PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrDESCOVY®

(emtricitabine/tenofovir alafenamide) tablets

200 mg emtricitabine
10 mg* and 25 mg** tenofovir alafenamide

*as 11.2 mg tenofovir alafenamide hemifumarate
**as 28.0 mg tenofovir alafenamide hemifumarate

Antiretroviral Agent

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RECENT MAJOR LABEL CHANGES

Indications (1)	09/2019
Indications, Pediatrics (1.1)	09/2019
Dosage and Administration, Dosing Considerations (4.1)	09/2019
Dosage and Administration, Recommended Dose and Dose Adjustment (4.2)	09/2019
Warnings and Precautions, Immune (7)	05/2019
Warnings and Precautions, Musculoskeletal (7)	09/2019
Warnings and Precautions, Pediatrics (7.1)	09/2019

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DESCOVY®

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

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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.

1.1 Pediatrics (weighing ≥25 kg)

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

Safety and efficacy of DESCOVY in children weighing less than 25 kg have not been established.

1.2 Geriatrics (≥65 years of age)

No differences in safety or efficacy have been observed between elderly patients and those <65 years of age (see **ACTION and 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 **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

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 patients coinfected with HIV-1 and HBV. Discontinuation of DESCOVY therapy in patients coinfected with HIV-1 and 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 patients who are coinfected with HIV-1 and HBV and discontinue DESCOVY. If appropriate, initiation of anti-hepatitis B therapy may be warranted (see **WARNINGS AND PRECAUTIONS**, **Special Populations**).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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

4.2 Recommended Dose and Dosage Adjustment

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.

Pediatrics (weighing <25 kg)

DESCOVY is not indicated for use in pediatric patients weighing <25 kg.

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

No dose adjustment of DESCOVY is required in adult patients with estimated creatinine clearance ≥30 mL per minute. The safety of DESCOVY has not been established in patients with estimated creatinine clearance that declines below 30 mL per minute.

DESCOVY should not be initiated in patients with estimated creatinine clearance below 30 mL per minute as there are insufficient data available regarding the use of DESCOVY in this population.

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

Hepatic Impairment

No dose adjustment of DESCOVY is required in patients with hepatic impairment. (see **ACTION AND CLINICAL PHARMACOLOGY**).

4.3 Missed Dose

If a patient misses a dose of DESCOVY within 18 hours of the time it is usually taken, the patient 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 a patient misses a dose of DESCOVY by more than 18 hours, the patient should not take the missed dose, but resume the usual dosing schedule.

5 OVERDOSAGE

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

If overdose occurs the patient 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 patient.

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%.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

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.

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

7 WARNINGS AND PRECAUTIONS

Please see the **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.

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®).

DESCOVY is not indicated for use as a pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high-risk.

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.

Endocrine and Metabolism

Serum Lipids and Blood Glucose

Serum lipid and blood glucose levels may increase during antiretroviral therapy. Disease control and life style 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 **WARNINGS AND PRECAUTIONS**, **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 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 **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, 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 Patients Coinfected with HIV and HBV

The safety and efficacy of DESCOVY have not been established in patients coinfected with HIV-1 and HBV. It is recommended that all patients with HIV-1 be tested for hepatitis B virus (HBV) before or when initiating ART.

Severe acute exacerbations of hepatitis B (and associated with liver decompensation and liver failure in some patients) may occur in patients coinfected with HBV and HIV-1 after discontinuation of FTC and TAF, the two components of DESCOVY.

Hepatic function should be closely monitored with both clinical and laboratory follow-up for at least several months in patients who discontinue DESCOVY and are coinfected with HIV-1 and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, post-treatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure. Therefore, in these patients, discontinuation of treatment without initiation of alternative anti-hepatitis B therapy is not recommended.

7.1.2 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

7.1.3 Nursing Women

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 whose mothers are being treated with FTC may be at risk for developing viral resistance to FTC. Other FTC-associated risks in infants breastfed by mothers being treated with 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**.

7.1.4 Pediatrics (weighing <25 kg)

Safety and efficacy of DESCOVY in children weighing less than 25 kg have not been established.

7.1.5 Geriatrics (≥65 years of age):

No dose adjustment of DESCOVY is required for elderly patients. In clinical trials, 80 of the 97 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 **ACTION and CLINICAL PHARMACOLOGY**).

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 **SERIOUS WARNINGS AND PRECAUTIONS BOX**]
- Immune Reconstitution Inflammatory Syndrome [see **WARNINGS AND PRECAUTIONS**].
- Lactic Acidosis/Severe Hepatomegaly with Steatosis [See **WARNINGS AND PRECAUTIONS**]

8.2 Clinical Trial Adverse Drug 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 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 2 displays the frequency of adverse reactions (Grades 2-4) greater than or equal to 1%, respectively.

Table 2. 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.

8.3 Less Common Clinical Trial Adverse Drug Reactions (<1%)

In addition to the adverse reactions presented in Table 1, 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 Laboratory Abnormalities

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 3.

Table 3. 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)

	Week 48		Week 144	
Laboratory Parameter Abnormality[a]	**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 4.

Table 4. 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-292-0111[a] (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.

8.5 Clinical Trials in 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).

8.6 Clinical Trials in 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 **CLINICAL TRIALS**).

8.7 Clinical Trials in Pediatric Patients (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 **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 **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 **CLINICAL TRIALS**, **Study results**).

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 (administered as GENVOYA)

		Mean Change from Baseline			
	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)

8.8 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

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Skin and subcutaneous tissue disorders: Angioedema, urticaria

9 DRUG INTERACTIONS

9.1 Drug-Drug Interactions

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 6). 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 **DRUG INTERACTIONS**, Table 6).

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 **WARNINGS AND PRECAUTIONS**, **General**).

Table 6 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 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)		
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.
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.

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
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 **ACTION AND 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 7. The effects of TAF on the exposure of coadministered drugs are shown in Table 8.

Table 7. 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 8. 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%)
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/	25 once daily[c]	15	↑ 17% (↑ 7%, ↑ 26%)	↑ 12% (↑ 7%, ↑ 17%)	↑ 16% (↑ 8%, ↑ 24%)

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}
Norgestrel	0.250 once daily / ethinyl estradiol 0.025 once daily			↑ 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%, ↑ 13 %)	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%)
Voxilaprevir				↑ 92% (↑ 63%, ↑ 126%)	↑ 171% (↑ 130%, ↑ 219%)	↑ 350% (↑ 268%, ↑ 450%)

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}
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.

9.2 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.

9.3 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.

9.4 Drug-Laboratory Interactions

Interactions of DESCOVY with laboratory tests have not been established.

10 ACTION AND 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 and Bioavailability

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.

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 CYP3A *in vivo*.

Excretion

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)

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

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

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.

Race

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.

Gender

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

Hepatic Impairment

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 Impairment

No clinically relevant differences in TAF or tenofovir pharmacokinetics were observed between healthy patients and patients with severe renal impairment (estimated

creatinine clearance <30 mL/min) in studies of TAF. There are no pharmacokinetic data on TAF in patients with estimated creatinine clearance <15 mL/min.

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 DESCOVY in patients with mild to moderate renal impairment was similar to that in patients with normal renal function.

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

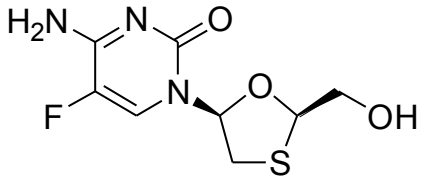
Common Name: emtricitabine (USAN)

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

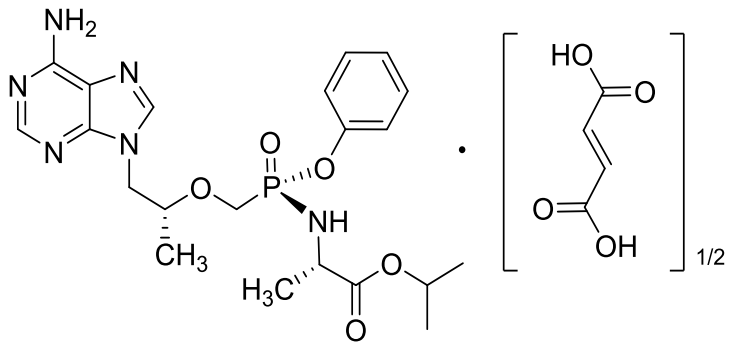
Common Name: Tenofovir alafenamide hemifumarate
Tenofovir alafenamide fumarate (USAN)

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

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 Study Demographics and Trial Design

Description of Clinical Studies

The clinical efficacy of DESCOVY in 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 treatment-naïve patients with DESCOVY.

Pivotal 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 9.

Table 9. 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 10.

Table 10. 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.

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 11.

Table 11. 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

14.2 Study Results

Study Results

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 12.

Table 12. 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 13, 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 13. 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 14, 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 14. 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 14) 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 **ADVERSE REACTIONS**).

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 15.

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 15.

Table 15. 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

Study results

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.

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.

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 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 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.

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

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.

Carcinogenesis

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.

Mutagenesis

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 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.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

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 also 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.**

What is Descovy used for?
Descovy is used to treat people with HIV infection. **Descovy** is for adults and children who weigh at least 25 kg (55 lbs).

Descovy is for people who do not have an HIV virus that is resistant to **Descovy**. **Descovy** has not been studied in children weighing less than 25 kg (55 lbs).

How does Descovy work?
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**.

Descovy has not been shown to reduce the risk of passing HIV to others through sexual contact or blood. 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.

What are the ingredients in Descovy?
Medicinal ingredients: emtricitabine and tenofovir alafenamide*
(* as tenofovir alafenamide hemifumarate)

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

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?**).

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:

- Also have hepatitis B virus (HBV) infection at the same time 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 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. 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 breast-feeding or plan to breast-feed:
Do not breast-feed 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.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

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. 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.

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.

Usual dose:

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.

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.

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. 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	
<u>RARE</u> **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		✓	
<u>VERY RARE</u> **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		✓	
<u>VERY RARE</u> **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 help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect: www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - — Fax to 1-866-678-6789 (toll-free), or
  - — Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect at www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.

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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