

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Emtricitabine and Tenofovir alafenamide Tablets 200mg/25mg

2. Qualitative and quantitative composition

Each film-coated tablet contains 200 mg of Emtricitabine and 25 mg Tenofovir alafenamide equivalent to 28.043 mg of Tenofovir alafenamide hemifumarate.

For full list of excipients, see section 6.1.

3. Pharmaceutical form

Dosage form: Film coated tablet

Description: Pink, oval shaped, biconvex film coated tablets debossed with 'V' on one side and '21' on other side.

4. Clinical particulars

4.1 Therapeutic indications

Treatment of HIV-1 Infection

Emtricitabine and tenofovir alafenamide tablets are 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 tablets are 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.

HIV-1 Pre-Exposure Prophylaxis (PrEP)

Emtricitabine and tenofovir alafenamide tablets are indicated in at-risk adults and adolescents weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection

from sexual acquisition, excluding individuals at risk from receptive vaginal sex. Individuals must have a negative HIV-1 test immediately prior to initiating emtricitabine and tenofovir alafenamide tablets for HIV-1 PrEP [see Dosage and Administration (2.2) and Warnings and Precautions (5.2)].

Limitations of Use:

The indication does not include use of emtricitabine and tenofovir alafenamide tablets in individuals at risk of HIV-1 from receptive vaginal sex because effectiveness in this population has not been evaluated [see Clinical Studies (14.3)].

4.2 Posology and method of administration

Testing When Initiating and During Use of Emtricitabine and Tenofovir Alafenamide Tablets for Treatment of HIV-1 Infection or for HIV-1 PrEP

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

Prior to or when initiating emtricitabine and tenofovir alafenamide tablets, and during use of emtricitabine and tenofovir alafenamide 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 (5.4)].

HIV-1 Screening for Individuals Receiving Emtricitabine and Tenofovir Alafenamide Tablets for HIV-1 PrEP

Screen all individuals for HIV-1 infection immediately prior to initiating emtricitabine and tenofovir alafenamide tablets for HIV-1 PrEP and at least once every 3 months while taking emtricitabine and tenofovir alafenamide 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)].

Recommended Dosage for Treatment of HIV-1 Infection in Adults and Pediatric Patients Weighing at Least 25 kg

Emtricitabine and tenofovir alafenamide tablet 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 for treatment of HIV-1 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 coadministered 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.

Recommended Dosage for HIV-1 PrEP in Adults and Adolescents Weighing at Least 35 kg The dosage of emtricitabine and tenofovir alafenamide tablets for HIV-1 PrEP is one tablet (containing 200 mg of FTC and 25 mg of TAF) once daily taken orally with or without food in HIV-1 uninfected adults and adolescents weighing at least 35 kg and with a creatinine clearance greater than or equal to 30 mL per minute, excluding individuals at risk from receptive vaginal sex [see Clinical Pharmacology (12.3)].

Not Recommended in Individuals with Severe Renal Impairment for Treatment of HIV-1 Infection or for HIV-1 PrEP

Emtricitabine and tenofovir alafenamide tablets are not recommended in individuals with estimated creatinine clearance below 30 mL per minute [see Warnings and Precautions (5.4) and Use in Specific Populations (8.6)].

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Severe Acute Exacerbation of Hepatitis B in Individuals with HBV Infection

All individuals should be tested for the presence of hepatitis B virus (HBV) before or when initiating emtricitabine and tenofovir alafenamide [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 products containing FTC and/or tenofovir disoproxil fumarate (TDF) and may occur with discontinuation of emtricitabine and tenofovir alafenamide. Individuals infected with HBV who discontinue emtricitabine and tenofovir alafenamide 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 post-treatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure. HBV-uninfected individuals should be offered vaccination.

Comprehensive Management to Reduce the Risk of Sexually Transmitted Infections, Including HIV-1, and Development of HIV-1 Resistance When Emtricitabine and Tenofovir Alafenamide is Used for HIV-1 PrEP

Use emtricitabine and tenofovir alafenamide for HIV-1 PrEP to reduce the risk of HIV-1 infection as part of a comprehensive prevention strategy, 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 alafenamide for HIV-1 PrEP to maximal protection against HIV-1 infection is unknown.

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

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

Use emtricitabine and tenofovir alafenamide to reduce the risk of acquiring HIV-1 only in individuals confirmed to be HIV-1 negative. HIV-1 resistance substitutions may emerge in individuals with undetected HIV-1 infection who are taking only emtricitabine and tenofovir alafenamide, because emtricitabine and tenofovir alafenamide 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 alafenamide 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 alafenamide 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 alafenamide 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 alafenamide dosing schedule. The effectiveness of emtricitabine and tenofovir alafenamide in reducing the risk of acquiring HIV-1 is strongly correlated with adherence, as demonstrated by measurable drug levels in a clinical trial of emtricitabine and tenofovir alafenamide 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)].

Immune Reconstitution Syndrome

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

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

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) in HIV-1 infected patients 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 estimated creatinine clearance 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 estimated creatinine clearance 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 estimated creatinine clearance between 30 and 50 mL per minute [see Adverse Reactions (6.1)]. Emtricitabine and tenofovir alafenamide is not recommended in individuals with estimated creatinine clearance below 30 mL per minute because data in this population are insufficient.

Individuals 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.

Prior to or when initiating emtricitabine and tenofovir alafenamide, and during treatment with emtricitabine and tenofovir alafenamide 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. Discontinue emtricitabine and tenofovir alafenamide in individuals who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

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 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).

4.5 Interaction with other medicinal products and other forms of interaction

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 5). 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 and development of resistance. Coadministration of emtricitabine and tenofovir alafenamide 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 weak inhibitor of CYP3A in vitro. TAF is not an inhibitor or inducer of CYP3A in vivo.

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 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, valganciclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs [see Warnings and Precautions (5.4)].

Established and Other Potentially Significant Interactions

Table 5 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, the components of emtricitabine and tenofovir alafenamide tablets (emtricitabine and tenofovir alafenamide) as individual agents or are predicted drug interactions that may occur with emtricitabine and tenofovir alafenamide. For magnitude of interaction, see Clinical Pharmacology (12.3).

Table 5 Established and Other Potentially Significant 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 is not recommended.
Other Agents		
Anticonvulsants: carbamazepine oxcarbazepine phenobarbital phenytoin	↓ TAF	Consider alternative anticonvulsant.
Antimycobacterials: rifabutin rifampin rifapentine	↓ TAF	Coadministration of emtricitabine and tenofovir alafenamide with rifabutin, rifampin, or rifapentine is not recommended.
Herbal Products: St. John's wort (<i>Hypericum perforatum</i>)	↓ TAF	Coadministration of emtricitabine and tenofovir alafenamide with St. John's wort is not recommended.

a. This table is not all inclusive.

b. ↓=Decrease

Drugs without Clinically Significant Interactions with Emtricitabine and Tenofovir Alafenamide

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 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 is combined with the following drugs: buprenorphine, itraconazole, ketoconazole, lorazepam, methadone, midazolam, naloxone, norbuprenorphine, norgestimate/ethinyl estradiol, and sertraline.

4.6 Pregnancy and lactation Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

Available data from the APR show no increase in the risk of overall major birth defects for emtricitabine (FTC) 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). There are insufficient tenofovir alafenamide (TAF) data from the APR to adequately assess the risk of major birth defects. The rate of miscarriage for individual drugs 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 to 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 (see Data). 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. 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.

Data

Human Data

Emtricitabine: Based on prospective reports to the APR through January 2019 of over 4,450 exposures to FTC-containing regimens during pregnancy (including over 3,150 exposed in the first trimester and over 1,300 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: 1.9% to 3.0%) with first trimester exposure to FTC-containing regimens and 2.3% (95% CI: 1.5% to 3.2%) with the second/third trimester exposure to FTC-containing regimens.

Tenofovir Alafenamide: Based on prospective reports to the APR of over 220 exposures to TAF-containing regimens during pregnancy (including over 160 exposed in the first trimester and over 60 exposed in the second/third trimester), there have been 6 birth defects with first trimester exposure to TAF-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 (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. 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.

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-1.

Based on limited data, FTC has been shown to be present in human breast milk;

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

It is not known if emtricitabine and tenofovir alafenamide 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 taking emtricitabine and tenofovir alafenamide for the treatment of HIV-1 (see Data).

Data

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. 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.

Pediatric Use

Treatment of HIV-1 Infection

The safety and effectiveness of emtricitabine and tenofovir alafenamide, 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 Indications and Usage (1.1) and Dosage and Administration (2.3)].

Use of emtricitabine and tenofovir alafenamide 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 (14.2)].

Use of emtricitabine and tenofovir alafenamide 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 (14.2)].

Safety and effectiveness of emtricitabine and tenofovir alafenamide coadministered 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 (2.3)].

Safety and effectiveness of emtricitabine and tenofovir alafenamide for treatment of HIV-1 infection in pediatric patients less than 25 kg have not been established.

HIV-1 PrEP

Safety and effectiveness of emtricitabine and tenofovir alafenamide for HIV-1 PrEP in at-risk adolescents weighing at least 35 kg, excluding individuals at risk from receptive vaginal sex, is supported by data from an adequate and well-controlled trial of emtricitabine and tenofovir alafenamide 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 TAF, with EVG+COBI, in HIV-1 infected adults and pediatric subjects [see Dosage and Administration (2.4),

Adverse Reactions (6.1), Clinical Pharmacology (12.3 and 12.4), and Clinical Studies (14)].

While using emtricitabine and tenofovir alafenamide for HIV-1 PrEP, HIV-1 testing should be repeated at least every 3 months, and upon diagnosis of any other STIs. Previous studies in at-risk adolescents indicated waning adherence to a daily oral PrEP regimen once visits were switched from monthly to quarterly visits. Adolescents may therefore benefit from more frequent visits and counseling [see Warnings and Precautions (5.2)].

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

Geriatric Use

In clinical trials of an FTC+TAF-containing regimen for treatment of HIV-1, 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.

Renal Impairment

Emtricitabine and tenofovir alafenamide is not recommended in individuals with severe renal impairment (estimated creatinine clearance below 30 mL per minute). No dosage adjustment of emtricitabine and tenofovir alafenamide is recommended in individuals with estimated creatinine clearance greater than or equal to 30 mL per minute [see Dosage and Administration (2.5) and Clinical Studies (14.2)].

Hepatic Impairment

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

4.7 Undesirable Effects

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

- Severe Acute Exacerbations of Hepatitis B [see Warnings and Precautions (5.1)].
- Immune Reconstitution Syndrome [see Warnings and Precautions (5.3)].
- New Onset or Worsening Renal Impairment [see Warnings and Precautions (5.4)].
- Lactic Acidosis/Severe Hepatomegaly with Steatosis [see Warnings and Precautions (5.5)].

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 (14.2)]. 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 at Week 48; 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.

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.

Bone Mineral Density Effects

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/mm³ [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			
		Week 2	Week 4	Week 12	Week 24
CD4+ Cell Count (cells/mm ³)	966 (201.7) ^a	-162	-125	-162	-150
CD4%	40 (5.3) ^a	+0.5%	-0.1%	-0.8%	-1.5%

a. Mean (SD)

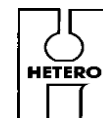
Adverse Reactions from Clinical Trial Experience in HIV-1 Uninfected Individuals Taking Emtricitabine and Tenofovir Alafenamide for HIV-1 PrEP

The safety profile of emtricitabine and tenofovir alafenamide for HIV-1 PrEP was comparable to that observed in clinical trials of HIV-infected subjects based on a double-blind, randomized, active-controlled trial (DISCOVER) in which a total of 5,387 HIV-1 uninfected adult men and transgender women who have sex with men received emtricitabine and tenofovir alafenamide (N=2,694) or TRUVADA (N=2,693) once daily for HIV-1 PrEP [see Clinical Studies (14.3)]. Median duration of exposure was 86 and 87 weeks, respectively. The most common adverse reaction in participants who received emtricitabine and tenofovir alafenamide (incidence greater than or equal to 5%, all grades) was diarrhea (5%). Table 2 provides a list of the most common adverse reactions that occurred in 2% or more of participants in either treatment group. The proportion of participants who discontinued treatment with emtricitabine and tenofovir alafenamide or TRUVADA due to adverse events, regardless of severity, was 1.3% and 1.8%, respectively.

Table 2 Adverse Reactions (All Grades) Reported in ≥2% in Either Arm in the DISCOVER Trial of HIV-1 Uninfected Participants

	Emtricitabine and Tenofovir Alafenamide (N=2,694)	TRUVA DA (N=2,693)
Diarrhea	5%	6%
Nausea	4%	5%
Headache	2%	2%
Fatigue	2%	3%
Abdominal pain ^a	2%	3%

a. Includes the following terms: abdominal pain, abdominal pain upper, abdominal pain lower, gastrointestinal pain, and abdominal discomfort

**Summary of Product Characteristics***Renal Laboratory Tests*

Changes from baseline to Week 48 in renal laboratory data are presented in Table 3. The long-term clinical significance of these renal laboratory changes on adverse reaction frequencies between emtricitabine and tenofovir alafenamide and TRUVADA is not known.

Table 3 Laboratory Assessments of Renal Function Reported in HIV-1 Uninfected Participants Receiving Emtricitabine and Tenofovir Alafenamide or TRUVADA in the DISCOVER Trial

	Emtricitabine and Tenofovir Alafenamide (N=2,694)	TRUVADA (N=2,693)
Serum Creatinine (mg/dL) ^a Change at Week 48	-0.01 (0.107)	0.01 (0.111)
eGFR _{CG} (mL/min) ^b Change at Week 48	1.8 (-7.2, 11.1)	-2.3 (-10.8, 7.2)
Percentage of Participants who Developed UPCR >200 mg/g ^c At Week 48	0.7%	1.5%

eGFR_{CG}=estimated Glomerular Filtration Rate by Cockcroft-Gault; UPCR=urine protein/creatinine ratio

a. Mean (SD).

b. Median (Q1, Q3).

c. Based on N who had normal UPCR ($\leq$ 200 mg/g) at baseline.

Bone Mineral Density Effects

In the DISCOVER trial, mean increases from baseline to Week 48 of 0.5% at the lumbar spine (N=159) and 0.2% at the total hip (N=158) were observed in participants receiving emtricitabine and tenofovir alafenamide, compared to mean decreases of 1.1% at the lumbar spine (N=160) and 1.0% at the total hip (N=158) in participants receiving TRUVADA. BMD declines of 5% or greater at the lumbar spine and 7% or greater at the total hip were experienced by 4% and 1% of participants, respectively, in both treatment groups at Week 48. The long-term

clinical significance of these BMD changes is not known.

Serum Lipids

Changes from baseline to Week 48 in total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, and total cholesterol to HDL ratio are presented in Table 4

Table 4 Fasting Lipid Values, Mean Change from Baseline, Reported in HIV-1 Uninfected Participants Receiving Emtricitabine and Tenofovir Alafenamide or TRUVADA in the DISCOVER Trials³

	Emtricitabine and Tenofovir Alafenamide (N=2,694)		TRUVA DA (N=2,693)	
	Baseline	Week 48	Baseline	Week 48
	mg/dL	Change ^b	mg/dL	Change ^b
Total Cholesterol (fasted)	176 ^c	0 ^c	176 ^d	-12 ^d
HDL-Cholesterol (fasted)	51 ^c	-2 ^c	51 ^d	-5 ^d
LDL-Cholesterol (fasted)	103 ^e	0 ^e	103 ^f	-7 ^f
Triglycerides (fasted)	109 ^c	+9 ^c	111 ^d	-1 ^d
Total Cholesterol to HDL ratio	3.7 ^c	0.2 ^c	3.7 ^d	0.1 ^d

a. Excludes subjects who received lipid lowering agents during the treatment period.

b. The baseline and change from baseline are for subjects with both baseline and Week 48 values.

c. N=1,098

d. N=1,124

e. N=1,079

f. N=1,107

Postmarketing Experience

The following reactions have been identified during post approval use of products containing TAF. Because these events 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.

4.8 Overdose

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

Emtricitabine (FTC): Limited clinical experience is available at doses higher than the recommended dose of FTC in emtricitabine and tenofovir alafenamide. In one clinical pharmacology study, single doses of FTC 1200 mg (6 times the FTC dose in emtricitabine and tenofovir alafenamide) 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) 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%.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after Authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Pharmacovigilance Electronic Reporting System (PvERS)

<https://pv.pharmacyboardkenya.org/>

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: *Anti-retroviral*

ATC code: J05AR17 Emtricitabine and Tenofovir alafenamide

Pharmaco-dynamic properties

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, FTC, or the combination of FTC and TAF on the QT interval is not known.

5.2 Pharmacokinetic properties

Absorption, Distribution, Metabolism, and Excretion

The pharmacokinetic (PK) properties of the components of emtricitabine and tenofovir alafenamide are provided in Table 6. The multiple dose PK parameters of FTC and TAF and its metabolite tenofovir are provided in Table 7. HIV status has no effect on the pharmacokinetics of FTC and TAF in adults.

Table 6 Pharmacokinetic Properties of the Components of Emtricitabine and Tenofovir Alafenamide

	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	<i>In vitro</i>	<i>Ex vivo</i>
Blood-to-plasma ratio	0.6	1.0
Metabolism		
Metabolism	Not significantly metabolized	Cathepsin A ^b (PBMCs) CES1 (hepatocytes) CYP3A (minimal)
Elimination		

Major route of elimination	Glomerular filtration and active tubular secretion	Metabolism (>80% of oral dose)
t _{1/2} (h) ^c	10	0.51
% Of dose excreted in urine ^d	70	<1
% Of dose excreted in feces ^d	13.7	31.7

PBMCs=peripheral blood mononuclear cells; CES1=carboxylesterase 1

- 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.
- 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.
- 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 to 180 hours within PBMCs.
- Dosing in mass balance studies: FTC (single dose administration of [¹⁴C] emtricitabine after multiple dosing of emtricitabine for 10 days); TAF (single dose administration of [¹⁴C] tenofovir alafenamide).

Table 7 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 ^b	Tenofovir ^c
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

- From Intensive PK analysis in a phase 2 trial in HIV-infected adults treated with FTC+TAF and EVG+COBI.
- From Population PK analysis in two trials of treatment-naïve adults with HIV-1 infection treated with FTC+TAF with EVG+COBI (N=539).
- 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

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)].

Pediatric Patients

Treatment of HIV-1 Infection: 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 8).

Table 8 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 _{tau} (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 (38.9)	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 9) [see Use in Specific Populations (8.4)].

Table 9 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 _{tau} (microgram•hour per mL)	20.6 ^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

HIV-1 PrEP: The pharmacokinetic data for FTC and TAF following administration of emtricitabine and tenofovir alafenamide in HIV-1 uninfected adolescents weighing 35 kg and above are not available. The dosage recommendations of emtricitabine and tenofovir alafenamide for HIV-1 PrEP in this population are based on known pharmacokinetic information in HIV-infected adolescents taking FTC and TAF for treatment [see Use in Specific Populations (8.4)].

Race and Gender

Based on population pharmacokinetic analyses, there are no clinically meaningful differences based on race or gender.

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 10).

Table 10 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

Creatinine Clearance	AUC_{tau} (microgram · hour per mL) Mean (CV%)		
	≥90 mL per minute (N=18)^b	60 to 89 mL per minute (N=11)^c	30 to 59 mL per minute (N=18)
Emtricitabine	11.4 (11.9)	17.6 (18.2)	23.0 (23.6)
Tenofovir Alafenamide*	0.23 (47.2)	0.24 (45.6)	0.26 (58.8)
Tenofovir	0.32 (14.9)	0.46 (31.5)	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 Infection

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

Drug Interaction Studies

The effects of coadministered drugs on the exposure of TAF are shown in Table 11 and the effects of emtricitabine and tenofovir alafenamide or its components on the exposure of coadministered drugs are shown in Table 12 [these studies were conducted with emtricitabine and tenofovir alafenamide or the components of emtricitabine and tenofovir alafenamide (FTC or TAF)

administered alone]. For information regarding clinical recommendations, see *Drug Interactions* (7).

Table 11 Drug Interactions: Changes in TAF Pharmacokinetic Parameters in the Presence of Coadministered Drug(s)^a

Coadministered Drug	Coadministered Drug(s) 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	2.83 (2.20, 3.65)	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	40 ^b	11	0.78 (0.58, 1.05)	0.86 (0.72, 1.02)	NC
				2.19	1.47	

Lopinavir	800 (+200 ritonavir)	10	10	(1.72, 2.79)	(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

- All interaction studies conducted in healthy volunteers.
- Study conducted with emtricitabine and tenofovir alafenamide (FTC/TAF).
- Study conducted with FTC+TAF with EVG+COBI.

Table 12 Drug Interactions: Changes in PK Parameters for Coadministered Drug in the Presence of Emtricitabine and Tenofovir Alafenamide 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 Parameters (90% CI); No effect = 1.00		
				C _{max}	AUC	C _{min}
Atazanavir	300 +100 ritonavir	10	10	0.98 (0.89, 1.07)	0.99 (0.96, 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 (0.82, 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)
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NC=Not Calculated

- a. All interaction studies conducted in healthy volunteers.
- b. Study conducted with emtricitabine and tenofovir alafenamide (FTC/TAF).
- c. A sensitive CYP3A4 substrate.
- d. Study conducted with FTC+TAF with EVG+COBI.

5.3 Preclinical safety data

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) 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).

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. 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.

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 55 times (rat) those observed in humans after administration of the daily recommended dose of emtricitabine and tenofovir alafenamide. 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) 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.

Animal Toxicology and/or Pharmacology

Minimal to slight infiltration of mononuclear cells in the posterior uvea 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 toxicity 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.

6. Pharmaceutical particulars

6.1 List of excipients

Microcrystalline Cellulose (Avicel-PH 112) USP/NF, Croscarmellose Sodium, (Ac-di-sol) USP/NF, Magnesium stearate, (Ligamed MF-2-V) USP/NF, Purified water IHS/USP/Ph.Eur, Opadry II Pink 85F94172.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

<3 Years>

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of container

Blister pack: 30's HDPE Container, 60's HDPE Container 90's HDPE Container & 100's HDPE Container

6.6 Special precautions for disposal

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

7. Market Authorisation Holder

Hetero Labs Limited

Business Address:

7-2-A2, Hetero Corporate,
Industrial Estates, Sanath Nagar,
Hyderabad-500 018 Telangana,
INDIA.

8. Market authorisation Number

H2022/CTD9303/18618

9. Date of authorisation/renewal of authorisation

15/12/2022

10. Date of revision of the text

22/08/2026