215F/Y, K219Q/E/N/R), or multinucleoside resistant HIV-1 with a T69S double insertion mutation or with a Q151M substitution complex including K65R, showed reduced susceptibility to TAF in cell culture.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Emtricitabine

In long-term carcinogenicity studies of FTC, no drug-related increases in tumor incidence were found in mice at doses up to 750 mg per kg per day (23 times the human systemic exposure at the recommended dose of 200 mg per day in emtricitabine and tenofovir alafenamide tablets) or in rats at doses up to 600 mg per kg per day (28 times the human systemic exposure at the recommended dose in emtricitabine and tenofovir alafenamide tablets).

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

FTC did not affect fertility in male rats at approximately 140 times or in male and female mice at approximately 60 times higher exposures (AUC) than in humans given the recommended 200 mg daily dosage in emtricitabine and tenofovir alafenamide tablets. 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 times higher than human exposures at the recommended 200 mg daily dosage in emtricitabine and tenofovir alafenamide tablets.

Tenofovir Alafenamide

Since TAF is rapidly converted to tenofovir and a lower tenofovir exposure in rats and mice was observed after TAF administration compared to TDF administration, carcinogenicity studies were conducted only with TDF. Long-term oral carcinogenicity studies of TDF in mice and rats were carried out at exposures up to approximately 10 times (mice) and 4 times (rats) those observed in humans at the recommended dose of TDF (300 mg) for HIV-1 infection. The tenofovir exposure in these studies was approximately 167 times (mice) and 13 times (rat) those observed in humans after administration of the daily recommended dose of emtricitabine and tenofovir alafenamide tablets. At the high dose in female mice, liver adenomas were increased at tenofovir exposures approximately 10 times (300 mg TDF) and 167 times (emtricitabine and tenofovir alafenamide tablets) the exposure observed in humans. In rats, the study was negative for carcinogenic findings.

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

There were no effects on fertility, mating performance or early embryonic development when TAF was administered to male rats at a dose equivalent to 62 times (25 mg TAF) the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 14 days prior to mating through Day 7 of gestation.

13.2 Animal Toxicology and/or Pharmacology

Minimal to slight infiltration of mononuclear cells in the posterior urea was observed in dogs with similar severity after three and nine month administration of TAF; reversibility was seen after a three month recovery period. No eye toxic was observed in the dog at systemic exposures of 5 (TAF) and 15 (tenofovir) times the exposure seen in humans with the recommended daily TAF dose in emtricitabine and tenofovir alafenamide tablets.

14 CLINICAL STUDIES

In trials of FTC + TAF with EVG + COBI in HIV-1 infected adults as initial therapy in those with no antiretroviral treatment history (N = 866) and to replace a stable antiretroviral regimen in those who were virologically suppressed for at least 6 months with no known resistance substitutions (N = 799), 92% and 96% of patients in the two populations, respectively, had HIV-1 RNA less than 50 copies per mL at Week 48.

An open-label, single arm trial of FTC + TAF with EVG + COBI enrolled 50 treatment-naïve HIV-1 infected adolescents aged 12 to less than 18 years weighing at least 35 kg (cohort 1) and 23 virologically suppressed children aged 6 to less than 12 years weighing at least 25 kg (cohort 2). In cohort 1, the virologic response rate (i.e., HIV-1 RNA less than 50 copies per mL) was 92% (46/50) and the mean increase from baseline in CD4+ cell count was 224 cells per mm^3 at Week 48. In cohort 2, 100% of subjects remained virologically suppressed at Week 24. From a mean (SD) baseline CD4+ cell count of 906 (201.7), the mean change from baseline in CD4+ cell count was -150 cells/mm^3 and the mean (SD) change in CD4% was -1.5% (3.7%) at Week 24. All subjects maintained CD4+ cell counts above 400 cells/mm*(see Adverse Reactions (6.1) and Use in Specific Populations (8.4))*.

In a trial in 248 HIV-1 infected adult patients with estimated creatinine clearance greater than 30 mL per minute but less than 70 mL per minute, 95% (235/248) of the combined population of treatment-naïve subjects (N = 8) began on FTC + TAF with EVG + COBI and those previously virologically suppressed on other regimens (N = 240) and switched to FTC + TAF with EVG + COBI had HIV-1 RNA less than 50 copies per mL at Week 24.

16 HOW SUPPLIED/STORAGE AND HANDLING

Emtricitabine and Tenofovir alafenamide tablets **Pink, oval shaped, biconvex film coated tablets debossed with 'V' on one side and '21' on other side.** Each film-coated tablet contains 200 mg of Emtricitabine and 25 mg Tenofovir alafenamide equivalent to 28.04 mg of Tenofovir alafenamide hemifumarate. They are supplied as follows:

Bottle of 30 tablets NDC: 71785-1024-0

STORAGE CONDITION:

Store at temperatures not exceeding 30°C.

- Keep container tightly closed.
- Dispense only in original container.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Post-treatment Acute Exacerbation of Hepatitis B in Patients with HBV Coinfection

Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued products containing FTC and/or TDF, and may likewise occur with discontinuation of emtricitabine and tenofovir alafenamide tablets *(see Warnings and Precautions (5.1))*. Advise the patient to not discontinue emtricitabine and tenofovir alafenamide tablets without first informing their healthcare provider.

Immune Reconstitution Syndrome

Advise patients to inform their healthcare provider immediately of any symptoms of infection, as 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.*(see Warnings and Precautions (5.2))*.

New Onset or Worsening Renal Impairment

Advise patients to avoid taking emtricitabine and tenofovir alafenamide tablets with concurrent or recent use of nephrotoxic agents. Renal impairment, including cases of acute renal failure, has been reported in association with the use of tenofovir prodrugs.*(see Warnings and Precautions (5.3))*.

Lactic Acidosis and Severe Hepatomegaly

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with use of drugs similar to emtricitabine and tenofovir alafenamide tablets. Advise patients that they should stop emtricitabine and tenofovir alafenamide tablets if they develop clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity.*(see Warnings and Precautions (5.4))*.

Missed Dosage

Inform patients that it is important to take emtricitabine and tenofovir alafenamide tablets on a regular dosing schedule with or without food and to avoid missing doses as it can result in development of resistance.*(see Dosage and Administration (2.2))*.

Pregnancy Registry

Inform patients that there is an antiretroviral pregnancy registry to monitor fetal outcomes of pregnant women exposed to emtricitabine and tenofovir alafenamide tablets *(see Use in Specific Populations (8.1))*.

Lactation

Instruct women with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in breast milk.*(see Use in Specific Populations (8.2))*.

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

ADR REPORTING STATEMENT: For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Please seek medical attention immediately at the first sign of any adverse drug reaction.

TAFNEXT-EM Emtricitabine and Tenofovir Alafenamide Tablets is manufactured under a license from Gilead Sciences, Inc.

Manufactured for Hetero Labs Limited by:
ANNORA PHARMA PRIVATE LIMITED
Sy. No. 261, Annaram Village, Gummadidala Mandal,
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Patient Information

EMTRICITABINE AND TENOFOVIR ALAFENAMIDE

200 mg / 25 mg film-coated tablet

Antiretroviral

Important: Ask your healthcare provider or pharmacist about medicines that should not be taken with emtricitabine and tenofovir alafenamide tablets. For more information, see the section "What should I tell my healthcare provider before taking emtricitabine and tenofovir alafenamide tablets?"

What is the most important information I should know about Emtricitabine and Tenofovir alafenamide tablets?

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

- **Worsening of Hepatitis B virus infection. Emtricitabine and tenofovir alafenamide tablets is not for use to treat chronic hepatitis B virus (HBV) infection. If you have hepatitis B virus (HBV) infection and take emtricitabine and tenofovir alafenamide tablets, your HBV may get worse (flare-up) if you stop taking emtricitabine and tenofovir alafenamide tablets. A "flare-up" is when your HBV infection suddenly returns in a worse way than before.**
- It is not known if emtricitabine and tenofovir alafenamide tablets is safe and effective in people who have both HIV-1 and HBV infection.
- Do not run out of emtricitabine and tenofovir alafenamide tablets. Refill your prescription or talk to your healthcare provider before your emtricitabine and tenofovir alafenamide tablets is all gone.
- Do not stop taking emtricitabine and tenofovir alafenamide tablets without first talking to your healthcare provider.
- If you stop taking emtricitabine and tenofovir alafenamide tablets, your healthcare provider will need to check your health often and do blood tests regularly for several months to check your HBV infection. Tell your healthcare provider about any new or unusual symptoms you may have after you stop taking emtricitabine and tenofovir alafenamide tablets.

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

What is emtricitabine and tenofovir alafenamide tablets?

Emtricitabine and tenofovir alafenamide tablets is a prescription medicine that is used to treat Human Immunodeficiency Virus 1 (HIV-1) in adults and children who weigh at least 77 pounds (35 kg) together with other anti-HIV-1 medicines in children who weigh at least 55 pounds (25 kg) and less than 77 pounds (35 kg) together with certain other anti-HIV-1 medicines. Your healthcare provider will determine which other anti-HIV-1 medicines are used with emtricitabine and tenofovir alafenamide tablets. HIV-1 is the virus that causes AIDS (Acquired Immune Deficiency Syndrome). Emtricitabine and tenofovir alafenamide tablets is not for use to help reduce the risk of getting HIV-1 infection by sexual contact in adults at high risk. Emtricitabine and tenofovir alafenamide tablets contains the prescription medicines emtricitabine (EMTRIVA®) and tenofovir alafenamide. It is not known if emtricitabine and tenofovir alafenamide tablets is safe and effective in children who weigh less than 55 pounds (25 kg).

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

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

- have liver problems, including hepatitis B virus infection
- have kidney problems
- are pregnant or plan to become pregnant. It is not known if emtricitabine and tenofovir alafenamide tablets can harm your unborn baby. Tell your healthcare provider if you become pregnant during treatment with emtricitabine and tenofovir alafenamide tablets.

Pregnancy Registry: There is a pregnancy registry for women who take antiretroviral medicines 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. Do not breastfeed if you take emtricitabine and tenofovir alafenamide tablets.
- You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.
- At least one of the medicines in emtricitabine and tenofovir alafenamide tablets can pass to your baby in your breast milk. It is not known if the other medicine in emtricitabine and tenofovir alafenamide tablets can pass into your breast milk. Talk with your healthcare provider about the best way to feed your baby during treatment with emtricitabine and tenofovir alafenamide tablets.

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 alafenamide 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 alafenamide 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 alafenamide tablets with other medicines.

How should I take emtricitabine and tenofovir alafenamide tablets?

- Take emtricitabine and tenofovir alafenamide tablets exactly as your healthcare provider tells you to take it. Emtricitabine and tenofovir alafenamide tablets must be taken together with other HIV-1 medicines to treat HIV-1 infection.
- Take emtricitabine and tenofovir alafenamide tablets 1 time each day with or without food.
- Do not change your dose or stop taking emtricitabine and tenofovir alafenamide tablets without first talking with your healthcare provider. Stay under a healthcare provider's care during treatment with emtricitabine and tenofovir alafenamide tablets.
- Do not miss a dose of emtricitabine and tenofovir alafenamide tablets.
- If you take too much emtricitabine and tenofovir alafenamide tablets, call your healthcare provider or go to the nearest hospital emergency room right away.
- When your emtricitabine and tenofovir alafenamide tablets supply starts to run low, get more from your healthcare provider or pharmacy. This is very important because 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 alafenamide tablets and become harder to treat.

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

Emtricitabine and tenofovir alafenamide tablet may cause serious side effects, including:

- **See "What is the most important information I should know about emtricitabine and tenofovir alafenamide tablets?" Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV-1 medicines. 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.
- **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 alafenamide tablets. Your healthcare provider may tell you to stop taking emtricitabine and tenofovir alafenamide tablets if you develop new or worse kidney problems.
- **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 effect of emtricitabine and tenofovir alafenamide tablets is nausea. These are not all the possible side effects of emtricitabine and tenofovir alafenamide 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 ALAFENAMIDE TABLETS?

- Store emtricitabine and tenofovir alafenamide tablets below 30 °C.
- Keep emtricitabine and tenofovir alafenamide tablets in its original container.
- Keep the container tightly closed.

Keep emtricitabine and tenofovir alafenamide tablets and all medicines out of the reach and sight of children.

General information about the safe and effective use of emtricitabine and tenofovir alafenamide tablets.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use emtricitabine and tenofovir alafenamide tablets for a condition for which it was not prescribed. Do not give emtricitabine and tenofovir alafenamide 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 alafenamide tablets that is written for health professionals. For more information, call 1-866-495-1995.

What are the ingredients in emtricitabine and tenofovir alafenamide tablets?

Active ingredients: emtricitabine and tenofovir alafenamide.

Inactive ingredients: croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The tablets are film-coated with a coating material containing polyvinyl alcohol, titanium dioxide, macrogol/peg 3350, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

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