Brand Name	Descovy
Active Ingredient(s)	emtricitabine, tenofovir alafenamide
Strength	200-25 mg
Dosage Form	tablet
Inactive Ingredients	microcrystalline cellulose, film-coated with a coating material containing polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and indigo carmine aluminum lake croscarmellose sodium, and magnesium stearate.
NDC	61958-2002-1
DIN	02454424
Canadian Distributor	Gilead Sciences Canada Inc. 600 6711 Mississauga Road, Mississauga, Ontario, Canada L5N 2W3
NDA Number	NDA208215
US Distributor (NDA Holder)	Gilead Sciences, Inc. 333 Lakeside Drive, Foster City, CA 94404
Manufacturer (Final Packager)	Not available
API Manufacturer	Not available
Relationship to Sponsor	The Sponsor may have or have had agreements with the U.S. manufacturer for rebates. The Sponsor has no relationship with the foreign manufacturer.

Current FDA-approved Package Insert

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use DESCOVY safely and effectively. See full prescribing information for DESCOVY.

DESCOVY® (emtricitabine and tenofovir alafenamide) tablets, for oral use
Initial U.S. Approval: 2015

WARNING: POST-TREATMENT ACUTE EXACERBATION OF HEPATITIS B and RISK OF DRUG RESISTANCE WITH USE OF DESCOVY FOR HIV-1 PRE-EXPOSURE PROPHYLAXIS (PrEP) IN UNDIAGNOSED EARLY HIV-1 INFECTION
See full prescribing information for complete boxed warning.

Severe acute exacerbations of hepatitis B (HBV) have been reported in HBV-infected individuals who have discontinued products containing emtricitabine (FTC) and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of DESCOVY. Hepatic function should be monitored closely in these individuals. If appropriate, anti-hepatitis B therapy may be warranted. (5.1)

DESCOVY used for HIV-1 PrEP must only be prescribed to individuals confirmed to be HIV-negative immediately prior to initiating and at least every 3 months during use. Drug-resistant HIV-1 variants have been identified with use of FTC/TDF for HIV-1 PrEP following undetected acute HIV-1 infection. Do not initiate DESCOVY for HIV-1 PrEP if signs or symptoms of acute HIV-1 infection are present unless negative infection status is confirmed. (5.2)

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.1)	01/2022
Dosage and Administration (2.4)	01/2022
Warnings and Precautions (5.4)	03/2021

----------INDICATIONS AND USAGE----------
HIV-1 Treatment (1.1):
DESCOVY 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 35 kg.
- 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 14 kg and less than 35 kg.

HIV-1 PrEP (1.2):
DESCOVY is 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 DESCOVY for HIV-1 PrEP.
Limitations of Use (1.2):
The indication does not include use of DESCOVY in individuals at risk of HIV-1 from receptive vaginal sex because effectiveness in this population has not been evaluated.

----------DOSAGE AND ADMINISTRATION----------

- Testing: Prior to or when initiating DESCOVY, test for hepatitis B virus infection. Prior to or when initiating DESCOVY, and during use 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. (2.1)
- HIV-1 Screening: Screen all individuals for HIV-1 infection immediately prior to initiating DESCOVY for HIV-1 PrEP and at least once every 3 months while taking DESCOVY, and upon diagnosis of any other sexually transmitted infections (STIs). (2.2)
- Recommended dosage:
  - Treatment of HIV-1 Infection:
    - Adult and pediatric patients weighing at least 35 kg: One 200 mg/25 mg tablet once daily with or without food. (2.3)
    - Pediatric patients not receiving a protease inhibitor administered with ritonavir or cobicistat, and weighing:
      - at least 25 to less than 35 kg: One 200 mg/25 mg tablet once daily with or without food. (2.4)
      - at least 14 to less than 25 kg: One 120 mg/15 mg tablet once daily with or without food. (2.4)
  - HIV-1 PrEP: One 200 mg/ 25 mg tablet once daily with or without food in individuals with body weight at least 35 kg. (2.5)
- Renal impairment: DESCOVY is not recommended in individuals with estimated creatinine clearance of 15 to below 30 mL per minute, or below 15 mL per minute who are not receiving chronic hemodialysis. (2.6)

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 200 mg/25 mg and 120 mg/15 mg of FTC and TAF respectively (3)

----------CONTRAINDICATIONS----------
DESCOVY for HIV-1 PrEP is contraindicated in individuals with unknown or positive HIV-1 status. (4)

----------WARNINGS AND PRECAUTIONS----------

- Comprehensive management to reduce the risk of sexually transmitted infections (STIs), including HIV-1, when DESCOVY is used for HIV-1 PrEP: Counsel on adherence to daily dosing and safer sex practices, including condoms, to reduce the risk of STIs. (5.2)
- Management to reduce the risk of acquiring HIV-1 drug resistance when DESCOVY is used for HIV-1 PrEP: refer to full prescribing information for additional detail. (5.2)
- Immune reconstitution syndrome during treatment of HIV-1 infection: May necessitate further evaluation and treatment. (5.3)
- New onset or worsening renal impairment: Assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein when initiating DESCOVY and during use on a clinically appropriate schedule in all individuals. Also assess serum phosphorus in individuals with chronic kidney disease. (5.4)
- Lactic acidosis/severe hepatomegaly with steatosis: Discontinue DESCOVY in individuals who develop symptoms or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity. (5.5)

----------ADVERSE REACTIONS----------

- In HIV-1 infected patients, the most common adverse reaction (incidence greater than or equal to 10%, all grades) was nausea. (6.1)
- In HIV-1 uninfected adults in a PrEP trial, the most common adverse reaction (incidence greater than or equal to 5%, all grades) was diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Gilead Sciences, Inc. at 1-800-GILEAD-5 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
Consult the Full Prescribing Information prior to and during use for potential drug interactions. (7, 12.3)

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Mothers infected with HIV-1 should be instructed not to breastfeed, due to the potential for HIV transmission. (8.2)
- Pediatrics:
  - Treatment of HIV-1 Infection: Not recommended for patients weighing less than 14 kg. (8.4)
  - HIV-1 PrEP: Not recommended for individuals weighing less than 35 kg. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 01/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: POST-TREATMENT ACUTE EXACERBATION OF HEPATITIS B and RISK OF DRUG RESISTANCE WITH USE OF DESCOVY FOR HIV-1 PRE-EXPOSURE PROPHYLAXIS (PrEP) IN UNDIAGNOSED EARLY HIV-1 INFECTION

Severe acute exacerbations of hepatitis B (HBV) have been reported in HBV-infected individuals who have discontinued products containing emtricitabine (FTC) and/or tenofovir disoproxil fumarate (TDF) and may occur with discontinuation of DESCOVY.

Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in individuals who are infected with HBV and discontinue DESCOVY. If appropriate, anti-hepatitis B therapy may be warranted *[see Warnings and Precautions (5.1)]*.

DESCOVY used for HIV-1 PrEP must only be prescribed to individuals confirmed to be HIV-negative immediately prior to initiating and at least every 3 months during use. Drug-resistant HIV-1 variants have been identified with use of FTC/TDF for HIV-1 PrEP following undetected acute HIV-1 infection. Do not initiate DESCOVY for HIV-1 PrEP if signs or symptoms of acute HIV-1 infection are present unless negative infection status is confirmed *[see Warnings and Precautions (5.2)].*

1 INDICATIONS AND USAGE

1.1 Treatment of HIV-1 Infection

DESCOVY 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.

DESCOVY is 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 14 kg and less than 35 kg.

1.2 HIV-1 Pre-Exposure Prophylaxis (PrEP)

DESCOVY is 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 DESCOVY 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 DESCOVY 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)].*

2 DOSAGE AND ADMINISTRATION

2.1 Testing When Initiating and During Use of DESCOVY for Treatment of HIV-1 Infection or for HIV-1 PrEP

Prior to or when initiating DESCOVY, test individuals for hepatitis B virus infection *[see Warnings and Precautions (5.1)]*.

Prior to or when initiating DESCOVY, and during use of DESCOVY 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)].*

2.2 HIV-1 Screening for Individuals Receiving DESCOVY for HIV-1 PrEP

Screen all individuals for HIV-1 infection immediately prior to initiating DESCOVY for HIV-1 PrEP and at least once every 3 months while taking DESCOVY, 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)].*

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

DESCOVY is a two-drug fixed dose combination product containing emtricitabine (FTC) and tenofovir alafenamide (TAF).

The recommended dosage of DESCOVY for treatment of HIV-1 is one tablet containing 200 mg FTC and 25 mg of TAF taken orally once daily with or without food in:

- adults and pediatric patients with body weight at least 35 kg and estimated creatinine clearance greater than or equal to 30 mL per minute; or
- adults with creatinine clearance below 15 mL per minute who are receiving chronic hemodialysis. On days of hemodialysis, administer the daily dose of DESCOVY after completion of hemodialysis treatment *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

The safety and effectiveness of DESCOVY coadministered with an HIV-1 protease inhibitor that is administered with either ritonavir or cobicistat have not been established in adults with creatinine clearance below 15 mL per minute, with or without hemodialysis.

For specific dosing recommendations for coadministered antiretroviral drugs, refer to their respective prescribing information *[see Drug Interactions (7)]*.

2.4 Recommended Dosage for Treatment of HIV-1 Infection in Pediatric Patients Weighing at Least 14 kg to Less than 35 kg

The recommended dosage of DESCOVY in pediatric patients weighing at least 14 kg to 35 kg is based on body weight and provided in Table 1. This dosing information is applicable to pediatric patients with estimated creatinine clearance greater than or equal to 30 mL per minute *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]* who are not receiving an HIV protease inhibitor that is administered with either ritonavir or cobicistat.

Table 1 Dosing for Treatment of HIV-1 Infection in Pediatric Patients Weighing 14 to Less than 35 kg

Body Weight (kg)	**DESCOVY Dose**
25 kg to less than 35 kg	One tablet containing 200 mg FTC and 25 mg of TAF taken orally once daily
14 kg to less than 25 kg	One tablet containing 120 mg FTC and 15 mg TAF taken orally once daily

The safety and effectiveness of DESCOVY 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.

For specific dosing recommendations for coadministered antiretroviral drugs, refer to their respective prescribing information *[see Drug Interactions (7)]*.

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

The dosage of DESCOVY 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; or
- adults with creatinine clearance below 15 mL per minute who are receiving chronic hemodialysis. On days of hemodialysis, administer the daily dose of DESCOVY after completion of hemodialysis treatment *[see Indications and Usage (1.2) and Clinical Pharmacology (12.3)].*

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

DESCOVY is not recommended in individuals with:

- severe renal impairment (estimated creatinine clearance of 15 to below 30 mL per minute); or
- end stage renal disease (ESRD; estimated creatinine clearance below 15 mL per minute) who are not receiving chronic hemodialysis *[see Dosage and Administration (2.3, 2.5) and Use in Specific Populations (8.6)]*.

3 DOSAGE FORMS AND STRENGTHS

DESCOVY tablets are available in two dose strengths:

- 200 mg/25 mg tablets: 200 mg of emtricitabine (FTC) and 25 mg of tenofovir alafenamide (TAF) (equivalent to 28 mg of tenofovir alafenamide fumarate). These tablets are blue, rectangular-shaped, film-coated, debossed with “GSI” on one side and “225” on the other side.

- 120 mg/15 mg tablets: 120 mg of FTC and 15 mg of TAF (equivalent to 16.8 mg of tenofovir alafenamide fumarate). These tablets are white, round-shaped, film coated, debossed with “GSI” on one side and “15” on the other side.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

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

All individuals should be tested for the presence of hepatitis B virus (HBV) before or when initiating DESCOVY *[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 DESCOVY. Individuals infected with HBV who discontinue DESCOVY 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.

5.2 Comprehensive Management to Reduce the Risk of Sexually Transmitted Infections, Including HIV-1, and Development of HIV-1 Resistance When DESCOVY Is Used for HIV-1 PrEP

Use DESCOVY 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 DESCOVY 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 DESCOVY 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 DESCOVY, because DESCOVY 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 DESCOVY 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 DESCOVY 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 DESCOVY 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 DESCOVY dosing schedule. The effectiveness of DESCOVY in reducing the risk of acquiring HIV-1 is strongly correlated with adherence, as demonstrated by measurable drug levels in a clinical trial of DESCOVY 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)].*

5.3 Immune Reconstitution Syndrome

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

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

5.4 New Onset or Worsening Renal Impairment

Postmarketing cases of renal impairment, including acute renal failure, proximal renal tubulopathy (PRT), and Fanconi syndrome have been reported with TAF-containing products; while most of these cases were characterized by potential confounders that may have contributed to the reported renal events, it is also possible these factors may have predisposed patients to tenofovir-related adverse events *[see Adverse Reactions (6.1, 6.2)]*. DESCOVY is not recommended in individuals with estimated creatinine clearance of 15 to below 30 mL per minute, or in individuals with estimated creatinine clearance below 15 mL per minute who are not receiving chronic hemodialysis.

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 DESCOVY, and during treatment with DESCOVY 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 DESCOVY in individuals who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

5.5 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 DESCOVY, and tenofovir DF, another prodrug of tenofovir, alone or in combination with other antiretrovirals. Treatment with DESCOVY 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).

6 ADVERSE REACTIONS

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)].*

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 Elvitegravir (EVG) plus Cobicistat (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. Across these trials, 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 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. FTC+TAF with EVG+COBI was permanently discontinued due to worsening renal function in two of 80 (3%) subjects.

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 a Clinical Trial of FTC+TAF with EVG+COBI in Virologically-Suppressed Adults with End Stage Renal Disease (ESRD) Receiving Chronic Hemodialysis

In a 48-week trial of virologically-suppressed HIV-1 infected adult subjects with end stage renal disease (ESRD) (estimated creatinine clearance of less than 15 mL/min) on chronic hemodialysis treated with FTC+TAF with EVG+COBI (N=55), the most commonly reported adverse reaction (adverse event assessed as

causally related by investigator and all grades) was nausea (7%). Serious adverse events were reported in 53% of subjects and the most common serious adverse events were pneumonia (13%), fluid overload (7%), hyperkalemia (7%) and osteomyelitis (7%). Overall 5% of subjects permanently discontinued treatment due to an adverse event.

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

Pediatric Subjects Weighing at Least 25 kg:

The safety profile of FTC+TAF in pediatric subjects weighing at least 25 kg is informed by 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=52; Cohort 2). Subjects received FTC+TAF with EVG+COBI through 48 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 in 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 48, +3.9% at the lumbar spine and +4.2% for TBLH. Mean changes from baseline BMD Z-scores were -0.24 for lumbar spine and -0.19 for TBLH at Week 48. Six subjects had significant (at least 4%) lumbar spine BMD loss at Week 48 and 2 subjects also had at least 4% TBLH BMD loss at Week 48.

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=52) 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 Weeks 24 and 48. The mean baseline and mean change from baseline in CD4+ cell count and in

CD4% from Week 2 to Week 48 are presented in Table 2. All subjects maintained their CD4+ cell counts above 400 cells/mm^3 *[see Use in Specific Populations (8.4)].*

Table 2 Mean Change in CD4+ Count and CD4 Percentage from Baseline to Week 48 in Virologically-Suppressed Pediatric Patients from 6 to <12 Years Who Switched to FTC+TAF with EVG+COBI

		Mean Change from Baseline					
	Baseline	**Week 2**	**Week 4**	**Week 12**	**Week 24**	**Week 32**	**Week 48**
CD4+ Cell Count (cells/mm^3)	961 (275.5)[a]	-117	-114	-112	-118	-62	-66
CD4%	38 (6.4)[a]	+0.3%	-0.1%	-0.8%	-0.8%	-1.0%	-0.6%

a. Mean (SD)

Pediatric Subjects Weighing at Least 14 to Less Than 25 kg:

In a separate open-label trial of virologically-suppressed subjects at least 2 years of age and weighing at least 14 to less than 25 kg (N=22; Cohort 3) who received FTC+TAF with bictegravir through 24 weeks, no new adverse reactions or laboratory abnormalities were identified compared to those observed in adults. In this trial, the mean (SD) change from baseline to Week 24 in CD4+ cell count was −126 (264) cells per mm^3 and the mean (SD) change in CD4% from baseline to Week 24 was 0.2% (4.4%).

Adverse Reactions from Clinical Trial Experience in HIV-1 Uninfected Individuals Taking DESCOVY for HIV-1 PrEP

The safety profile of DESCOVY 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 DESCOVY (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 DESCOVY (incidence greater than or equal to 5%, all grades) was diarrhea (5%). Table 3 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 DESCOVY or TRUVADA due to adverse events, regardless of severity, was 1.3% and 1.8%, respectively.

Table 3 Adverse Reactions (All Grades) Reported in ≥2% in Either Arm in the DISCOVER Trial of HIV-1 Uninfected Participants

	DESCOVY (N=2,694)	TRUVADA (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

Renal Laboratory Tests

Changes from baseline to Week 48 in renal laboratory data are presented in Table 4. The long-term clinical significance of these renal laboratory changes on adverse reaction frequencies between DESCOVY and TRUVADA is not known.

Table 4 Laboratory Assessments of Renal Function Reported in HIV-1 Uninfected Participants Receiving DESCOVY or TRUVADA in the DISCOVER Trial

	DESCOVY (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 (≤ 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 DESCOVY, 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 5.

Table 5 Fasting Lipid Values, Mean Change from Baseline, Reported in HIV-1 Uninfected Participants Receiving DESCOVY or TRUVADA in the DISCOVER Trial[a]

	DESCOVY (N=2,694)		**TRUVADA (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

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of products containing TAF. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and Subcutaneous Tissue Disorders
Angioedema, urticaria, and rash

Renal and Urinary Disorders
Acute renal failure, acute tubular necrosis, proximal renal tubulopathy, and Fanconi syndrome

7 DRUG INTERACTIONS

7.1 Potential for Other Drugs to Affect One or More Components of DESCOVY

TAF, a component of DESCOVY, 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 DESCOVY and development of resistance. Coadministration of DESCOVY 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 DESCOVY 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 (5.4)]*.

7.3 Established and Other Potentially Significant Interactions

Table 6 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 DESCOVY, the components of DESCOVY (emtricitabine and tenofovir alafenamide) as individual agents, or are predicted drug interactions that may occur with DESCOVY. For magnitude of interaction, *see Clinical Pharmacology (12.3)*.

Table 6 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 DESCOVY is not recommended.
Other Agents		
Anticonvulsants: carbamazepine oxcarbazepine phenobarbital phenytoin	↓ TAF	Consider alternative anticonvulsant.
Antimycobacterials: rifabutin rifampin rifapentine	↓ TAF	Coadministration of DESCOVY with rifabutin, rifampin, or rifapentine is not recommended.
Herbal Products: St. John's wort *(Hypericum perforatum)*	↓ TAF	Coadministration of DESCOVY with St. John's wort is not recommended.

a. This table is not all inclusive.
b. ↓=Decrease

7.4 Drugs without Clinically Significant Interactions with DESCOVY

Based on drug interaction studies conducted with the components of DESCOVY, no clinically significant drug interactions have been either observed or are expected when DESCOVY 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 DESCOVY 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

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to DESCOVY 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 statistically significant difference in the overall risk of major birth defects for emtricitabine (FTC) or tenofovir alafenamide (TAF) compared with the background rate for major birth defects of 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) *(see Data)*. The rate of miscarriage for individual drugs is not reported in the APR. 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 DESCOVY 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 DESCOVY *(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 DESCOVY. 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 DESCOVY.

Data

Human Data

Prospective reports from the APR of overall major birth defects in pregnancies exposed to the components of DESCOVY are compared with a U.S. background major birth defect rate. Methodological 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 less than 20 weeks gestation.

Emtricitabine (FTC):

Based on prospective reports to the APR of over 5,400 exposures to FTC-containing regimens during pregnancy resulting in live births (including over 3,900 exposed in the first trimester and over 1,500 exposed in the second/third trimester), the prevalence of birth defects in live births was 2.6% (95% CI: 2.2% to 3.2%) and 2.7% (95% CI: 1.9% to 3.7%) following first and second/third trimester exposure, respectively, to FTC-containing regimens.

Tenofovir Alafenamide (TAF):

Based on prospective reports to the APR of over 660 exposures to TAF-containing regimens during pregnancy resulting in live births (including over 520 exposed in the first trimester and over 130 exposed in the second/third trimester), the prevalence of birth defects in live births was 4.2 % (95% CI: 2.6 % to 6.3 %) and 3.0% (95% CI: 0.8% to 7.5 %) following first and second/third trimester exposure, respectively, to TAF-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 DESCOVY. 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 DESCOVY.

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-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 DESCOVY 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 DESCOVY 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.

8.4 Pediatric Use

Treatment of HIV-1 Infection

The safety and effectiveness of DESCOVY, 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 14 kg *[see Indication and Usage (1.1) and Dosage and Administration (2.3, 2.4)]*.

Use of DESCOVY in pediatric patients between 6 to less than 18 years of age and 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 antiretroviral treatment-naïve HIV-1 infected pediatric subjects aged 12 to less than 18 years and weighing at least 35 kg through Week 48 (N=50; cohort 1) and in virologically-suppressed pediatric subjects aged 6 to less than 12 years and weighing at least 25 kg through Week 48 (N=52; cohort 2). The safety and efficacy of FTC+TAF with EVG+COBI in adolescent subjects was similar to that in adults on this regimen. The safety and efficacy of FTC+TAF with EVG+COBI in subjects 6 to 12 years of age weighing at least 25 kg was similar to that in antiretroviral treatment-naïve adults and adolescents on this regimen, with the exception of a decrease from baseline in CD4+ cell count *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies (14.2)]*.

Use of DESCOVY in pediatric patients between 2 to less than 6 years of age and weighing at least 14 to less than 25 kg is supported by adequate and well controlled studies of FTC+TAF with EVG+COBI in adults and by a separate open-label trial of FTC+TAF with bictegravir in virologically-suppressed pediatric patients at least 2 years of age and weighing at least 14 to less than 25 kg through Week 24 (N=22; cohort 3). The safety and efficacy of FTC+TAF in these pediatric subjects were similar to that observed in adults who received FTC+TAF with bictegravir *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies (14.2)]*.

Safety and effectiveness of DESCOVY coadministered with an HIV-1 protease inhibitor that is administered with either ritonavir or cobicistat have not been

established in pediatric patients weighing less than 35 kg *[see Dosage and Administration (2.4)]*.

Safety and effectiveness of DESCOVY for treatment of HIV-1 infection in pediatric patients weighing less than 14 kg have not been established.

HIV-1 PrEP

Safety and effectiveness of DESCOVY 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 DESCOVY 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 (2.5), Adverse Reactions (6.1), Clinical Pharmacology (12.3 and 12.4), and Clinical Studies (14)].*

While using DESCOVY 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 DESCOVY for HIV-1 PrEP in pediatric patients weighing less than 35 kg have not been established.

8.5 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.

8.6 Renal Impairment

No dosage adjustment of DESCOVY is recommended in individuals with estimated creatinine clearance greater than or equal to 30 mL per minute, or in adults with ESRD (estimated creatinine clearance below 15 mL per minute) who are receiving chronic hemodialysis. On days of hemodialysis, administer the daily dose of DESCOVY after completion of hemodialysis treatment.

Safety and effectiveness of DESCOVY coadministered with an HIV-1 protease inhibitor that is administered with either ritonavir or cobicistat have not been established in patients with ESRD *[see Dosage and Administration (2.3)]*.

DESCOVY is not recommended in individuals with severe renal impairment (estimated creatinine clearance of 15 to below 30 mL per minute), or in individuals with ESRD who are not receiving chronic hemodialysis, as the safety of DESCOVY has not been established in these populations *[see Dosage and Administration (2.6) and Clinical Studies (14.2)].*

8.7 Hepatic Impairment

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

10 OVERDOSAGE

No data are available on overdose of DESCOVY in patients. If overdose occurs, monitor the individual for evidence of toxicity. Treatment of overdose with DESCOVY 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 DESCOVY. In one clinical pharmacology study, single doses of FTC 1200 mg (6 times the FTC dose in DESCOVY) 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 DESCOVY) 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

DESCOVY (emtricitabine and tenofovir alafenamide) is a fixed dose combination tablet containing emtricitabine (FTC) and tenofovir alafenamide (TAF) for oral administration.

- FTC, a synthetic nucleoside analog of cytidine, is an HIV nucleoside analog reverse transcriptase inhibitor (HIV NRTI).
- TAF, an HIV NRTI, is converted in vivo to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate.

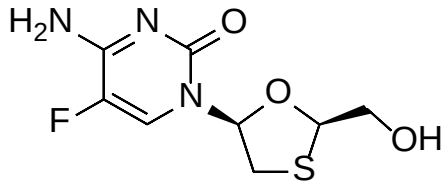
DESCOVY tablets are available in two dose strengths:

- 200 mg/25 mg tablets: 200 mg of FTC and 25 mg of TAF (equivalent to 28 mg of tenofovir alafenamide fumarate).
- 120 mg/15 mg tablets: 120 mg of FTC and 15 mg of TAF (equivalent to 16.8 mg of tenofovir alafenamide fumarate).

Both dose strengths of DESCOVY tablets include the following inactive ingredients: croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The 200 mg/ 25 mg tablets are film-coated with a coating material containing indigo carmine aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide. The 120 mg/15 mg tablets are film-coated with a coating material containing polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc.

Emtricitabine: The chemical name of FTC is 4-amino-5-fluoro-1-(2*R*-hydroxymethyl-1,3-oxathiolan-5*S*-yl)-(1H)-pyrimidin-2-one. 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.

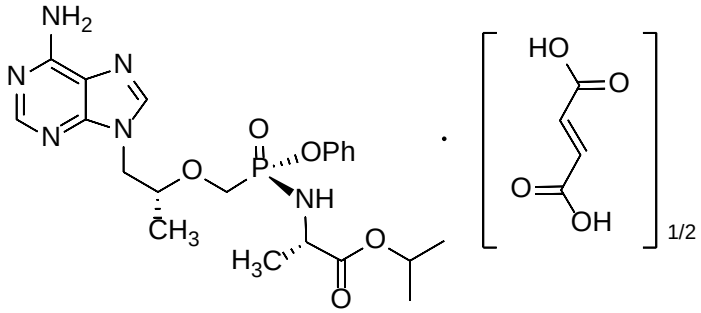
FTC has a molecular formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.24 and has the following structural formula:



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

Tenofovir Alafenamide: The chemical name of tenofovir alafenamide fumarate drug substance is L-alanine, *N*-[(*S*)-[[(1*R*)-2-(6-amino-9*H*-purin-9-yl)-1-methylethoxy]methyl]phenoxyphosphinyl]-, 1-methylethyl ester, (2*E*)-2-butenedioate (2:1).

Tenofovir alafenamide fumarate has an empirical formula of $C_{21}H_{29}O_5N_6P \bullet ½(C_4H_4O_4)$ and a formula weight of 534.50 and has the following structural formula:



Tenofovir alafenamide fumarate is a white to off-white or tan powder with a solubility of 4.7 mg per mL in water at 20 °C.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

DESCOVY 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 DESCOVY, 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 DESCOVY are provided in Table 7. The multiple dose PK parameters of FTC and TAF and its metabolite tenofovir are provided in Table 8. HIV status has no effect on the pharmacokinetics of FTC and TAF in adults.

Table 7 Pharmacokinetic Properties of the Components of DESCOVY

	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)
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

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 10 days); TAF (single dose administration of [^{14}C] tenofovir alafenamide).

Table 8 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

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

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 9).

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 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 receiving this same dosage regimen; the increases were not considered clinically significant (Table 10) *[see Use in Specific Populations (8.4)]*.

Table 10 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

Exposures of FTC and TAF (AUC_{tau} and C_{max}) achieved in 22 pediatric patients at least 2 years of age and weighing from 14 to less than 25 kg who received FTC+TAF with bictegravir were higher than exposures in adults; the increases were not considered clinically significant as the safety profiles were similar in adult and pediatric patients (Table 11) *[see Use in Specific Populations (8.4)]*.

Table 11 Multiple Dose Pharmacokinetic Parameters of Emtricitabine and Tenofovir Alafenamide Following Oral Administration of FTC+TAF with Bictegravir in HIV-Infected Pediatric Subjects at least 2 Years of age and Weighing from 14 to Less than 25 kg[a]

Parameter Mean (CV%)	Emtricitabine[b]	Tenofovir Alafenamide[b]
C_{max} (microgram per mL)	3.85 (34.7)	0.414 (31.0)
AUC_{tau} (microgram•h per mL)	15.0 (21.9)	0.305 (42.6)
C_{trough} (microgram per mL)	0.210 (243)	NA

CV = Coefficient of Variation; NA = Not Applicable

a. This trial enrolled virologically-suppressed pediatric subjects with HIV-1 infection from 3 to 9 years of age.

b. From Intensive PK analysis (n=12 except n=11 for C_{trough} for FTC).

HIV-1 PrEP: The pharmacokinetic data for FTC and TAF following administration of DESCOVY in HIV-1 uninfected adolescents weighing 35 kg and above are not available. The dosage recommendations of DESCOVY 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-1 infected subjects with renal impairment (eGFR 30 to 69 mL per minute by Cockcroft-Gault method), and in HIV-1 infected subjects with ESRD (eGFR less than 15 mL per minute by Cockcroft-Gault method) receiving chronic hemodialysis were evaluated in subsets of virologically-suppressed subjects in open-label trials. The pharmacokinetics of TAF were similar among healthy subjects, subjects with mild or moderate renal impairment, and subjects with ESRD receiving chronic hemodialysis; increases in FTC and TFV exposures in subjects with renal impairment were not considered clinically relevant (Table 12).

Table 12 Pharmacokinetics of the Components of DESCOVY and a Metabolite of TAF (Tenofovir) in HIV-Infected Adults with Renal Impairment Compared to Subjects with Normal Renal Function

	AUC_{tau} (microgram·hour per mL) Mean (CV%)			
Estimated Creatinine Clearance[a]	**≥90 mL per minute (N=18)[b]**	**60–89 mL per minute (N=11)[c]**	**30–59 mL per minute (N=18)[d]**	**<15 mL per minute (N=12)[e]**
Emtricitabine	11.4 (11.9)	17.6 (18.2)	23.0 (23.6)	62.9 (48.0)[f]
Tenofovir	0.32 (14.9)	0.46 (31.5)	0.61 (28.4)	8.72 (39.4)[g]

a. By Cockcroft-Gault method.
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.
d. From a phase 3 trial in HIV-1 infected adults with renal impairment treated with FTC+TAF with EVG+COBI.
e. From a phase 3 trial in HIV-1 infected adults with ESRD receiving chronic hemodialysis treated with FTC+TAF with EVG+COBI; PK assessed prior to hemodialysis following 3 consecutive daily doses of FTC+TAF with EVG+COBI.
f. N = 11.
g. N = 10.

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 13 and the effects of DESCOVY or its components on the exposure of coadministered drugs are shown in Table 14 [these studies were conducted with DESCOVY or the components of DESCOVY (FTC or TAF) administered alone]. For information regarding clinical recommendations, *see Drug Interactions (7)*.

Table 13 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
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 DESCOVY (FTC/TAF).
c. Study conducted with FTC+TAF with EVG+COBI.

Table 14 Drug Interactions: Changes in PK Parameters for Coadministered Drug in the Presence of DESCOVY 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)
Lopinavir	800 +200 ritonavir	10	10	1.00 (0.95, 1.06)	1.00 (0.92, 1.09)	0.98 (0.85, 1.12)
Midazolam[c]	2.5 (single dose, orally)	25	18	1.02 (0.92, 1.13)	1.13 (1.04, 1.23)	NC
	1 (single dose, intravenous)			0.99 (0.89, 1.11)	1.08 (1.04, 1.14)	NC
Rilpivirine	25	25	16	0.93 (0.87, 0.99)	1.01 (0.96, 1.06)	1.13 (1.04, 1.23)
Sertraline	50 (single dose)	10[d]	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 DESCOVY (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, Ɛ, 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. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there is no evidence of toxicity to mitochondria in cell culture.

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 1.3–640 nM. FTC displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, and G (EC_{50} values ranged from 7-75 nM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 7–1,500 nM).

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 monocyte/macrophage cells 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.

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

Emtricitabine and Tenofovir Alafenamide: The prophylactic activity of the combination of oral FTC and TAF was evaluated in a controlled study of macaques administered once weekly intra-rectal inoculations of chimeric simian/human immunodeficiency type 1 virus (SHIV) for up to 19 weeks (n=6). All 6 macaques that received FTC and TAF at doses resulting in PBMC exposures

consistent with those achieved in humans administered a dose of FTC/TAF 200/25 mg remained SHIV uninfected.

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 L429I substitutions; in addition, a K70E substitution in HIV-1 RT was observed.

In Clinical Trials

Treatment of HIV-1

The resistance profile of DESCOVY 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 a 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 Q207 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).

HIV-1 PrEP

In the DISCOVER trial of HIV-1 uninfected men and transgender women who have sex with men and who are at risk of HIV-1 infection receiving DESCOVY or TRUVADA for HIV-1 PrEP, genotyping was performed on participants found to be infected during the trial who had HIV-1 RNA ≥400 copies/mL (6 of 7 participants receiving DESCOVY and 13 of 15 participants receiving TRUVADA). The development of FTC resistance-associated substitutions, M184I and/or M184V, was observed in 4 HIV-1 infected participants in the TRUVADA group who had suspected baseline infections.

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 DESCOVY) or in rats at doses up to 600 mg per kg per day (28 times the human systemic exposure at the recommended dose in DESCOVY).

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 DESCOVY. 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 DESCOVY.

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 DESCOVY. At the high dose in female mice, liver adenomas were increased at tenofovir exposures approximately 10 times (300

mg TDF) and 167 times (DESCOVY) 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 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 DESCOVY.

14 CLINICAL STUDIES

14.1 Overview of Clinical Trials

The efficacy and safety of DESCOVY have been evaluated in the trials summarized in Table 15.

Table 15 Trials Conducted with FTC+TAF-Containing Products for HIV-1 Treatment and DESCOVY for HIV-1 PrEP

Trial	Population	Study Arms (N)	Timepoint
Study 104 [a] (NCT01780506) Study 111 [a] (NCT01797445)	HIV-1 infected treatment-naïve adults	FTC+TAF with EVG+COBI [b] (866) FTC+TDF with EVG+COBI [c] (867)	48 Weeks
Study 109 [d] (NCT01815736)	HIV-1 infected virologically-suppressed [f] adults	FTC+TAF with EVG+COBI [b] (799) ATRIPLA® or TRUVADA®+atazanavir+cobicistat or ritonavir or FTC+TDF with EVG+COBI [c] (397)	48 Weeks
Study 112 [e] (NCT01818596)	HIV-1 infected virologically-suppressed [f] adults with renal impairment [g]	FTC+TAF with EVG+COBI [b] (242)	24 Weeks
Study 1825 [e] (NCT02600819)	HIV-1 infected virologically-suppressed [f] adults with ESRD [h] receiving chronic hemodialysis	FTC+TAF with EVG+COBI [b] (55)	48 Weeks
Study 106 [e] (Cohort 1) (NCT01854775)	HIV-1 infected treatment-naïve adolescents between the ages of 12 to less than 18 years (at least 35 kg)	FTC+TAF with EVG+COBI [b] (50)	48 Weeks
Study 106 [e] (Cohort 2) (NCT01854775)	HIV-1 infected, virologically suppressed [f] children between the ages of 6 to less than 12 years (at least 25 kg)	FTC+TAF with EVG+COBI [b] (52)	48 Weeks
Study 1474 [e] (Cohort 3) (NCT02881320)	HIV-1 infected, virologically suppressed [f] children at least 2 years (at least 14 kg and less than 25 kg)	FTC+TAF with bictegravir [i] (22)	24 Weeks
DISCOVER [a] (NCT02842086)	HIV-1 uninfected men or transgender women who have sex with men	DESCOVY (2,670) TRUVADA® (2,665)	4,370 person-years [j]

a. Randomized, double-blind, active-controlled study.
b. Administered as GENVOYA®.
c. Administered as STRIBILD®.
d. Randomized, open-label, active controlled trial.
e. Open label trial
f. HIV-1 RNA less than 50 copies per mL.
g. Estimated creatinine clearance between 30 and 69 mL per minute by Cockcroft-Gault method.
h. End stage renal disease (estimated creatinine clearance of less than 15 mL per minute by Cockcroft-Gault method).
i. Administered as BIKTARVY®.
j. Exposure in the DESCOVY group.

14.2 Clinical Trial Results for Treatment of HIV-1

Clinical Trials in Adults with HIV-1

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.

Clinical Trials in Pediatric Patients with HIV-1

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 52 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, 98% (51/52) of subjects remained virologically suppressed at Week 48. From a mean (SD) baseline CD4+ cell count of 961 (275.5) cells per mm^3, the mean change from baseline in CD4+ cell count was -66 cells per mm^3 and the mean (SD) change in CD4% was -0.6% (4.4%) at Week 48. All subjects maintained CD4+ cell counts above 400 cells/mm^3 *[see Adverse Reactions (6.1) and Use in Specific Populations (8.4)].*

In a separate open-label single arm trial of FTC+TAF with bictegravir that enrolled 24 virologically-suppressed children at least 2 years of age and weighing at least 14 to less than 25 kg (cohort 3), 91% (20/22) of subjects remained virologically suppressed at Week 24. From a mean (SD) baseline CD4+ count of 1104 (440), the mean (SD) change from baseline in CD4+ cell count was −126 (264) cells per mm^3, and the mean (SD) change in CD4% was 0.2% (4.4%) at Week 24.

Clinical Trials in Adults with HIV-1 and Renal Insufficiency

In a trial in 248 HIV-1 infected adults 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 began on FTC+TAF with EVG+COBI (N=6) and those previously virologically-suppressed on other regimens and switched to FTC+TAF with EVG+COBI (N=242) had HIV-1 RNA less than 50 copies per mL at Week 24.

In a trial in 55 HIV-1 infected virologically-suppressed adults with ESRD (estimated creatinine clearance of less than 15 mL per minute) receiving chronic hemodialysis for at least 6 months who switched to FTC+TAF with EVG+COBI, 82% (45/55) maintained HIV-1 RNA less than 50 copies per mL at Week 48. Two subjects had HIV-1 RNA ≥ 50 copies per mL by Week 48, 7 discontinued due to AE or other reasons while suppressed, and 1 did not have an HIV-1 RNA measurement at Week 48.

14.3 Clinical Trial Results for HIV-1 PrEP

The efficacy and safety of DESCOVY to reduce the risk of acquiring HIV-1 infection were evaluated in a randomized, double-blind multinational trial (DISCOVER) in HIV-seronegative men (N=5,262) or transgender women (N=73) who have sex with men and are at risk of HIV-1 infection, comparing once daily DESCOVY (N=2,670) to TRUVADA (FTC/TDF 200 mg/300 mg; N=2,665). Evidence of risk behavior at entry into the trial included at least one of the following: two or more unique condomless anal sex partners in the past 12 weeks or a diagnosis of rectal gonorrhea/chlamydia or syphilis in the past 24 weeks. The median age of participants was 34 years (range, 18-76); 84% were White, 9% Black/Mixed Black, 4% Asian, and 24% Hispanic/Latino. At baseline, 897 participants (17%) reported receiving TRUVADA for PrEP.

At weeks 4, 12, and every 12 weeks thereafter, all participants received local standard of care HIV-1 prevention services, including HIV-1 testing, evaluation of adherence, safety evaluations, risk-reduction counseling, condoms, management of sexually transmitted infections, and assessment of sexual behavior.

Trial participants maintained a high risk of sexual HIV-1 acquisition, with high rates of rectal gonorrhea (DESCOVY, 24%; TRUVADA, 25%), rectal chlamydia (DESCOVY, 30%; TRUVADA, 31%), and syphilis (14% in both treatment groups) during the trial.

The primary outcome was the incidence of documented HIV-1 infection per 100 person-years in participants randomized to DESCOVY and TRUVADA (with a minimum follow-up of 48 weeks and at least 50% of participants having 96 weeks of follow-up). DESCOVY was non-inferior to TRUVADA in reducing the risk of acquiring HIV-1 infection (Table 16). The results were similar across the subgroups of age, race, gender identity, and baseline TRUVADA for PrEP use.

Table 16 HIV-1 Infection Results in DISCOVER Trial – Full Analysis Set

	DESCOVY (N=2,670)	**TRUVADA (N=2,665)**	**Rate Ratio (95% CI)**
	4,370 person-years	**4,386 person-years**	
HIV-1 infections, n	7	15	
Rate of HIV-1 infections per 100 person-years	0.16	0.34	0.468 (0.19, 1.15)

CI = Confidence interval.

Of the 22 participants diagnosed with HIV-1 infection in the trial, five had suspected baseline infection prior to study entry (DESCOVY, 1; TRUVADA, 4). In a case-control substudy of intracellular drug levels and estimated number of daily doses as measured by dried blood spot testing, median intracellular tenofovir diphosphate concentrations were substantially lower in participants infected with HIV-1 at the time of diagnosis compared with uninfected matched control participants. For both DESCOVY and TRUVADA, efficacy was therefore strongly correlated to adherence to daily dosing.

16 HOW SUPPLIED/STORAGE AND HANDLING

DESCOVY tablets are available in bottles and blister packs containing 30 tablets:

Bottles

- 200 mg/25 mg tablets each contain 200 mg of emtricitabine (FTC) and 25 mg of tenofovir alafenamide (TAF). These tablets are blue, rectangular-shaped, and film-coated with “GSI” debossed on one side and “225” on the other side (NDC 61958-2002-1).

- 120 mg/15 mg tablets each contain 120 mg of FTC and 15 mg of TAF. These tablets are white, round-shaped, and film coated with “GSI” debossed on one side and “15” on the other side (NDC 61958-2005-1).

Bottles contain a silica gel desiccant, polyester coil, and child resistant closure.

Keep bottle tightly closed.

Blister Pack

- 200 mg/25 mg tablets each contain 200 mg of FTC and 25 mg of TAF. These tablets are blue, rectangular-shaped, and film-coated with “GSI” debossed on one side and “225” on the other side (NDC 61958-2002-2).

Blister packs are sealed with a child-resistant laminated foil lidding material (peel-push) and each blister cavity contains a die-cut desiccant film which is heat staked to the foil lidding material.

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (see USP Controlled Room Temperature).

Dispense only in original container.

17 PATIENT COUNSELING INFORMATION

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

Important Information for Uninfected Individuals Taking DESCOVY for HIV-1 PrEP

Advise HIV-1 uninfected individuals about the following *[see Warnings and Precautions (5.2)]:*

- The need to confirm that they are HIV-negative before starting to take DESCOVY to reduce the risk of acquiring HIV-1.
- That HIV-1 resistance substitutions may emerge in individuals with undetected HIV-1 infection who are taking DESCOVY, because DESCOVY alone does not constitute a complete regimen for HIV-1 treatment.
- The importance of taking DESCOVY on a regular dosing schedule and strict adherence to the recommended dosing schedule to reduce the risk of acquiring HIV-1. Uninfected individuals who miss doses are at greater risk of acquiring HIV-1 than those who do not miss doses.
- That DESCOVY does not prevent other sexually acquired infections and should be used as part of a complete prevention strategy including other prevention measures.
- To use condoms consistently and correctly to lower the chances of sexual contact with any body fluids such as semen, vaginal secretions, or blood.
- The importance of knowing their HIV-1 status and the HIV-1 status of their partner(s).
- The importance of virologic suppression in their partner(s) with HIV-1.
- The need to get tested regularly for HIV-1 (at least every 3 months, or more frequently for some individuals such as adolescents) and to ask their partner(s) to get tested as well.
- To report any symptoms of acute HIV-1 infection (flu-like symptoms) to their healthcare provider immediately.
- That the signs and symptoms of acute infection include fever, headache, fatigue, arthralgia, vomiting, myalgia, diarrhea, pharyngitis, rash, night sweats, and adenopathy (cervical and inguinal).
- To get tested for other sexually transmitted infections, such as syphilis, chlamydia, and gonorrhea, that may facilitate HIV-1 transmission.
- To assess their sexual risk behavior and get support to help reduce sexual risk behavior.

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

Inform individuals that severe acute exacerbations of hepatitis B have been reported in patients who are infected with HBV and have discontinued products containing FTC and/or TDF and may likewise occur with discontinuation of DESCOVY *[see Warnings and Precautions (5.1)]*. Advise HBV-infected individuals to not discontinue DESCOVY without first informing their healthcare provider.

Immune Reconstitution Syndrome

Advise HIV-1 infected patients to inform their healthcare provider immediately of any symptoms of infection. 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 (5.3)]*.

New Onset or Worsening Renal Impairment

Advise HIV-1 infected patients and uninfected individuals to avoid taking DESCOVY with concurrent or recent use of nephrotoxic agents. Postmarketing cases of renal impairment, including acute renal failure, have been reported *[see Warnings and Precautions (5.4)].*

Lactic Acidosis and Severe Hepatomegaly

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with use of drugs similar to DESCOVY. Advise HIV-1 infected patients and uninfected individuals that they should stop DESCOVY if they develop clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity *[see Warnings and Precautions (5.5)]*.

Dosage Recommendations for Treatment of HIV-1 Infection

Inform HIV-1 infected patients that it is important to take DESCOVY with other antiretroviral drugs for the treatment of HIV-1 on a regular dosing schedule with or without food and to avoid missing doses as it can result in development of resistance *[see Dosage and Administration (2.3, 2.4)]*.

Pregnancy Registry

Inform individuals using DESCOVY that there is an antiretroviral pregnancy registry to monitor fetal outcomes of pregnant women exposed to DESCOVY *[see Use in Specific Populations (8.1)].*

Lactation

Instruct mothers with HIV-1 infection not to breastfeed because of the risk of passing the HIV-1 virus to the baby *[see Use in Specific Populations (8.2)]*.

Medication Guide
DESCOVY® (des-KOH-vee)
(emtricitabine and tenofovir alafenamide)
tablets

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

This Medication Guide provides information about two different ways that DESCOVY may be used. See the section **"What is DESCOVY?"** for detailed information about how DESCOVY may be used.

What is the most important information I should know about DESCOVY?

DESCOVY can cause serious side effects, including:

- **Worsening of hepatitis B virus (HBV) infection. Your healthcare provider will test you for HBV infection before or when you start treatment with DESCOVY. If you have HBV infection and take DESCOVY, your HBV may get worse (flare-up) if you stop taking DESCOVY. A "flare-up" is when your HBV infection suddenly returns in a worse way than before.**
  - Do not run out of DESCOVY. Refill your prescription or talk to your healthcare provider before your DESCOVY is all gone.
  - Do not stop taking DESCOVY without first talking to your healthcare provider.
  - If you stop taking DESCOVY, your healthcare provider will need to check your health often and do blood tests regularly for several months to check your liver, and may give you a medicine to treat hepatitis B. Tell your healthcare provider about any new or unusual symptoms you may have after you stop taking DESCOVY.

For more information about side effects, see the section "What are the possible side effects of DESCOVY?"

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

Before taking DESCOVY to reduce your risk of getting HIV-1:

- **You must be HIV-1 negative to start DESCOVY. You must get tested to make sure that you do not already have HIV-1 infection.**
- **Do not take DESCOVY for HIV-1 PrEP unless you are confirmed to be HIV-1 negative.**
- Some HIV-1 tests can miss HIV-1 infection in a person who has recently become infected. If you have flu-like symptoms, you could have recently become infected with HIV-1. Tell your healthcare provider if you had a flu-like illness within the last month before starting DESCOVY or at any time while taking DESCOVY. Symptoms of new HIV-1 infection include:
  - tiredness
  - fever
  - joint or muscle aches
  - headache
  - sore throat
  - vomiting or diarrhea
  - rash
  - night sweats
  - enlarged lymph nodes in the neck or groin

While you are taking DESCOVY for HIV-1 PrEP:

- **DESCOVY does not prevent other sexually transmitted infections (STIs). Practice safer sex by using a latex or polyurethane condom to reduce the risk of getting STIs.**
- **You must stay HIV-1 negative to keep taking DESCOVY for HIV-1 PrEP.**
  - Know your HIV-1 status and the HIV-1 status of your partners.
  - Ask your partners with HIV-1 if they are taking HIV-1 medicines and have an undetectable viral load. An undetectable viral load is when the amount of virus in the blood is too low to be measured in a lab test. To maintain an undetectable viral load, your partners must keep taking HIV-1 medicines every day. Your risk of getting HIV-1 is lower if your partners with HIV-1 are taking effective treatment.
  - Get tested for HIV-1 at least every 3 months or when your healthcare provider tells you.
  - Get tested for other STIs such as syphilis, chlamydia, and gonorrhea. These infections make it easier for HIV-1

to infect you.
  - If you think you were exposed to HIV-1, tell your healthcare provider right away. They may want to do more tests to be sure you are still HIV-1 negative.
  - Get information and support to help reduce sexual risk behaviors.
  - Do not miss any doses of DESCOVY. Missing doses increases your risk of getting HIV-1 infection.
- If you do become HIV-1 positive, you need more medicine than DESCOVY alone to treat HIV-1. DESCOVY by itself is not a complete treatment for HIV-1.

If you have HIV-1 and take only DESCOVY, over time your HIV-1 may become harder to treat.

What is DESCOVY?

DESCOVY is a prescription medicine that may be used in two different ways. DESCOVY is used:

- to treat HIV-1 infection
  - in adults and children who weigh at least 77 pounds (35 kg) together with other HIV-1 medicines
  - in children who weigh at least 31 pounds (14 kg) and less than 77 pounds (35 kg) together with certain other HIV-1 medicines. Your healthcare provider will determine which other HIV-1 medicines may be used with DESCOVY.
- for HIV-1 PrEP to reduce the risk of getting HIV-1 infection in adults and adolescents who weigh at least 77 pounds (35 kg). It is not known if DESCOVY is effective in reducing the risk of getting HIV-1 from certain types of sex.
  - DESCOVY for PrEP is not for use in people born female (assigned female at birth) who are at risk of getting HIV-1 infection from vaginal sex, because its effectiveness has not been studied.

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

DESCOVY contains the prescription medicines emtricitabine and tenofovir alafenamide.

It is not known if DESCOVY for treatment of HIV-1 infection is safe and effective in children who weigh less than 31 pounds (14 kg).

It is not known if DESCOVY is safe and effective in reducing the risk of HIV-1 infection in people who weigh less than 77 pounds (35 kg).

For people taking DESCOVY for HIV-1 PrEP:
Do not take DESCOVY for HIV-1 PrEP if:

- **you already have HIV-1 infection.** If you are HIV-1 positive, you need to take other medicines with DESCOVY to treat HIV-1. DESCOVY by itself is not a complete treatment for HIV-1.
- **you do not know your HIV-1 infection status.** You may already be HIV-1 positive. You need to take other HIV-1 medicines with DESCOVY to treat HIV-1 infection.

DESCOVY can only help reduce your risk of getting HIV-1 infection **before** you are infected.

What should I tell my healthcare provider before taking DESCOVY?

Before taking DESCOVY, tell your healthcare provider about all of your medical conditions, including if you:

- have liver problems, including HBV infection
- have kidney problems
- are pregnant or plan to become pregnant. It is not known if DESCOVY can harm your unborn baby. Tell your healthcare provider if you become pregnant during treatment with DESCOVY.

  Pregnancy Registry: There is a pregnancy registry for people who take DESCOVY 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 DESCOVY for treatment of HIV-1 because of the risk of passing HIV-1 to your baby.
  - One of the ingredients in DESCOVY (emtricitabine) passes into your breast milk.

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 DESCOVY. 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 DESCOVY.

- **Do not start a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take DESCOVY with other medicines.

How should I take DESCOVY?

- Take DESCOVY exactly as your healthcare provider tells you to take it. If you take DESCOVY to treat HIV-1 infection, you need to take DESCOVY with other HIV-1 medicines. Your healthcare provider will tell you what medicines to take and how to take them.
- Take DESCOVY 1 time each day with or without food.
- If you are on dialysis, take your daily dose of DESCOVY following dialysis.
- Do not change your dose or stop taking DESCOVY without first talking with your healthcare provider. Stay under a healthcare provider's care when taking DESCOVY. Do not miss a dose of DESCOVY.
- If you take too much DESCOVY, call your healthcare provider or go to the nearest hospital emergency room right away.
- When your DESCOVY supply starts to run low, get more from your healthcare provider or pharmacy.
  - If you are taking DESCOVY for treatment of HIV-1, the amount of virus in your blood may increase if the medicine is stopped for even a short time. The virus may develop resistance to DESCOVY and become harder to treat.
  - If you are taking DESCOVY for HIV-1 PrEP, missing doses increases your risk of getting HIV-1 infection.

What are the possible side effects of DESCOVY?

DESCOVY may cause serious side effects, including:

- **See "What is the most important information I should know about DESCOVY?"**
- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking medicines to treat HIV-1 infection. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider right away if you start having any new symptoms after starting your HIV-1 medicine.
- **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 while taking DESCOVY. Your healthcare provider may tell you to stop taking DESCOVY 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 DESCOVY for treatment of HIV-1 is nausea.

The most common side effect of DESCOVY for HIV-1 PrEP is diarrhea.

These are not all of the possible side effects of DESCOVY.

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 DESCOVY?

- Store DESCOVY between 68°F to 77°F (20°C to 25°C).
- Keep DESCOVY in its original bottle or blister pack.
- Keep the bottle tightly closed.

Keep DESCOVY and all medicines out of reach of children.

General information about the safe and effective use of DESCOVY.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use DESCOVY for a condition for which it was not prescribed. Do not give DESCOVY 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 DESCOVY that is written for health professionals.

What are the ingredients in DESCOVY?

Active ingredients: emtricitabine and tenofovir alafenamide.

Inactive ingredients: croscarmellose sodium, magnesium stearate, and microcrystalline cellulose.

The 200 mg/25 mg tablets are film-coated with a coating material containing indigo carmine aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide. The 120 mg/15 mg tablets are film-coated with a coating material containing polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc.

Manufactured and distributed by: Gilead Sciences, Inc. Foster City, CA 94404

208215-GS-009

For more information, call 1-800-445-3235 or go to www.DESCOVY.com.

This Medication Guide has been approved by the U.S. Food and Drug Administration Revised: 01/2022

Proposed Package Insert

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use DESCOVY safely and effectively. See full prescribing information for DESCOVY.

DESCOVY® (emtricitabine and tenofovir alafenamide) tablets, for oral use
Initial U.S. Approval: 2015

WARNING: POST-TREATMENT ACUTE EXACERBATION OF HEPATITIS B and RISK OF DRUG RESISTANCE WITH USE OF DESCOVY FOR HIV-1 PRE-EXPOSURE PROPHYLAXIS (PrEP) IN UNDIAGNOSED EARLY HIV-1 INFECTION
See full prescribing information for complete boxed warning.

Severe acute exacerbations of hepatitis B (HBV) have been reported in HBV-infected individuals who have discontinued products containing emtricitabine (FTC) and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of DESCOVY. Hepatic function should be monitored closely in these individuals. If appropriate, anti-hepatitis B therapy may be warranted. (5.1)

DESCOVY used for HIV-1 PrEP must only be prescribed to individuals confirmed to be HIV-negative immediately prior to initiating and at least every 3 months during use. Drug-resistant HIV-1 variants have been identified with use of FTC/TDF for HIV-1 PrEP following undetected acute HIV-1 infection. Do not initiate DESCOVY for HIV-1 PrEP if signs or symptoms of acute HIV-1 infection are present unless negative infection status is confirmed. (5.2)

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.1)	01/2022
Dosage and Administration (2.4)	01/2022
Warnings and Precautions (5.4)	03/2021

----------INDICATIONS AND USAGE----------
HIV-1 Treatment (1.1):
DESCOVY 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 35 kg.
- 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 14 kg and less than 35 kg.

HIV-1 PrEP (1.2):
DESCOVY is 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 DESCOVY for HIV-1 PrEP.
Limitations of Use (1.2):
The indication does not include use of DESCOVY in individuals at risk of HIV-1 from receptive vaginal sex because effectiveness in this population has not been evaluated.

----------DOSAGE AND ADMINISTRATION----------

- Testing: Prior to or when initiating DESCOVY, test for hepatitis B virus infection. Prior to or when initiating DESCOVY, and during use 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. (2.1)
- HIV-1 Screening: Screen all individuals for HIV-1 infection immediately prior to initiating DESCOVY for HIV-1 PrEP and at least once every 3 months while taking DESCOVY, and upon diagnosis of any other sexually transmitted infections (STIs). (2.2)
- Recommended dosage:
  - Treatment of HIV-1 Infection:
    - Adult and pediatric patients weighing at least 35 kg: One 200 mg/25 mg tablet once daily with or without food. (2.3)
    - Pediatric patients not receiving a protease inhibitor administered with ritonavir or cobicistat, and weighing:
      - at least 25 to less than 35 kg: One 200 mg/25 mg tablet once daily with or without food. (2.4)
      - at least 14 to less than 25 kg: One 120 mg/15 mg tablet once daily with or without food. (2.4)
  - HIV-1 PrEP: One 200 mg/ 25 mg tablet once daily with or without food in individuals with body weight at least 35 kg. (2.5)
- Renal impairment: DESCOVY is not recommended in individuals with estimated creatinine clearance of 15 to below 30 mL per minute, or below 15 mL per minute who are not receiving chronic hemodialysis. (2.6)

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 200 mg/25 mg of FTC and TAF respectively (3)

----------CONTRAINDICATIONS----------
DESCOVY for HIV-1 PrEP is contraindicated in individuals with unknown or positive HIV-1 status. (4)

----------WARNINGS AND PRECAUTIONS----------

- Comprehensive management to reduce the risk of sexually transmitted infections (STIs), including HIV-1, when DESCOVY is used for HIV-1 PrEP: Counsel on adherence to daily dosing and safer sex practices, including condoms, to reduce the risk of STIs. (5.2)
- Management to reduce the risk of acquiring HIV-1 drug resistance when DESCOVY is used for HIV-1 PrEP: refer to full prescribing information for additional detail. (5.2)
- Immune reconstitution syndrome during treatment of HIV-1 infection: May necessitate further evaluation and treatment. (5.3)
- New onset or worsening renal impairment: Assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein when initiating DESCOVY and during use on a clinically appropriate schedule in all individuals. Also assess serum phosphorus in individuals with chronic kidney disease. (5.4)
- Lactic acidosis/severe hepatomegaly with steatosis: Discontinue DESCOVY in individuals who develop symptoms or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity. (5.5)

----------ADVERSE REACTIONS----------

- In HIV-1 infected patients, the most common adverse reaction (incidence greater than or equal to 10%, all grades) was nausea. (6.1)
- In HIV-1 uninfected adults in a PrEP trial, the most common adverse reaction (incidence greater than or equal to 5%, all grades) was diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact LifeScience Logistics at 1-855-738-6171 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
Consult the Full Prescribing Information prior to and during use for potential drug interactions. (7, 12.3)

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Mothers infected with HIV-1 should be instructed not to breastfeed, due to the potential for HIV transmission. (8.2)
- Pediatrics:
  - Treatment of HIV-1 Infection: Not recommended for patients weighing less than 14 kg. (8.4)
  - HIV-1 PrEP: Not recommended for individuals weighing less than 35 kg. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 01/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: POST-TREATMENT ACUTE EXACERBATION OF HEPATITIS B and RISK OF DRUG RESISTANCE WITH USE OF DESCOVY FOR HIV-1 PRE-EXPOSURE PROPHYLAXIS (PrEP) IN UNDIAGNOSED EARLY HIV-1 INFECTION

Severe acute exacerbations of hepatitis B (HBV) have been reported in HBV-infected individuals who have discontinued products containing emtricitabine (FTC) and/or tenofovir disoproxil fumarate (TDF) and may occur with discontinuation of DESCOVY.

Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in individuals who are infected with HBV and discontinue DESCOVY. If appropriate, anti-hepatitis B therapy may be warranted *[see Warnings and Precautions (5.1)]*.

DESCOVY used for HIV-1 PrEP must only be prescribed to individuals confirmed to be HIV-negative immediately prior to initiating and at least every 3 months during use. Drug-resistant HIV-1 variants have been identified with use of FTC/TDF for HIV-1 PrEP following undetected acute HIV-1 infection. Do not initiate DESCOVY for HIV-1 PrEP if signs or symptoms of acute HIV-1 infection are present unless negative infection status is confirmed *[see Warnings and Precautions (5.2)].*

1 INDICATIONS AND USAGE

1.1 Treatment of HIV-1 Infection

DESCOVY 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.

DESCOVY is 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 14 kg and less than 35 kg.

1.2 HIV-1 Pre-Exposure Prophylaxis (PrEP)

DESCOVY is 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 DESCOVY 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 DESCOVY 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)].*

2 DOSAGE AND ADMINISTRATION

2.1 Testing When Initiating and During Use of DESCOVY for Treatment of HIV-1 Infection or for HIV-1 PrEP

Prior to or when initiating DESCOVY, test individuals for hepatitis B virus infection *[see Warnings and Precautions (5.1)]*.

Prior to or when initiating DESCOVY, and during use of DESCOVY 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)].*

2.2 HIV-1 Screening for Individuals Receiving DESCOVY for HIV-1 PrEP

Screen all individuals for HIV-1 infection immediately prior to initiating DESCOVY for HIV-1 PrEP and at least once every 3 months while taking DESCOVY, 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)].*

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

DESCOVY is a two-drug fixed dose combination product containing emtricitabine (FTC) and tenofovir alafenamide (TAF).

The recommended dosage of DESCOVY for treatment of HIV-1 is one tablet containing 200 mg FTC and 25 mg of TAF taken orally once daily with or without food in:

- adults and pediatric patients with body weight at least 35 kg and estimated creatinine clearance greater than or equal to 30 mL per minute; or
- adults with creatinine clearance below 15 mL per minute who are receiving chronic hemodialysis. On days of hemodialysis, administer the daily dose of DESCOVY after completion of hemodialysis treatment *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

The safety and effectiveness of DESCOVY coadministered with an HIV-1 protease inhibitor that is administered with either ritonavir or cobicistat have not been established in adults with creatinine clearance below 15 mL per minute, with or without hemodialysis.

For specific dosing recommendations for coadministered antiretroviral drugs, refer to their respective prescribing information *[see Drug Interactions (7)]*.

2.4 Recommended Dosage for Treatment of HIV-1 Infection in Pediatric Patients Weighing at Least 14 kg to Less than 35 kg

The recommended dosage of DESCOVY in pediatric patients weighing at least 14 kg to 35 kg is based on body weight and provided in Table 1. This dosing information is applicable to pediatric patients with estimated creatinine clearance greater than or equal to 30 mL per minute *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]* who are not receiving an HIV protease inhibitor that is administered with either ritonavir or cobicistat.

Table 1 Dosing for Treatment of HIV-1 Infection in Pediatric Patients Weighing 14 to Less than 35 kg

Body Weight (kg)	**DESCOVY Dose**
25 kg to less than 35 kg	One tablet containing 200 mg FTC and 25 mg of TAF taken orally once daily
	The 120 mg / 15 mg tablets are not being imported by LifeScience Logistics.

The safety and effectiveness of DESCOVY 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.

For specific dosing recommendations for coadministered antiretroviral drugs, refer to their respective prescribing information *[see Drug Interactions (7)]*.

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

The dosage of DESCOVY 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; or
- adults with creatinine clearance below 15 mL per minute who are receiving chronic hemodialysis. On days of hemodialysis, administer the daily dose of DESCOVY after completion of hemodialysis treatment *[see Indications and Usage (1.2) and Clinical Pharmacology (12.3)].*

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

DESCOVY is not recommended in individuals with:

- severe renal impairment (estimated creatinine clearance of 15 to below 30 mL per minute); or
- end stage renal disease (ESRD; estimated creatinine clearance below 15 mL per minute) who are not receiving chronic hemodialysis *[see Dosage and Administration (2.3, 2.5) and Use in Specific Populations (8.6)]*.

3 DOSAGE FORMS AND STRENGTHS

DESCOVY tablets are available in two dose strengths:

- 200 mg/25 mg tablets: 200 mg of emtricitabine (FTC) and 25 mg of tenofovir alafenamide (TAF) (equivalent to 28 mg of tenofovir alafenamide fumarate). These tablets are blue, rectangular-shaped, film-coated, debossed with “GSI” on one side and “225” on the other side.

- The 120 mg / 15 mg tablets are not being imported by LifeScience Logistics.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

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

All individuals should be tested for the presence of hepatitis B virus (HBV) before or when initiating DESCOVY *[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 DESCOVY. Individuals infected with HBV who discontinue DESCOVY 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.

5.2 Comprehensive Management to Reduce the Risk of Sexually Transmitted Infections, Including HIV-1, and Development of HIV-1 Resistance When DESCOVY Is Used for HIV-1 PrEP

Use DESCOVY 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 DESCOVY 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 DESCOVY 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 DESCOVY, because DESCOVY 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 DESCOVY 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 DESCOVY 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 DESCOVY 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 DESCOVY dosing schedule. The effectiveness of DESCOVY in reducing the risk of acquiring HIV-1 is strongly correlated with adherence, as demonstrated by measurable drug levels in a clinical trial of DESCOVY 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)].*

5.3 Immune Reconstitution Syndrome

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

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

5.4 New Onset or Worsening Renal Impairment

Postmarketing cases of renal impairment, including acute renal failure, proximal renal tubulopathy (PRT), and Fanconi syndrome have been reported with TAF-containing products; while most of these cases were characterized by potential confounders that may have contributed to the reported renal events, it is also possible these factors may have predisposed patients to tenofovir-related adverse events *[see Adverse Reactions (6.1, 6.2)]*. DESCOVY is not recommended in individuals with estimated creatinine clearance of 15 to below 30 mL per minute, or in individuals with estimated creatinine clearance below 15 mL per minute who are not receiving chronic hemodialysis.

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 DESCOVY, and during treatment with DESCOVY 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 DESCOVY in individuals who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

5.5 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 DESCOVY, and tenofovir DF, another prodrug of tenofovir, alone or in combination with other antiretrovirals. Treatment with DESCOVY 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).

6 ADVERSE REACTIONS

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)].*

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 Elvitegravir (EVG) plus Cobicistat (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. Across these trials, 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 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. FTC+TAF with EVG+COBI was permanently discontinued due to worsening renal function in two of 80 (3%) subjects.

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.

<u>Adverse Reactions in a Clinical Trial of FTC+TAF with EVG+COBI in Virologically-Suppressed Adults with End Stage Renal Disease (ESRD) Receiving Chronic Hemodialysis</u>

In a 48-week trial of virologically-suppressed HIV-1 infected adult subjects with end stage renal disease (ESRD) (estimated creatinine clearance of less than 15 mL/min) on chronic hemodialysis treated with FTC+TAF with EVG+COBI (N=55), the most commonly reported adverse reaction (adverse event assessed as

causally related by investigator and all grades) was nausea (7%). Serious adverse events were reported in 53% of subjects and the most common serious adverse events were pneumonia (13%), fluid overload (7%), hyperkalemia (7%) and osteomyelitis (7%). Overall 5% of subjects permanently discontinued treatment due to an adverse event.

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

Pediatric Subjects Weighing at Least 25 kg:

The safety profile of FTC+TAF in pediatric subjects weighing at least 25 kg is informed by 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=52; Cohort 2). Subjects received FTC+TAF with EVG+COBI through 48 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 in 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 48, +3.9% at the lumbar spine and +4.2% for TBLH. Mean changes from baseline BMD Z-scores were -0.24 for lumbar spine and -0.19 for TBLH at Week 48. Six subjects had significant (at least 4%) lumbar spine BMD loss at Week 48 and 2 subjects also had at least 4% TBLH BMD loss at Week 48.

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=52) 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 Weeks 24 and 48. The mean baseline and mean change from baseline in CD4+ cell count and in

CD4% from Week 2 to Week 48 are presented in Table 2. All subjects maintained their CD4+ cell counts above 400 cells/mm^3 *[see Use in Specific Populations (8.4)].*

Table 2 Mean Change in CD4+ Count and CD4 Percentage from Baseline to Week 48 in Virologically-Suppressed Pediatric Patients from 6 to <12 Years Who Switched to FTC+TAF with EVG+COBI

		Mean Change from Baseline					
	Baseline	**Week 2**	**Week 4**	**Week 12**	**Week 24**	**Week 32**	**Week 48**
CD4+ Cell Count (cells/mm^3)	961 (275.5)[a]	-117	-114	-112	-118	-62	-66
CD4%	38 (6.4)[a]	+0.3%	-0.1%	-0.8%	-0.8%	-1.0%	-0.6%

a. Mean (SD)

Pediatric Subjects Weighing at Least 14 to Less Than 25 kg:

In a separate open-label trial of virologically-suppressed subjects at least 2 years of age and weighing at least 14 to less than 25 kg (N=22; Cohort 3) who received FTC+TAF with bictegravir through 24 weeks, no new adverse reactions or laboratory abnormalities were identified compared to those observed in adults. In this trial, the mean (SD) change from baseline to Week 24 in CD4+ cell count was −126 (264) cells per mm^3 and the mean (SD) change in CD4% from baseline to Week 24 was 0.2% (4.4%).

Adverse Reactions from Clinical Trial Experience in HIV-1 Uninfected Individuals Taking DESCOVY for HIV-1 PrEP

The safety profile of DESCOVY 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 DESCOVY (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 DESCOVY (incidence greater than or equal to 5%, all grades) was diarrhea (5%). Table 3 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 DESCOVY or TRUVADA due to adverse events, regardless of severity, was 1.3% and 1.8%, respectively.

Table 3 Adverse Reactions (All Grades) Reported in ≥2% in Either Arm in the DISCOVER Trial of HIV-1 Uninfected Participants

	DESCOVY (N=2,694)	TRUVADA (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

Renal Laboratory Tests

Changes from baseline to Week 48 in renal laboratory data are presented in Table 4. The long-term clinical significance of these renal laboratory changes on adverse reaction frequencies between DESCOVY and TRUVADA is not known.

Table 4 Laboratory Assessments of Renal Function Reported in HIV-1 Uninfected Participants Receiving DESCOVY or TRUVADA in the DISCOVER Trial

	DESCOVY (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 (≤ 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 DESCOVY, 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 5.

Table 5 Fasting Lipid Values, Mean Change from Baseline, Reported in HIV-1 Uninfected Participants Receiving DESCOVY or TRUVADA in the DISCOVER Trial[a]

	DESCOVY (N=2,694)		**TRUVADA (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

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of products containing TAF. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and Subcutaneous Tissue Disorders
Angioedema, urticaria, and rash

Renal and Urinary Disorders
Acute renal failure, acute tubular necrosis, proximal renal tubulopathy, and Fanconi syndrome

7 DRUG INTERACTIONS

7.1 Potential for Other Drugs to Affect One or More Components of DESCOVY

TAF, a component of DESCOVY, 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 DESCOVY and development of resistance. Coadministration of DESCOVY 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 DESCOVY 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 (5.4)]*.

7.3 Established and Other Potentially Significant Interactions

Table 6 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 DESCOVY, the components of DESCOVY (emtricitabine and tenofovir alafenamide) as individual agents, or are predicted drug interactions that may occur with DESCOVY. For magnitude of interaction, *see Clinical Pharmacology (12.3)*.

Table 6 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 DESCOVY is not recommended.
Other Agents		
Anticonvulsants: carbamazepine oxcarbazepine phenobarbital phenytoin	↓ TAF	Consider alternative anticonvulsant.
Antimycobacterials: rifabutin rifampin rifapentine	↓ TAF	Coadministration of DESCOVY with rifabutin, rifampin, or rifapentine is not recommended.
Herbal Products: St. John's wort *(Hypericum perforatum)*	↓ TAF	Coadministration of DESCOVY with St. John's wort is not recommended.

a. This table is not all inclusive.
b. ↓=Decrease

7.4 Drugs without Clinically Significant Interactions with DESCOVY

Based on drug interaction studies conducted with the components of DESCOVY, no clinically significant drug interactions have been either observed or are expected when DESCOVY 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 DESCOVY 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

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to DESCOVY 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 statistically significant difference in the overall risk of major birth defects for emtricitabine (FTC) or tenofovir alafenamide (TAF) compared with the background rate for major birth defects of 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) *(see Data)*. The rate of miscarriage for individual drugs is not reported in the APR. 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 DESCOVY 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 DESCOVY *(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 DESCOVY. 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 DESCOVY.

Data

Human Data

Prospective reports from the APR of overall major birth defects in pregnancies exposed to the components of DESCOVY are compared with a U.S. background major birth defect rate. Methodological 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 less than 20 weeks gestation.

Emtricitabine (FTC):

Based on prospective reports to the APR of over 5,400 exposures to FTC-containing regimens during pregnancy resulting in live births (including over 3,900 exposed in the first trimester and over 1,500 exposed in the second/third trimester), the prevalence of birth defects in live births was 2.6% (95% CI: 2.2% to 3.2%) and 2.7% (95% CI: 1.9% to 3.7%) following first and second/third trimester exposure, respectively, to FTC-containing regimens.

Tenofovir Alafenamide (TAF):

Based on prospective reports to the APR of over 660 exposures to TAF-containing regimens during pregnancy resulting in live births (including over 520 exposed in the first trimester and over 130 exposed in the second/third trimester), the prevalence of birth defects in live births was 4.2 % (95% CI: 2.6 % to 6.3 %) and 3.0% (95% CI: 0.8% to 7.5 %) following first and second/third trimester exposure, respectively, to TAF-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 DESCOVY. 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 DESCOVY.

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-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 DESCOVY 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 DESCOVY 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.

8.4 Pediatric Use

Treatment of HIV-1 Infection

The safety and effectiveness of DESCOVY, 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 14 kg *[see Indication and Usage (1.1) and Dosage and Administration (2.3, 2.4)]*.

Use of DESCOVY in pediatric patients between 6 to less than 18 years of age and 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 antiretroviral treatment-naïve HIV-1 infected pediatric subjects aged 12 to less than 18 years and weighing at least 35 kg through Week 48 (N=50; cohort 1) and in virologically-suppressed pediatric subjects aged 6 to less than 12 years and weighing at least 25 kg through Week 48 (N=52; cohort 2). The safety and efficacy of FTC+TAF with EVG+COBI in adolescent subjects was similar to that in adults on this regimen. The safety and efficacy of FTC+TAF with EVG+COBI in subjects 6 to 12 years of age weighing at least 25 kg was similar to that in antiretroviral treatment-naïve adults and adolescents on this regimen, with the exception of a decrease from baseline in CD4+ cell count *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies (14.2)]*.

Use of DESCOVY in pediatric patients between 2 to less than 6 years of age and weighing at least 14 to less than 25 kg is supported by adequate and well controlled studies of FTC+TAF with EVG+COBI in adults and by a separate open-label trial of FTC+TAF with bictegravir in virologically-suppressed pediatric patients at least 2 years of age and weighing at least 14 to less than 25 kg through Week 24 (N=22; cohort 3). The safety and efficacy of FTC+TAF in these pediatric subjects were similar to that observed in adults who received FTC+TAF with bictegravir *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies (14.2)]*.

Safety and effectiveness of DESCOVY coadministered with an HIV-1 protease inhibitor that is administered with either ritonavir or cobicistat have not been

established in pediatric patients weighing less than 35 kg *[see Dosage and Administration (2.4)]*.

Safety and effectiveness of DESCOVY for treatment of HIV-1 infection in pediatric patients weighing less than 14 kg have not been established.

HIV-1 PrEP

Safety and effectiveness of DESCOVY 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 DESCOVY 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 (2.5), Adverse Reactions (6.1), Clinical Pharmacology (12.3 and 12.4), and Clinical Studies (14)].*

While using DESCOVY 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 DESCOVY for HIV-1 PrEP in pediatric patients weighing less than 35 kg have not been established.

8.5 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.

8.6 Renal Impairment

No dosage adjustment of DESCOVY is recommended in individuals with estimated creatinine clearance greater than or equal to 30 mL per minute, or in adults with ESRD (estimated creatinine clearance below 15 mL per minute) who are receiving chronic hemodialysis. On days of hemodialysis, administer the daily dose of DESCOVY after completion of hemodialysis treatment.

Safety and effectiveness of DESCOVY coadministered with an HIV-1 protease inhibitor that is administered with either ritonavir or cobicistat have not been established in patients with ESRD *[see Dosage and Administration (2.3)]*.

DESCOVY is not recommended in individuals with severe renal impairment (estimated creatinine clearance of 15 to below 30 mL per minute), or in individuals with ESRD who are not receiving chronic hemodialysis, as the safety of DESCOVY has not been established in these populations *[see Dosage and Administration (2.6) and Clinical Studies (14.2)].*

8.7 Hepatic Impairment

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

10 OVERDOSAGE

No data are available on overdose of DESCOVY in patients. If overdose occurs, monitor the individual for evidence of toxicity. Treatment of overdose with DESCOVY 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 DESCOVY. In one clinical pharmacology study, single doses of FTC 1200 mg (6 times the FTC dose in DESCOVY) 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 DESCOVY) 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

DESCOVY (emtricitabine and tenofovir alafenamide) is a fixed dose combination tablet containing emtricitabine (FTC) and tenofovir alafenamide (TAF) for oral administration.

- FTC, a synthetic nucleoside analog of cytidine, is an HIV nucleoside analog reverse transcriptase inhibitor (HIV NRTI).
- TAF, an HIV NRTI, is converted in vivo to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate.

DESCOVY tablets are available in strength:

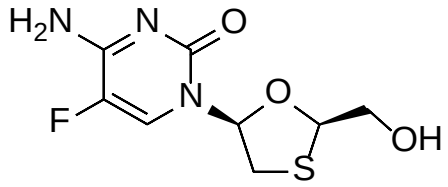
- 200 mg/25 mg tablets: 200 mg of FTC and 25 mg of TAF (equivalent to 28 mg of tenofovir alafenamide fumarate).

- The 120 mg / 15 mg tablets are not being imported by LifeScience Logistics.

DESCOVY tablets include the following inactive ingredients: croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The 200 mg/ 25 mg tablets are film-coated with a coating material containing indigo carmine aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide. The 120 mg / 15 mg tablets are not being imported by LifeScience Logistics.

Emtricitabine: The chemical name of FTC is 4-amino-5-fluoro-1-(2*R*-hydroxymethyl-1,3-oxathiolan-5*S*-yl)-(1H)-pyrimidin-2-one. 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.

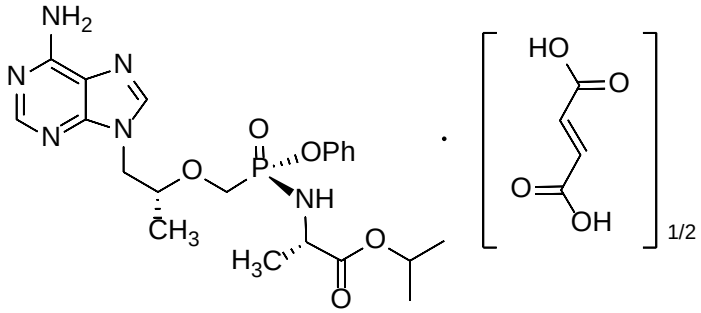
FTC has a molecular formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.24 and has the following structural formula:



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

Tenofovir Alafenamide: The chemical name of tenofovir alafenamide fumarate drug substance is L-alanine, *N*-[(*S*)-[[(1*R*)-2-(6-amino-9*H*-purin-9-yl)-1-methylethoxy]methyl]phenoxyphosphinyl]-, 1-methylethyl ester, (2*E*)-2-butenedioate (2:1).

Tenofovir alafenamide fumarate has an empirical formula of $C_{21}H_{29}O_5N_6P \bullet ½(C_4H_4O_4)$ and a formula weight of 534.50 and has the following structural formula:



Tenofovir alafenamide fumarate is a white to off-white or tan powder with a solubility of 4.7 mg per mL in water at 20 °C.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

DESCOVY 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 DESCOVY, 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 DESCOVY are provided in Table 7. The multiple dose PK parameters of FTC and TAF and its metabolite tenofovir are provided in Table 8. HIV status has no effect on the pharmacokinetics of FTC and TAF in adults.

Table 7 Pharmacokinetic Properties of the Components of DESCOVY

	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)
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

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 10 days); TAF (single dose administration of [^{14}C] tenofovir alafenamide).

Table 8 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

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

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 9).

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 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 receiving this same dosage regimen; the increases were not considered clinically significant (Table 10) *[see Use in Specific Populations (8.4)]*.

Table 10 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

Exposures of FTC and TAF (AUC_{tau} and C_{max}) achieved in 22 pediatric patients at least 2 years of age and weighing from 14 to less than 25 kg who received FTC+TAF with bictegravir were higher than exposures in adults; the increases were not considered clinically significant as the safety profiles were similar in adult and pediatric patients (Table 11) *[see Use in Specific Populations (8.4)]*.

Table 11 Multiple Dose Pharmacokinetic Parameters of Emtricitabine and Tenofovir Alafenamide Following Oral Administration of FTC+TAF with Bictegravir in HIV-Infected Pediatric Subjects at least 2 Years of age and Weighing from 14 to Less than 25 kg[a]

Parameter Mean (CV%)	Emtricitabine[b]	Tenofovir Alafenamide[b]
C_{max} (microgram per mL)	3.85 (34.7)	0.414 (31.0)
AUC_{tau} (microgram•h per mL)	15.0 (21.9)	0.305 (42.6)
C_{trough} (microgram per mL)	0.210 (243)	NA

CV = Coefficient of Variation; NA = Not Applicable

a. This trial enrolled virologically-suppressed pediatric subjects with HIV-1 infection from 3 to 9 years of age.

b. From Intensive PK analysis (n=12 except n=11 for C_{trough} for FTC).

HIV-1 PrEP: The pharmacokinetic data for FTC and TAF following administration of DESCOVY in HIV-1 uninfected adolescents weighing 35 kg and above are not available. The dosage recommendations of DESCOVY 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-1 infected subjects with renal impairment (eGFR 30 to 69 mL per minute by Cockcroft-Gault method), and in HIV-1 infected subjects with ESRD (eGFR less than 15 mL per minute by Cockcroft-Gault method) receiving chronic hemodialysis were evaluated in subsets of virologically-suppressed subjects in open-label trials. The pharmacokinetics of TAF were similar among healthy subjects, subjects with mild or moderate renal impairment, and subjects with ESRD receiving chronic hemodialysis; increases in FTC and TFV exposures in subjects with renal impairment were not considered clinically relevant (Table 12).

Table 12 Pharmacokinetics of the Components of DESCOVY and a Metabolite of TAF (Tenofovir) in HIV-Infected Adults with Renal Impairment Compared to Subjects with Normal Renal Function

	AUC_{tau} (microgram·hour per mL) Mean (CV%)			
Estimated Creatinine Clearance[a]	**≥90 mL per minute (N=18)[b]**	**60–89 mL per minute (N=11)[c]**	**30–59 mL per minute (N=18)[d]**	**<15 mL per minute (N=12)[e]**
Emtricitabine	11.4 (11.9)	17.6 (18.2)	23.0 (23.6)	62.9 (48.0)[f]
Tenofovir	0.32 (14.9)	0.46 (31.5)	0.61 (28.4)	8.72 (39.4)[g]

a. By Cockcroft-Gault method.
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.
d. From a phase 3 trial in HIV-1 infected adults with renal impairment treated with FTC+TAF with EVG+COBI.
e. From a phase 3 trial in HIV-1 infected adults with ESRD receiving chronic hemodialysis treated with FTC+TAF with EVG+COBI; PK assessed prior to hemodialysis following 3 consecutive daily doses of FTC+TAF with EVG+COBI.
f. N = 11.
g. N = 10.

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 13 and the effects of DESCOVY or its components on the exposure of coadministered drugs are shown in Table 14 [these studies were conducted with DESCOVY or the components of DESCOVY (FTC or TAF) administered alone]. For information regarding clinical recommendations, *see Drug Interactions (7)*.

Table 13 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
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 DESCOVY (FTC/TAF).
c. Study conducted with FTC+TAF with EVG+COBI.

Table 14 Drug Interactions: Changes in PK Parameters for Coadministered Drug in the Presence of DESCOVY 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)
Lopinavir	800 +200 ritonavir	10	10	1.00 (0.95, 1.06)	1.00 (0.92, 1.09)	0.98 (0.85, 1.12)
Midazolam[c]	2.5 (single dose, orally)	25	18	1.02 (0.92, 1.13)	1.13 (1.04, 1.23)	NC
	1 (single dose, intravenous)			0.99 (0.89, 1.11)	1.08 (1.04, 1.14)	NC
Rilpivirine	25	25	16	0.93 (0.87, 0.99)	1.01 (0.96, 1.06)	1.13 (1.04, 1.23)
Sertraline	50 (single dose)	10[d]	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 DESCOVY (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, Ɛ, 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. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there is no evidence of toxicity to mitochondria in cell culture.

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 1.3–640 nM. FTC displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, and G (EC_{50} values ranged from 7-75 nM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 7–1,500 nM).

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 monocyte/macrophage cells 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.

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

Emtricitabine and Tenofovir Alafenamide: The prophylactic activity of the combination of oral FTC and TAF was evaluated in a controlled study of macaques administered once weekly intra-rectal inoculations of chimeric simian/human immunodeficiency type 1 virus (SHIV) for up to 19 weeks (n=6). All 6 macaques that received FTC and TAF at doses resulting in PBMC exposures

consistent with those achieved in humans administered a dose of FTC/TAF 200/25 mg remained SHIV uninfected.

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 L429I substitutions; in addition, a K70E substitution in HIV-1 RT was observed.

In Clinical Trials

Treatment of HIV-1

The resistance profile of DESCOVY 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 a 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 Q207 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).

HIV-1 PrEP

In the DISCOVER trial of HIV-1 uninfected men and transgender women who have sex with men and who are at risk of HIV-1 infection receiving DESCOVY or TRUVADA for HIV-1 PrEP, genotyping was performed on participants found to be infected during the trial who had HIV-1 RNA ≥400 copies/mL (6 of 7 participants receiving DESCOVY and 13 of 15 participants receiving TRUVADA). The development of FTC resistance-associated substitutions, M184I and/or M184V, was observed in 4 HIV-1 infected participants in the TRUVADA group who had suspected baseline infections.

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 DESCOVY) or in rats at doses up to 600 mg per kg per day (28 times the human systemic exposure at the recommended dose in DESCOVY).

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 DESCOVY. 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 DESCOVY.

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 DESCOVY. At the high dose in female mice, liver adenomas were increased at tenofovir exposures approximately 10 times (300

mg TDF) and 167 times (DESCOVY) 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 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 DESCOVY.

14 CLINICAL STUDIES

14.1 Overview of Clinical Trials

The efficacy and safety of DESCOVY have been evaluated in the trials summarized in Table 15.

Table 15 Trials Conducted with FTC+TAF-Containing Products for HIV-1 Treatment and DESCOVY for HIV-1 PrEP

Trial	Population	Study Arms (N)	Timepoint
Study 104 [a] (NCT01780506) Study 111 [a] (NCT01797445)	HIV-1 infected treatment-naïve adults	FTC+TAF with EVG+COBI [b] (866) FTC+TDF with EVG+COBI [c] (867)	48 Weeks
Study 109 [d] (NCT01815736)	HIV-1 infected virologically-suppressed [f] adults	FTC+TAF with EVG+COBI [b] (799) ATRIPLA® or TRUVADA®+atazanavir+cobicistat or ritonavir or FTC+TDF with EVG+COBI [c] (397)	48 Weeks
Study 112 [e] (NCT01818596)	HIV-1 infected virologically-suppressed [f] adults with renal impairment [g]	FTC+TAF with EVG+COBI [b] (242)	24 Weeks
Study 1825 [e] (NCT02600819)	HIV-1 infected virologically-suppressed [f] adults with ESRD [h] receiving chronic hemodialysis	FTC+TAF with EVG+COBI [b] (55)	48 Weeks
Study 106 [e] (Cohort 1) (NCT01854775)	HIV-1 infected treatment-naïve adolescents between the ages of 12 to less than 18 years (at least 35 kg)	FTC+TAF with EVG+COBI [b] (50)	48 Weeks
Study 106 [e] (Cohort 2) (NCT01854775)	HIV-1 infected, virologically suppressed [f] children between the ages of 6 to less than 12 years (at least 25 kg)	FTC+TAF with EVG+COBI [b] (52)	48 Weeks
Study 1474 [e] (Cohort 3) (NCT02881320)	HIV-1 infected, virologically suppressed [f] children at least 2 years (at least 14 kg and less than 25 kg)	FTC+TAF with bictegravir [i] (22)	24 Weeks
DISCOVER [a] (NCT02842086)	HIV-1 uninfected men or transgender women who have sex with men	DESCOVY (2,670) TRUVADA® (2,665)	4,370 person-years [j]

a. Randomized, double-blind, active-controlled study.
b. Administered as GENVOYA®.
c. Administered as STRIBILD®.
d. Randomized, open-label, active controlled trial.
e. Open label trial
f. HIV-1 RNA less than 50 copies per mL.
g. Estimated creatinine clearance between 30 and 69 mL per minute by Cockcroft-Gault method.
h. End stage renal disease (estimated creatinine clearance of less than 15 mL per minute by Cockcroft-Gault method).
i. Administered as BIKTARVY®.
j. Exposure in the DESCOVY group.

14.2 Clinical Trial Results for Treatment of HIV-1

Clinical Trials in Adults with HIV-1

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.

Clinical Trials in Pediatric Patients with HIV-1

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 52 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, 98% (51/52) of subjects remained virologically suppressed at Week 48. From a mean (SD) baseline CD4+ cell count of 961 (275.5) cells per mm^3, the mean change from baseline in CD4+ cell count was -66 cells per mm^3 and the mean (SD) change in CD4% was -0.6% (4.4%) at Week 48. All subjects maintained CD4+ cell counts above 400 cells/mm^3 *[see Adverse Reactions (6.1) and Use in Specific Populations (8.4)].*

In a separate open-label single arm trial of FTC+TAF with bictegravir that enrolled 24 virologically-suppressed children at least 2 years of age and weighing at least 14 to less than 25 kg (cohort 3), 91% (20/22) of subjects remained virologically suppressed at Week 24. From a mean (SD) baseline CD4+ count of 1104 (440), the mean (SD) change from baseline in CD4+ cell count was −126 (264) cells per mm^3, and the mean (SD) change in CD4% was 0.2% (4.4%) at Week 24.

Clinical Trials in Adults with HIV-1 and Renal Insufficiency

In a trial in 248 HIV-1 infected adults 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 began on FTC+TAF with EVG+COBI (N=6) and those previously virologically-suppressed on other regimens and switched to FTC+TAF with EVG+COBI (N=242) had HIV-1 RNA less than 50 copies per mL at Week 24.

In a trial in 55 HIV-1 infected virologically-suppressed adults with ESRD (estimated creatinine clearance of less than 15 mL per minute) receiving chronic hemodialysis for at least 6 months who switched to FTC+TAF with EVG+COBI, 82% (45/55) maintained HIV-1 RNA less than 50 copies per mL at Week 48. Two subjects had HIV-1 RNA ≥ 50 copies per mL by Week 48, 7 discontinued due to AE or other reasons while suppressed, and 1 did not have an HIV-1 RNA measurement at Week 48.

14.3 Clinical Trial Results for HIV-1 PrEP

The efficacy and safety of DESCOVY to reduce the risk of acquiring HIV-1 infection were evaluated in a randomized, double-blind multinational trial (DISCOVER) in HIV-seronegative men (N=5,262) or transgender women (N=73) who have sex with men and are at risk of HIV-1 infection, comparing once daily DESCOVY (N=2,670) to TRUVADA (FTC/TDF 200 mg/300 mg; N=2,665). Evidence of risk behavior at entry into the trial included at least one of the following: two or more unique condomless anal sex partners in the past 12 weeks or a diagnosis of rectal gonorrhea/chlamydia or syphilis in the past 24 weeks. The median age of participants was 34 years (range, 18-76); 84% were White, 9% Black/Mixed Black, 4% Asian, and 24% Hispanic/Latino. At baseline, 897 participants (17%) reported receiving TRUVADA for PrEP.

At weeks 4, 12, and every 12 weeks thereafter, all participants received local standard of care HIV-1 prevention services, including HIV-1 testing, evaluation of adherence, safety evaluations, risk-reduction counseling, condoms, management of sexually transmitted infections, and assessment of sexual behavior.

Trial participants maintained a high risk of sexual HIV-1 acquisition, with high rates of rectal gonorrhea (DESCOVY, 24%; TRUVADA, 25%), rectal chlamydia (DESCOVY, 30%; TRUVADA, 31%), and syphilis (14% in both treatment groups) during the trial.

The primary outcome was the incidence of documented HIV-1 infection per 100 person-years in participants randomized to DESCOVY and TRUVADA (with a minimum follow-up of 48 weeks and at least 50% of participants having 96 weeks of follow-up). DESCOVY was non-inferior to TRUVADA in reducing the risk of acquiring HIV-1 infection (Table 16). The results were similar across the subgroups of age, race, gender identity, and baseline TRUVADA for PrEP use.

Table 16 HIV-1 Infection Results in DISCOVER Trial – Full Analysis Set

	DESCOVY (N=2,670)	**TRUVADA (N=2,665)**	**Rate Ratio (95% CI)**
	4,370 person-years	**4,386 person-years**	
HIV-1 infections, n	7	15	
Rate of HIV-1 infections per 100 person-years	0.16	0.34	0.468 (0.19, 1.15)

CI = Confidence interval.

Of the 22 participants diagnosed with HIV-1 infection in the trial, five had suspected baseline infection prior to study entry (DESCOVY, 1; TRUVADA, 4). In a case-control substudy of intracellular drug levels and estimated number of daily doses as measured by dried blood spot testing, median intracellular tenofovir diphosphate concentrations were substantially lower in participants infected with HIV-1 at the time of diagnosis compared with uninfected matched control participants. For both DESCOVY and TRUVADA, efficacy was therefore strongly correlated to adherence to daily dosing.

16 HOW SUPPLIED/STORAGE AND HANDLING

DESCOVY tablets are available in bottles containing 30 tablets:

Bottles

- 200 mg/25 mg tablets each contain 200 mg of emtricitabine (FTC) and 25 mg of tenofovir alafenamide (TAF). These tablets are blue, rectangular-shaped, and film-coated with “GSI” debossed on one side and “225” on the other side (NDC 42067-110-01).

Bottles contain a silica gel desiccant, polyester coil, and child resistant closure.

Keep bottle tightly closed.

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (see USP Controlled Room Temperature).

Dispense only in original container.

The 120 mg / 15 mg tablets are not being imported by LifeScience Logistics.

This drug was imported from Canada without the authorization of Gilead Sciences Inc. under the State of Florida Section 804 Importation Program.

Imported by: LifeScience Logistics, 310 N. Galloway Rd., Lakeland, FL 33815

17 PATIENT COUNSELING INFORMATION

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

Important Information for Uninfected Individuals Taking DESCOVY for HIV-1 PrEP

Advise HIV-1 uninfected individuals about the following *[see Warnings and Precautions (5.2)]:*

- The need to confirm that they are HIV-negative before starting to take DESCOVY to reduce the risk of acquiring HIV-1.
- That HIV-1 resistance substitutions may emerge in individuals with undetected HIV-1 infection who are taking DESCOVY, because DESCOVY alone does not constitute a complete regimen for HIV-1 treatment.
- The importance of taking DESCOVY on a regular dosing schedule and strict adherence to the recommended dosing schedule to reduce the risk of acquiring HIV-1. Uninfected individuals who miss doses are at greater risk of acquiring HIV-1 than those who do not miss doses.
- That DESCOVY does not prevent other sexually acquired infections and should be used as part of a complete prevention strategy including other prevention measures.
- To use condoms consistently and correctly to lower the chances of sexual contact with any body fluids such as semen, vaginal secretions, or blood.
- The importance of knowing their HIV-1 status and the HIV-1 status of their partner(s).
- The importance of virologic suppression in their partner(s) with HIV-1.
- The need to get tested regularly for HIV-1 (at least every 3 months, or more frequently for some individuals such as adolescents) and to ask their partner(s) to get tested as well.
- To report any symptoms of acute HIV-1 infection (flu-like symptoms) to their healthcare provider immediately.
- That the signs and symptoms of acute infection include fever, headache, fatigue, arthralgia, vomiting, myalgia, diarrhea, pharyngitis, rash, night sweats, and adenopathy (cervical and inguinal).
- To get tested for other sexually transmitted infections, such as syphilis, chlamydia, and gonorrhea, that may facilitate HIV-1 transmission.
- To assess their sexual risk behavior and get support to help reduce sexual risk behavior.

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

Inform individuals that severe acute exacerbations of hepatitis B have been reported in patients who are infected with HBV and have discontinued products containing FTC and/or TDF and may likewise occur with discontinuation of DESCOVY *[see Warnings and Precautions (5.1)]*. Advise HBV-infected individuals to not discontinue DESCOVY without first informing their healthcare provider.

Immune Reconstitution Syndrome

Advise HIV-1 infected patients to inform their healthcare provider immediately of any symptoms of infection. 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 (5.3)]*.

New Onset or Worsening Renal Impairment

Advise HIV-1 infected patients and uninfected individuals to avoid taking DESCOVY with concurrent or recent use of nephrotoxic agents. Postmarketing cases of renal impairment, including acute renal failure, have been reported *[see Warnings and Precautions (5.4)].*

Lactic Acidosis and Severe Hepatomegaly

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with use of drugs similar to DESCOVY. Advise HIV-1 infected patients and uninfected individuals that they should stop DESCOVY if they develop clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity *[see Warnings and Precautions (5.5)]*.

Dosage Recommendations for Treatment of HIV-1 Infection

Inform HIV-1 infected patients that it is important to take DESCOVY with other antiretroviral drugs for the treatment of HIV-1 on a regular dosing schedule with or without food and to avoid missing doses as it can result in development of resistance *[see Dosage and Administration (2.3, 2.4)]*.

Pregnancy Registry

Inform individuals using DESCOVY that there is an antiretroviral pregnancy registry to monitor fetal outcomes of pregnant women exposed to DESCOVY *[see Use in Specific Populations (8.1)].*

Lactation

Instruct mothers with HIV-1 infection not to breastfeed because of the risk of passing the HIV-1 virus to the baby *[see Use in Specific Populations (8.2)]*.

Medication Guide
DESCOVY® (des-KOH-vee)
(emtricitabine and tenofovir alafenamide)
tablets

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

This Medication Guide provides information about two different ways that DESCOVY may be used. See the section **"What is DESCOVY?"** for detailed information about how DESCOVY may be used.

What is the most important information I should know about DESCOVY?

DESCOVY can cause serious side effects, including:

- **Worsening of hepatitis B virus (HBV) infection. Your healthcare provider will test you for HBV infection before or when you start treatment with DESCOVY. If you have HBV infection and take DESCOVY, your HBV may get worse (flare-up) if you stop taking DESCOVY. A "flare-up" is when your HBV infection suddenly returns in a worse way than before.**
  - Do not run out of DESCOVY. Refill your prescription or talk to your healthcare provider before your DESCOVY is all gone.
  - Do not stop taking DESCOVY without first talking to your healthcare provider.
  - If you stop taking DESCOVY, your healthcare provider will need to check your health often and do blood tests regularly for several months to check your liver, and may give you a medicine to treat hepatitis B. Tell your healthcare provider about any new or unusual symptoms you may have after you stop taking DESCOVY.

For more information about side effects, see the section "What are the possible side effects of DESCOVY?"

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

Before taking DESCOVY to reduce your risk of getting HIV-1:

- **You must be HIV-1 negative to start DESCOVY. You must get tested to make sure that you do not already have HIV-1 infection.**
- **Do not take DESCOVY for HIV-1 PrEP unless you are confirmed to be HIV-1 negative.**
- Some HIV-1 tests can miss HIV-1 infection in a person who has recently become infected. If you have flu-like symptoms, you could have recently become infected with HIV-1. Tell your healthcare provider if you had a flu-like illness within the last month before starting DESCOVY or at any time while taking DESCOVY. Symptoms of new HIV-1 infection include:
  - tiredness
  - fever
  - joint or muscle aches
  - headache
  - sore throat
  - vomiting or diarrhea
  - rash
  - night sweats
  - enlarged lymph nodes in the neck or groin

While you are taking DESCOVY for HIV-1 PrEP:

- **DESCOVY does not prevent other sexually transmitted infections (STIs). Practice safer sex by using a latex or polyurethane condom to reduce the risk of getting STIs.**
- **You must stay HIV-1 negative to keep taking DESCOVY for HIV-1 PrEP.**
  - Know your HIV-1 status and the HIV-1 status of your partners.
  - Ask your partners with HIV-1 if they are taking HIV-1 medicines and have an undetectable viral load. An undetectable viral load is when the amount of virus in the blood is too low to be measured in a lab test. To maintain an undetectable viral load, your partners must keep taking HIV-1 medicines every day. Your risk of getting HIV-1 is lower if your partners with HIV-1 are taking effective treatment.
  - Get tested for HIV-1 at least every 3 months or when your healthcare provider tells you.
  - Get tested for other STIs such as syphilis, chlamydia, and gonorrhea. These infections make it easier for HIV-1

to infect you.
  - If you think you were exposed to HIV-1, tell your healthcare provider right away. They may want to do more tests to be sure you are still HIV-1 negative.
  - Get information and support to help reduce sexual risk behaviors.
  - Do not miss any doses of DESCOVY. Missing doses increases your risk of getting HIV-1 infection.
- If you do become HIV-1 positive, you need more medicine than DESCOVY alone to treat HIV-1. DESCOVY by itself is not a complete treatment for HIV-1.

If you have HIV-1 and take only DESCOVY, over time your HIV-1 may become harder to treat.

What is DESCOVY?

DESCOVY is a prescription medicine that may be used in two different ways. DESCOVY is used:

- to treat HIV-1 infection
  - in adults and children who weigh at least 77 pounds (35 kg) together with other HIV-1 medicines
  - in children who weigh at least 31 pounds (14 kg) and less than 77 pounds (35 kg) together with certain other HIV-1 medicines. Your healthcare provider will determine which other HIV-1 medicines may be used with DESCOVY.
- for HIV-1 PrEP to reduce the risk of getting HIV-1 infection in adults and adolescents who weigh at least 77 pounds (35 kg). It is not known if DESCOVY is effective in reducing the risk of getting HIV-1 from certain types of sex.
  - DESCOVY for PrEP is not for use in people born female (assigned female at birth) who are at risk of getting HIV-1 infection from vaginal sex, because its effectiveness has not been studied.

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

DESCOVY contains the prescription medicines emtricitabine and tenofovir alafenamide.

It is not known if DESCOVY for treatment of HIV-1 infection is safe and effective in children who weigh less than 31 pounds (14 kg).

It is not known if DESCOVY is safe and effective in reducing the risk of HIV-1 infection in people who weigh less than 77 pounds (35 kg).

For people taking DESCOVY for HIV-1 PrEP:
Do not take DESCOVY for HIV-1 PrEP if:

- **you already have HIV-1 infection.** If you are HIV-1 positive, you need to take other medicines with DESCOVY to treat HIV-1. DESCOVY by itself is not a complete treatment for HIV-1.
- **you do not know your HIV-1 infection status.** You may already be HIV-1 positive. You need to take other HIV-1 medicines with DESCOVY to treat HIV-1 infection.

DESCOVY can only help reduce your risk of getting HIV-1 infection **before** you are infected.

What should I tell my healthcare provider before taking DESCOVY?

Before taking DESCOVY, tell your healthcare provider about all of your medical conditions, including if you:

- have liver problems, including HBV infection
- have kidney problems
- are pregnant or plan to become pregnant. It is not known if DESCOVY can harm your unborn baby. Tell your healthcare provider if you become pregnant during treatment with DESCOVY.

  Pregnancy Registry: There is a pregnancy registry for people who take DESCOVY 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 DESCOVY for treatment of HIV-1 because of the risk of passing HIV-1 to your baby.
  - One of the ingredients in DESCOVY (emtricitabine) passes into your breast milk.

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 DESCOVY. 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 DESCOVY.

- **Do not start a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take DESCOVY with other medicines.

How should I take DESCOVY?

- Take DESCOVY exactly as your healthcare provider tells you to take it. If you take DESCOVY to treat HIV-1 infection, you need to take DESCOVY with other HIV-1 medicines. Your healthcare provider will tell you what medicines to take and how to take them.
- Take DESCOVY 1 time each day with or without food.
- If you are on dialysis, take your daily dose of DESCOVY following dialysis.
- Do not change your dose or stop taking DESCOVY without first talking with your healthcare provider. Stay under a healthcare provider's care when taking DESCOVY. Do not miss a dose of DESCOVY.
- If you take too much DESCOVY, call your healthcare provider or go to the nearest hospital emergency room right away.
- When your DESCOVY supply starts to run low, get more from your healthcare provider or pharmacy.
  - If you are taking DESCOVY for treatment of HIV-1, the amount of virus in your blood may increase if the medicine is stopped for even a short time. The virus may develop resistance to DESCOVY and become harder to treat.
  - If you are taking DESCOVY for HIV-1 PrEP, missing doses increases your risk of getting HIV-1 infection.

What are the possible side effects of DESCOVY?

DESCOVY may cause serious side effects, including:

- **See "What is the most important information I should know about DESCOVY?"**
- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking medicines to treat HIV-1 infection. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider right away if you start having any new symptoms after starting your HIV-1 medicine.
- **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 while taking DESCOVY. Your healthcare provider may tell you to stop taking DESCOVY 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 DESCOVY for treatment of HIV-1 is nausea.

The most common side effect of DESCOVY for HIV-1 PrEP is diarrhea.

These are not all of the possible side effects of DESCOVY.

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 DESCOVY?

- Store DESCOVY between 68°F to 77°F (20°C to 25°C).
- Keep DESCOVY in its original bottle.
- Keep the bottle tightly closed.

Keep DESCOVY and all medicines out of reach of children.

General information about the safe and effective use of DESCOVY.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use DESCOVY for a condition for which it was not prescribed. Do not give DESCOVY 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 DESCOVY that is written for health professionals.

What are the ingredients in DESCOVY?

Active ingredients: emtricitabine and tenofovir alafenamide.

Inactive ingredients: croscarmellose sodium, magnesium stearate, and microcrystalline cellulose.

The 200 mg/25 mg tablets are film-coated with a coating material containing indigo carmine aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide. The 120 mg / 15 mg tablets are not being imported by LifeScience Logistics.

Manufactured and distributed by: Gilead Sciences, Inc. Foster City, CA 94404

208215-GS-009

For more information, call 1-800-445-3235 or go to www.DESCOVY.com.

This Medication Guide has been approved by the U.S. Food and Drug Administration Revised: 01/2022

This drug was imported from Canada without the authorization of Gilead Sciences, Inc. under the State of Florida Section 804 Importation Program. Imported by: LifeScience Logistics, 310 N. Galloway Rd., Lakeland, FL 33815

Annotated Label Comparisons

PI Comparisons FDA VS. FLCPDIP
Differences
Updated information Adverse Reactions Contact
How Supplied/Storage and Handling added SIP804 language
Patient Information added SIP804 language
Listed new NDC #
Added Importation language & Importer name & address
Listed only drug strength purchased for program

FDA

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 200 mg/25 mg and 120 mg/15 mg of FTC and TAF respectively (3)

----------ADVERSE REACTIONS----------
- In HIV-1 infected patients, the most common adverse reaction (incidence greater than or equal to 10%, all grades) was nausea. (6.1)

diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Gilead Sciences, Inc. at 1-800-GILEAD-5 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Table 1 Dosing for Treatment of HIV-1 Infection in Pediatric Patients Weighing 14 to Less than 35 kg

Body Weight (kg)	DESCOVY Dose
25 kg to less than 35 kg	One tablet containing 200 mg FTC and 25 mg of TAF taken orally once daily
14 kg to less than 25 kg	One tablet containing 120 mg FTC and 15 mg TAF taken orally once daily

3 DOSAGE FORMS AND STRENGTHS

DESCOVY tablets are available in two dose strengths:

- 200 mg/25 mg tablets: 200 mg of emtricitabine (FTC) and 25 mg of tenofovir alafenamide (TAF) (equivalent to 28 mg of tenofovir alafenamide fumarate). These tablets are blue, rectangular-shaped, film-coated, debossed with "GSI" on one side and "225" on the other side.
- 120 mg/15 mg tablets: 120 mg of FTC and 15 mg of TAF (equivalent to 16.8 mg of tenofovir alafenamide fumarate). These tablets are white, round-shaped, film coated, debossed with "GSI" on one side and "15" on the other side.

FLSIP 804

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 200 mg/25 mg of FTC and TAF respectively (3)

----------ADVERSE REACTIONS----------
- In HIV-1 infected patients, the most common adverse reaction (incidence greater than or equal to 10%, all grades) was nausea. (6.1)
- In HIV-1 uninfected adults in a PrEP trial, the most common adverse reaction (incidence greater than or equal to 5%, all grades) was diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact LifeScience Logistics at 1-855-738-6171 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Table 1 Dosing for Treatment of HIV-1 Infection in Pediatric Patients Weighing 14 to Less than 35 kg

Body Weight (kg)	DESCOVY Dose
25 kg to less than 35 kg	One tablet containing 200 mg FTC and 25 mg of TAF taken orally once daily
	The 120 mg / 15 mg tablets are not being imported by LifeScience Logistics.

3 DOSAGE FORMS AND STRENGTHS

DESCOVY tablets are available in two dose strengths:

- 200 mg/25 mg tablets: 200 mg of emtricitabine (FTC) and 25 mg of tenofovir alafenamide (TAF) (equivalent to 28 mg of tenofovir alafenamide fumarate). These tablets are blue, rectangular-shaped, film-coated, debossed with "GSI" on one side and "225" on the other side.
- The 120 mg / 15 mg tablets are not being imported by LifeScience Logistics.

FDA

11 DESCRIPTION

DESCOVY (emtricitabine and tenofovir alafenamide) is a fixed dose combination tablet containing emtricitabine (FTC) and tenofovir alafenamide (TAF) for oral administration.

- FTC, a synthetic nucleoside analog of cytidine, is an HIV nucleoside analog reverse transcriptase inhibitor (HIV NRTI).
- TAF, an HIV NRTI, is converted in vivo to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate.

DESCOVY tablets are available in two dose strengths:

- 200 mg/25 mg tablets: 200 mg of FTC and 25 mg of TAF (equivalent to 28 mg of tenofovir alafenamide fumarate).
- 120 mg/15 mg tablets: 120 mg of FTC and 15 mg of TAF (equivalent to 16.8 mg of tenofovir alafenamide fumarate).

Both dose strengths of DESCOVY tablets include the following inactive ingredients: croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The 200 mg/ 25 mg tablets are film-coated with a coating material containing indigo carmine aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide. The 120 mg/15 mg tablets are film-coated with a coating material containing polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc.

16 HOW SUPPLIED/STORAGE AND HANDLING

DESCOVY tablets are available in bottles and blister packs containing 30 tablets:

Bottles

- 200 mg/25 mg tablets each contain 200 mg of emtricitabine (FTC) and 25 mg of tenofovir alafenamide (TAF). These tablets are blue, rectangular-shaped, and film-coated with "GSI" debossed on one side and "225" on the other side (NDC 61958-2002-1).
- 120 mg/15 mg tablets each contain 120 mg of FTC and 15 mg of TAF. These tablets are white, round-shaped, and film coated with "GSI" debossed on one side and "15" on the other side (NDC 61958-2005-1).

Bottles contain a silica gel desiccant, polyester coil, and child resistant closure.

Keep bottle tightly closed.

Blister Pack

- 200 mg/25 mg tablets each contain 200 mg of FTC and 25 mg of TAF. These tablets are blue, rectangular-shaped, and film-coated with "GSI" debossed on one side and "225" on the other side (NDC 61958-2002-2).

Blister packs are sealed with a child-resistant laminated foil lidding material (peel-push) and each blister cavity contains a die-cut desiccant film which is heat staked to the foil lidding material.

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (see USP Controlled Room Temperature).

Dispense only in original container.

FLSIP 804

11 DESCRIPTION

DESCOVY (emtricitabine and tenofovir alafenamide) is a fixed dose combination tablet containing emtricitabine (FTC) and tenofovir alafenamide (TAF) for oral administration.

- FTC, a synthetic nucleoside analog of cytidine, is an HIV nucleoside analog reverse transcriptase inhibitor (HIV NRTI).
- TAF, an HIV NRTI, is converted in vivo to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate.

DESCOVY tablets are available in strength:

- 200 mg/25 mg tablets: 200 mg of FTC and 25 mg of TAF (equivalent to 28 mg of tenofovir alafenamide fumarate).
- The 120 mg / 15 mg tablets are not being imported by LifeScience Logistics.

DESCOVY tablets include the following inactive ingredients: croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The 200 mg/ 25 mg tablets are film-coated with a coating material containing indigo carmine aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide. The 120 mg / 15 mg tablets are not being imported by LifeScience Logistics.

16 HOW SUPPLIED/STORAGE AND HANDLING

DESCOVY tablets are available in bottles containing 30 tablets:

Bottles

- 200 mg/25 mg tablets each contain 200 mg of emtricitabine (FTC) and 25 mg of tenofovir alafenamide (TAF). These tablets are blue, rectangular-shaped, and film-coated with "GSI" debossed on one side and "225" on the other side (NDC 42067-110-01).

Bottles contain a silica gel desiccant, polyester coil, and child resistant closure.

Keep bottle tightly closed.

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (see USP Controlled Room Temperature).

Dispense only in original container.

The 120 mg / 15 mg tablets are not being imported by LifeScience Logistics.

This drug was imported from Canada without the authorization of Gilead Sciences Inc. under the State of Florida Section 804 Importation Program.

Imported by: LifeScience Logistics, 310 N. Galloway Rd., Lakeland, FL 33815

FDA

How should I store DESCOVY?

- Store DESCOVY between 68°F to 77°F (20°C to 25°C).
- Keep DESCOVY in its original bottle or blister pack.
- Keep the bottle tightly closed.

Keep DESCOVY and all medicines out of reach of children.

What are the ingredients in DESCOVY?

Active ingredients: emtricitabine and tenofovir alafenamide.

Inactive ingredients: croscarmellose sodium, magnesium stearate, and microcrystalline cellulose.

The 200 mg/25 mg tablets are film-coated with a coating material containing indigo carmine aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide. The 120 mg/15 mg tablets are film-coated with a coating material containing polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc.

Manufactured and distributed by: Gilead Sciences, Inc. Foster City, CA 94404

208215-GS-009

For more information, call 1-800-445-3235 or go to www.DESCOVY.com.

This Medication Guide has been approved by the U.S. Food and Drug Administration Revised: 01/2022

FLSIP 804

How should I store DESCOVY?

- Store DESCOVY between 68°F to 77°F (20°C to 25°C).
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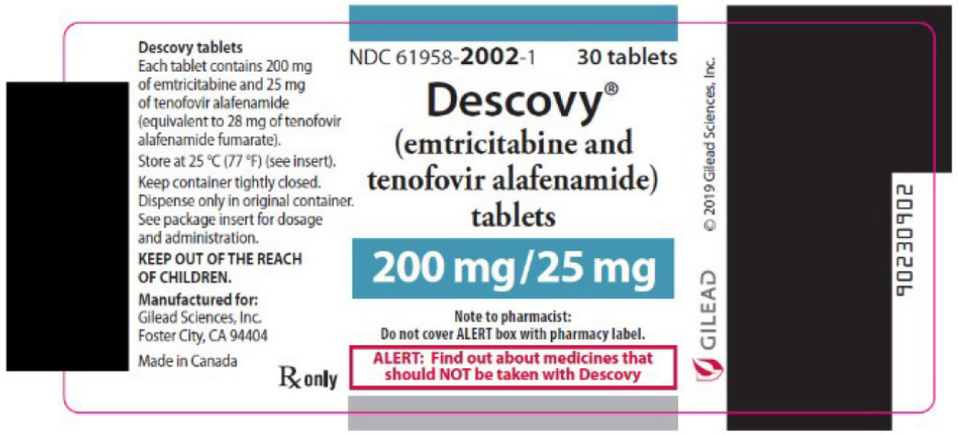
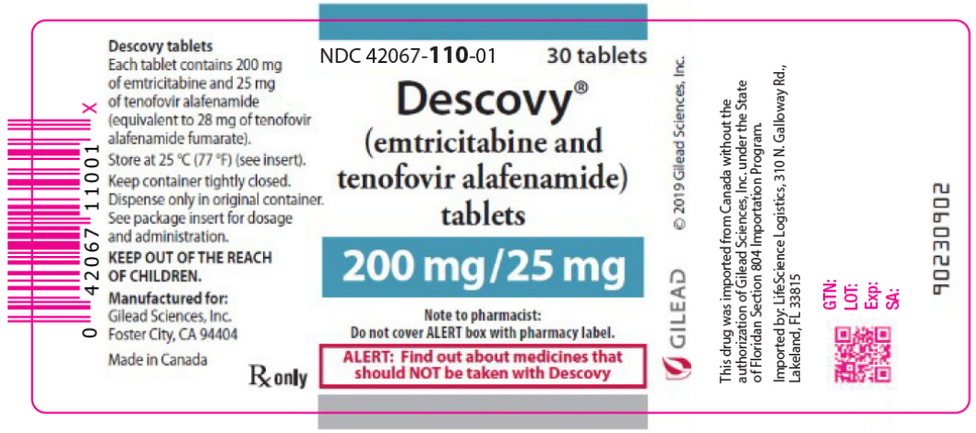
Proposed Package Label





Label Comparisons FDA VS. FLCPDIP
Differences
NDC
GTN
Bar Codes FPO with Associated NDCs
SIP804 Importation Language
Label SIZE due to production process & adding SIP804 language
Importer Name & Address
Brand logos FPO low resolution. Native art files requested upon SIP804 approval.

Comparisons
FDA to FLSIP

Recent FDA Approved Label	US Proprietary Name	US Generic Name	US Strength	NDC	NDA or ANDA	Applicant Holder Name	Applicant Holder Address	US Active Ingredients	Date Labeling Prepared for FLSIP	FLSIP Proprietary Name	FLSIP Generic Name	FLSIP Strength	LSL NDC	Relabeler Name	Applicant Holder Name	Applicant Holder Address	Active Ingredients	FDA Comments
Jan-22	Descovy	None	200-25 mg	61958-2002-1	208215	Gilead Sciences, Inc.	334 Lakeside Dr Foster City, CA 94404	emtricitabine/tenofovir alafenamide	Aug-23	Descovy	None	200-25 mg	42067-110-1	LifeScience Logistics, LLC	Gilead Sciences, Inc.	Foster City, CA 94405	emtricitabine/tenofovir alafenamide	none

Canadian and FDA Comparisons

Comparisons
Canada to FDA

Active Ingredient	Canadian Submission Number	Canadian Proprietary Name	Canadian Generic Name	DIN	Date Labeling Approved	Company Name	Address	Canadian Strength	Dosage Form	# of active Ingred.	Canadian Ingredients	US Proprietary Name	US Generic Name	US Strength	NDC	NDA or ANDA	Applicant Holder Name	US Active Ingredients	Comments for FDA
emtricitabine/tenofovir alafenamide	261849	Descovy	emtricitabine/tenofovir alafenamide	02454416	Revision: 8/5/2022	Gilead Sciences Canada, Inc.	6712 Mississauga Rd, Suite 600 Mississauga, ON L5N 2W3	200-25 mg	Oral Tablet, Once daily	2	emtricitabine/tenofovir alafenamide	Descovy	None	200-25 mg	61958-2002-1	208215	Gilead Sciences, Inc. Foster City, CA 94405	emtricitabine/tenofovir alafenamide	Generic not available.

Canadian Monograph

PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrDESCOVY®

emtricitabine/tenofovir alafenamide tablets

200 mg emtricitabine/ 10 mg* and 25 mg** tenofovir alafenamide, Oral

*as 11.2 mg tenofovir alafenamide hemifumarate

**as 28.0 mg tenofovir alafenamide hemifumarate

Antiretroviral Agent

Gilead Sciences Canada, Inc.
Mississauga, ON L5N 2W3

www.gilead.ca

Submission Control No: 261849

Date of Initial Authorization:
April 28, 2016

Date of Revision:
August 5, 2022

RECENT MAJOR LABEL CHANGES

1 Indications	11/2020
1 Indications, 1.1 Pediatrics	11/2020
2 Contraindications	11/2020
3 Serious Warnings and Precautions Box	11/2020
4 Dosage and Administration, 4.1 Dosing Considerations	11/2020
4 Dosage and Administration, 4.2 Recommended Dose and Dose Adjustment	11/2020
4 Dosage and Administration, 4.5 Missed Dose	11/2020
7 Warnings and Precautions, General	11/2020
7 Warnings and Precautions, Renal	11/2020
7 Warnings and Precautions, 7.1.2 Breast-feeding	11/2020
7 Warnings and Precautions, 7.1.5 Hepatitis B Virus (HBV) Infection	11/2020
7 Warnings and Precautions, 7.1.3 Pediatrics	11/2020
7 Warnings and Precautions, 7.1.5 Comprehensive Management to Reduce the Risk of Sexually Acquired Infections and Development of HIV-1 Resistance When DESCOVY is Used for HIV-1 PrEP	11/2020

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Treatment of HIV-1 Infection

DESCOVY is indicated in combination with other antiretrovirals (such as non-nucleoside reverse transcriptase inhibitors or protease inhibitors) for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and pediatric patients weighing ≥ 25 kg.

HIV-1 Pre-Exposure Prophylaxis (PrEP)

DESCOVY is indicated for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in at-risk adults and adolescents weighing ≥ 35 kg, excluding individuals at risk from receptive vaginal sex.

For more information on the DESCOVY HIV-1 PrEP Education Program (Checklist for Prescribers, Important Safety Information Fact Sheet for HCPs, and Uninfected Individual Safety Brochure), log onto www.descovyeducation.ca.

1.1 Pediatrics

Treatment of HIV-1 Infection

Pediatrics (weighing ≥ 25 kg): The safety and efficacy of DESCOVY in HIV-1 infected children weighing ≥ 25 kg are based on data from an open-label clinical study (see **8 ADVERSE REACTIONS** and **14 CLINICAL TRIALS**).

Pediatrics (weighing < 25 kg): Safety and efficacy of DESCOVY for the treatment of HIV-1 infection in children weighing < 25 kg have not been established.

HIV-1 PrEP

Pediatrics (weighing ≥ 35 kg): The safety and efficacy of DESCOVY for HIV-1 PrEP in at-risk adolescents weighing ≥ 35 kg (excluding individuals at risk from receptive vaginal sex) is supported by data from an adequate and well-controlled trial of DESCOVY for HIV-1 PrEP in adults together 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 **8 ADVERSE REACTIONS**, **10 CLINICAL PHARMACOLOGY** and **14 CLINICAL TRIALS**).

Pediatrics (weighing < 35 kg): Safety and efficacy of DESCOVY for HIV-1 PrEP in children weighing < 35 kg have not been established.

1.2 Geriatrics (≥ 65 years of age)

Geriatrics (≥ 65 years of age): No differences in safety or efficacy have been observed between elderly patients and those < 65 years of age (see **10 CLINICAL PHARMACOLOGY**).

2 CONTRAINDICATIONS

DESCOVY is contraindicated in patients with known hypersensitivity to any of the components of the product. For a complete listing, see the **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING** section of the Product Monograph.

DESCOVY for PrEP is contraindicated in individuals with unknown or positive HIV-1 status.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **Post-treatment Exacerbation of Hepatitis B Virus**

DESCOVY is not approved for the treatment of chronic hepatitis B virus (HBV) infection and the safety and efficacy of DESCOVY have not been established in individuals infected with HBV. Discontinuation of DESCOVY therapy in individuals infected with HBV may be associated with severe acute exacerbations of hepatitis due to the emtricitabine (FTC) or tenofovir alafenamide (TAF) components of DESCOVY. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in individuals infected with HBV who discontinue DESCOVY. If appropriate, initiation of anti-hepatitis B therapy may be warranted (see **7.1 Special Populations**).

- **Risk of Drug Resistance with Use of DESCOVY for HIV-1 PrEP in Undiagnosed Early HIV-1 Infection**

DESCOVY used for HIV-1 PrEP must only be prescribed to individuals confirmed to be HIV-negative immediately prior to initiating and at least every 3 months during use. Drug-resistant HIV-1 variants have been identified with use of FTC/TDF for HIV-1 PrEP following undetected acute HIV-1 infection. Do not initiate DESCOVY for HIV-1 PrEP if signs or symptoms of acute HIV-1 infection are present unless negative infection status is confirmed (see **7.1 Special Populations**).

Prior to or when initiating DESCOVY, and during use of DESCOVY, assess serum creatinine, estimated creatinine clearance (CrCl), urine glucose, and urine protein in all individuals as clinically appropriate. In individuals with chronic kidney disease, also assess serum phosphorus.

Treatment of HIV-1 Infection

In adults and pediatric patients weighing ≥ 25 kg, DESCOVY is taken orally once daily with or without food (see **9.2 Drug-Food Interactions**).

HIV-1 PrEP

DESCOVY is not recommended in individuals at risk of HIV-1 from receptive vaginal sex because the efficacy in this population has not been established.

When prescribing DESCOVY for PrEP, healthcare providers must:

- counsel all uninfected individuals to strictly adhere to the recommended DESCOVY dosing schedule because the effectiveness of DESCOVY in reducing the risk of acquiring HIV-1 was strongly correlated with adherence as demonstrated by measurable drug levels in a clinical trial (see **4.5 Missed Dose** and **7 WARNINGS AND PRECAUTIONS**); and

- screen all individuals for HIV-1 infection immediately prior to initiating DESCOVY for HIV-1 PrEP and at least once every 3 months while taking DESCOVY, and upon diagnosis of any other sexually transmitted infections (STIs) (see **7 WARNINGS AND PRECAUTIONS**).

4.2 Recommended Dose and Dosage Adjustment

Treatment of HIV-1 Infection

The choice of dose of DESCOVY depends on the other antiretroviral agents being coadministered:

- the 200/10 mg dose is recommended when DESCOVY is used in combination with an HIV-1 protease inhibitor that is administered with either ritonavir or COBI.

- the 200/25 mg dose is recommended when DESCOVY is used in combination with other antiretrovirals (i.e. non-nucleoside reverse transcriptase inhibitors, integrase inhibitors, maraviroc). This dose should not be used in combination with an HIV-1 protease inhibitor that is administered with either ritonavir or COBI.

Table 1 includes dosing recommendations based upon clinical data from third agents evaluated with DESCOVY in Study GS-US-311-1089 or drug interactions studies.

Table 1. Dose of DESCOVY according to third agent in the HIV treatment regimen

Dose of DESCOVY	Third agent in HIV treatment regimen
DESCOVY 200/10 mg once daily	Atazanavir with ritonavir or COBI[a] Darunavir with ritonavir or COBI[a] Lopinavir with ritonavir
DESCOVY 200/25 mg once daily	Dolutegravir, efavirenz, maraviroc, nevirapine, rilpivirine, raltegravir

a. Atazanavir with COBI and darunavir with COBI were not evaluated in Study GS-US-311-1089 (see **DRUG INTERACTIONS**).

For specific dosing recommendations for coadministered antiretroviral agents, refer to their respective Product Monograph.

HIV-1 PrEP

The recommended DESCOVY dosage in HIV-1 uninfected adults (excluding individuals at risk from receptive vaginal sex) is 200/25 mg once daily with or without food.

Geriatrics (≥ 65 years of age)

No dose adjustment is required for elderly patients. No differences in safety or efficacy have been observed between elderly patients and those < 65 years of age.

Renal Impairment

Adults with Renal Impairment:

No dose adjustment of DESCOVY is required in adult individuals with estimated CrCl ≥ 30 mL per minute or in adult individuals with end stage renal disease (ESRD) (estimated CrCl < 15 mL/minute) on chronic hemodialysis. On days of hemodialysis, administer the daily dose of DESCOVY after completion of hemodialysis treatment. DESCOVY is not recommended in individuals with severe renal impairment (estimated CrCl ≥ 15 and < 30 mL/minute), or with ESRD (estimated CrCl < 15 mL/minute) who are not on chronic hemodialysis, as the safety of DESCOVY has not been established in these populations.

Pediatrics with Renal Impairment:

DESCOVY is not recommended in pediatric individuals with renal impairment as no data are available in this population.

Hepatic Impairment

No dose adjustment of DESCOVY is required in individuals with hepatic impairment. (see **10 CLINICAL PHARMACOLOGY**).

4.4 Administration

DESCOVY is one tablet (containing 200 mg of FTC and 10 mg of TAF or 200 mg of FTC and 25 mg of TAF) taken orally once daily with or without food.

4.5 Missed Dose

If an individual misses a dose of DESCOVY within 18 hours of the time it is usually taken, the individual should take DESCOVY with or without food as soon as possible, and then take the next dose of DESCOVY at the regularly scheduled time.

If an individual misses a dose of DESCOVY by more than 18 hours, the individual should not take the missed dose, but resume the usual dosing schedule.

Uninfected individuals who miss doses are at greater risk of acquiring HIV-1 than those who do not miss doses (see **7 WARNINGS AND PRECAUTIONS**).

5 OVERDOSAGE

If overdose occurs the individual must be monitored for evidence of toxicity. Treatment of overdose with DESCOVY consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the individual.

Emtricitabine

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

Emtricitabine can be removed by hemodialysis, which removes approximately 30% of the FTC dose over a 3 hour dialysis period starting within 1.5 hours of FTC dosing.

It is not known whether FTC can be removed by peritoneal dialysis.

Tenofovir Alafenamide

Limited clinical experience is available at doses higher than the therapeutic dose of TAF. A single supratherapeutic dose of 125 mg TAF 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%.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2. Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form/ Strength/Composition	Non-medicinal Ingredients
Oral	Film-coated tablet 200 mg emtricitabine/ 10 mg* and 25 mg** tenofovir alafenamide (*as 11.2 mg tenofovir alafenamide hemifumarate **as 28.0 mg tenofovir alafenamide hemifumarate)	croscarmellose sodium, magnesium stearate and microcrystalline cellulose. The grey tablets are film-coated with a coating material containing iron oxide black, polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide. The blue tablets are film-coated with a coating material containing indigo carmine aluminum lake, polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

DESCOVY is available as rectangular-shaped, film-coated tablets containing 200 mg of FTC and either 10 mg or 25 mg of TAF (grey tablets and blue tablets, respectively). Each tablet is debossed with “GSI” on one side and either “210” (200/10 mg strength) or “225” (200/25 mg strength) on the other side. Each bottle contains 30 tablets and a silica gel desiccant and is closed with a child-resistant closure.

7 WARNINGS AND PRECAUTIONS

Please see the **3 SERIOUS WARNINGS AND PRECAUTIONS BOX** at the beginning of Part I: Health Professional Information.

General

DESCOVY is a fixed dose combination (FDC) of FTC and TAF.

For the treatment of HIV-1, DESCOVY should not be used alone and should be administered in combination with other antiretrovirals such as non-nucleoside reverse transcriptase inhibitors, protease inhibitors, or integrase inhibitors.

In the presence of a pharmacokinetic enhancer (i.e., ritonavir or cobicistat (COBI)), the dose of DESCOVY should be 200 mg/10 mg (FTC/TAF).

DESCOVY should not be coadministered with products containing any of the same components, FTC or TAF (ATRIPLA®, BIKTARVY®, COMPLERA®, EMTRIVA®, GENVOYA®, ODEFSEY®, STRIBILD®, Symtuza™, TRUVADA®, and VEMLIDY®); or with products containing lamivudine (3TC®, Combivir®, Kivexa®, Triumeq®, and Trizivir®) or tenofovir disoproxil fumarate (TDF) (ATRIPLA®, COMPLERA®, STRIBILD®, TRUVADA®, and VIREAD®); and DESCOVY should not be administered with adefovir dipivoxil (HEPSERA®).

Triple nucleoside regimens are not recommended.

The safety and efficacy of DESCOVY has not been established in patients with virologic failure.

In treatment-experienced patients, the use of DESCOVY should be guided by laboratory testing and treatment history.

The safety and efficacy of DESCOVY for HIV-1 PrEP in individuals at risk from receptive vaginal sex have not been studied (see **14 CLINICAL TRIALS**).

Endocrine and Metabolism

Serum Lipids and Blood Glucose

Serum lipid and blood glucose levels may increase during antiretroviral therapy. Disease control and lifestyle changes may also be contributing factors. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders and blood glucose elevations should be managed as clinically appropriate.

Hepatic/Biliary/Pancreatic

Hepatic Impairment

Tenofovir and TAF are not metabolized by liver enzymes. Clinically relevant pharmacokinetic changes in patients with hepatic impairment were not observed. Therefore, no dose adjustment of DESCOVY is required in patients with hepatic impairment. FTC has not been evaluated in patients with hepatic impairment; however, FTC is not significantly metabolized by liver enzymes, so the impact of liver impairment is likely to be limited.

The safety and efficacy of DESCOVY have not been studied specifically in patients with underlying liver disorders. Patients with chronic hepatitis B or C who are treated with ART are at increased risk for severe and potentially fatal hepatic adverse events (see **7.1 Special Populations**).

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including FTC, a component of DESCOVY, and TDF, another prodrug of tenofovir, alone or in combination with other antiretrovirals. Treatment with DESCOVY 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).

Pancreatitis

Caution should be exercised in the use of DESCOVY in patients with a history of pancreatitis or risk factors for the development of pancreatitis. Pancreatitis has occurred during the use of nucleoside analogues. Therapy should be suspended in patients with suspected pancreatitis.

Immune

Immune Reconstitution Inflammatory Syndrome

Immune reconstitution inflammatory syndrome has been reported in HIV-1 infected patients treated with combination ART, including FTC, a component of DESCOVY. 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, 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.

Musculoskeletal

Bone Effects

Tenofovir alafenamide and tenofovir have been shown to be associated with decreases in bone mineral density (BMD) in animal toxicology studies and in human clinical trials.

In a pooled analysis of two Phase 3 clinical studies in HIV-1 infected ART treatment-naïve adults who received FTC+TAF in combination with elvitegravir (EVG) and COBI as a FDC tablet, the percentage of patients who had more than a 3% decrease from baseline in hip and spine BMD at Week 48 was 17% and 27%, respectively, at Week 96 was 23% and 26%, respectively, and at Week 144 was 28% and 30%, respectively (see **14 CLINICAL TRIALS**).

The effects of TAF-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown.

Renal

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 with EVG/COBI/FTC/TAF and with DESCOVY for PrEP, there have been no cases of Fanconi syndrome or proximal renal tubulopathy.

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.

7.1 Special Populations

7.1.1 Pregnant Women

DESCOVY has not been studied in pregnant women. DESCOVY should not be used in pregnant women unless the potential benefits outweigh the potential risks to the fetus.

In the embryo-fetal development study in rats, administration of TAF was associated with reduced fetal body weight and delayed ossification rate at ≥100 mg/kg. The no-observed-adverse-effect-level (NOAEL) for embryo-fetal development was 25 mg/kg (approximately 10 times the clinical tenofovir exposure based on AUC).

In the embryo-fetal toxicity study in pregnant rabbits, administration of TAF resulted in significantly increased number of litters with minor external and visceral anomalies at 100 mg/kg (approximately 90 times the clinical tenofovir exposure based on AUC). The NOAEL for embryo-fetal development was 30 mg/kg/day (approximately 17 times the clinical tenofovir exposure based on AUC).

In the peri- and postnatal development study, administration of TDF, another prodrug of tenofovir, to pregnant rats resulted in increased peri/postpartum pup mortality, reduced pup survival, reduced pup body weights, reduced survival of F1 generation, reduced body weight/food consumption of F1 generation and delayed sexual maturation of F1 generation at ≥400 mg/kg (approximately 90 times the clinical tenofovir exposure based on AUC). The NOAEL for these effects was 150 mg/kg (approximately 25 times the clinical tenofovir exposure based on AUC). These results are considered relevant to TAF.

Antiretroviral Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to ART including DESCOVY, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients, http://www.apregistry.com
Telephone: (800) 258-4263
Fax: (800) 800-1052

7.1.2 Breast-feeding

Treatment of HIV-1 Infection

HIV-1 infected mothers should not breastfeed their infants to avoid risking postnatal transmission of HIV. Studies in rats have demonstrated that tenofovir is secreted into milk. It is not known whether TAF is excreted in human milk. Tenofovir-associated risks, including the risk

of developing viral resistance to tenofovir, in infants breastfed by mothers being treated with TAF are unknown.

In humans, samples of breast milk obtained from five HIV-1 infected mothers show that FTC is secreted in human milk at estimated neonatal concentrations 3 to 12 times higher than the FTC IC_{50} but 3 to 12 times lower than the C_{min} achieved from oral administration of FTC. Breastfeeding infants infected with HIV-1 whose mothers are taking FTC may be at risk for developing viral resistance to FTC. Other FTC-associated risks in infants breastfed by mothers who are taking FTC are unknown.

Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving DESCOVY**.

7.1.3 Pediatrics

HIV-1 Treatment: Safety and efficacy of DESCOVY for the treatment of HIV-1 in children weighing < 25 kg have not been established.

HIV-1 PrEP: DESCOVY is not indicated for HIV-1 PrEP in uninfected pediatric patients weighing < 35 kg.

7.1.4 Geriatrics

No dose adjustment of DESCOVY is required for elderly patients. In clinical trials, 80 of the 97 HIV-1 infected patients enrolled aged 65 years and over received FTC+TAF given with EVG+COBI as a FDC tablet (administered as GENVOYA). No differences in safety or efficacy have been observed between elderly patients and those <65 years of age (see **10 CLINICAL PHARMACOLOGY**).

7.1.5 Others

Hepatitis B Virus (HBV) Infection

The safety and efficacy of DESCOVY have not been established in individuals infected with HBV. It is recommended that all individuals be tested for hepatitis B virus (HBV) before or when initiating DESCOVY.

Severe acute exacerbations of hepatitis B (and associated with liver decompensation and liver failure) may occur in individuals infected with HBV after discontinuation of DESCOVY.

Hepatic function should be closely monitored with both clinical and laboratory follow-up for at least several months in individuals who discontinue DESCOVY and are infected with HBV. If appropriate, initiation of 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. Discontinuation of treatment without initiation of alternative anti-hepatitis B therapy in these individuals is not recommended.

Comprehensive Management to Reduce the Risk of Sexually Acquired Infections and Development of HIV-1 Resistance When DESCOVY is Used for HIV-1 PrEP

Comprehensive Prevention Strategy

Use DESCOVY for PrEP to reduce the risk of HIV-1 infection. As part of a comprehensive prevention strategy to reduce the risk of sexually acquired infections, counsel individuals on the use of other prevention measures (e.g., consistent and correct condom use, knowledge of partner HIV-1 status, regular testing for sexually transmitted infections that can facilitate HIV-1 transmission). The time from initiation of DESCOVY for HIV-1 PrEP to maximal protection against HIV-1 infection is unknown.

Risk of Resistance with Undetected HIV-1 Infection

DESCOVY should only be used to reduce the risk of acquiring HIV-1 in individuals confirmed to be HIV-negative. Confirm HIV-1 negative status prior to initiating DESCOVY for PrEP and routinely in individuals taking DESCOVY for PrEP. HIV-1 resistance substitutions may emerge in individuals with undetected HIV-1 infection who are taking only DESCOVY, because DESCOVY alone does not constitute a complete regimen for HIV-1 treatment. (see **14 CLINICAL TRIALS**).

Many HIV-1 tests, such as rapid tests, detect anti-HIV antibodies and may not identify HIV-1 during the acute stage of infection. Prior to initiating DESCOVY for PrEP, evaluate seronegative individuals for current or recent signs or symptoms consistent with acute viral infections (e.g., fever, fatigue, myalgia, skin rash, etc.) and ask about potential exposure events (e.g., unprotected, or condom broke during sex with an HIV-1 infected partner) that may have occurred within the last month.

If clinical symptoms consistent with acute HIV-1 infection are present, and recent (<1 month) exposures to HIV-1 are suspected, follow local clinical guidelines and use a test approved or cleared by Health Canada to aid in the diagnosis of acute or primary HIV-1 infection.

While using DESCOVY for PrEP, HIV-1 screening tests should be repeated at least every 3 months. 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 Health Canada.

Seroconversion while on DESCOVY for HIV-1 PrEP is considered an adverse event and should be reported to the Canadian Vigilance Program by:

- Visiting the Web page on Adverse Reaction Reporting: www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada for information on how to report online, by mail or by fax; or
- Calling 1-866-234-2345 (toll-free).

For more information on the DESCOVY HIV-1 PrEP Education Program (Checklist for Prescribers, Important Safety Information Fact Sheet for HCPs, and Uninfected Individual Safety Brochure), log onto www.descovyeducation.ca.

Importance of Adherence

Counsel HIV-1 uninfected individuals to strictly adhere to the recommended DESCOVY dosing schedule. The effectiveness of DESCOVY in reducing the risk of acquiring HIV-1 is strongly correlated with adherence as demonstrated by measurable drug levels (see **14 CLINICAL**

TRIALS). Some individuals, such as adolescents, may benefit from more frequent visits and counseling to support adherence.

For more information on the DESCOVY HIV-1 PrEP Education Program (Checklist for Prescribers, Important Safety Information Fact Sheet for HCPs, and Uninfected Individual Safety Brochure), log onto www.descovyeducation.ca.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of DESCOVY is based on studies of FTC+TAF when given with EVG+COBI as the FDC tablet, GENVOYA (EVG/COBI/FTC/TAF).

The following adverse drug reactions are discussed in other sections of the product monograph:

- Severe Acute Exacerbations of Hepatitis B [see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX]**
- Immune Reconstitution Inflammatory Syndrome [see **7 WARNINGS AND PRECAUTIONS**].
- Lactic Acidosis/Severe Hepatomegaly with Steatosis [See **7 WARNINGS AND PRECAUTIONS**]

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Clinical Trials in HIV-1 Infected Treatment-Naïve Adults

The safety assessment of FTC and TAF is based on Weeks 48, 96, and 144 pooled data from 1733 patients in two comparative clinical trials, GS-US-292-0104 (Study 104) and GS-US-292-0111 (Study 111), in antiretroviral treatment-naive HIV-1 infected adult patients who received FTC+TAF (N = 866) given with EVG+COBI as a FDC tablet (administered as GENVOYA) once daily. The proportion of patients who discontinued treatment with FTC+TAF (administered as GENVOYA) or FTC+TDF (administered as STRIBILD) due to adverse events, regardless of severity, was 0.9% and 1.5% at Week 48 and 1.3% and 3.3% at Week 144, respectively. Table 3 displays the frequency of adverse reactions (Grades 2-4) greater than or equal to 1%, respectively.

Table 3. Adverse Drug Reactions[a] (Grades 2-4) Reported in ≥ 1% of HIV-1 Infected Treatment-Naïve Adults Receiving FTC+TAF (administered as GENVOYA) in Studies GS-US-292-0104 and GS-US-292-0111 (Week 48 and Week 144 Analyses[b])

	Week 48 and Week 144	
	FTC+TAF (Administered as GENVOYA) (N=866)	FTC+TDF (Administered as STRIBILD) (N=867)
GASTROINTESTINAL DISORDERS		
Nausea	1%	1%
Diarrhea	1%	<1%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Fatigue	1%	1%
NERVOUS SYSTEM DISORDERS		
Headache	1%	1%

FTC=emtricitabine; TAF= tenofovir alafenamide; TDF= tenofovir disoproxil fumarate

a. Frequencies of adverse reactions are based on Grades 2-4 adverse events attributed to study drugs by the investigator.

b. Frequencies of adverse reactions at Week 48 and at Week 144 were the same.

Clinical Trials in HIV-1 Uninfected Adults

No new adverse reactions to DESCOVY were identified in a double-blind, randomized, active-controlled study (GS-US-412-2055 [the DISCOVER Study]) in which a total of 5387 HIV-1 uninfected adult men or transgender women who have sex with men received DESCOVY (N = 2694) or TRUVADA (N = 2693) once daily for HIV-1 PrEP. Median duration of exposure to DESCOVY and TRUVADA was 86 and 87 weeks, respectively. The most common adverse reaction in participants who received DESCOVY (incidence greater than or equal to 5%, all grades) was diarrhea (5%). Table 4 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 DESCOVY or TRUVADA due to adverse events, regardless of severity, was 1.3% and 1.8%, respectively.

Table 4. Adverse Reactions (All Grades) Reported in ≥ 2% in Either Arm in the DISCOVER Study of HIV-1 Uninfected Participants

	DESCOVY (N=2694)	TRUVADA (N=2693)
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

Clinical Trials in HIV-1 Infected Virologically Suppressed Patients

No new adverse reactions to DESCOVY were identified through Week 96 in the double-blind clinical study GS-US-311-1089 of virologically suppressed patients who changed their background regimen from TRUVADA to DESCOVY while maintaining their third antiretroviral agent (N = 333).

Clinical Trials in HIV-1 Infected Adult Patients with Renal Impairment

The safety of FTC+TAF was evaluated through Week 144 in an open-label clinical study GS-US-292-0112 (Study 112) in which 248 HIV-1 infected patients with mild to moderate renal impairment (estimated CrCl by Cockcroft-Gault method 30-69 mL/min) received FTC+TAF in combination with EVG+COBI as a FDC tablet (administered as GENVOYA). The safety profile of FTC+TAF in patients with mild to moderate renal impairment was similar to that in patients with normal renal function (estimated CrCl ≥ 80 mL/min). The safety results were consistent through Week 144 (see **14 CLINICAL TRIALS**).

The safety of FTC+TAF was evaluated through Week 48 in a single arm, open-label clinical study (GS-US-292-1825), in which 55 virologically suppressed HIV-1 infected patients with end stage renal disease (estimated CrCl by Cockcroft-Gault method < 15 mL/min) on chronic hemodialysis received FTC+TAF in combination with EVG+COBI as a fixed-dose combination tablet. The safety profile of FTC+TAF in patients with end stage renal disease on chronic hemodialysis was similar to that in patients with normal renal function.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Pediatrics (6 to < 18 years of age)

The safety of FTC+TAF was evaluated in 50 HIV-1 infected, treatment-naïve pediatric patients between the ages of 12 to < 18 years (≥ 35 kg) through Week 48 in Cohort 1, and in 23 virologically suppressed pediatric patients between the ages of 6 to <12 years (≥ 25 kg) through Week 24 in Cohort 2 of an open-label clinical trial GS-US-292-0106 (Study 106) where patients received FTC+TAF administered in combination with EVG+COBI as a FDC tablet (administered as GENVOYA) (see **14 CLINICAL TRIALS**). In this study, the safety profile of DESCOVY in pediatric patients who received treatment with FTC+TAF was similar to that in adults.

One 13 year old female subject in Cohort 1 developed unexplained uveitis while receiving GENVOYA that resolved and did not require discontinuation of GENVOYA.

In Cohort 1 of Study 106, 4 patients experienced treatment-emergent worsening in the spine (N = 39) and/or TBLH (N = 37) height-age-adjusted BMD Z-score clinical status from baseline at Week 24, where a relationship to FTC and TAF could not be excluded. However, two of these patients subsequently showed improvements in BMD at Week 48. In Cohort 2 of Study 106, 2 patients had significant (at least 4%) lumbar spine BMD loss at Week 24 (see **7 WARNINGS AND PRECAUTIONS**).

Also within Cohort 2 of Study 106, although all subjects had HIV-1 RNA < 50 copies/mL, there was a decrease from baseline in mean CD4+ cell count at Week 24 (all subjects' CD4+ cell counts remained above 400 cells/mm^3) (see **14 CLINICAL TRIALS**).

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 5.

Table 5: 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, given with EVG+COBI as a FDC tablet (GENVOYA)

	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)

8.3 Less Common Clinical Trial Adverse Reactions

In addition to the adverse reactions presented in Table 3, abdominal pain, dyspepsia, flatulence, rash, and vomiting occurred at a frequency of < 1% and/or at severity of Grade 1 in the FTC+TAF group (administered as GENVOYA).

Adverse Reactions from Clinical Trials of the Components of DESCOVY

For information on the safety profile of FTC, consult the Product Monograph for EMTRIVA.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

The frequency of laboratory abnormalities (Grades 3-4) occurring in at least 2% of patients receiving FTC+TAF given with EVG+COBI as a FDC tablet (administered as GENVOYA) in Studies 104 and 111 are presented in Table 6.

Table 6. Laboratory Abnormalities (Grades 3-4) Reported in ≥ 2% of Patients Receiving FTC+TAF (administered as GENVOYA) in Studies GS-US-292-0104 and GS-US-292-0111 (Week 48 and Week 144 Analyses)

Laboratory Parameter Abnormality[a]	Week 48		Week 144	
	FTC+TAF (Administered as GENVOYA) (N=866)	FTC+TDF (Administered as STRIBILD) (N=867)	FTC+TAF (Administered as GENVOYA) (N=866)	FTC+TDF (Administered as STRIBILD) (N=867)
Amylase (> 2.0 x ULN)	<2%	3%	3%	5%
ALT (> 5.0 x ULN)	<2%	<2%	3%	3%
AST (>5.0 x ULN)	<2%	<2%	3%	4%
Creatine Kinase (≥10.0 x ULN)	7%	6%	11%	10%
LDL-cholesterol (fasted) (>4.92mmol/L)	5%	2%	11%	5%
Total Cholesterol (fasted) (>7.77 mmol/L)	<2%	1%	4%	3%
Lipase[b] (≥3.0 x ULN)	4%	8%	5%	8%
Urine RBC (Hematuria) (>75 RBC/HPF)	<2%	2%	3%	3%

FTC=emtricitabine; TAF= tenofovir alafenamide; TDF= tenofovir disoproxil fumarate

a. Frequencies are based on treatment-emergent laboratory abnormalities.

b. Lipase test was performed only for patients with serum amylase >1.5 x ULN (N=90 for GENVOYA arm, N=113 for STRIBILD arm at Week 48; N=127 for GENVOYA arm, N=154 for STRIBILD arm at Week 144).

Serum Lipids

Patients receiving FTC+TAF (administered as GENVOYA) experienced higher increases in serum lipids than those receiving FTC+TDF (administered as STRIBILD). In the clinical trials of FTC+TAF and of FTC+TDF, both given with EVG+COBI as a FDC tablet (administered as GENVOYA and STRIBILD, respectively), a similar percentage of patients receiving FTC+TAF and FTC+TDF were on lipid lowering agents at baseline (2% and 3%, respectively). Similar percentages of subjects in each treatment group initiated lipid-modifying medications through Week 144, 5.5% and 5.8% in subjects FTC+TAF and FTC+TDF, respectively.

Changes from baseline in total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides and total cholesterol to HDL ratio at Week 48 and Week 144 are presented in Table 7.

Table 7. Lipid Values, Mean Change from Baseline, Reported in Patients Receiving FTC+TAF (Administered as GENVOYA) or FTC+TDF (Administered as STRIBILD) in Studies GS-US-292-0104 and GS-US-292-0111a (Week 48 and Week 144 Analyses)

	Week 48				Week 144			
	FTC+TAF (Administered as GENVOYA) N=866		FTC+TDF (Administered as STRIBILD) N=867		FTC+TAF (Administered as GENVOYA) N=866		FTC+TDF (Administered as STRIBILD) N=867	
	Baseline	Change[b] at Week 48	Baseline	Change[b] at Week 48	Baseline	Change[c] at Week 144	Baseline	Change[c] at Week 144
Total Cholesterol (fasted), mmol/L	4.19 [N=757]	+0.78 [N=757]	4.29 [N=742]	+034 [N=742]	4.19 [N=647]	+0.80 [N=647]	4.27 [N=627]	+0.36 [N=627]
HDL-cholesterol (fasted), mmol/L	1.19 [N=757]	+0.18 [N=757]	1.16 [N=742]	+0.10 [N=742]	1.21 [N=647]	+0.18 [N=647]	1.19 [N=627]	+0.08 [N=627]
LDL-cholesterol (fasted), mmol/L	2.69 [N=753]	+0.39 [N=753]	2.77 [N=744]	+0.08 [N=744]	2.66 [N=643]	+0.52 [N=643]	2.77 [N=628]	+0.21 [N=628]
Triglycerides (fasted), mmol/L	1.28 [N=757]	+0.33 [N=757]	1.34 [N=742]	+0.11 [N=742]	1.25 [N=647]	+0.33 [N=647]	1.30 [N=627]	+0.19 [N=627]
Total Cholesterol to HDL ratio	3.7 [N=757]	0.2 [N=757]	3.9 [N=742]	0 [N=742]	3.7 [N=647]	0.2 [N=647]	3.8 [N=627]	0.1 [N=627]

FTC = emtricitabine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

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

b. The change from baseline is the mean of within patient changes from baseline for patients with both baseline and Week 48 values.

c. The change from baseline is the mean of within patient changes from baseline for patients with both baseline and Week 144 values.

Laboratory Abnormalities

The frequency of laboratory abnormalities (Grades 3-4) occurring in at least 2% of patients receiving DESCOVY in the DISCOVER study are presented in Table 8.

Table 8. Laboratory Abnormalities (Grades 3-4) Reported in ≥ 2% in Either Arm in the DISCOVER Study of HIV-1 Uninfected Participants

Laboratory Parameter Abnormality[a]	DESCOVY (N=2694)	TRUVADA (N=2693)
AST (>5.0 x ULN)	2%	2%
LDL-cholesterol (fasted) (>4.92 mmol/L)	2%	1%
Lipase[b] (≥3.0 x ULN)	18%	26%

a. Frequencies are based on treatment-emergent laboratory abnormalities.
b. Lipase test was only performed for participants with serum amylase > 1.5 x ULN.

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 9.

Table 9. Fasting Lipid Values, Mean Change from Baseline, Reported in HIV-1 Uninfected Participants Receiving DESCOVY or TRUVADA in the DISCOVER Study[a]

	DESCOVY (N=2694)		TRUVADA (N=2693)	
	Baseline	Week 48	Baseline	Week 48
	mmol/L	Change[b]	mmol/L	Change[b]
Total Cholesterol (fasted)	4.56[c]	0[c]	4.56[d]	-0.31[d]
HDL-Cholesterol (fasted)	1.32[c]	-0.05[c]	1.32[d]	-0.13[d]
LDL-Cholesterol (fasted)	2.67[e]	0[e]	2.67[f]	-0.18[f]
Triglycerides (fasted)	1.23[c]	0.10[c]	1.25[d]	-0.01[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

8.5 Post-Market Adverse Drug Reactions

In addition to the adverse reaction reports from clinical trials, the following possible adverse reactions have been identified during post-approval use of products containing FTC or TAF. Because these events have been reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been considered possible adverse

reactions due to a combination of their seriousness, frequency of reporting or potential causal relationship with treatment.

Emtricitabine

The following adverse experiences have been reported in post-marketing experience without regard to causality; some events represent a single report.

Blood and lymphatic system disorders:	Thrombocytopenia
Gastrointestinal disorders:	Pancreatitis
General disorders and administrative site conditions:	Pyrexia
Metabolism and nutrition disorders:	Lactic acidosis

Tenofovir Alafenamide

Skin and subcutaneous tissue disorders:	Angioedema, urticaria

9 DRUG INTERACTIONS

9.1 Drug Interactions Overview

Potential for Other Drugs to Affect One or More Components of DESCOVY

Emtricitabine

In vitro and clinical pharmacokinetic drug-drug interaction studies have shown that the potential for CYP-mediated interactions involving FTC with other medicinal products is low.

Emtricitabine is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. No drug-drug interactions due to competition for renal excretion have been observed; however, coadministration of FTC with drugs that are eliminated by active tubular secretion may increase concentrations of FTC, and/or the coadministered drug.

Drugs that decrease renal function may increase concentrations of FTC.

Tenofovir Alafenamide

Tenofovir alafenamide, a component of DESCOVY, is a substrate of P-glycoprotein (P-gp), and breast cancer resistance protein (BCRP). Drugs that strongly affect P-gp and BCRP activity may lead to changes in TAF absorption (see Table 9). 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 DESCOVY and development of resistance.

Coadministration of DESCOVY with other drugs that inhibit P-gp or BCRP may increase the absorption and plasma concentration of TAF.

In vitro and clinical pharmacokinetic drug-drug interactions studies have shown that the potential for CYP-mediated interactions involving TAF with other medicinal products is low.

Coadministration of DESCOVY with drugs that inhibit the lysosomal carboxypeptidase cathepsin A may decrease metabolism of TAF to tenofovir in target cells, which may lead to reduced therapeutic effect of DESCOVY and development of resistance (see Table 10).

9.2 Drug-Behavioural Interactions

Interactions of DESCOVY with individual behavioural risks have not been established.

9.3 Drug-Drug Interactions

Established and Other Potentially Significant Interactions

DESCOVY should not be coadministered with products containing any of the same components, FTC or TAF; or with products containing lamivudine or TDF; and DESCOVY should not be administered with adefovir dipivoxil (see **7 WARNINGS AND PRECAUTIONS**, **General**).

Table 10 provides a listing of established or potentially clinically significant drug interactions. The drug interactions described are based on studies conducted with either DESCOVY, the components of DESCOVY (FTC and TAF) as individual agents or are predicted drug interactions that may occur with DESCOVY. The table includes potentially significant interactions but is not all inclusive.

Table 10. Established and Other Potentially Significant[a] Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Antiretroviral Agents: Protease Inhibitors (PI)		
Atazanavir/cobicistat[c]	↑ tenofovir alafenamide	TAF exposure is increased when atazanavir/COBI is used in combination with DESCOVY. The recommended dose of DESCOVY is 200/10 mg once daily.
Atazanavir/ritonavir[c]	↑ tenofovir alafenamide	TAF exposure is increased when atazanavir/ritonavir is used in combination with DESCOVY. The recommended dose of DESCOVY is 200/10 mg once daily.
Darunavir/cobicistat[c]	↔ tenofovir alafenamide ↑ tenofovir[d]	Tenofovir[d] exposure is increased when darunavir/ COBI is used in combination with DESCOVY. The recommended dose of DESCOVY is 200/10 mg once daily TAF exposure is not impacted.
Darunavir/ritonavir[c]	↔ tenofovir alafenamide ↑ tenofovir[d]	Tenofovir[d] exposure is increased when darunavir/ritonavir is used in combination with DESCOVY. The recommended dose of DESCOVY is 200/10 mg once daily. TAF exposure is not impacted.
Lopinavir/ritonavir[c]	↑ tenofovir alafenamide	TAF exposure is increased when lopinavir/ritonavir is used in combination with DESCOVY. The recommended dose of DESCOVY is 200/10 mg once daily.

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Tipranavir/ritonavir	↓ tenofovir alafenamide	TAF exposure may decrease when tipranavir/ritonavir is used in combination with DESCOVY. There are no data available to make dosing recommendations. Coadministration with DESCOVY is not recommended.
Other Protease Inhibitors	Effect is unknown	There are no data available to make dosing recommendations for coadministration with other protease inhibitors.
Other Agents		
Anticonvulsants: carbamazepine[c] oxcarbazepine phenobarbital phenytoin	↓ tenofovir alafenamide	Coadministration of carbamazepine, oxcarbazepine, phenobarbital, or phenytoin, all of which are P-gp inducers, may decrease TAF plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Alternative anticonvulsants should be considered.
Antifungals: itraconazole ketoconazole	↑ tenofovir alafenamide	Coadministration of itraconazole or ketoconazole, both of which are P-gp inhibitors, may increase plasma concentrations of TAF. No dose adjustment is required.
Antimycobacterial: rifabutin rifampin rifapentine*	↓ tenofovir alafenamide	Coadministration of rifampin, rifabutin, and rifapentine, all of which are P-gp inducers, may decrease TAF plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Coadministration of DESCOVY with rifabutin, rifampin, or rifapentine* is not recommended.
Herbal Products: St. John's wort *(Hypericum perforatum)*	↓ tenofovir alafenamide	Coadministration of St. John's wort, a P-gp inducer, may decrease TAF plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Coadministration of DESCOVY with St. John's wort is not recommended.

TAF = tenofovir alafenamide
* Not marketed in Canada
a. This table is not all inclusive.
b. ↑ = increase, ↓ = decrease ↔ = no effect
c. Indicates that a drug-drug interaction study was conducted.
d. Tenofovir is the major circulating metabolite of tenofovir alafenamide (see **10 CLINICAL PHARMACOLOGY**).

Drugs without Clinically Significant Interactions with DESCOVY

Based on drug interaction studies conducted with the components of DESCOVY, no clinically significant drug interactions have been either observed or are expected when DESCOVY is combined with the following antiretroviral agents: dolutegravir, efavirenz, famciclovir, ledipasvir/sofosbuvir, maraviroc, nevirapine, raltegravir, rilpivirine, sofosbuvir, sofosbuvir/velpatasvir, and sofosbuvir/velpatasvir/voxilaprevir. No clinically significant drug interactions have been either observed or expected when DESCOVY is combined with the following drugs: buprenorphine, ethinyl estradiol, methadone, midazolam, naloxone, norbuprenorphine, norgestimate, and sertraline.

Assessment of Drug Interactions

Drug Interaction Studies

Drug-drug interaction studies were conducted with DESCOVY or the components of DESCOVY (FTC or TAF) as individual agents.

The effects of coadministered drugs on the exposure of TAF are shown in Table 11. The effects of TAF on the exposure of coadministered drugs are shown in Table 12.

Table 11. Drug Interactions: Changes in Pharmacokinetic Parameters for TAF in the Presence of the Coadministered Drug[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	TAF (mg)	N	Percent Change of TAF Pharmacokinetic Parameters (90% CI)[b]; No Effect = 0%		
				C_{max}	AUC	C_{min}
Atazanavir	300 + 100 ritonavir once daily	10 once daily	10	↑ 77% (↑ 28%, ↑ 144%)	↑ 91% (↑ 55%, ↑ 135%)	NA
Atazanavir	300 + 150 cobicistat once daily	10 once daily	20	↑ 80% (↑ 48%, ↑ 118%)	↑ 75% (↑ 55%, ↑ 98%)	NA
Carbamazepine	300 twice daily	25 once daily[c]	26	↓ 57% (↓ 64%, ↓ 49%)	↓ 55% (↓ 60%, ↓ 49%)	NA
Cobicistat	150 once daily	8 once daily	12	↑ 183% (↑ 120%, ↑ 265%)	↑ 165% (↑ 129%, ↑ 207 %)	NA
Darunavir	800 + 150 cobicistat once daily	25 once daily[c]	11	↓ 7%[d] (↓ 28%, ↑ 21%)	↓ 2%[d] (↓ 20%, ↑ 19%)	NA
Darunavir	800 + 100 ritonavir once daily	10 once daily	10	↑ 42%[e] (↓ 4%, ↑109)	↑ 6%[e] (↓ 16%, ↑ 35%)	NA
Dolutegravir	50 once daily	10 once daily	10	↑ 24% (↓ 12%, ↑ 74%)	↑ 19% (↓ 4%, ↑ 48%)	NA
Efavirenz	600 once daily	40 once daily[c]	11	↓ 22% (↓ 42%, ↑ 5%)	↓ 14% (↓ 28%, ↑ 2%)	NA
Ledipasvir/ sofosbuvir	90/400 once daily	10 once daily[f]	30	↓ 10% (↓ 27%, ↑ 11%)	↓ 14% (↓ 22%, ↓ 5%)	NA
Ledipasvir/ sofosbuvir	90/400 once daily	25 once daily[g]	42	↑ 3% (↓ 6%, ↑ 14%)	↑ 32% (↑ 25%, ↑ 40%)	NA
Lopinavir	800 + 200 ritonavir once daily	10 once daily	10	↑ 119% (↑ 72%, ↑179%)	↑ 47% (↑ 17%, ↑ 85%)	NA

Coadministered Drug	Dose of Coadministered Drug (mg)	TAF (mg)	N	Percent Change of TAF Pharmacokinetic Parameters (90% CI)[b]; No Effect = 0%		
				C_{max}	AUC	C_{min}
Rilpivirine	25 once daily	25 once daily	17	↑ 1% (↓ 16%, ↑ 22%)	↑ 1% (↓ 6%, ↑ 9%)	NA
Sertraline	50 single dose	10 once daily[f]	19	0% (↓ 14%, ↑ 16 %)	↓ 4% (↓ 11%, ↑ 3%)	NA
Sofosbuvir/ velpatasvir	400/100 once daily	10 once daily[f]	24	↓ 20% (↓ 32%, ↓ 6%)	↓13% (↓ 19%, ↓ 6%)	NA
Sofosbuvir/ velpatasvir/ voxilaprevir	400/100/100 + 100 voxilaprevir[h] once daily	10 once daily[f]	29	↓ 21% (↓ 32%, ↓ 8%)	↓ 7% (↓ 15%, ↑ 1%)	NA
Sofosbuvir/ velpatasvir/ voxilaprevir	400/100/100 + 100 voxilaprevir[h] once daily	25 once daily[g]	30	↑ 32% (↑ 17%, ↑ 48%)	↑ 52% (↑ 43%, ↑ 61%)	NA

NA=Not Available/Not Applicable

a. All interaction studies conducted in healthy volunteers.
b. All No Effect Boundaries are ↓ 30% -↑43% unless otherwise specified.
c. Study conducted with DESCOVY (FTC/TAF) (FTC=emtricitabine; TAF=tenofovir alafenamide)
d. Percent change of tenofovir PK parameters (90% CI) was ↑216% (↑200%, ↑233%) for C_{max}, ↑224% (↑202%, ↑247%) for AUC_{tau}, and ↑221% (↑190%, ↑254%) for C_{min}.
e. Percent change of tenofovir PK parameters (90% CI) was ↑142% (↑ 98%, ↑195%) for C_{max}, ↑ 105% (↑54%, ↑172%) for $AUC_{inf.}$
f. Study conducted with GENVOYA.
g. Study conducted with ODEFSEY.
h. Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

Table 12. Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of TAF or the Individual Components[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	TAF (mg)	N	Percent Change of Coadministered Drug Pharmacokinetic Parameters (90% CI)[b]; No Effect = 0%		
				C_{max}	AUC	C_{min}
Atazanavir	300 + 100 ritonavir once daily	10 once daily	10	↓ 2% (↓ 11 %, ↑ 7%)	↓ 1% (↓ 4%, ↑ 1%)	0% (↓ 4%, ↑ 4%)
Atazanavir	300 + 150 cobicistat once daily	10 once daily	20	↓ 2% (↓ 6%, ↑ 2%)	↑ 6% (↑ 1%, ↑ 11%)	↑ 18% (↑ 6%, ↑ 31%)
Darunavir	800 + 150 cobicistat once daily	25 once daily[c]	11	↑ 2% (↓ 4%, ↑ 9%)	↓ 1% (↓ 8%, ↑ 7%)	↓ 3% (↓ 18%, ↑ 15%)
Darunavir	800 + 100 ritonavir once daily	10 once daily[c]	10	↓ 1% (↓ 9%, ↑ 8%)	↑ 1% (↓ 4%, ↑ 6%)	↑ 13% (↓ 5%, ↑ 34%)
Dolutegravir	50 once daily	10 once daily[c]	10	↑ 15% (↑ 4%, ↑ 27%)	↑ 2% (↓ 3%, ↑ 8%)	↑ 5% (↓ 3%, ↑ 13%)
Ledipasvir	90/400 once daily	10 once daily[e]	30	↑ 65 % (↑ 53 %, ↑ 78%)	↑ 79 % (↑ 64 %, ↑ 96%)	↑ 93% (↑ 74 %, ↑ 115%)
Sofosbuvir				↑ 28 % (↑ 13 %, ↑ 47%)	↑ 47 % (↑ 35 %, ↑ 59%)	NA
GS-331007[f]				↑ 29 % (↑ 24 %, ↑ 35%)	↑ 48 % (↑ 44 %, ↑ 53%)	↑ 66 % (↑ 60 %, ↑ 73%)
Ledipasvir	90/400 once daily	25 once daily[g]	41	↑ 1 % (↓ 3 %, ↑ 5%)	↑ 2 % (↓ 3 %, ↑ 6%)	↑ 2 % (↓ 2 %, ↑ 7%)
Sofosbuvir				↓ 4 % (↓ 11 %, ↑ 4%)	↑ 5 % (↑ 1 %, ↑ 9%)	NA
GS-331007[f]				↑ 8 % (↑ 5 %, ↑ 11%)	↑ 8 % (↑ 6 %, ↑ 10%)	↑ 10 % (↑ 7%, ↑ 12%)
Lopinavir	800 + 200 ritonavir once daily	10 once daily[c]	10	0% (↓ 5%, ↑ 6%)	0% (↓ 8%, ↑ 9%)	↓ 2% (↓ 15%, ↑ 12%)

Coadministered Drug	Dose of Coadministered Drug (mg)	TAF (mg)	N	Percent Change of Coadministered Drug Pharmacokinetic Parameters (90% CI)[b]; No Effect = 0%		
				C_{max}	AUC	C_{min}
Midazolam[d]	2.5 single dose, orally	25 once daily	18	↑ 2% (↓ 8%, ↑ 13%)	↑ 13% (↑4 %, ↑ 23%)	NA
	1 single dose, IV			↓ 1% (↓ 11%, ↑ 11%)	↑ 8% (↑ 4%, ↑ 14%)	NA
Norelgestromin	norgestimate 0.180/0.215/ 0.250 once daily / ethinyl estradiol 0.025 once daily	25 once daily[c]	15	↑ 17% (↑ 7%, ↑ 26%)	↑ 12% (↑ 7%, ↑ 17%)	↑ 16% (↑ 8%, ↑ 24%)
Norgestrel				↑ 10% (↑ 2%, ↑ 18%)	↑ 9% (↑ 1%, ↑ 18%)	↑ 11% (↑ 3%, ↑ 20%)
Ethinyl estradiol				↑ 22% (↑ 15%, ↑ 29%)	↑ 11% (↑ 7%, ↑ 16%)	↑ 2% (↓ 8%, ↑ 12%)
Rilpivirine	25 once daily	25 once daily	16	↓ 7% (↓ 13%, ↓ 1%)	↑ 1% (↓ 4%, ↑ 6%)	↑ 13% (↑ 4%, ↑ 23%)
Sertraline	50 single dose	10 once daily[e]	19	↑ 14% (↓ 6%, ↑ 38%)	↓ 7% (↓ 23%, ↑ 1 3 %)	NA
Sofosbuvir	400/100 once daily	10 once daily[e]	24	↑ 23% (↑ 7%, ↑ 42%)	↑ 37% (↑ 24%, ↑ 52%)	NA
GS-331007[f]				↑ 29% (↑ 25%, ↑ 33%)	↑ 48% (↑ 43%, ↑ 53%)	↑ 58% (↑ 52%, ↑ 65%)
Velpatasvir				↑ 30% (↑ 17%, ↑ 45%)	↑ 50% (↑ 35%, ↑ 66%)	↑ 60% (↑ 44%, ↑ 78%)
Sofosbuvir	400/100/100 + 100[h] once daily	10 once daily[e]	29	↑ 27% (↑ 9%, ↑ 48%)	↑ 22% (↑ 12%, ↑ 32%)	NA
GS-331007[f]				↑ 28% (↑ 25%, ↑ 32%)	↑ 43% (↑ 39%, ↑ 47%)	NA
Velpatasvir				↓ 4% (↓ 11%, ↑ 4%)	↑ 16% (↑ 6%, ↑ 27%)	↑ 46% (↑ 30%, ↑ 64%)

Coadministered Drug	Dose of Coadministered Drug (mg)	TAF (mg)	N	Percent Change of Coadministered Drug Pharmacokinetic Parameters (90% CI)[b]; No Effect = 0%		
				C_{max}	AUC	C_{min}
Voxilaprevir				↑ 92% (↑ 63%, ↑ 126%)	↑ 171% (↑ 130%, ↑ 219%)	↑ 350% (↑ 268%, ↑ 450%)
Sofosbuvir	400/100/100 + 100[h] once daily	25 once daily[g]	30	↓ 5% (↓ 14%, ↑ 5%)	↑ 1% (↓ 3%, ↑ 6%)	NA
GS-331007[f]				↑ 2% (↓ 2%, ↑ 6%)	↑ 4% (↑ 1%, ↑ 6%)	NA
Velpatasvir				↑ 5% (↓ 4%, ↑ 16%)	↑ 1% (↓ 6%, ↑ 7%)	↑ 1% (↓ 5%, ↑ 9%)
Voxilaprevir				↓ 4% (↓ 16%, ↑ 11%)	↓ 6% (↓ 16%, ↑ 5%)	↑ 2% (↓ 8%, ↑ 12%)

NA=Not Available/Not Applicable

a. All interaction studies conducted in healthy volunteers
b. All No Effect Boundaries are ↓30% -↑43% unless otherwise specified.
c. Study conducted with DESCOVY (FTC/TAF) (FTC=emtricitabine; TAF=tenofovir alafenamide).
d. A sensitive CYP3A4 substrate.
e. Study conducted with GENVOYA.
f. The predominant circulating metabolite of sofosbuvir.
g. Study conducted with ODEFSEY.
h. Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

9.4 Drug-Food Interactions

Emtricitabine

Relative to fasting conditions, the administration of TAF with a high fat meal (~800 kcal, 50% fat), resulted in a decrease in FTC C_{max} and AUC_{last} of 27% and 9%, respectively. These changes are not considered clinically meaningful. DESCOVY can be taken without regard to food.

Tenofovir Alafenamide

Relative to fasting conditions, the administration of DESCOVY with a high fat meal (~800 kcal, 50% fat) resulted in a decrease in TAF C_{max} (15-37%) and an increase in AUC_{last} (17-77%). These modest changes are not considered clinically meaningful.

DESCOVY can be taken without regard to food.

9.5 Drug-Herb Interactions

Coadministration of St. John's wort, a P-gp inducer, may decrease TAF plasma concentrations, which may result in loss of therapeutic effect and development of resistance.

Coadministration of DESCOVY with St. John's wort is not recommended.

9.6 Drug-Laboratory Interactions

Interactions of DESCOVY with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

DESCOVY is a FDC of antiviral drugs FTC and TAF.

Emtricitabine

Emtricitabine is a nucleoside analogue of 2'-deoxycytidine. Emtricitabine is phosphorylated by cellular enzymes to form FTC triphosphate. Emtricitabine triphosphate inhibits HIV replication through incorporation into viral DNA by the HIV reverse transcriptase, which results in DNA chain-termination.

Emtricitabine has activity that is specific to human immunodeficiency virus (HIV-1 and HIV-2) and hepatitis B virus.

Emtricitabine triphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there was no evidence of toxicity to mitochondria *in vitro* and *in vivo*.

Tenofovir Alafenamide

Tenofovir alafenamide is a phosphonamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analogue) and differs from TDF which is another prodrug of tenofovir. Tenofovir alafenamide is permeable into cells and due to increased plasma stability, and intracellular activation through hydrolysis by cathepsin A, TAF is efficient in loading tenofovir into peripheral blood mononuclear cells (PBMCs) (including lymphocytes and other HIV target cells) and macrophages. Intracellular tenofovir is subsequently phosphorylated to the pharmacologically active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HIV replication through incorporation into viral DNA by the HIV reverse transcriptase, which results in DNA chain-termination.

Tenofovir has activity that is specific to human immunodeficiency virus (HIV-1 and HIV-2). Tenofovir alafenamide displayed antiviral activity in cell culture against all HIV-1 groups. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ. In the *in vitro* study, TAF did not significantly affect mitochondrial DNA in HepG2 cells.

10.2 Pharmacodynamics

Effects on Electrocardiogram

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

10.3 Pharmacokinetics

Comparative Bioavailability

The bioavailabilities of FTC and TAF from a single dose administration of DESCOVY (F/TAF) 200 mg/10 mg FDC tablet with concomitant administration of COBI 150 mg tablet and EVG 150 mg tablet or a single dose of GENVOYA (E/C/F/TAF) 150 mg/150 mg/200 mg/10 mg fixed dose combination tablet in healthy male and female subjects (N = 100) under moderate fat, moderate calorie fed conditions were comparable.

The bioavailabilities of FTC and TAF from a single dose administration of DESCOVY (F/TAF) 200 mg/25 mg FDC tablet or a single dose of GENVOYA (E/C/F/TAF) 150 mg/150 mg/200 mg/10 mg fixed dose combination tablet in healthy male and female subjects (N = 116) under moderate fat, moderate calorie fed conditions were comparable.

Absorption

Following administration of FTC/TAF hemifumarate 200 mg/25 mg fixed dose combination tablets with a high fat, high calorie meal, there was a delay in the mean T_{max} for FTC by approximately 1 hour, and a decrease in AUC_T and C_{max} for FTC by approximately 9% and 26%, respectively when compared to administration under fasting conditions. For TAF, there was a delay in the mean T_{max} for TAF by approximately 0.5 hours, an increase in the AUC_T for TAF by approximately 74% and a decrease in C_{max} for TAF by approximately 10% when compared to administration under fasting conditions.

HIV status has no effect on exposures of FTC and TAF in adults.

Distribution

Emtricitabine

In vitro binding of FTC to human plasma proteins is < 4% and is independent of concentration over the range of 0.02 to 200 µg/mL. At peak plasma concentration, the mean plasma to blood drug concentration ratio was ~1.0 and the mean semen to plasma drug concentration ratio was ~4.0.

Tenofovir Alafenamide

The binding of tenofovir to human plasma proteins is < 0.7% and is independent of concentration over the range of 0.01–25 µg/mL. The binding of TAF to human plasma proteins in samples collected during clinical studies was approximately 80%.

Metabolism

Emtricitabine

Emtricitabine is not significantly metabolized.

Tenofovir Alafenamide

Metabolism is a major elimination pathway for TAF in humans, accounting for > 80% of an oral dose. *In vitro* studies have shown that TAF is metabolized to tenofovir (major metabolite) by

cathepsin A in peripheral blood mononuclear cells (PBMCs) (including lymphocytes and other HIV target cells) and macrophages; and by carboxylesterase-1 in hepatocytes. Tenofovir alafenamide is a substrate of P-gp and BCRP transporters, and is minimally metabolized by CYP3A4. Upon coadministration with the moderate CYP3A inducer probe efavirenz, TAF exposure was unaffected.

In vivo, TAF is hydrolyzed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite, tenofovir diphosphate. In human clinical studies, a 10 mg oral dose of TAF in a FDC of EVG/COBI/FTC/TAF resulted in tenofovir diphosphate concentrations > 4-fold higher in PBMCs and > 90% lower concentrations of tenofovir in plasma as compared to a 300 mg oral dose of TDF in STRIBILD.

In vitro, TAF is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or UGT1A1.

Tenofovir alafenamide is not an inhibitor or inducer of CYP3A4 *in vivo*.

Elimination

Emtricitabine

Emtricitabine is primarily excreted in the urine by a combination of glomerular filtration and active tubular secretion.

Tenofovir Alafenamide

Tenofovir alafenamide is eliminated following metabolism to tenofovir. Tenofovir is renally eliminated by both glomerular filtration and active tubular secretion. Tenofovir alafenamide and tenofovir have a median plasma half-life of 0.51 and 32.37 hours, respectively. Renal excretion of intact TAF is a minor pathway with less than 1% of the dose eliminated in urine. The pharmacologically active metabolite, tenofovir diphosphate, has a half-life of 150-180 hours within PBMCs.

Special Populations and Conditions

- **Pediatrics (≥ 6 to < 18 years of age)**

Treatment of HIV-1 infection: Exposures of FTC and TAF achieved in 24 HIV-1 infected pediatric patients aged 12 to < 18 years (Study 106) were similar to exposures achieved in HIV-1 infected treatment-naïve adults.

Exposures of FTC and TAF achieved in 23 HIV-1 infected pediatric patients between the ages of 6 to < 12 years (≥ 25 kg) (Study 106) were generally higher (20-80%) than exposures achieved in HIV-1 infected adults; however, the increase was not considered clinically relevant as the safety profiles were similar in adult and pediatric patients.

HIV-1 PrEP: The pharmacokinetic data for FTC and TAF following administration of DESCOVY in HIV-1 uninfected adolescents weighing ≥ 35 kg are not available. The dosage recommendations of DESCOVY for HIV-1 PrEP in HIV-1 uninfected adolescents weighing ≥ 35 kg (excluding individuals at risk from receptive vaginal sex) are based on known pharmacokinetic information in HIV-infected adolescents taking FTC and TAF for treatment.

- **Geriatrics (≥65 years of age)**

Pharmacokinetic-pharmacodynamic analysis of HIV-infected patients in Phase 2 and Phase 3 trials of FTC+TAF given with EVG+COBI as a FDC tablet (administered as GENVOYA) showed that within the age range studied (8 to 82 years), age did not have a clinically relevant effect on exposures of TAF.

- **Sex**

No clinically relevant pharmacokinetic differences have been observed between men and women for FTC and TAF.

- **Ethnic Origin**

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

Tenofovir Alafenamide: Pharmacokinetics-pharmacodynamics analyses of TAF in HIV-1 infected patients indicated that race had no clinically relevant effect on the exposure of TAF.

- **Hepatic Insufficiency**

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

Tenofovir Alafenamide: Clinically relevant changes in the pharmacokinetics of TAF or its metabolite tenofovir were not observed in patients with mild, moderate, or severe hepatic impairment; no TAF dose adjustment is required in patients with hepatic impairment.

- **Renal Insufficiency**

Mild to Moderate Renal Impairment

The safety, virologic, and immunologic responses of DESCOVY in HIV-1 infected patients with mild to moderate renal impairment (estimated CrCl by Cockcroft-Gault method 30-69 mL/min) were evaluated with FTC+TAF given with EVG+COBI as a FDC tablet (administered as GENVOYA) in an open-label trial, Study 112. The safety profile of FTC+TAF in patients with mild to moderate renal impairment was similar to that in patients with normal renal function.

Severe Renal Impairment

No clinically relevant differences in TAF or tenofovir pharmacokinetics were observed between healthy subjects and patients with severe renal impairment (estimated CrCl ≥ 15 and < 30 mL/min) in Phase I studies of TAF. In a separate Phase 1 study of FTC alone, FTC exposures were increased in subjects with severe renal impairment. The safety of FTC+TAF has not been established in subjects with estimated creatinine clearance ≥ 15 mL and < 30 mL/min.

End Stage Renal Disease

Exposures of FTC and tenofovir in 12 subjects with end stage renal disease (estimated CrCl < 15 mL/minute) on chronic hemodialysis who received FTC+TAF in combination with

EVG+COBI as a fixed-dose combination tablet in Study 1825 were significantly higher than in subjects with normal renal function. However, the safety profile of FTC+TAF in subjects with end stage renal disease on chronic hemodialysis in this study was similar to that in subjects with normal renal function. No clinically relevant differences in TAF pharmacokinetics were observed in patients with end stage renal disease as compared to those with normal renal function. There are no pharmacokinetic data on TAF in patients with estimated CrCl < 15 mL/minute not on chronic hemodialysis.

- **Hepatitis B and/or Hepatitis C Virus Coinfection**

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

11 STORAGE, STABILITY AND DISPOSAL

Store below 30 °C (86 °F).

- Keep container tightly closed.
- Dispense only in original container.
- Do not use if seal over bottle opening is broken or missing.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

DESCOVY is a FDC tablet containing emtricitabine (FTC) and TAF hemifumarate. FTC is a synthetic nucleoside analog of cytidine. Tenofovir alafenamide, a nucleoside reverse transcriptase inhibitor (NRTI), is a prodrug of tenofovir converted *in vivo* to tenofovir, and acyclic nucleoside phosphanate (nucleotide) analog of adenosine 5'-monophosphate.

DESCOVY tablets are for oral administration. Each tablet contains 200 mg of FTC and either 10 mg or 25 mg of TAF (which is equivalent to 11.2 mg and 28.0 mg of TAF hemifumarate, respectively). The tablets include the following inactive ingredients: microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The 200/10 mg strength tablets are film-coated with a coating material containing polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and iron oxide black. The 200/25 mg strength tablets are film-coated with a coating material containing polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and indigo carmine aluminum lake.

Emtricitabine (FTC)

Drug Substance

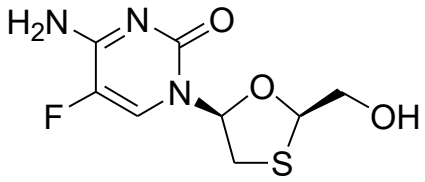
Common Name: emtricitabine (USAN)

Chemical Name: 5-fluoro-1-(2R,5S)-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine

Empirical Formula: $C_8H_{10}FN_3O_3S$

Molecular Weight: 247.24

Structural Formula:



Physicochemical Properties:

Description: Emtricitabine is a white to off-white crystalline powder.

Solubility: The solubility is approximately 112 mg/mL in water at 25°C. The partition coefficient (log P) is −0.43 and the pKa is 2.65.

Tenofovir Alafenamide (TAF)

Drug Substance

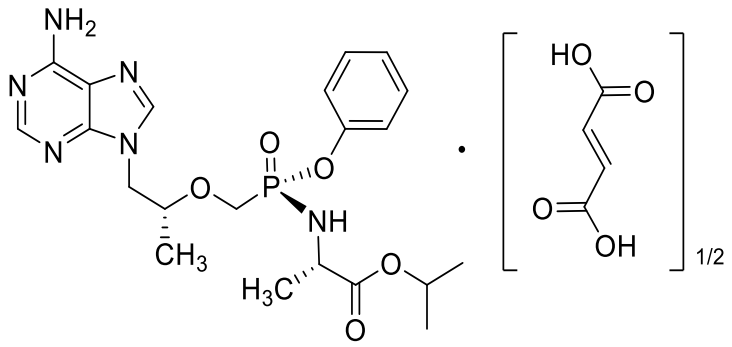
Common Name: Tenofovir alafenamide hemifumarate
Tenofovir alafenamide fumarate (USAN)

Chemical Name: Propan-2-yl N-[(S)-({[(2R)-1-(6-amino-9H-purin-9-yl)propan-2-yl]-oxy}methyl)(phenoxy)phosphoryl]-l-alaninate, (2E)-but-2-enedioate (2:1)

Empirical Formula: $C_{21}H_{29}O_5N_6P \cdot 1/2(C_4H_4O_4)$

Molecular Weight: 534.5

Structural Formula:



Physicochemical Properties:

Description: TAF hemifumarate is a white to off-white or tan powder.

Solubility: The solubility of TAF hemifumarate in water, pH 8.0 (50 mM phosphate buffer) at 20°C is 4.86 mg/mL. The partition coefficient (log P) is 1.6 and the pKa is 3.96.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Treatment of HIV-1 Infection

The clinical efficacy of DESCOVY in HIV-1 infected treatment-naïve patients was established from studies conducted with FTC+TAF when given with EVG+COBI in a FDC (GENVOYA [E/C/F/TAF]). There are no efficacy and safety studies conducted in HIV-1 infected treatment-naïve patients with DESCOVY. The efficacy and safety of FTC+TAF in HIV-1 infected, virologically-suppressed patients with end stage renal disease (ESRD) on chronic hemodialysis is based on 48-week data from a single arm, open-label study, GS-US-292-1825 (Study 1825) (N=55).

Treatment-Naïve HIV-1 Infected Patients

In both Studies GS-US-292-0104 (Study 104) and GS-US-292-0111 (Study 111), patients were randomized in a 1:1 ratio to receive either FTC+TAF (N=866) or FTC+TDF (N=867) once daily, both given with EVG+COBI as a FDC tablet (GENVOYA and STRIBILD, respectively).

In Studies 104 and 111, the mean age was 36 years (range 18-76), 85% were male, 57% were White, 25% were Black, and 10% were Asian. Nineteen percent of patients identified as Hispanic/Latino. The mean baseline plasma HIV-1 RNA was 4.5 $\log_{10}$ copies per mL (range 1.3–7.0). The mean baseline CD4+ cell count was 427 cells per mm^3 (range 0-1360) and 13% had CD4+ cell counts < 200 cells per mm^3. Twenty-three percent of patients had baseline viral loads > 100,000 copies per mL.

For demographic and baseline characteristics for Studies 104 and 111, see Table 13.

Table 13. Pooled Demographic and Baseline Characteristics of Antiretroviral Treatment-naïve HIV-1 Infected Adult Patients in Studies GS-US-292-0104 and GS-US-292-0111

	FTC+TAF (Administered as GENVOYA) (N=866)	FTC+TDF (Administered as STRIBILD) (N=867)
Demographic characteristics		
Median age, years (range)	33 (18-74)	35 (18-76)
Sex		
Male	733	740
Female	133	127
Race		
American Indian/Alaska Native	5	8
White	485	498
Black	223	213
Native Hawaiian/Pacific Islander	5	4
Asian	91	89
Other	57	55
Baseline disease characteristics		
Median baseline plasma HIV-1 RNA $\log_{10}$ copies/mL (range)	4.58 (2.57-6.89)	4.58(1.28-6.98)
Percentage of subjects with viral load ≤100,000 copies/mL	77.4	77.5
Percentage of subjects with viral load > 100,000 to ≤400,000 copies/mL	17.0	17.8
Percentage of subjects with viral load >400,000 copies/mL	5.7	4.7
Median baseline CD4+ cell count /µL (range)	404 (0-1311)	406 (1-1360)
Percentage of subjects with CD4+ cell counts <200 cells/mm^3	13.0	13.5
HIV disease status		
Asymptomatic	779	800
Symptomatic HIV infection	53	34
AIDS	31	29
Unknown	3	4
Estimated CrCl by Cockcroft-Gault method (mL/min), median (Q1, Q3)	117.0 (99.6, 135.6)	113.9 (99.0, 133.6)
Proteinuria by urinalysis (dipstick)		
Grade 0	778	780
Grade 1	80	67
Grade 2	8	18
Grade 3	0	1
-Missing-	0	1

FTC=emtricitabine; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate

In both studies, patients were stratified by baseline HIV-1 RNA (≤ 100,000 copies per mL, > 100,000 copies per mL to ≤ 400,000 copies per mL, or > 400,000 copies per mL), by CD4 count (<50 cells per µL, 50-199 cells per µL, or ≥ 200 cells per µL), and by region (US or ex-US).

Treatment outcomes of Studies 104 and 111 through Week 48 and Week 144 are presented in Table 14.

Table 14. Pooled Virologic Outcomes of Studies GS-US-292-0104 and GS-US-292-0111 at Week 48[a] and Week 144[b]

	Week 48		Week 144	
	FTC+TAF (Administered as GENVOYA) (N=866)	**FTC+TDF (Administered as STRIBILD) (N=867)**	**FTC+TAF (Administered as GENVOYA) (N=866)**	**FTC+TDF (Administered as STRIBILD) (N=867)**
Virologic Success HIV-1 RNA < 50 copies/mL	92%	90%	84%	80%
Treatment Difference	2.0% (95% CI: -0.7% to 4.7%)		4.2% (95% CI: 0.6% to 7.8%)	
Virologic Failure HIV-1 RNA ≥ 50 copies/mL[c]	4%	4%	5%	4%
No Virologic Data at Week 48 or Week 144 Window	4%	6%	11%	16%
Discontinued Study Drug Due to AE or Death[d]	1%	2%	1%	3%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA <50 copies/ mL[e]	2%	4%	9%	11%
Missing Data During Window but on Study Drug	1%	<1%	1%	1%
Proportion (%) of Subjects with HIV-1 RNA <50 copies/mL by Subgroup				
Age				
< 50 years	716/777 (92%)	680/753 (90%)	647/777 (83%)	602/753 (80%)
≥ 50 years	84/89 (94%)	104/114 (91%)	82/89 (92%)	92/114 (81%)
Sex				
Male	674/733 (92%)	673/740 (91%)	616/733 (84%)	603/740 (81%)
Female	126/133 (95%)	111/127 (87%)	113/133 (85%)	91/127 (72%)
Race				
Black	197/223 (88%)	177/213 (83%)	168/223 (75%)	152/213 (71%)
Nonblack	603/643 (94%)	607/654 (93%)	561/643 (87%)	542/654 (83%)
Baseline Viral Load				
≤ 100,000 copies/mL	629/670 (94%)	610/672 (91%)	567/670 (85%)	537/672 (80%)
> 100,000 copies/mL	171/196 (87%)	174/195 (89%)	162/196 (83%)	157/195 (81%)

	Week 48		Week 144	
	FTC+TAF (Administered as GENVOYA) (N=866)	**FTC+TDF (Administered as STRIBILD) (N=867)**	**FTC+TAF (Administered as GENVOYA) (N=866)**	**FTC+TDF (Administered as STRIBILD) (N=867)**
Baseline CD4+ cell count				
< 200 cells/mm^3	96/112 (86%)	104/117 (89%)	93/112 (83%)	94/117 (80%)
≥ 200 cells/mm^3	703/753 (93%)	680/750 (91%)	635/753 (84%)	600/750 (80%)

FTC=emtricitabine; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate

a. Week 48 window was between Day 294 and 377 (inclusive).
b. Week 144 window was between Day 966 and 1049 (inclusive).
c. Included patients who had ≥50 copies/mL in the Week 48 or Week 144 window; patients who discontinued early due to lack or loss of efficacy; patients who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥50 copies/mL.
d. Includes patients who discontinued due to AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.
e. Includes patients who discontinued for reasons other than an AE, death or lack or loss of efficacy; e.g., withdrew consent, loss to follow-up, etc.

In Studies 104 and 111, FTC+TAF met the noninferiority criteria in achieving HIV-1 RNA <50 copies/mL at Week 48 and Week 96, when compared to FTC+TDF, both given with EVG+COBI as a FDC tablet (GENVOYA and STRIBILD, respectively). At Week 144, FTC+TAF (administered as GENVOYA) demonstrated statistical superiority (p = 0.021) in achieving HIV-1 RNA < 50 copies/mL when compared to FTC+TDF (administered as STRIBILD). In Studies 104 and 111, the 95% CIs for differences in virologic success between treatment groups included zero for most subgroups evaluated suggesting no differences between the treatments.

The mean increase from baseline in CD4+ cell count at Week 48, Week 96, and Week 144 was 230 cells/mm^3, 280 cells/mm^3, and 326 cells/mm3, respectively, in patients receiving FTC+TAF, and 211 cells/mm^3, 266 cells/mm^3, and 305 cells/mm^3, respectively, in patients receiving FTC+TDF (p=0.024, p=0.14, and p=0.06 at Week 48, Week 96, and Week 144, respectively).

Bone Mineral Density

In the pooled analysis of Studies 104 and 111, the effects of FTC+TAF compared to that of FTC+TDF on bone mineral density (BMD) from baseline to Week 48, Week 96, and Week 144 were assessed by dual-energy X-ray absorptiometry (DXA). As shown in Table 15, in patients who had both baseline and Week 48, 96, and Week 144 measurements (Week 48: N = 780 and 784 in patients receiving FTC+TAF and N = 767 and 773 in patients receiving FTC+TDF, for hip and spine, respectively; Week 96: N = 716 and 722 in patients receiving FTC+TAF and N = 711 and 714 in patients receiving FTC+TDF, for hip and spine, respectively; Week 144: N = 690 and 702 in patients receiving FTC+TAF and N = 683 and 686 in patients receiving FTC+TDF, for hip and spine, respectively), there were smaller decreases in BMD in patients receiving FTC+TAF as compared to patients receiving FTC+TDF, both given with EVG+COBI as a FDC tablet (GENVOYA and STRIBILD, respectively).

Table 15. Measures of Bone Mineral Density in Studies GS-US-292-0104 and GS-US-292-0111 (Week 48, Week 96, and Week 144 Analyses)

	Week 48				Week 96				Week 144			
	FTC+TAF (Administered as GENVOYA)	FTC+TDF (Administered as STRIBILD)	Treatment Difference		FTC+TAF (Administered as GENVOYA)	FTC+TDF (Administered as STRIBILD)	Treatment Difference		FTC+TAF (Administered as GENVOYA)	FTC+TDF (Administered as STRIBILD	Treatment Difference	
Hip DXA Analysis	**N=780**	**N=767**	**Difference in LSM (95% CI)**	**P-value**	**N=716**	**N=711**	**Difference in LSM (95% CI)**	**P-value**	**N=690**	**N=683**	**Difference in LSM (95% CI)**	**P-value**
Mean (SD) Percent Change in BMD	-0.7% (3.3%)	-3.0% (3.4%)	2.3% (2.0 to 2.6)	p < 0.001	-0.7% (3.9%)	-3.3% (4.0%)	2.6% (2.2 to 3.0)	p < 0.001	-0.8% (4.4%)	-3.4% (4.3%)	2.6% (2.2 to 3.1)	p < 0.001
Patients with Categorical Change:												
> 3% Decrease in BMD	17%	50%	--	--	23%	56%	--	--	28%	55%	--	--
> 3% Increase in BMD	7%	3%			12%	6%			13%	6%		
Patients with No Decrease (≥ zero % change) in BMD	35%	14%	--	--	39%	16%	--	--	40%	19%	--	--
Lumbar Spine DXA Analysis	**N=784**	**N=773**			**N=722**	**N=714**			**N=702**	**N=686**		
Mean (SD) Percent Change in BMD	-1.3% (3.1%)	-2.9% (3.2%)	1.6% (1.2 to 1.9)	p < 0.001	-1.0% (3.7%)	-2.8% (3.9%)	1.8% (1.4 to 2.2)	p < 0.001	-0.9% (4.1%)	-3.0% (4.3%)	2.0% (1.6 to 2.5)	p < 0.001

	Week 48				Week 96				Week 144			
	FTC+TAF (Administered as GENVOYA)	FTC+TDF (Administered as STRIBILD)	Treatment Difference		FTC+TAF (Administered as GENVOYA)	FTC+TDF (Administered as STRIBILD)	Treatment Difference		FTC+TAF (Administered as GENVOYA)	FTC+TDF (Administered as STRIBILD	Treatment Difference	
Patients with Categorical Change:												
> 3% Decrease in BMD	27%	46%	--	--	26%	48%	--	--	30%	49%	--	--
> 3% Increase in BMD	7%	3%			11%	6%			13%	7%		
Patients with No Decrease (≥ zero % change) in BMD	34%	17%	--	--	37%	21%	--	--	39%	22%	--	--

FTC=emtricitabine; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate

Changes in Renal Laboratory Tests and Renal Safety

In the pooled analysis of Studies 104 and 111, laboratory tests were performed to compare the effect of TAF to that of TDF on renal laboratory parameters. As shown in Table 16, statistically significant differences were observed between treatment groups that favored TAF for increases in serum creatinine and changes in proteinuria, including urine protein to creatinine ratio (UPCR), urine albumin to creatinine ratio (UACR), urine retinol binding protein (RBP) to creatinine ratio, and urine beta-2-microglobulin to creatinine ratio. There were zero cases of Fanconi syndrome or Proximal Renal Tubulopathy (PRT) in the FTC+TAF group through Week 144.

Table 16. Change from Baseline in Renal Laboratory Tests in Studies GS-US-292-0104 and GS-US-292-0111 (Week 48, Week 96, and Week 144 Analyses)

	Week 48			Week 96			Week 144		
	FTC+TAF (Administered as GENVOYA) (N=866)	FTC+TDF (Administered as STRIBILD) (N=867)	Treatment Difference	FTC+TAF (Administered as GENVOYA) (N=866)	FTC+TDF (Administered as STRIBILD) (N=867)	Treatment Difference	FTC+TAF (Administered as GENVOYA) (N=866)	FTC+TDF (Administered as STRIBILD) (N=867)	Treatment Difference
Serum Creatinine (µmol/L)[a]	7.07 ± 10.96	9.72 ± 19.18	-3.54 p < 0.001	3.54 ± 10.08	6.19 ± 11.23	-2.65 p < 0.001	3.54 ± 10.61	6.19 ± 11.23	-3.54 p < 0.001
Proteinuria by Urine Dipstick[b]	31%	37%	p = 0.022	36%	41%	p = 0.034	40%	45%	p = 0.027
Urine Protein to Creatinine Ratio [UPCR][c]	-3.4%	19.8%	p < 0.001	-9.1%	16.2%	p < 0.001	-10.5%	25.2%	p < 0.001
Urine Albumin to Creatinine Ratio [UACR][c,d]	-4.7%	7.1%	p < 0.001	-5.2%	4.9%	p < 0.001	[d]	[d]	[d]
Urine RBP to Creatinine Ratio[c]	9.2%	51.2%	p < 0.001	13.8%	74.2%	p < 0.001	34.8%	111%	p < 0.001
Urine Beta-2-Microglobulin to Creatinine Ratio[c]	-31.7%	24.1%	p < 0.001	-32.1%	33.5%	p < 0.001	-25.7%	53.8%	p < 0.001

FTC=emtricitabine; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate

a. Mean change ± SD
b. Includes all severity grades (1-3)
c. Median percent change
d.. UACR was assessed up to Week 96

In addition to the tabulated differences (shown in Table 16) in serum creatinine and proteinuria, there were other differences in tests of proximal renal tubular function that favored TAF. At Weeks 48, 96, and 144, the proportion of patients with any grade hypophosphatemia was 3.6%, 5.6%, and 6.8%, respectively, in patients receiving FTC+TAF, and 4.0%, 5.4%, and 7.6%, respectively, in patients receiving FTC+TDF, both given with EVG+COBI as a FDC tablet (GENVOYA and STRIBILD, respectively). The median (Q1, Q3) change from baseline in $FEPO_4$ was 2.0% (-1.2%, 5.6%), 2.1% (-1.3%, 5.5%), and 3.0% (-0.7%, 7.2%) at Weeks 48, 96, and 144, respectively, in patients receiving FTC+TAF, and 2.6% (-0.7%, 6.4%), 2.7% (-0.8%, 7.0%), and 4.1% (0.2%, 8.0%) at Weeks 48, 96, and 144, respectively, in patients receiving FTC+TDF (p = 0.006, p = 0.009, and p = 0.001 at Weeks 48, 96, and 144, respectively).

The median (Q1, Q3) change from baseline in the ratio of the renal tubular maximum reabsorption rate of phosphate to the glomerular filtration rate (TmP/GFR) was -0.2 mg/dL (-0.7 mg/dL, 0.2 mg/dL), −0.3 mg/dL (-0.9 mg/dL, 0.2 mg/dL), and -0.4 mg/dL (-1.0 mg/dL, 0.1 mg/dL) at Weeks 48, 96, and 144, respectively, in patients receiving FTC+TAF, and -0.3 mg/dL (-0.7 mg/dL, 0.2 mg/dL), -0.4 mg/dL (-0.8 mg/dL, 0.1 mg/dL), and -0.5 mg/dL (-1.0 mg/dL, 1.0 mg/dL) at Weeks 48, 96, and 144, respectively, in patients receiving FTC+TDF (p=0.21, p=0.35, and p=0.011 at Weeks 48 and, 96, and 144, respectively).

Changes in Lipid Laboratory Tests

Increases from baseline were observed in both treatment groups for the fasting lipid parameters total cholesterol, direct LDL, HDL, and triglycerides at Week 48, 96, and 144. The median increase from baseline for these parameters was greater in patients receiving FTC+TAF compared with patients receiving FTC+TDF, both given with EVG+COBI as a FDC tablet (p<0.001 for the difference between treatment groups for fasting total cholesterol, direct LDL, HDL, and triglycerides). Median (Q1, Q3) change from baseline at Week 48, 96, and 144 in total cholesterol to HDL ratio was 0.1 (-0.3, 0.5), 0.1 (-0.3, 0.7), and 0.2 (-0.3, 0.7), respectively, in patients receiving FTC+TAF and 0.0 (-0.5, 0.4), 0.0 (-0.4, 0.5) and 0.1 (-0.4, 0.6), respectively, in patients receiving FTC+TDF (p<0.001 for the difference between treatment groups at Weeks 48 and 96; p=0.006 at Week 144) (see **8 ADVERSE REACTIONS**).

HIV-1 Infected Patients with Renal Impairment

In Study 1825, the efficacy and safety of FTC+TAF given with EVG+COBI were evaluated in a single arm, open-label clinical study in which 55 HIV-1 infected adults with end stage renal disease (estimated CrCl by Cockcroft-Gault method < 15 mL/min) receiving chronic hemodialysis for at least 6 months switched to FTC+TAF in combination with EVG+COBI as a fixed-dose combination tablet. Patients were virologically suppressed (HIV-1 RNA < 50 copies/mL) for at least 6 months before switching.

The mean age was 48 years (range 23−64). Seventy-six percent were male, 82% were Black and 18% were White. Fifteen percent of patients identified as Hispanic/Latino. The mean baseline CD4+ cell count was 545 cells/mm^3 (range 205−1473).

At Week 48, 81.8% (45/55 patients) maintained HIV-1 RNA < 50 copies/mL after switching to FTC+TAF given with EVG+COBI. There were no clinically significant changes in fasting lipid laboratory tests in patients who switched.

HIV-1 Infected Pediatric Patients

In Study 106, the efficacy, safety, and pharmacokinetics of FTC+TAF, given with EVG+COBI as a FDC tablet (administered as GENVOYA), were evaluated in an open-label study in HIV-1-infected treatment-naïve adolescents between the ages of 12 to < 18 years (> 35 kg) (N = 50) through Week 48, and in virologically suppressed pediatric patients between the ages of 6 to < 12 years (≥ 25 kg) (N = 23) through Week 24.

Cohort 1: Treatment-Naïve Adolescents (12 to < 18 Years of Age and Weighing ≥ 35 kg)

Patients in Cohort 1 had a mean age of 15 years (range: 12 to 17), 44% were male, 12% were Asian, and 88% were Black. At baseline, mean plasma HIV-1 RNA was 4.6 $\log_{10}$ copies/mL, median CD4+ cell count was 456 cells/mm^3 (range: 95 to 1110), and median CD4+% was 23% (range: 7% to 45%). Twenty-two percent had baseline plasma HIV-1 RNA > 100,000 copies/mL as shown in Table 17.

Cohort 2: Virologically Suppressed Children (6 to < 12 Years of Age and Weighing ≥ 25 kg)

Patients in Cohort 2 had a mean age of 10 years (range: 8 to 11), a mean baseline weight of 31.6 kg (range: 26 to 58), 39% were male, 13% were Asian, and 78% were Black. At baseline, median CD4+ cell count was 969 cells/mm^3 (range: 603 to 1421), and median CD4+% was 39% (range: 30% to 51%). All 23 patients had baseline plasma HIV-1 RNA < 50 copies/mL as shown in Table 17.

Table 17. Demographic and Baseline Characteristics of Treatment-Naïve HIV-1 Infected Adolescents (Cohort 1) and Virologically Suppressed Children (Cohort 2) in Study GS-US-292-0106

	Cohort 1	Cohort 2
	FTC+TAF (Administered as GENVOYA) (N=50)	FTC+TAF (Administered as GENVOYA) (N=23)
Demographic characteristics		
Median age, years (range)	15 (12-17)	10 (8-11)
Sex		
Male	22	9
Female	28	14
Race		
Asian	6	3
Black	44	18
White	0	2
BMI (kg/m^2), median (Q1, Q3)	20.0 (18.1, 23.1)	15.9 (15.2, 18.1)
Baseline disease characteristics		
HIV-1 RNA (log_{10} copies/mL), median (Q1, Q3)	4.65 (4.25, 4.94)	N/A
HIV-1 RNA >100,000 copies/mL	11	0
HIV-1 RNA < 50 copies/mL	0	23
CD4+ cell count (cells/µL), median (Q1, Q3)	456 (332, 574)	969 (843, 1087)
Mode of infection (HIV risk factors)		
Heterosexual sex	12	0
Homosexual sex	8	0
IV drug use	1	0
Vertical transmission	32	23
HIV disease status		
Asymptomatic	42	23
Symptomatic HIV infection	8	0
Estimated CrCl by Schwartz formula ($mL/min/1.73\ m^2$), median (Q1, Q3)	156 (129.0, 185.0)	150.0 (134.7, 165.6)
Proteinuria by urinalysis (dipstick)		
Grade 0	48	22
Grade 1	1	1
Grade 2	1	0
Grade 3	0	0

FTC=emtricitabine; TAF=tenofovir alafenamide

Cohort 1: Treatment-naïve Adolescents (≥ 12 to < 18 Years of Age and Weighing ≥ 35 kg)

At Week 24, out of 23 patients assessed for efficacy, 91% achieved HIV-1 RNA < 50 copies/mL, and at Week 48, 92% (46/50) achieved HIV-1 RNA <50 copies/mL, similar to response rates in trials of treatment-naïve HIV-1 infected adults. The mean increase from baseline in CD4+ cell count at Week 24 and Week 48 was 212 and 224 cells/mm^3, respectively. Two patients had virologic failure by snapshot at Week 24 and three of the 50 patients had virologic failure by snapshot at Week 48; no emergent resistance to FTC and TAF was detected through Week 24 and Week 48.

Fifty patients in Cohort 1 were assessed for safety at Week 24 and Week 48 (these patients received FTC+TAF (10 mg) given with EVG+COBI as a FDC tablet (GENVOYA) for 24 and 48 weeks). BMD by DXA was assessed in 47 patients for spine at both Week 24 and Week 48. BMD by DXA was assessed in 45 and 44 patients for total body less head (TBLH) at Week 24 and Week 48, respectively. Mean (SD) BMD increased from baseline to Week 24, +1.6% (3.9%) at the lumbar spine and +0.6% (2.5%) for TBLH. Mean (SD) BMD increased from baseline to Week 48, +4.2% (5.0%) at the lumbar spine and +1.3% (2.7%) for TBLH.

Cohort 2: Virologically Suppressed Children (6 to < 12 Years of Age and Weighing ≥ 25 kg)

At Week 24, 100% (23/23) of patients in Cohort 2 remained suppressed (HIV-1 RNA < 50 copies/mL) after switching to FTC+TAF (10 mg) given with EVG+COBI as a FDC tablet (GENVOYA). The mean change from baseline in CD4+ cell count at Week 24 was -150 cells/mm^3. No emergent resistance was detected through Week 24.

Among the patients in Cohort 2 who had both baseline and Week 24 measurements, BMD by DXA was assessed in 21 patients for spine and 23 patients for TBLH. Mean (SD) BMD increased from baseline to Week 24, +2.9% (4.9%) at the lumbar spine and +1.7% (2.5%) for TBLH.

HIV-1 PrEP

The efficacy and safety of DESCOVY to reduce the risk of acquiring HIV-1 infection were evaluated in a randomized, double-blind multinational study (DISCOVER) comparing once daily DESCOVY (FTC/TAF 200 mg/25 mg; N = 2670) to TRUVADA (FTC/TDF 200 mg/300 mg; N=2665) in HIV-seronegative men (N=5262) or transgender women (N=73) who have sex with men and are at risk of HIV-1 infection. Evidence of risk behavior at entry into the study included at least one of the following: two or more unique condomless anal sex partners in the past 12 weeks or a diagnosis of rectal gonorrhea/chlamydia or syphilis in the past 24 weeks. The median age of participants was 34 years (range, 18-76); 84% were White, 9% Black, 4% Asian, and 24% Hispanic/Latino. At baseline, 905 participants (17%) reported receiving TRUVADA for PrEP, of which 465 were randomized to DESCOVY.

At weeks 4, 12, and every 12 weeks thereafter, all participants received local standard of care HIV-1 prevention services, including HIV-1 testing, evaluation of adherence, safety evaluations, risk-reduction counseling, condoms, management of sexually transmitted infections, and assessment of sexual behavior.

Study participants maintained a high risk of sexual HIV-1 acquisition, with high rates of rectal gonorrhea (DESCOVY, 22/100 person-years; TRUVADA, 21/100 person-years), rectal

chlamydia (28/100 person-years in both treatment groups), and syphilis (10/100 person-years in both treatment groups) during the study.

The primary outcome was the incidence of documented HIV-1 infection per 100 person-years in participants randomized to DESCOVY and TRUVADA (with a minimum follow-up of 48 weeks and at least 50% of participants having 96 weeks of follow-up). DESCOVY was non-inferior to TRUVADA in reducing the risk of acquiring HIV-1 infection (Table 18). The results were similar across the subgroups of age, race, baseline TRUVADA for PrEP use, and gender identity.

Table 18. HIV-1 Infection Results in DISCOVER Study – Full Analysis Set

	DESCOVY (N=2670)	**TRUVADA (N=2665)**	
	4370 person-years	**4386 person-years**	**Rate Ratio (95% CI)**
HIV-1 infections n (%)	7 (0.26%)	15 (0.56%)	
Rate of HIV-1 infections per 100 person-years	0.16	0.34	0.468 (0.19, 1.15[a])

CI = Confidence interval.
a. Noninferiority margin: 1.62

Of the 22 participants with diagnosed HIV-1 infections, 5 had suspected baseline infection prior to study entry (DESCOVY, 1; TRUVADA, 4). In a PK case-control substudy of intracellular study drug levels in RBC and estimated number of daily doses as measured by dried blood spot (DBS) testing, median intracellular TFV-DP concentrations were substantially lower in participants infected with HIV-1 at the time of diagnosis compared with uninfected matched control participants. The results showed a positive correlation between the efficacy of PrEP and adherence to daily dosing in both arms.

Bone Mineral Density

In the DISCOVER study, changes in BMD from baseline were assessed by DXA. Observed changes at Week 48 are summarized in Table 19.

Table 19. Measures of Bone Mineral Density in DISCOVER Study (Week 48)

	DESCOVY	**TRUVADA**	**Treatment Difference**
Hip DXA Analysis	**N=158**	**N=158**	
Mean Percent Change in BMD	0.2%	−1.0%	1.12% p<0.001
Participants with Categorical Change:			
≥3% Decrease in BMD	4%	18%	-
≥3% Increase in BMD	9%	6%	
Participants with No Decrease (≥ zero % increase) in BMD	50%	34%	-

Lumbar Spine DXA Analysis	N=159	N=160	
Mean Percent Change in BMD	0.5%	−1.1%	1.61% p<0.001
Participants with Categorical Change: ≥3% Decrease in BMD ≥3% Increase in BMD	 10% 17%	 27% 9%	-
Participants with No Decrease (≥ zero % increase) in BMD	61%	33%	-

Changes in Renal Laboratory Tests

In the DISCOVER Study, tests were performed to compare the effect of TAF to that of TDF on renal laboratory parameters. As shown in Table 20, statistically significant differences were observed between treatment groups for changes in glomerular and proximal tubular renal function that favored TAF.

Table 20. Change from Baseline in Renal Laboratory Tests in DISCOVER Study (Week 48)

	DESCOVY N=2694	TRUVADA N=2693	Treatment Difference
Serum Creatinine (mmol/L)[a]	−0.001 ± 0.009	0.001 ± 0.010	p<0.001
estimated CrCl by Cockcroft-Gault method (mL/min)[a]	2.0 ± 15.84	−2.0 ± 15.79	p<0.001
Urine Retinol Binding Protein to Creatinine Ratio[b]	0.2%	19.9%	p<0.001
Urine Beta-2-Microglobulin to Creatinine Ratio[b]	−10.7%	15.3%	p<0.001

a. Mean change ± SD
b. Median percent change

Participants with renal laboratory data at Week 48 who were receiving TRUVADA for PrEP at baseline and were randomized to DESCOVY (N = 433) had a mean (±SD) increase in estimated CrCl by Cockcroft-Gault method of +3.8 mL/min (14.90), whereas those who were randomized to TRUVADA (N = 400) had a mean decrease in estimated CrCl of −0.6 mL/min (15.98) (p < 0.001).

Changes in Lipid Laboratory Tests

Minimal declines or no change from baseline was observed in the DESCOVY treatment group for mean fasting total cholesterol, direct LDL, and HDL, whereas modest declines were observed in the TRUVADA treatment group at Week 48 (p < 0.002 for the difference between treatment groups for fasting total cholesterol, direct LDL, and HDL). There was no significant change from baseline in the total cholesterol to HDL ratio (DESCOVY, 0.1 [−0.2, 0.5] and TRUVADA 0.1 [−0.3, 0.5]) at Week 48, with no differences between DESCOVY and TRUVADA.

14.2 Comparative Bioavailability Studies

Study GS-US-311-1472 was a randomized, open-label, single-dose, 2-way crossover study conducted in 100 healthy male and female subjects to compare the bioavailabilities of FTC and TAF from a single dose of DESCOVY (F/TAF) 200 mg/10 mg fixed dose combination tablet administered concomitantly with COBI 150 mg tablet and EVG 150 mg tablet, and a single dose of GENVOYA (E/C/F/TAF) 150/150/200/10 mg fixed dose combination tablet under moderate calorie, moderate fat fed conditions. A summary of the data is provided in Table 21.

Table 21. Summary Table of the Comparative Bioavailability Data for Study GS-US-311-1472

Emtricitabine (FTC)
(1 x 200 mg FTC/10 mg TAF hemifumarate + 150 mg EVG + 150 mg COBI or 1 x 150 mg EVG/150 mg COBI/200 mg FTC/ 10 mg TAF hemifumarate)
From measured data
Geometric Least Squares Mean
Arithmetic Mean (CV %)

Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng.h/mL)	9975.14 10159.2 (17.2)	9991.25 10086.8 (15.9)	99.84	98.41 – 101.29
AUC_{Inf} (ng.h/mL)	10259.33 10535.1 (27.0)	10191.26 10294.4 (15.8)	100.67	98.24 – 103.16
C_{max} (ng/mL)	1629.68 1660.8 (20.6)	1636.72 1662.6 (19.1)	99.57	96.78 – 102.44
T_{max}§ (h)	2.02 (1.00 - 5.00)	2.00 (0.75 - 5.00)		
$T_{1/2}$ψ (h)	18.11 (46.8)	19.08 (57.0)		

Tenofovir alafenamide (TAF)
(1 x 200 mg FTC /10 mg TAF hemifumarate + 150 mg EVG + 150 mg COBI or 1 x 150 mg EVG /150 mg COBI /200 mg FTC / 10 mg TAF hemifumarate)
From measured data
Geometric Least Squares Mean
Arithmetic Mean (CV %)

Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng.h/mL)	317.27 335.7 (34.0)	323.89 342.5 (33.8 34.0)	97.96	94.69 – 101.34
AUC_{Inf} (ng.h/mL)	330.89 352.4 (30.8)	336.49 356.7 (33.2)	98.34	94.81 – 101.99
C_{max} (ng/mL)	267.18 299.4 (49.2)	275.85 311.7 (48.4)	96.86	89.36 – 104.99
T_{max}§ (h)	1.50 (0.50 – 4.00)	1.02 (0.48 – 4.00)		
$T_{1/2}$ψ (h)	0.41 (39.5)	0.43 (35.4)		

* DESCOVY (200 mg FTC/10 mg TAF hemifumarate fixed dose combination tablet) + 150 mg COBI tablet + 150 mg EVG tablet administered under moderate fat, moderate calorie fed conditions.
† GENVOYA (EVG/COBI/FTC/TAF hemifumarate) 150 mg/150 mg/200 mg/10 mg fixed dose combination tablet administered under moderate fat, moderate calorie conditions.
§ Expressed as the median (range) only.
ψ Expressed as the arithmetic mean (CV%) only.

Study GS-US-311-1473 was a randomized, open-label, single-dose, 2-way crossover study conducted in 116 healthy male and female subjects to compare the bioavailabilities of FTC and TAF from a single dose of DESCOVY (F/TAF) 200/25 mg FDC tablet and a single dose of GENVOYA (E/C/F/TAF) 150/150/200/10 mg FDC tablet under moderate calorie, moderate fat fed conditions. A summary of the data is provided in Table 22.

Table 22. Summary Table of the Comparative Bioavailability Data for Study GS-US-311-1473

Emtricitabine (FTC)
(1 x 200 mg FTC/25 mg TAF hemifumarate or
1 x 150 mg EVG/150 mg COBI/200 mg FTC/10 mg TAF hemifumarate)
From measured data
Geometric Least Squares Mean
Arithmetic Mean (CV %)

Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng.h/mL)	9263.96 9423.9 (19.3)	10291.82 10475.3 (19.7)	90.01	88.88 – 91.16
AUC_{Inf} (ng.h/mL)	9490.42 9654.6 (19.3)	10521.69 10706.6 (19.6)	90.20	89.06 – 91.35
C_{max} (ng/mL)	1528.45 1577.4 (26.8)	1571.43 1601.7 (19.6)	97.26	94.57 – 100.03
T_{max}§ (h)	2.00 (1.00 - 5.00)	3.00 (1.00 - 5.00)		
$T_{1/2}$ψ (h)	22.31 (52.0)	21.87 (55.6)		

Tenofovir alafenamide (TAF)
(1 x 200 mg FTC/25 mg TAF hemifumarate or
1 x 150 mg EVG/150 mg COBI/200 mg FTC/10 mg TAF hemifumarate)
From measured data
Geometric Least Squares Mean
Arithmetic Mean (CV %)

Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng.h/mL)	344.12 374.0 (43.4)	343.03 369.3 (40.6)	100.32	96.48 - 104.31
AUC_{Inf} (ng.h/mL)	357.37 396.4 (42.6)	362.68 389.5 (39.3)	98.54	94.61 - 102.62
C_{max} (ng/mL)	242.52 280.5 (62.9)	234.03 267.8 (59.8)	103.63	95.46 - 112.49
T_{max}§ (h)	1.50 (0.50 - 4.00)	1.50 (0.50 - 3.00)		
$T_{1/2}$ψ (h)	0.47 (27.1)	0.48 (38.5)		

* DESCOVY (200 mg FTC/25 mg TAF hemifumarate) fixed dose combination tablet administered under moderate fat, moderate calorie fed conditions.
† GENVOYA (EVG/COBI/FTC/TAF hemifumarate) 150 mg/150 mg/200 mg/10 mg fixed dose combination tablet administered under moderate fat, moderate calorie conditions.
§ Expressed as the median (range) only.
ψ Expressed as the arithmetic mean (CV%) only.

15 MICROBIOLOGY

Antiviral Activity

Emtricitabine: The antiviral activity of FTC against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and primary peripheral blood mononuclear cells. The 50% effective concentration (EC_{50}) values for FTC were in the range of 0.0013 to 0.64 µM. Emtricitabine displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, and G (EC_{50} values ranged from 0.007 to 0.075 µM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 0.007 to 1.5 µM).

In two-drug combination studies of FTC with NRTIs (abacavir, didanosine, lamivudine, stavudine, tenofovir, and zidovudine), non-nucleoside reverse transcriptase inhibitors (NNRTIs) (delavirdine, efavirenz, nevirapine, and rilpivirine), protease inhibitors (PIs) (amprenavir, nelfinavir, ritonavir, and saquinavir), and the integrase strand transfer inhibitor EVG, additive to synergistic effects were observed. 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 monocyte/macrophage cells and CD4-T lymphocytes. The EC_{50} values for TAF were in the range of 2.0 to 14.7 nM. Tenofovir alafenamide 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). Overall, TAF showed potent antiviral activity against the HIV-1 groups/subtypes evaluated.

In a study of TAF with a broad panel of representatives from the major classes of approved anti-HIV agents (NRTIs, NNRTIs, integrase strand transfer inhibitors (INSTIs), and PIs), additive to synergistic effects were observed. No antagonism was observed for these combinations.

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

Emtricitabine and Tenofovir Alafenamide: The prophylactic activity of the combination of daily oral FTC and TAF was evaluated in a controlled study of macaques administered once weekly inoculations of intra-rectal SIV/HIV-1 chimeric virus (SHIV) for up to 19 weeks (n = 6) and a controlled study of pigtailed macaques administered once weekly inoculations of intravaginal SHIV for up to 16 weeks (n = 6). All 6 macaques and 5 of 6 pigtail macaques that received FTC and TAF at doses resulting in PBMC exposures consistent with those achieved in humans administered a dose of FTC/TAF 200/25 mg remained SHIV antibody seronegative and SHIV RNA negative during all viral challenges.

Resistance

In Cell Culture

Emtricitabine*:* HIV-1 isolates with reduced susceptibility to FTC have been selected in cell culture. Reduced susceptibility to FTC was associated with M184V/I substitutions in HIV-1 RT.

Tenofovir Alafenamide*:* HIV-1 isolates with reduced susceptibility to TAF have been selected in cell culture. HIV-1 isolates selected by TAF expressed a K65R mutation in HIV-1 RT; in addition, a K70E mutation in HIV-1 RT has been transiently observed. HIV-1 isolates with the K65R substitution have low-level reduced susceptibility to abacavir, FTC, TAF, tenofovir, and

lamivudine. *In vitro* drug resistance selection studies with TAF have shown no development of resistance increases above 2.5-fold after 6 months in culture.

In Clinical Trials

In HIV-1 Infected Treatment-Naïve Patients: In a pooled analysis of antiretroviral-naive patients receiving FTC+TAF given with EVG+COBI as a FDC tablet in Phase 3 Studies, 104 and 111, genotyping was performed on plasma HIV-1 isolates from all patients with HIV-1 RNA ≥ 400 copies/mL at confirmed virologic failure, at Week 144, or at time of early study drug discontinuation. As of Week 144, the development of one or more primary EVG, FTC, or TAF resistance-associated with resistance was observed in 12 of 22 patients with evaluable genotypic data from paired baseline and FTC+TAF given with EVG+COBI as a FDC tablet treatment-failure isolates (12 of 866 patients [1.4%]) compared with 12 of 20 treatment-failure isolates from patients with evaluable genotypic data in the FTC+TDF given with EVG+COBI as a FDC tablet group (12 of 867 patients [1.4%]). Of the 12 patients with resistance development in the FTC+TAF given with EVG+COBI as a FDC tablet group, the mutations that emerged against FTC and/or TAF were M184V/I (N=11) and K65R/N (N=2) in reverse transcriptase and T66T/A/I/V (N=2), E92Q (N=4), Q148Q/R (N=1), and N155H (N=2) in integrase. Of the 12 patients with resistance development in the FTC+TDF given with EVG+COBI as a FDC tablet group, the mutations that emerged against FTC and/or TDF were M184V/I (N=9) and K65R/N (N=4), and L210W (N=1) in reverse transcriptase and E92Q/V (N=4), Q148R (N=2), and N155H/S (N=3) in integrase.

In phenotypic analyses of patients in the final resistance analysis population, 8 of 22 patients (36%) receiving FTC+TAF given with EVG+COBI as a FDC tablet had HIV-1 isolates with reduced susceptibility to FTC compared with 7 of 20 patients with data (35%) receiving FTC+TDF given with EVG+COBI as a FDC tablet. One patient receiving FTC+TAF given with EVG+COBI as a FDC tablet (1 of 22 [4.5%]) and 2 patients receiving FTC+TDF given with EVG+COBI as a FDC tablet (2 of 20 with data, [10%]) had reduced susceptibility to tenofovir. Finally, 7 of 22 patients (32%) had reduced susceptibility to EVG in the FTC+TAF given with EVG+COBI as a FDC tablet group compared with 7 of 20 patients (35%) in the FTC+TDF given with EVG+COBI as a FDC tablet group.

In HIV-1 Infected Virologically Suppressed Patients: In a Week 96 analysis of virologically suppressed patients who changed their background regimen from FTC+TDF to DESCOVY while maintaining their third antiretroviral agent (GS-US-311-1089), 1 of 4 patients analyzed in the DESCOVY+third agent group (1 of 333 [0.3%]) developed M184V in reverse transcriptase in the first 48 weeks with reduced susceptibility to FTC. In the FTC/TDF+third agent group, 0 of 3 patients analyzed (0 of 333 [0%]) developed resistance to any components of their regimen.

In HIV-1 Uninfected Adults at Risk for HIV-1 Infection: In the DISCOVER study of HIV-1 uninfected adult men and transgender women who have sex with men and who are at risk of HIV-1 infection receiving DESCOVY or TRUVADA for HIV-1 PrEP, genotyping was performed on participants found to be infected during the study who had HIV-1 RNA ≥ 400 copies/mL (6 of 7 participants receiving DESCOVY and 13 of 15 participants receiving TRUVADA). With approximately 4370 and 4386 person-years of follow-up (87 weeks, median) in the DESCOVY and TRUVADA groups, respectively, the development of resistance-associated mutations was observed in 0 of 6 HIV-1 infected participants in the DESCOVY group compared to 4 of 13 HIV-1 infected participants in the TRUVADA group. The 4 HIV-1 infected participants in the TRUVADA group had suspected baseline HIV-1 infections, and the study drug mutation that emerged in these participants was M184V.

Cross Resistance

No cross-resistance has been demonstrated for elvitegravir-resistant HIV-1 isolates and FTC or tenofovir, or for FTC- or tenofovir-resistant isolates and EVG.

Emtricitabine: Cross-resistance has been observed among NRTIs. Emtricitabine-resistant isolates harboring an M184V/I substitution in HIV-1 RT were cross-resistant to lamivudine. HIV-1 isolates containing the K65R RT substitution, selected *in vivo* by abacavir, didanosine, and tenofovir, demonstrated reduced susceptibility to inhibition by FTC.

Tenofovir Alafenamide: The K65R and K70E mutations result in reduced susceptibility to abacavir, didanosine, lamivudine, FTC, and tenofovir, but retain sensitivity to zidovudine. Multinucleoside resistant HIV-1 with a T69S double insertion mutation or with a Q151M mutation complex including K65R showed reduced susceptibility to TAF.

HIV-1 containing the K103N or Y181C mutations associated with resistance to NNRTIs were susceptible to TAF. HIV-1 containing mutations associated with resistance to PIs, such as M46I, I54V, V82F/T, and L90M were susceptible to TAF.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

No toxicology studies have been conducted with DESCOVY tablets. The toxicology information is based on studies conducted with FTC or TAF as individual agents.

Tenofovir Alafenamide

The general toxicology profile of TAF has been studied in mice, rats and dogs.

The target organs were the kidney and bone. The effects on the kidneys included cortical tubular basophilia and tubular karyomegaly in both rats and dogs and additionally cortical tubular degeneration/regeneration in dogs. These effects did not appear to meaningfully affect renal function except for possibly related reduction in serum calcitriol (1,25-dihydroxyvitamin D3) that may be implicated in the bone effects (see below). The TAF-related effects on the bone included decreases in bone mineral density and mineral content observed in both rats and dogs. In the 9-month dog study, animals dosed at 18/12 mg/kg/day (approximately 47 times the clinical exposure based on AUC) failed to mature skeletally. The NOAEL in the rat and dog was 25 mg/kg/day (approximately 13 times clinical tenofovir exposure based on AUC) and 2 mg/kg/day (approximately 4 times the clinical tenofovir exposure based on AUC), respectively. These effects were partially reversible upon treatment discontinuation. Electrocardiographic effects occurred in the 9-month dog study and included prolongation of PR intervals at ≥6 mg/kg (approximately 15 times the clinical exposure based on AUC) and reduction in heart rate with an associated QT prolongation at 18/12 mg/kg (approximately 47 times the clinical exposure based on AUC); the heart rate changes were reversible following a three-month recovery period. The NOAEL was 2 mg/kg (approximately 4 times the clinical tenofovir exposure based on AUC). These effects might have been due to a reduction in triiodothyronine (T3) levels.

Carcinogenicity

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/kg/day (23 times the human systemic exposure at the therapeutic dose of 200 mg/day) or in rats at doses up to 600 mg/kg/day (28 times the human systemic exposure at the therapeutic dose).

Tenofovir Alafenamide: Because there is a lower tenofovir exposure in rats and mice after TAF administration compared to TDF, 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 300 mg therapeutic dose of TDF for HIV-1 infection. At the high dose in female mice, liver adenomas were increased at exposures 10 times that in humans. In rats, the study was negative for carcinogenic findings at exposures up to 4 times that observed in humans at the therapeutic dose.

Genotoxicity

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

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

Reproductive and Developmental Toxicology

Emtricitabine: The incidence of fetal variations and malformations was not increased in embryo-fetal toxicity studies performed with FTC in mice at exposures (AUC) approximately 60 times higher and in rabbits at approximately 120 times higher than human exposures at the recommended daily dose.

Emtricitabine did not affect fertility in male rats at approximately 140-fold or in male and female mice at approximately 60 fold higher exposures (AUC) than in humans given the recommended 200 mg daily dose. Fertility was normal in the offspring of mice exposed daily from before birth (in utero) through sexual maturity at daily exposures (AUC) of approximately 60-fold higher than human exposures at the recommended 200 mg daily dose.

Tenofovir Alafenamide: There were no effects on fertility, mating performance or early embryonic development when TAF was administered to male rats at a dose equivalent to 155 times 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 seven of gestation.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrDESCOVY®

emtricitabine/tenofovir alafenamide* tablets
*** as tenofovir alafenamide hemifumarate**

Read this carefully before you start taking **Descovy** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Descovy**.

Serious Warnings and Precautions

- **"Flare-ups" of Hepatitis B Virus infection, in which the disease suddenly returns in a worse way than before, can occur if you have hepatitis B and stop taking Descovy. Do not stop taking Descovy without your doctor's advice. If you stop taking Descovy, tell your doctor immediately about any new, unusual or worsening symptoms that you notice after stopping treatment. After you stop taking Descovy, your doctor will still need to check your health and take blood tests to check your liver. Descovy is not approved for the treatment of hepatitis B virus infection.**
- **Descovy should only be used for pre-exposure prophylaxis (PrEP) if you are HIV-negative before and during treatment. Discuss with your healthcare professional if you have had a recent flu-like illness. Your healthcare professional will run tests to confirm that you are HIV-negative before and during Descovy treatment.**

What is Descovy used for?

Descovy is used to:

- treat HIV infection in adults and children who weigh at least 25 kg (55 lbs)
- help reduce the risk of getting HIV-1 infection in adults and adolescents who weigh at least 35 kg (77 lbs). This is called pre-exposure prophylaxis or PrEP.
    - **Descovy** for PrEP is not for use in people born female (assigned female at birth) who are at risk of getting HIV-1 infection from vaginal sex, because its effectiveness has not been studied.

Descovy is for people who do not have an HIV virus that is resistant to **Descovy.**

Descovy has not been studied in children with HIV-1 infection weighing less than 25 kg (55 lbs) or HIV-1 uninfected children weighing less than 35 kg.

For more information on the DESCOVY HIV-1 PrEP Education Program (Important Safety Information for People Taking DESCOVY for PrEP), log onto www.descovyeducation.ca.

How does Descovy work?

Using Descovy to treat HIV-1 Infection:

Descovy lowers the amount of HIV in the blood (viral load).

HIV infection destroys CD4+ (T) cells. These cells are important to help the immune system fight infections. After a large number of T cells are destroyed, acquired immune deficiency syndrome (AIDS) develops.

Descovy may help increase the count of CD4+ (T) cells. Lowering the amount of HIV in the blood and increasing the CD4+ (T) cells lower the chance of getting infections that happen when your immune system is weak.

Descovy does not cure HIV infection or AIDS. The long-term effects of **Descovy** are not known. People taking **Descovy** may still get infections or other conditions that happen with HIV infection. Some of these conditions are pneumonia and *Mycobacterium avium* complex (MAC) infections. **It is very important that you see your doctor on a regular basis while taking Descovy**.

Using Descovy for HIV-1 PrEP:

Descovy works better to reduce the risk of getting HIV-1 when the medicines are in your bloodstream before you are exposed to HIV-1. Continue to practice safe sex. Use condoms to lower the chance of sexual contact with body fluids such as semen, vaginal secretions, or blood. Do not re-use or share needles.

For more information on the DESCOVY HIV-1 PrEP Education Program (Important Safety Information for People Taking DESCOVY for PrEP), log onto www.descovyeducation.ca.

What are the ingredients in Descovy?

Medicinal ingredients: emtricitabine and tenofovir alafenamide*
(* as tenofovir alafenamide hemifumarate)

Non-medicinal ingredients: croscarmellose sodium, magnesium stearate and microcrystalline cellulose. The grey tablets are film-coated with a coating material containing iron oxide black, polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide. The blue tablets are film-coated with a coating material containing indigo carmine aluminum lake, polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

Descovy comes in the following dosage forms:

Descovy is available as tablets.

Descovy is available as rectangular-shaped, film-coated tablets containing 200 mg of emtricitabine and either 10 mg or 25 mg of tenofovir alafenamide (grey tablets and blue tablets, respectively). Each tablet is debossed with “GSI” on one side and either “210” (200/10 mg strength) or “225” (200/25 mg strength) on the other side. Each bottle contains 30 tablets and a silica gel desiccant and is closed with a child-resistant closure.

Do not use Descovy if:

- you are taking any medication that is listed in this pamphlet under "**Drugs that should not be taken with Descovy**"
- you are allergic to **Descovy** or any of its ingredients (see: **What are the ingredients in Descovy?**).

Do not take Descovy for HIV-1 PrEP if:

- **you already have HIV-1 infection**. If you are HIV-1 positive, you need to take other HIV-1 medicines with **Descovy** to treat HIV-1. **Descovy** by itself is not a complete treatment for HIV-1.
- **you do not know your HIV-1 infection status.** You may already be HIV-1 positive. You need to take other HIV-1 medicines with **Descovy** to treat HIV-1 infection.

Descovy can only help reduce your risk of getting HIV-1 infection before you are infected.

To help avoid side effects and ensure proper use, talk to your doctor before you take Descovy. Talk about any health conditions or problems you may have, including if you:

- Have hepatitis B virus (HBV) infection and take **Descovy**. Your HBV infection may get worse (flare-up) and symptoms worsen if you stop taking **Descovy** (see **Serious Warnings and Precautions** box and **Serious Side Effects** table).
- Have a history of pancreatitis (swelling of the pancreas). If you develop symptoms of pancreatitis, such as nausea, vomiting and severe pain in the abdomen and/or back, contact your doctor.
- Have kidney problems. Kidney problems, including kidney failure, have occurred in patients taking tenofovir. If you have kidney problems and are taking **Descovy** along with certain medicines such as non-steroidal anti inflammatory drugs, your kidney problems could get worse.
- Have a history of bone fracture, bone loss or osteoporosis. Bone loss has happened in some people who took **Descovy**.
- Have lactic acidosis (high levels of acid in the blood). See the Serious Side Effects table for symptoms and contact your doctor right away if you get these symptoms.
- Have severe liver problems including enlarged or fatty liver. See the **Serious Side Effects** table for symptoms and contact your doctor right away if you get these symptoms.

Do not run out of **Descovy**. Refill your prescription or talk to your doctor before your **Descovy** is all gone.

Do not stop taking **Descovy** without first talking to your doctor.

If you have HBV infection and you stop taking **Descovy**, your doctor will need to check your health often and do blood tests regularly for several months to check your HBV infection. Tell your doctor about any new or unusual symptoms you may have after you stop taking **Descovy**.

Other warnings you should know about:

If you are pregnant or plan to become pregnant:

It is not known if **Descovy** can harm your unborn child. You and your doctor will decide if you should take **Descovy**.

Pregnancy Registry: There is a pregnancy registry for women who take antiviral medicines during pregnancy. This registry collects information about your health and your baby's health. If you become pregnant while taking **Descovy**, talk with your doctor about taking part in this registry.

If you are breastfeeding or plan to breastfeed:

Do not breastfeed if you have HIV because of the chance of passing the HIV virus to your baby. One of the ingredients of **Descovy**, emtricitabine, can be passed to your baby in your breast milk and may cause harm to your baby. It is not known if the other components can be passed to your baby in breast milk. If you are a woman who has or will have a baby, talk with your doctor about the best way to feed your baby.

Blood Sugar and Fat Levels

Your blood sugar levels (glucose) or level of fats (lipids) in your blood may increase with HIV treatment. Your doctor may order blood tests for you.

Before taking Descovy for HIV-1 PrEP:

- You must be HIV-1 negative to start **Descovy**. You must get tested to make sure that you do not already have HIV-1 infection.
- Do not take **Descovy** for HIV-1 PrEP unless you are confirmed to be HIV-1 negative.
- Many HIV-1 tests can fail to pick up that you are HIV-1 infected if you have just recently become infected with HIV-1. If you have flu-like symptoms, you could have recently become infected with HIV-1. Tell your healthcare provider if you had a flu-like illness within the last month before starting **Descovy** or at any time while taking **Descovy**. Symptoms of new HIV-1 infection include: tiredness, fever, joint or muscle aches, headache, sore throat, vomiting or diarrhea, rash, night sweats or enlarged lymph nodes in the neck or groin.

For more information on the DESCOVY HIV-1 PrEP Education Program (Important Safety Information for People Taking DESCOVY for PrEP), log onto www.descovyeducation.ca.

While you are taking Descovy for HIV-1 PrEP:

- **You must stay HIV-1 negative to keep taking Descovy for HIV-1 PrEP. It is important that you get tested for HIV-1 at least every 3 months or as recommended by your healthcare provider while taking Descovy.**
- If you do become HIV-1 positive, you need more medicine than **Descovy** alone to treat HIV-1. **Descovy** by itself is not a complete treatment for HIV-1.

For more information on the DESCOVY HIV-1 PrEP Education Program (Important Safety Information for People Taking DESCOVY for PrEP), log onto www.descovyeducation.ca.

If you have HIV-1 and take only Descovy, over time your HIV-1 may become harder to treat.

Avoid doing things that can increase your risk of getting HIV infection or other STIs or spreading HIV infection to other people:

- Do not re-use or share needles or other injection equipment.
- Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.
- Do not have any kind of sex without protection. Always practice safer sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vagina secretions, or blood.

Ask your healthcare professional if you have any questions on how to prevent getting HIV infection or other STIs or spreading HIV infection to other people.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Drugs that should not be taken with Descovy:

- Any other medicines that contain tenofovir alafenamide (BIKTARVY®, GENVOYA®, ODEFSEY®, Symtuza™, VEMLIDY®).
- Any other medicines that contain tenofovir disoproxil fumarate (ATRIPLA®, COMPLERA®, STRIBILD®, TRUVADA®, VIREAD®).
- Any other medicines that contain emtricitabine or lamivudine (ATRIPLA, BIKTARVY, COMPLERA, EMTRIVA®, GENVOYA, ODEFSEY, STRIBILD, Symtuza, TRUVADA; 3TC, Combivir®, Heptovir®, Kivexa®, Triumeq®, Trizivir®).
- adefovir (HEPSERA®).

Drugs that interact with Descovy and when the dose of Descovy or the dose of the other drug should be changed or further instruction from your doctor are needed:

Drug Class	Medicinal Ingredient (Brand Name)
Anticonvulsants	carbamazepine (Carbatrol®, Epitol®, Tegretol®), oxcarbazepine (Trileptal®), phenobarbital and phenytoin (Dilantin®)
Antifungals	ketoconazole (Nizoral®), itraconazole (Sporanox®)
Antimycobacterials	rifampin (Rifater®, Rifamate®, Rofact®, Rifadin®), rifapentine* (Priftin®)
Antiretrovirals	tipranavir (Aptivus®)
Herbal products	*Hypericum perforatum* (St. John's wort)

These are not all the medicines that may cause problems if you take Descovy. Be sure to tell your doctor about all the medicines you take.

Keep a complete list of all the prescription, nonprescription and herbal medicines that you are taking, how much you take and how often you take them. Make a new list when medicines or herbal medicines are added or stopped, or if the dose changes. Give copies of this list to all your doctors and pharmacists **every** time you visit them or fill a prescription. This will give your

doctor a complete picture of the medicines you use. Then he or she can decide the best approach for the situation.

How to take Descovy:

Stay under a doctor's care when taking **Descovy**. Do not change your treatment or stop treatment without first talking with your doctor.

When your **Descovy** supply starts to run low, get more from your doctor or pharmacy. If you are taking **Descovy** for HIV-1 treatment, this is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short time. If **Descovy** is not taken on a regular basis, as prescribed, HIV may become harder to treat.

If you are on dialysis, take your daily dose of **Descovy** following dialysis.

Only take medicine that has been prescribed specifically for you.

Do not give **Descovy** to others or take medicine prescribed for someone else.

Do not use if seal over bottle opening is broken or missing.

If you take Descovy for HIV-1 PrEP:

- you must also use other methods to reduce your risk of getting other STIs.
- take **Descovy** every day, not just when you think you have been exposed to HIV-1.

Usual dose:

For treatment of HIV-1 infection

Adults and children weighing 25 kg or more:

- The usual dose of **Descovy** is one tablet orally (by mouth) once a day.
- Try to take the tablet at the same time each day. Swallow with plenty of water.
- Take **Descovy** with or without food.

For prevention of HIV-1 infection (PrEP)

Adults and children weighing 35 kg or more:

- The dose of **Descovy** is one 200/25 mg tablet orally (by mouth) once a day.
- Try to take the tablet at the same time each day. Swallow with plenty of water.
- Take **Descovy** with or without food.

Overdose:

If you think you have taken too much **Descovy**, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

It is important that you do not miss any doses. If you miss a dose of **Descovy** and it is less than 18 hours from the time you usually take **Descovy**, then take the dose. If more than 18 hours has passed from the time you usually take **Descovy**, then wait until the next scheduled

daily dose. **Do not** take more than 1 dose of **Descovy** in a day. **Do not** take 2 doses at the same time. Call your doctor or pharmacist if you are not sure what to do.

If you are taking **Descovy** for HIV-1 PrEP, missing doses increases your risk of getting HIV-1 infection.

What are possible side effects from using Descovy?

These are not all the possible side effects you may feel when taking **Descovy**. If you get any side effects not listed here, contact your doctor. Please also see **Serious Warnings and Precautions** box.

The most common side effects of **Descovy** are:

- Nausea.
- Diarrhea.
- Headache.
- Fatigue.

Additional side effects may include:

- Gas.
- Swelling in the face, lips, tongue or throat (angioedema).
- Hives (urticaria).

Changes in your immune system (Immune Reconstitution Inflammatory Syndrome) can happen when you start taking HIV-1 medicines for HIV-1 treatment. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time.

Autoimmune disorders (when the immune system attacks healthy body tissue), may also occur after you start taking medicines for HIV infection. Examples of this include: Grave's disease (which affects the thyroid gland), Guillain-Barré syndrome (which affects the nervous system), polymyositis (which affects the muscles), or autoimmune hepatitis (which affects the liver). Autoimmune disorders may occur many months after the start of treatment. Look for any other symptoms such as:

- high temperature (fever), redness, rash or swelling
- joint or muscle pain
- numbness or weakness beginning in the hands and feet and moving up towards the trunk of the body
- palpitations (chest pain) or rapid heart rate

If you notice these or any symptoms of inflammation or infection, tell your doctor immediately.

Bone problems can happen in some people who take **Descovy**. Bone problems may include bone pain, softening or thinning (which may lead to fractures). Your doctor may need to do tests to check your bones.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
RARE			
Effect: Lactic acidosis **Symptoms:** feeling very weak or tired, unusual muscle pain, stomach pain with nausea and vomiting, feeling unusually cold especially in arms and legs, feeling dizzy or lightheaded, fast or irregular heartbeat, fast and deep breathing		✓	
VERY RARE			
Effect: Flare-ups of hepatitis B virus infection following drug discontinuation **Symptoms:** jaundice (skin or the white part of eyes turns yellow), urine turns dark, bowel movements (stools) turn light in color, loss of appetite for several days or longer, feeling sick to your stomach (nausea), lower stomach pain		✓	
Effect: Hepatotoxicity (severe liver problems) with hepatomegaly (liver enlargement) and steatosis (fat in the liver) **Symptoms:** jaundice (skin or the white part of eyes turns yellow), urine turns dark, bowel movements (stools) turn light in color, loss of appetite for several days or longer, feeling sick to your stomach (nausea), lower stomach pain		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- **Descovy** should be stored below 30°C (86°F). It should remain stable until the expiration date printed on the label.
- Keep **Descovy** in its original container and keep the container tightly closed.
- Keep out of reach and sight of children.

If you want more information about Descovy:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (www.gilead.ca); or by calling 1-866-207-4267.

This leaflet was prepared by Gilead Sciences Canada, Inc.

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Marketing Status in United States

Drug Databases (https://www.fda.gov/Drugs/InformationOnDrugs/)

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Home (index.cfm?resetfields=1) | Back to Search Results

Product Details for NDA 208215

Collapse All

DESCOVY (EMTRICITABINE; TENOFOVIR ALAFENAMIDE FUMARATE) 120MG;EQ 15MG BASE
Marketing Status: Prescription

Active Ingredient: EMTRICITABINE; TENOFOVIR ALAFENAMIDE FUMARATE
Proprietary Name: DESCOVY
Dosage Form; Route of Administration: TABLET; ORAL
Strength: 120MG;EQ 15MG BASE
Reference Listed Drug: Yes
Reference Standard: No
TE Code:
Application Number: N208215
Product Number: 002
Approval Date: Jan 7, 2022
Applicant Holder Full Name: GILEAD SCIENCES INC
Marketing Status: Prescription
Patent and Exclusivity Information (patent_info.cfm?Product_No=002&Appl_No=208215&Appl_type=N)

DESCOVY (EMTRICITABINE; TENOFOVIR ALAFENAMIDE FUMARATE) 200MG;EQ 25MG BASE
Marketing Status: Prescription

Active Ingredient: EMTRICITABINE; TENOFOVIR ALAFENAMIDE FUMARATE
Proprietary Name: DESCOVY
Dosage Form; Route of Administration: TABLET; ORAL
Strength: 200MG;EQ 25MG BASE
Reference Listed Drug: Yes

Reference Standard: Yes
TE Code:
Application Number: N208215
Product Number: 001
Approval Date: Apr 4, 2016
Applicant Holder Full Name: GILEAD SCIENCES INC
Marketing Status: Prescription
Patent and Exclusivity Information (patent_info.cfm?Product_No=001&Appl_No=208215&Appl_type=N)