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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www.gilead.ca

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

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet	*For a complete listing see **Dosage Forms, Composition and Packaging** section.*
	200 mg emtricitabine/ 10 mg tenofovir alafenamide* * as 11.2 mg tenofovir alafenamide hemifumarate	None
	200 mg emtricitabine/ 25 mg tenofovir alafenamide* * as 28.0 mg tenofovir alafenamide hemifumarate	None

INDICATIONS AND CLINICAL USE

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 12 years of age and older (and weighing ≥35 kg).

Additional important information regarding the use of DESCOVY for the treatment of HIV-1 infection:

- It is not recommended that DESCOVY be used as a component of a triple nucleoside regimen (see **WARNINGS AND PRECAUTIONS**).
- In treatment-experienced patients, the use of DESCOVY should be guided by laboratory testing and treatment history (see **MICROBIOLOGY**).
- The safety and efficacy of DESCOVY has not been established in patients with virologic failure.

Geriatrics (≥65 years of age)

No differences in safety or efficacy have been observed between elderly patients and those ≥12 and <65 years of age (see **ACTION and CLINICAL PHARMACOLOGY**).

Pediatrics (≥12 and <18 years of age)

Safety and efficacy of DESCOVY in children younger than 12 years or weighing <35 kg have not been established. The safety and efficacy in children between 12 years and <18 years of age (and ≥35 kg) are based on Week 24 data from an open-label clinical study (see **WARNINGS AND PRECAUTIONS, Musculoskeletal, ADVERSE REACTIONS** and **CLINICAL TRIALS**).

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.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Lactic Acidosis and Severe Hepatomegaly with Steatosis**
  In patients receiving nucleoside analogs in combination with other antiretrovirals, cases of lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Treatment with DESCOVY should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (see **WARNINGS AND PRECAUTIONS**, **Hepatic/Biliary/Pancreatic**).
- **Post-treatment Exacerbation of Hepatitis**
  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 or tenofovir alafenamide 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**).

General

DESCOVY is a fixed dose combination of emtricitabine and tenofovir alafenamide.

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

DESCOVY should not be coadministered with products containing any of the same components, emtricitabine or tenofovir alafenamide (ATRIPLA®, COMPLERA®,

EMTRIVA®, STRIBILD®, TRUVADA® and GENVOYA®); or with products containing lamivudine (3TC®, COMBIVIR®, TRIUMEQ® and TRIZIVIR®) or tenofovir disoproxil fumarate (ATRIPLA®, COMPLERA®, VIREAD®, STRIBILD®, and TRUVADA®); 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.

Clinical studies in HIV-infected patients have demonstrated that certain regimens that only contain three nucleoside reverse transcriptase inhibitors (NRTI) are generally less effective than triple drug regimens containing two NRTIs in combination with either a non-nucleoside reverse transcriptase inhibitor or a HIV-1 protease inhibitor. In particular, early virological failure and high rates of resistance mutations have been reported. Triple nucleoside regimens should therefore be used with caution. Patients on a therapy utilizing a triple nucleoside-only regimen should be carefully monitored and considered for treatment modification.

Endocrine and Metabolism

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy (ART). The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Hepatic/Biliary/Pancreatic

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 in combination with other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. 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).

Hepatic Impairment

Tenofovir and tenofovir alafenamide 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. Emtricitabine has not been evaluated in patients with hepatic impairment; however, emtricitabine has not been

shown to be metabolized by liver enzymes, so the impact of liver impairment is likely to be limited.

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

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 emtricitabine, 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, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable, and can occur many months after initiation of treatment.

Musculoskeletal

Bone Effects of Tenofovir Alafenamide

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 emtricitabine and tenofovir alafenamide in combination with elvitegravir and cobicistat as a fixed-dose combination 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 (see **CLINICAL TRIALS**).

In an open-label clinical study of HIV-1 infected ART treatment-naïve adolescents (≥12 to <18 years of age), treated with emtricitabine and tenofovir alafenamide 10 mg in combination with elvitegravir and cobicistat as a fixed-dose combination tablet, 4 patients experienced treatment-emergent worsening in the spine (N=39) and/or total body less head

(TBLH) (N=37) height-age-adjusted BMD Z-score clinical status from baseline to Week 24 where a relationship to DESCOVY could not be excluded. However, two of these patients showed improvements in BMD at Week 48; skeletal growth (height) appeared to be unaffected in these 4 patients when assessed at Week 24 (see **ADVERSE REACTIONS** and **CLINICAL TRIALS**).

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

Assessment of BMD should be considered in adolescents and in adults who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. If bone abnormalities are suspected, appropriate consultation should be obtained.

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 elvitegravir/cobicistat/ emtricitabine/tenofovir alafenamide, 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.

Special Populations

Patients Co-infected 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 the presence of chronic hepatitis B virus (HBV) before initiating ART.

Severe acute exacerbations of hepatitis B (and association with liver decompensation and liver failure in some patients), may occur in patients coinfected with HBV and HIV-1 after discontinuation of emtricitabine and tenofovir alafenamide, two of the 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 co-infected 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.

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 tenofovir alafenamide 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 tenofovir alafenamide 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 tenofovir disoproxil fumarate, another prodrug of tenofovir, to pregnant rats resulted in increased peri/postparturn 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 tenofovir alafenamide.

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

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 tenofovir alafenamide 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 tenofovir alafenamide are unknown.

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

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.**

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 emtricitabine and tenofovir alafenamide given with elvitegravir and cobicistat as a fixed-dose combination tablet. No differences in safety or efficacy have been observed between elderly patients and those older than 12 and <65 years of age (see **ACTION and CLINICAL PHARMACOLOGY**).

Pediatrics (≥12 and <18 years of age)

Safety and efficacy of DESCOVY in children younger than 12 years or weighing <35 kg have not been established.

ADVERSE REACTIONS

The safety of DESCOVY is based on studies of emtricitabine and tenofovir alafenamide when given with elvitegravir and cobicistat as the fixed-dose combination tablet GENVOYA (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide).

Adverse Drug Reaction Overview

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

- Lactic Acidosis/Severe Hepatomegaly with Steatosis [see **Boxed Warning, WARNINGS AND PRECAUTIONS**]
- Severe Acute Exacerbations of Hepatitis B [see **Boxed Warning**, **WARNINGS AND PRECAUTIONS**]
- Immune Reconstitution Inflammatory Syndrome [see **WARNINGS AND PRECAUTIONS**].

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 emtricitabine and tenofovir alafenamide is based on Week 48 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 emtricitabine and tenofovir alafenamide (N=866) given with elvitegravir and cobicistat as a fixed-dose combination tablet once daily.

The proportion of patients who discontinued treatment with emtricitabine and tenofovir alafenamide (administered as GENVOYA) or emtricitabine and tenofovir disoproxil fumarate (administered as STRIBILD) due to adverse events, regardless of severity, was 0.9% and 1.5%, respectively. Table 1 displays the frequency of adverse reactions (Grades 2-4) greater than or equal to 1%.

Table 1. Adverse Drug Reactions[a] (Grades 2-4) Reported in ≥ 1% of HIV-1 Infected Treatment-Naïve Adults in Any Treatment Arm in Studies GS-US-292-0104 and GS-US-292-0111 (Week 48 analysis)

	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.

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 emtricitabine and tenofovir alafenamide group (administered as GENVOYA).

Adverse Reactions from Clinical Trials of the Components of DESCOVY

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

Laboratory Abnormalities

The frequency of laboratory abnormalities (Grades 3-4) occurring in at least 2% of patients receiving emtricitabine and tenofovir alafenamide given with elvitegravir and cobicistat as a fixed-dose combination tablet (administered as GENVOYA) in Studies 104 and 111 are presented in Table 2.

Table 2. 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 Analysis)

Laboratory Parameter Abnormality[a]	FTC+TAF (Administered as GENVOYA) (N=866)	FTC+TDF (Administered as STRIBILD) (N=867)
Creatine Kinase (≥10.0 x ULN)	7%	6%
LDL-cholesterol (fasted) (>4.91mmol/L)	5%	2%
Lipase[b] (≥3.0 x ULN)	4%	8%

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).

Serum Lipids

In the clinical trials of emtricitabine and tenofovir alafenamide and emtricitabine and tenofovir disoproxil fumarate, both given with elvitegravir and cobicistat as a fixed-dose combination tablet (administered as GENVOYA and STRIBILD, respectively), a similar percentage of patients receiving emtricitabine and tenofovir alafenamide and emtricitabine and tenofovir disoproxil fumarate were on lipid lowering agents at baseline (4% and 5%, respectively). While receiving study drug through Week 48, an additional 4% of emtricitabine and tenofovir alafenamide patients were started on lipid lowering agents, compared to 3% of emtricitabine and tenofovir disoproxil fumarate patients.

Changes from baseline in total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides are presented in Table 3.

Table 3. 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]

	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
	mmol/L	mmol/L	mmol/L	mmol/L
Total Cholesterol (fasted)	4.19 [N=757]	+0.78 [N=757]	4.29 [N=742]	+034 [N=742]
HDL-cholesterol (fasted)	1.19 [N=757]	+0.18 [N=757]	1.16 [N=742]	+0.10 [N=742]
LDL-cholesterol (fasted)	2.69 [N=753]	+0.39 [N=753]	2.77 [N=744]	+0.08 [N=744]
Triglycerides (fasted)	1.28 [N=757]	+0.33 [N=757]	1.34 [N=742]	+0.11 [N=742]
Total Cholesterol to HDL ratio	3.7 [N=757]	0.2 [N=757]	3.9 [N=742]	0 [N=742]

FTC=emtricitabine; TAF= tenofovir alafenamide; TDF= tenofovir disoproxil fumarate
a Excludes subjects who received lipid lowering agents during the treatment period.
b The change from baseline is the mean of within-subject changes from baseline for subjects with both baseline and Week 48 values.

Clinical Trials in Virologically Suppressed Patients

No new adverse reactions to DESCOVY were identified through Week 48 in the double-blind clinical study GS-US-311-1089 of virologically suppressed patients who changed their background regimen from TRUVADA to DESCOVY while maintaining their third antiretroviral agent (N=333).

Clinical Trials in Adult Patients with Renal Impairment

The safety of emtricitabine and tenofovir alafenamide was evaluated through 24 weeks 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 (eGFR by Cockcroft-Gault method 30-69 mL/min) received emtricitabine and tenofovir alafenamide in combination with elvitegravir and cobicistat as a fixed-dose combination tablet (administered as GENVOYA). The safety profile of emtricitabine and tenofovir alafenamide in patients with mild to moderate renal impairment was similar to that in patients with normal renal function (eGFR ≥80 mL/min).

Clinical Trials in Pediatric Patients (12 to <18 years of age)

The safety of emtricitabine and tenofovir alafenamide in HIV-1 infected, treatment naïve pediatric patients aged 12 to <18 years was evaluated through 24 weeks in an open-label clinical trial GS-US-292-0106 (Study 106) in which HIV-1 infected, treatment naïve pediatric patients aged 12 to <18 years received emtricitabine and tenofovir alafenamide in combination with elvitegravir and cobicistat as a fixed-dose combination tablet (administered as GENVOYA) (see **CLINICAL TRIALS**). The safety profile in adolescent patients who received treatment with emtricitabine and tenofovir alafenamide was similar to that in adults. One 13 year old female subject developed unexplained uveitis while receiving GENVOYA that resolved and did not require discontinuation of GENVOYA.

In Study 106, 4 patients experienced treatment-emergent worsening in the spine (39 out of 47 patients assessed) and/or TBLH (37 out of 45 patients assessed) height-age-adjusted BMD Z-score clinical status from baseline at Week 24, where a relationship to emtricitabine and tenofovir alafenamide could not be excluded. However, two of these patients subsequently showed improvements in BMD at Week 48 (see **CLINICAL TRIALS**).

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 emtricitabine. 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

DRUG INTERACTIONS

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 emtricitabine 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 emtricitabine with drugs that are eliminated by active tubular secretion may increase concentrations of emtricitabine, and/or the coadministered drug.

Drugs that decrease renal function may increase concentrations of emtricitabine.

In drug interaction studies conducted with emtricitabine and with tenofovir disoproxil fumarate, coadministration of emtricitabine and famciclovir had no effect on the C_{max} or AUC of either drug.

Tenofovir Alafenamide

Tenofovir alafenamide, a component of DESCOVY, is transported by P-glycoprotein (P-gp). Drugs that strongly affect P-gp activity may lead to changes in tenofovir alafenamide absorption (see Table 4). Drugs that induce P-gp activity are expected to decrease the absorption of tenofovir alafenamide, resulting in decreased plasma concentration of tenofovir alafenamide, which may lead to loss of therapeutic effect of DESCOVY and development of resistance.

Coadministration of DESCOVY with other drugs that inhibit P-gp may increase the absorption and plasma concentration of tenofovir alafenamide.

Coadministration of DESCOVY with drugs that inhibit the lysosomal carboxypeptidase cathepsin A may decrease metabolism of tenofovir alafenamide to tenofovir in target cells, which may lead to reduced therapeutic effect of DESCOVY and development of resistance (see **DRUG INTERACTIONS**, Table 4).

Established and Other Potentially Significant Interactions

DESCOVY should not be coadministered with products containing any of the same components, emtricitabine or tenofovir alafenamide; or with products containing lamivudine or tenofovir disoproxil fumarate; and DESCOVY should not be administered with adefovir dipivoxil (see **WARNINGS AND PRECAUTIONS**, **General**).

Table 4 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 (emtricitabine and tenofovir alafenamide) 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 4. 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 expected to increase when atazanavir/cobicistat 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/cobicistat 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.
Other Protease Inhibitors	Effect is unknown	There are no data available to make dosing recommendations for coadministration with other protease inhibitors.

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Other Agents		
Anticonvulsants: carbamazepine 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, maraviroc, nevirapine, raltegravir, and rilpivirine,. No clinically significant drug interactions have been either observed or expected when DESCOVY is combined with the following drugs: buprenorphine, methadone, midazolam, naloxone, norbuprenorphine, norgestimate/ethinyl estradiol, and sertraline.

Assessment of Drug Interactions

Drug Interaction Studies

Drug-drug interaction studies were conducted with DESCOVY or the components of DESCOVY (emtricitabine or tenofovir alafenamide) as individual agents.

The effects of coadministered drugs on the exposure of tenofovir alafenamide are shown in Table 5. The effects of tenofovir alafenamide on the exposure of coadministered drugs are shown in Table 6.

Table 5. Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir Alafenamide 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%)	NC
Atazanavir	300 + 150 cobicistat once daily	10 once daily	20	↑ 80% (↑ 48%, ↑ 118%)	↑ 75% (↑ 55%, ↑ 98%)	NC
Cobicistat	150 once daily	8 once daily	12	↑ 183% (↑ 120%, ↑ 265%)	↑ 165% (↑ 129%, ↑ 207%)	NC
Darunavir	800 + 150 cobicistat once daily	25 once daily[c]	11	↓ 7%[d] (↓ 28%, ↑ 21%)	↓ 2%[d] (↓ 20%, ↑ 19%)	NC[d]
Darunavir	800 + 100 ritonavir once daily	10 once daily	10	↑ 42%[e] (↓ 4%, ↑109)	↑ 6%[e] (↓ 16%, ↑ 35%)	NC
Dolutegravir	50 once daily	10 once daily	10	↑ 24% (↓ 12%, ↑ 74%)	↑ 19% (↓ 4%, ↑ 48%)	NC
Efavirenz	600 once daily	40 once daily[c]	11	↓ 22% (↓ 42%, ↑ 5%)	↓ 14% (↓ 28%, ↑ 2%)	NC
Lopinavir	800 + 200 ritonavir once daily	10 once daily	10	↑ 119% (↑ 72%, ↑179%)	↑ 47% (↑ 17%, ↑ 85%)	NC
Rilpivirine	25 once daily	25 once daily	17	↑ 1% (↓ 16%, ↑ 22%)	↑ 1% (↓ 6%, ↑ 9%)	NC
Sertraline	50 single dose	10 once daily[f]	19	0% (↓ 14%, ↑ 16 %)	↓ 4% (↓ 11%, ↑ 3%)	NC

NC=Not Calculated

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.

Table 6. Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Tenofovir Alafenamide 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	10	↓ 1% (↓ 9%, ↑ 8%)	↑ 1% (↓ 4%, ↑ 6%)	↑ 13% (↓ 5%, ↑ 34%)
Dolutegravir	50 once daily	10 once daily	10	↑ 15% (↑ 4%, ↑ 27%)	↑ 2% (↓ 3%, ↑ 8%)	↑ 5% (↓ 3%, ↑ 13%)
Lopinavir	800 + 200 ritonavir once daily	10 once daily	10	0% (↓ 5%, ↑ 6%)	0% (↓ 8%, ↑ 9%)	↓ 2% (↓ 15%, ↑ 12%)
Midazolam[d]	2.5 once daily, orally	25 once daily	18	↑ 2% (↓ 8%, ↑ 13%)	↑ 12% (↑3 %, ↑ 22%)	NC
	1 once daily IV			↓ 1% (↓ 11%, ↑ 11%)	↑ 8% (↑ 4%, ↑ 14%)	NC
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%)	↑ 9% (↓ 10%, ↑ 32%)	NC

N/A=Not Applicable; NC=Not Calculated
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

Drug-Food Interactions

Emtricitabine

Relative to fasting conditions, the administration of tenofovir alafenamide with a high fat meal (~800 kcal, 50% fat), resulted in a decrease in emtricitabine 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 tenofovir alafenamide 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.

Drug-Herb Interactions

Coadministration of St. John's wort, a P-gp inducer, may decrease tenofovir alafenamide 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.

Drug-Laboratory Interactions

Interactions of DESCOVY with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

In adults and pediatric patients ≥12 years of age and weighing ≥35 kg, DESCOVY is taken orally once daily with or without food (see **DRUG INTERACTIONS**, **Drug-Food Interactions**).

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 cobicistat.
- 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 cobicistat.

Table 7 includes dosing recommendations based upon clinical data from third agents evaluated with DESCOVY in Study GS-US-311-1089 or drug interactions studies.

Table 7. 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 cobicistat[a] Darunavir with ritonavir or cobicistat[a] Lopinavir with ritonavir
DESCOVY 200/25 mg once daily	Dolutegravir, efavirenz, maraviroc, nevirapine, rilpivirine, raltegravir

a. Atazanavir with cobicistat and darunavir with cobicistat 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 (<12 years of age)

DESCOVY is not indicated for use in pediatric patients <12 years of age or weighing <35 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 between 12 and <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.

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

Hepatic Impairment

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

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.

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 EMTRIVA. In one clinical pharmacology study, single doses of emtricitabine 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 emtricitabine dose over a 3 hour dialysis period starting within 1.5 hours of emtricitabine dosing.

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

Tenofovir Alafenamide

Limited clinical experience is available at doses higher than the therapeutic dose of tenofovir alafenamide. A single supratherapeutic dose of 125 mg tenofovir alafenamide was administered to 48 healthy subjects. No serious adverse reactions were reported. The effects of higher doses are unknown. Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

DESCOVY is a fixed-dose combination of antiviral drugs emtricitabine and tenofovir alafenamide.

Emtricitabine

Emtricitabine is a nucleoside analogue of 2'-deoxycytidine. Emtricitabine is phosphorylated by cellular enzymes to form emtricitabine 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 tenofovir disoproxil fumarate 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, tenofovir alafenamide 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, tenofovir alafenamide did not significantly affect mitochondrial DNA in HepG2 cells.

Pharmacodynamics

Effects on Electrocardiogram

In a thorough QT/QTc study in 48 healthy patients, tenofovir alafenamide 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, emtricitabine, or the combination of emtricitabine and tenofovir alafenamide on the QT interval is not known.

Pharmacokinetics

Comparative Bioavailability

The bioavailabilities of emtricitabine and tenofovir alafenamide from a single dose administration of DESCOVY (F/TAF) 200 mg/10 mg fixed-dose combination tablet with concomitant administration of cobicistat 150 mg tablet and elvitegravir 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 emtricitabine and tenofovir alafenamide from a single dose administration of DESCOVY (F/TAF) 200 mg/25 mg fixed-dose combination 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 emtricitabine/tenofovir alafenamide 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 emtricitabine by approximately 1 hour, and a decrease in AUC_T and C_{max} for emtricitabine by approximately 9% and 26%, respectively when compared to administration under fasting conditions. For tenofovir alafenamide, there was a delay in the mean T_{max} for tenofovir alafenamide by approximately 0.5 hours, an increase in the AUC_T for tenofovir alafenamide by approximately 74% and a decrease in C_{max} for tenofovir alafenamide by approximately 10% when compared to administration under fasting conditions.

Distribution

Emtricitabine

In vitro binding of emtricitabine 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

In vitro binding of tenofovir to human plasma proteins is <0.7% and is independent of concentration over the range of 0.01–25 μg/mL. Ex-vivo binding of tenofovir alafenamide 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 tenofovir alafenamide in humans, accounting for >80% of an oral dose. *In vitro* studies have shown that tenofovir alafenamide 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, tenofovir alafenamide exposure was unaffected.

In vivo, tenofovir alafenamide 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 tenofovir alafenamide in a fixed dose combination of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide 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 tenofovir disoproxil fumarate in STRIBILD.

In vitro, tenofovir alafenamide is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or UGT1A1. Tenofovir alafenamide is a weak inhibitor of CYP3A *in vitro*.

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 eliminated from the body by the kidneys 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 tenofovir alafenamide 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 (≥12 to <18 years of age)

Exposures of emtricitabine and tenofovir alafenamide achieved in 24 pediatric patients aged 12 to <18 years were similar to exposures achieved in treatment-naïve adults.

Geriatrics (≥65 years of age)

Pharmacokinetics of emtricitabine and tenofovir alafenamide have not been fully evaluated in the elderly (65 years of age and older). Population pharmacokinetics analysis of HIV-infected patients in Phase 2 and Phase 3 trials of emtricitabine and tenofovir alafenamide given with elvitegravir and cobicistat as a fixed-dose combination tablet (administered as GENVOYA) showed that within the age range studied (12 to 82 years), age did not have a clinically relevant effect on exposures of tenofovir alafenamide.

Race

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

Tenofovir Alafenamide: Population pharmacokinetics analysis of tenofovir alafenamide in HIV-1 infected patients indicated that race had no clinically relevant effect on the exposure of tenofovir alafenamide.

Gender

No clinically relevant pharmacokinetic differences have been observed between men and women for emtricitabine and tenofovir alafenamide.

Hepatic Impairment

Emtricitabine: The pharmacokinetics of emtricitabine has not been studied in patients with hepatic impairment; however, emtricitabine 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 tenofovir alafenamide or its metabolite tenofovir were not observed in patients with mild, moderate, or severe hepatic impairment; no tenofovir alafenamide dose adjustment is required in patients with hepatic impairment.

Renal Impairment

No clinically relevant differences in tenofovir alafenamide or tenofovir pharmacokinetics were observed between healthy patients and patients with severe renal impairment (estimated creatinine clearance <30 mL/min) in studies of tenofovir alafenamide. There are no

pharmacokinetic data on tenofovir alafenamide 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 (eGFR by Cockcroft-Gault method 30-69 mL/min) were evaluated with emtricitabine and tenofovir alafenamide given with elvitegravir and cobicistat as a fixed-dose combination 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 safety data from patients with normal renal function.

Hepatitis B and/or Hepatitis C Virus Co-infection

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

STORAGE AND STABILITY

- 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.

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

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.

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.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

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

Emtricitabine (FTC)

Drug Substance

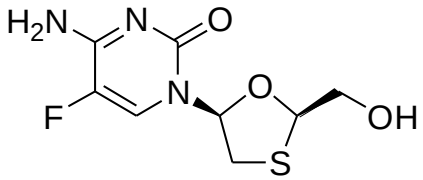
Common Name: emtricitabine (USAN)

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

Empirical Formula: $C_8H_{10}FN_3O_3S$

Molecular Weight: 247.24

Structural Formula:



Physicochemical Properties:

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

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

Tenofovir Alafenamide (TAF)

Drug Substance

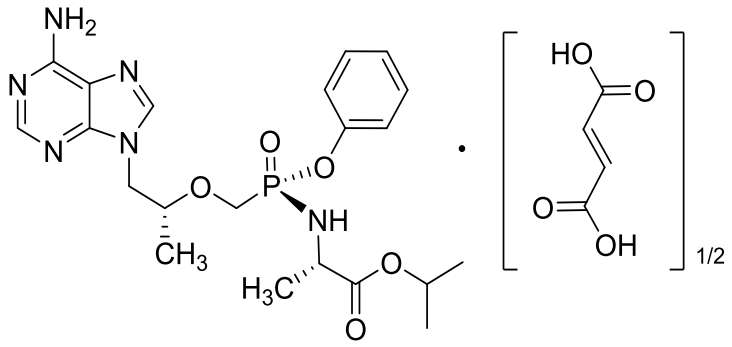
Common Name: Tenofovir alafenamide hemifumarate
Tenofovir alafenamide fumarate (USAN)

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

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

Molecular Weight: 534.5

Structural Formula:



Physicochemical Properties:

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

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

CLINICAL TRIALS

Study Demographics and Trial Design

Description of Clinical Studies

The clinical efficacy of DESCOVY in treatment-naïve patients was established from studies conducted with emtricitabine and tenofovir alafenamide when given with elvitegravir and cobicistat in a fixed-dose combination (GENVOYA). 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 emtricitabine and tenofovir alafenamide from a single dose of DESCOVY (F/TAF) 200 mg/10 mg fixed dose combination tablet administered concomitantly with cobicistat 150 mg tablet and elvitegravir 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 8.

Table 8. Summary Table of the Comparative Bioavailability Data for Study GS-US-311-1472

Emtricitabine
(1 x 200 mg emtricitabine/10 mg tenofovir alafenamide hemifumarate + 150 mg elvitegravir + 150 mg cobicistat or 1 x 150 mg elvitegravir/150 mg cobicistat/200 mg emtricitabine/10 mg tenofovir alafenamide 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
(1 x 200 mg emtricitabine/10 mg tenofovir alafenamide hemifumarate + 150 mg elvitegravir + 150 mg cobicistat or 1 x 150 mg elvitegravir/150 mg cobicistat/200 mg emtricitabine/10 mg tenofovir alafenamide 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 emtricitabine/10 mg tenofovir alafenamide hemifumarate fixed dose combination tablet) + 150 mg cobicistat tablet + 150 mg elvitegravir tablet administered under moderate fat, moderate calorie fed conditions.

† GENVOYA (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide 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 emtricitabine and tenofovir alafenamide from a single dose of DESCOVY (F/TAF) 200/25 mg fixed-dose combination 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-311-1473

Emtricitabine
(1 x 200 mg emtricitabine/25 mg tenofovir alafenamide hemifumarate or
1 x 150 mg elvitegravir/150 mg cobicistat/200 mg emtricitabine/10 mg tenofovir alafenamide 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
(1 x 200 mg emtricitabine/25 mg tenofovir alafenamide hemifumarate or
1 x 150 mg elvitegravir/150 mg cobicistat/200 mg emtricitabine/10 mg tenofovir alafenamide 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 emtricitabine/25 mg tenofovir alafenamide hemifumarate) fixed dose combination tablet administered under moderate fat, moderate calorie fed conditions.

† GENVOYA (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide 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 emtricitabine and tenofovir alafenamide (N=866) or emtricitabine and tenofovir disoproxil fumarate (N=867) once daily, both given with elvitegravir and cobicistat as a fixed-dose combination 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 10.

Table 10. 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	780	802
Symptomatic HIV infection	53	35
AIDS	30	26
Unknown	3	4
$eGFR_{CG}$ (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

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 48 weeks are presented in Table 11.

Table 11. Pooled Virologic Outcomes of Studies GS-US-292-0104 and GS-US-292-0111 at Week 48[a]

	FTC+TAF (Administered as GENVOYA) (N=866)	FTC+TDF (Administered as STRIBILD) (N=867)
HIV-1 RNA <50 copies/mL	92%	90%
Treatment Difference	2.0% (95% CI: -0.7% to 4.7%)	
HIV-1 RNA ≥50 copies/mL[b]	4%	4%
No Virologic Data at Week 48 Window	4%	6%
Discontinued Study Drug Due to AE or Death[c]	1%	2%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA <50 copies/mL[d]	2%	4%
Missing Data During Window but on Study Drug	1%	<1%
Proportion (%) of Subjects with HIV-1 RNA <50 copies/mL by Subgroup		
Age		
<50 years	716/777 (92%)	680/753 (90%)
≥50 years	84/89 (94%)	104/114 (91%)
Sex		
Male	674/733 (92%)	673/740 (91%)
Female	126/133 (95%)	111/127 (87%)
Race		
Black	197/223 (88%)	177/213 (83%)
Nonblack	603/643 (94%)	607/654 (93%)
Baseline Viral Load		
≤100,000 copies/mL	629/670 (94%)	610/672 (91%)
>100,000 copies/mL	171/196 (87%)	174/195 (89%)
Baseline CD4+ cell count		
<200 cells/mm^3	96/112 (86%)	104/117 (89%)
≥200 cells/mm^3	703/753 (93%)	680/750 (91%)

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

a Week 48 window was between Day 294 and 377 (inclusive).

b Included subjects who had ≥50 copies/mL in the Week 48 window; subjects who discontinued early due to lack or loss of efficacy; subjects 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.

c Includes subjects 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.

d Includes subjects who discontinued for reasons other than an AE, death or lack or loss of efficacy; e.g., withdrew consent, loss to follow-up, etc.

Emtricitabine and tenofovir alafenamide met the noninferiority criteria in achieving HIV-1 RNA <50 copies/mL at Week 48, when compared to emtricitabine and tenofovir disoproxil fumarate, both given with elvitegravir and cobicistat as a fixed-dose combination tablet (GENVOYA and STRIBILD, respectively). The mean increase from baseline in CD4+ cell count at Week 48 was 230 cells per mm^3 in patients receiving emtricitabine and tenofovir alafenamide and 211 cells per mm^3 in patients receiving emtricitabine and tenofovir disoproxil fumarate (p=0.024).

Bone Mineral Density

In the pooled analysis of Studies 104 and 111, bone mineral density (BMD) from baseline to Week 48 was assessed by dual-energy X-ray absorptiometry (DXA) to compare the bone safety of tenofovir alafenamide to that of tenofovir disoproxil fumarate. As shown in Table 12, there were smaller decreases in BMD in patients receiving emtricitabine and tenofovir alafenamide as compared with patients receiving emtricitabine and tenofovir disoproxil fumarate, both given with elvitegravir and cobicistat as a fixed-dose combination tablet (GENVOYA and STRIBILD, respectively).

Table 12. Measures of Bone Mineral Density in Studies GS-US-292-0104 and GS-US-292-0111 (Week 48 Analysis)

	FTC+TAF (Administered as GENVOYA)	FTC+TDF (Administered as STRIBILD)	Treatment Difference
Hip DXA Analysis	**N=780**	**N=767**	
Mean Percent Change in BMD	-0.7%	-3.0%	2.29% p<0.001
Patients with Categorical Change: >3% Decrease in BMD >3% Increase in BMD	 17% 7%	 50% 3%	 --
Patients with No Decrease in BMD	35%	14%	--
Lumbar Spine DXA Analysis	**N=784**	**N=773**	
Mean Percent Change in BMD	-1.3%	-2.9%	1.56% p<0.001
Patients with Categorical Change: >3% Decrease in BMD >3% Increase in BMD	 27% 7%	 46% 3%	 --
Patients with No Decrease in BMD	34%	17%	--

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

Changes in Renal Laboratory Tests

In the pooled analysis of Studies 104 and 111, tests were performed to compare the effect of tenofovir alafenamide to that of tenofovir disoproxil fumarate on renal laboratory parameters. As shown in Table 13, statistically significant differences were observed between treatment groups that favored tenofovir alafenamide 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.

Table 13. Change from Baseline in Renal Laboratory Tests in Studies GS-US-292-0104 and GS-US-292-0111 (Week 48 Analysis)

	FTC+TAF (Administered as GENVOYA) (N=866)	FTC+TDF (Administered as STRIBILD) (N=867)	Treatment Difference
Serum Creatinine (mg/dL)[a]	0.08 ± 0.12	0.11 ± 0.22	-0.04 p<0.001
Proteinuria by Urine Dipstick[b]	31%	37%	p=0.022
Urine Protein to Creatinine Ratio[c]	-3.4%	19.8%	p<0.001
Urine Albumin to Creatinine Ratio[c]	-4.7%	7.1%	p<0.001
Urine Retinol Binding Protein to Creatinine Ratio[c]	9.2%	51.2%	p<0.001
Urine Beta-2-Microglobulin to Creatinine Ratio[c]	-31.7%	24.1%	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

In addition to the tabulated differences (shown in Table 13) in serum creatinine and proteinuria, there were other differences in tests of proximal renal tubular function that favored tenofovir alafenamide. The proportion of patients with any grade hypophosphatemia was 3.6% in patients receiving emtricitabine and tenofovir alafenamide and 4.0% in patients receiving emtricitabine and tenofovir disoproxil fumarate, both given with elvitegravir and cobicistat as a fixed-dose combination tablet (GENVOYA and STRIBILD, respectively). The median (Q1, Q3) change from baseline in $FEPO_4$ at Week 48 was 2.0% (-1.2%, 5.6%) in patients receiving emtricitabine and tenofovir alafenamide and 2.6% (-0.7%, 6.4%) in patients receiving emtricitabine and tenofovir disoproxil fumarate (p=0.006). 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) at Week 48 was -0.2 mg/dL (-0.7 mg/dL, 0.2 mg/dL) in patients receiving emtricitabine and tenofovir alafenamide and -0.3 mg/dL (-0.7 mg/dL, 0.2 mg/dL) in patients receiving emtricitabine and tenofovir disoproxil fumarate (p=0.21).

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. The median increase from baseline for these parameters was greater in patients receiving emtricitabine and tenofovir alafenamide compared with patients receiving emtricitabine and tenofovir disoproxil fumarate, both given with elvitegravir and cobicistat as a fixed-dose combination 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 in total cholesterol to HDL ratio was 0.1 (–0.3, 0.5) in patients receiving emtricitabine and tenofovir alafenamide and 0.0 (-0.5, 0.4) in patients receiving emtricitabine and tenofovir disoproxil fumarate ($p<0.001$ for the difference between treatment groups).

Pediatric Patients

In Study 106, the efficacy, safety, and pharmacokinetics of emtricitabine and tenofovir alafenamide were evaluated in an open-label study, in which HIV-1-infected treatment-naïve adolescents received emtricitabine and tenofovir alafenamide in combination with elvitegravir and cobicistat as a fixed-dose combination tablet (GENVOYA). Twenty-three patients treated with GENVOYA for 24 weeks had a mean age of 14 years (range: 12 to 17), were 52% male, 17% Asian, and 83% Black. At baseline, mean plasma HIV-1 RNA was 4.8 log10 copies/mL, median CD4+ cell count was 456 cells/mm^3 (range: 104 to 748), and median CD4+% was 23% (range: 7% to 41%). Overall, 35% had baseline plasma HIV-1 RNA >100,000 copies/mL as shown in Table 14.

Table 14. Demographic and Baseline Characteristics of Treatment-naïve HIV-1 Infected Adolescent Patients in Study GS-US-292-0106

	Study GS-US-292-0106
	FTC+TAF (Administered as GENVOYA) (N=23)
Demographic characteristics	
Median age, years (range)	14 (12-17)
Sex	
Male	12
Female	11
Race	
Asian	4
Black	19
BMI (kg/m^2), median (Q1, Q3)	19.2 (17.8, 23.4)
Baseline disease characteristics	
HIV-1 RNA (log_{10} copies/mL), median (Q1, Q3)	4.73 (4.39, 5.27)
HIV-1 RNA >100,000 copies/mL	8
CD4+ cell count (cells/μL), median (Q1, Q3)	456 (313, 552)
Mode of infection (HIV risk factors)	
Heterosexual sex	3
Homosexual sex	4
IV drug use	1
Vertical transmission	17
HIV disease status	
Asymptomatic	17
Symptomatic HIV infection	6
eGFR by Schwartz formula (mL/min/1.73 m^2), median (Q1, Q3)	168 (137.0, 198.0)
Proteinuria by urinalysis (dipstick)	
Grade 0	23
Grade 1	0
Grade 2	0
Grade 3	0

FTC=emtricitabine; TAF=tenofovir alafenamide

Study results

At Week 24, out of 23 patients assessed for efficacy, 91% 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 was 212 cells per mm^3. Two patients had virologic failure at Week 24; neither patient had evidence of resistance to emtricitabine and tenofovir alafenamide.

Fifty patients were assessed for safety at Week 24 (these patients received emtricitabine and tenofovir alafenamide (10 mg) given with elvitegravir+cobicistat as a fixed-dose combination tablet (GENVOYA) for 24 weeks). BMD by DXA was assessed in 47 patients for spine and 45 patients for total body less head. Mean (SD) BMD increased from baseline to Week 24, +1.6% (3.9%) at the lumbar spine and +0.6% (2.5%) for total body less head. Only those patients who had a height-age-adjusted BMD Z-score both at baseline and at Week 24 were assessed. At Week 24, 4 patients experienced treatment-emergent worsening in the spine (39 out of 47 patients assessed) and/or TBLH (37 out of 45 patients assessed) height-age-adjusted BMD Z-score clinical status from baseline, where a relationship to GENVOYA could not be excluded. However, in 2 of these patients, improvements in BMD were subsequently observed at Week 48.

DETAILED PHARMACOLOGY

Pharmacokinetics

Antiviral Activity

Emtricitabine: The antiviral activity of emtricitabine 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 emtricitabine 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 emtricitabine 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 elvitegravir, additive to synergistic effects were observed. No antagonism was observed for these combinations.

Tenofovir Alafenamide: The antiviral activity of tenofovir alafenamide 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 tenofovir alafenamide 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, tenofovir alafenamide showed potent antiviral activity against the HIV-1 groups/subtypes evaluated.

In a study of tenofovir alafenamide 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.

MICROBIOLOGY

Resistance

In Cell Culture

Emtricitabine: HIV-1 isolates with reduced susceptibility to emtricitabine 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 tenofovir alafenamide have been selected in cell culture. HIV-1 isolates selected by tenofovir alafenamide 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, emtricitabine, tenofovir alafenamide, tenofovir, and lamivudine. *In vitro* drug resistance selection studies with tenofovir alafenamide 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 emtricitabine and tenofovir alafenamide given with elvitegravir and cobicistat as a fixed-dose combination tablet in GS-US-292-0104, GS-US-292-0111, and a Phase 2 study (GS-US-292-0102), genotyping was performed on plasma HIV-1 isolates from all patients with HIV-1 RNA >400 copies/mL at confirmed virologic failure, at Week 48, or at time of early study drug discontinuation. As of Week 48, the development of one or more primary elvitegravir, emtricitabine, or tenofovir alafenamide resistance-associated with resistance was observed in 7 of 14 patients with evaluable genotypic data from paired baseline and emtricitabine and tenofovir alafenamide given with elvitegravir and cobicistat as a fixed-dose combination tablet treatment-failure isolates (7 of 978 patients [0.7%]) compared with 7 of 15 treatment-failure isolates from patients in the emtricitabine and tenofovir disoproxil fumarate given with elvitegravir and cobicistat as a fixed-dose combination tablet group (7 of 925 patients [0.8%]). Of the 7 patients with resistance development in the emtricitabine and tenofovir alafenamide given with elvitegravir and cobicistat as a fixed-dose combination tablet group, the mutations that emerged against emtricitabine and/or tenofovir alafenamide were M184V/I (N=7) and K65R (N=1) in reverse transcriptase and T66T/A/I/V (N=2), E92Q (N=2), Q148Q/R (N=1), and N155H (N=1) in integrase. Of the 7 patients with resistance development in the emtricitabine and tenofovir disoproxil fumarate given with elvitegravir and cobicistat as a fixed-dose combination tablet group, the mutations that emerged against emtricitabine and/or tenofovir disoproxil fumarate were M184V/I (N=7) and K65R (N=2) in reverse transcriptase and E92E/Q (N=3) and Q148R (N=2) in integrase. All patients in both treatment groups who developed resistance mutations to emtricitabine in reverse transcriptase developed resistance mutations to elvitegravir in integrase.

In phenotypic analyses of patients in the resistance analysis population, 6 of 14 patients (43%) receiving emtricitabine and tenofovir alafenamide given with elvitegravir and cobicistat as a fixed-dose combination tablet had HIV-1 isolates with reduced susceptibility to FTC compared with 5 of 15 patients (33%) receiving emtricitabine and tenofovir disoproxil fumarate given with elvitegravir and cobicistat as a fixed-dose combination tablet. No patient receiving either treatment had HIV-1 isolates with reduced susceptibility to tenofovir. Finally, 4 of 14 patients (29%) had reduced susceptibility to elvitegravir in the emtricitabine and tenofovir alafenamide given with elvitegravir and cobicistat as a fixed-dose combination tablet group compared with 4 of 15 patients (27%) in the emtricitabine and tenofovir disoproxil fumarate given with elvitegravir and cobicistat as a fixed-dose combination tablet group.

In Virologically Suppressed Patients: In a Week 48 analysis of virologically suppressed patients who changed their background regimen from emtricitabine/tenofovir disoproxil fumarate to DESCOVY while maintaining their third antiretroviral agent (GS-US-311-1089), 1 of 2 patients analyzed in the DESCOVY+third agent group (1 of 333 [0.3%]) developed M184V in reverse transcriptase with reduced susceptibility to emtricitabine. In the emtricitabine/tenofovir disoproxil fumarate+third agent group, 0 of 1 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 emtricitabine or tenofovir, or for emtricitabine- or tenofovir-resistant isolates and elvitegravir.

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 emtricitabine.

Tenofovir Alafenamide: The K65R and K70E mutations result in reduced susceptibility to abacavir, didanosine, lamivudine, emtricitabine, 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 tenofovir alafenamide.

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

TOXICOLOGY

General

No toxicology studies have been conducted with DESCOVY tablets. The toxicology information is based on studies conducted with emtricitabine or tenofovir alafenamide as individual agents.

Tenofovir Alafenamide

The general toxicology profile of tenofovir alafenamide 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 tenofovir alafenamide-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 triiodothryonine (T3) levels.

Carcinogenesis

Emtricitabine: In long-term carcinogenicity studies of emtricitabine, 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 tenofovir alafenamide compared to tenofovir disoproxil fumarate, carcinogenicity studies were conducted only with tenofovir disoproxil fumarate. Long-term oral carcinogenicity studies of tenofovir disoproxil fumarate 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 tenofovir disoproxil fumarate 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 emtricitabine 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 tenofovir alafenamide 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.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PART III: 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

- Two of the ingredients of **Descovy**, emtricitabine and tenofovir alafenamide, are nucleoside reverse transcriptase inhibitors (NRTIs), which can cause lactic acidosis, a build-up of acid in the blood, including cases leading to death (see **Serious Side Effects** table).
- Severe liver problems such as enlarged or fatty liver, including cases leading to death, can occur in those taking **Descovy** or similar medicines (see **Serious Side Effects** table).
- **"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 12 years of age and older and who weigh at least 35 kg (77 lbs).

Descovy is for people who do not have an HIV virus that is resistant to **Descovy**. **Descovy** has not been studied in children under 12 years of age or weighing less than 35 kg (77 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:

- 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. You are more likely to get lactic acidosis if you are female, overweight or have been taking medicines such as **Descovy** for a long time.

- 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. You are more likely to get these liver problems if you are female, overweight or have been taking medicines such as **Descovy** for a long time.

- 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 serious liver problems or kidney problems.

- Have bone problems.

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.

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 (GENVOYA®).
- Any other medicines that contain tenofovir disoproxil fumarate (ATRIPLA®, COMPLERA®, STRIBILD®, TRUVADA®, VIREAD®).
- Any other medicines that contain emtricitabine or lamivudine (ATRIPLA, COMPLERA, EMTRIVA®, GENVOYA, STRIBILD, 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®)
Antiviral	tipranavir (Aptivus®)
Herbal products	Hypericum perforatum (St. John's wort)

* Not available in Canada

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 12 years of age and older and weighing 35 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.

Changes in body fat can happen in people who take HIV-1 medicine. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the middle of your body (trunk). Loss of fat from the legs, arms and face may also happen. The exact cause and long-term health effects of these conditions are not known.

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 or you could develop an autoimmune disease in which your immune system reacts against your own body [e.g. Grave's disease (which affects the thyroid gland), Guillain-Barre syndrome (which affects the nervous system) or polymyositis (which affects the muscles)] and it may develop at any time, sometimes months after the start of HIV therapy. Sometimes symptoms can be severe, so if you develop high temperature (fever), joint or muscle pain, redness, rash, swelling, or fatigue or any new symptoms, contact your doctor straight away.

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.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of **Descovy**. For more information, ask your doctor or pharmacist.

Serious side effects and what to do about them			
	Talk to your healthcare professional		Stop taking drug and get immediate medical help
Symptom/effect	**Only if severe**	**In all cases**	
RARE			
Effect: Lactic acidosis			
Symptoms:			
• Feeling very weak or tired		✓	
• Unusual muscle pain		✓	
• Stomach pain with nausea and vomiting		✓	
• Feeling unusually cold, especially in arms and legs		✓	
• Feeling dizzy or lightheaded		✓	
• Fast or irregular heartbeat		✓	
• Fast and deep breathing		✓	
VERY RARE			
Effect: 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		✓	
VERY RARE			
Effect: Flare-ups of hepatitis B virus infection following drug discontinuation			
Symptoms:			
• Jaundice (skin or the white part of eyes turns yellow)		✓	
• Urine turns dark		✓	
• Bowel movements (stools) turn light in color		✓	
• Loss of appetite for several days or longer		✓	
• Feeling sick to your stomach (nausea)		✓	
• Lower stomach pain		✓	

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.healthcanada.gc.ca/medeffect;
- 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.healthcanada.gc.ca/medeffect.

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 (www.health canada.gc.ca); the manufacturer's website (www.gilead.ca); or by calling 1-866-207-4267.

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