



# DESCOVY<sup>®</sup>

## Formulary Monograph

[Click here](#) for full Prescribing Information for DESCOVY, including **BOXED WARNING**.



**Descovy<sup>®</sup>**  
emtricitabine 200mg/  
tenofovir alafenamide 25mg tablets

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# EXECUTIVE SUMMARY

## BOXED WARNING

**WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B**

**Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs in combination with other antiretrovirals.**

**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 coinfecting with human immunodeficiency virus-1 (HIV-1) and HBV. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfecting with HIV-1 and HBV and have discontinued products containing emtricitabine (FTC) and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of DESCOVY. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are coinfecting with HIV-1 and HBV and discontinue DESCOVY. If appropriate, initiation of anti-hepatitis B therapy may be warranted.**

## INDICATION

DESCOVY is indicated, in combination with other antiretroviral agents, for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older.<sup>1</sup>

### Limitations of Use:

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

## DOSAGE AND ADMINISTRATION

- ◆ Prior to initiation of DESCOVY, patients should be tested for hepatitis B virus infection
- ◆ Estimated creatinine clearance, urine glucose, and urine protein should be assessed before initiating DESCOVY therapy and should be monitored during therapy in all patients
- ◆ The recommended dosage of DESCOVY is one tablet taken orally once daily, with or without food, in adults and pediatric patients 12 years of age and older weighing at least 35 kilograms and with creatinine clearance greater than or equal to 30 mL per minute. For specific dosing recommendations for coadministered third agents, refer to their respective prescribing information
- ◆ While dosage adjustment is not required in patients with estimated creatinine clearance greater than or equal to 30 mL per minute, DESCOVY is not recommended in patients with estimated creatinine clearance below 30 mL per minute, because data in this population are insufficient

# EXECUTIVE SUMMARY

## ADVERSE REACTIONS

The most common adverse reaction (incidence greater than or equal to 10%, all grades) is nausea. Please see Section 6 of the full Prescribing Information for DESCOVY for adverse reactions from clinical trials experience.

## MANUFACTURER

DESCOVY is manufactured and distributed by:

Gilead Sciences, Inc.  
Foster City, CA 94404

## DOSAGE FORMS AND HOW SUPPLIED

Each DESCOVY tablet contains:

- ◆ Emtricitabine (FTC), 200 mg
- ◆ Tenofovir alafenamide (TAF), 25 mg (equivalent to 28 mg of tenofovir alafenamide fumarate)

DESCOVY tablets are blue, rectangular-shaped, and film coated, with “GSI” debossed on one side and “225” on the other side of the tablet.

Each bottle contains 30 tablets (NDC 61958-2002-1), a silica gel desiccant, polyester coil, and is closed with a child-resistant closure.

## WHOLESALE ACQUISITION COST (WAC)

In the United States, the WAC for a 30-day supply of DESCOVY 200/25 mg is \$1,466.44 or about \$17,842 per year.

## FDA APPROVAL DATE

DESCOVY was approved by the US Food and Drug Administration on April 4, 2016.



Pill not actual size

[Click here](#) for full Prescribing Information for DESCOVY, including **BOXED WARNING**.

# EXECUTIVE SUMMARY

## CLINICAL DATA SUMMARY

Trials of FTC+TAF with EVG+COBI have been evaluated in HIV-1 infected adults as initial therapy in those with no antiretroviral treatment history and to replace a stable antiretroviral regimen in those who were virologically-suppressed for at least 6 months with no known resistance substitutions.

A trial of FTC+TAF with EVG+COBI included 23 treatment-naïve HIV-1 infected pediatric patients aged 12 to less than 18 years old and greater than 35 kg.

A trial of FTC+TAF with EVG+COBI included 248 HIV-1 infected patients with creatinine clearance greater than 30 mL per minute but less than 70 mL per minute. Six of the patients were treatment-naïve and 242 were virologically-suppressed (HIV-1 RNA less than 50 copies per mL for at least 6 months before switching to FTC+TAF with EVG+COBI).

**Table 1: Studies conducted with FTC/TAF in combination with other antiretroviral agents in subjects with HIV-1 infection<sup>2,3</sup>**

Population	Study	Treatment Arms (N)	Timepoint (Week)
Naïve adults	104/111 <sup>a</sup> (Pooled)	<b>FTC/TAF</b> + EVG/COBI <sup>e</sup> (866) <b>FTC/TDF</b> + EVG/COBI <sup>e</sup> (867)	48
Naïve adolescents	106 <sup>b</sup>	<b>FTC/TAF</b> + EVG/COBI <sup>e</sup> (23)	24
Virologically-suppressed adults	109 <sup>c</sup>	<b>FTC/TAF</b> + EVG/COBI <sup>e</sup> (959) <b>FTC/TDF</b> + third agent <sup>f</sup> (477)	48
Virologically-suppressed adults with renal impairment	112 <sup>d</sup>	<b>FTC/TAF</b> + EVG/COBI <sup>e</sup> (242)	24

FTC/TAF

<sup>a</sup>Randomized, double-blind, active-controlled studies.

<sup>b</sup>Open-label study in patients 12 to <18 years of age.

<sup>c</sup>Randomized, open-label, active-controlled study in adults with HIV-1 RNA <50 copies/mL.

<sup>d</sup>Open-label study in adults with HIV-1 RNA <50 copies/mL and CrCl 30-69 mL/min.

<sup>e</sup>Administered as a single-tablet regimen.

<sup>f</sup>Third agents included EVG + COBI<sup>e</sup>, EFV<sup>e</sup>, ATV + COBI, or ATV + RTV.\*

\*EVG = elvitegravir; COBI = cobicistat; EFV = efavirenz; ATV = atazanavir; RTV = ritonavir; FTC = emtricitabine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

# EXECUTIVE SUMMARY

## WARNINGS AND PRECAUTIONS

- ◆ **Fat redistribution** or accumulation has been observed in patients receiving antiretroviral therapy.
- ◆ **Immune reconstitution syndrome**, including the occurrence of autoimmune disorders with variable time to onset, has been reported.
- ◆ **New onset or worsening renal impairment:** Cases of acute renal failure and Fanconi syndrome have been reported with the use of tenofovir prodrugs. In clinical trials of emtricitabine and tenofovir alafenamide with elvitegravir and cobicistat, there have been no cases of Fanconi syndrome or proximal renal tubulopathy (PRT). Do not initiate DESCOVY in patients with estimated creatinine clearance (CrCl) <30 mL/min. Patients with impaired renal function and/or taking nephrotoxic agents (including NSAIDs) are at increased risk of renal-related adverse reactions. Discontinue DESCOVY in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

*Renal monitoring:* In all patients, monitor CrCl, urine glucose, and urine protein prior to initiating and during therapy. In patients with chronic kidney disease, additionally monitor serum phosphorus.

- ◆ **Bone loss and mineralization defects:** Decreases in bone mineral density (BMD) have been reported with the use of tenofovir prodrugs. Consider monitoring BMD in patients with a history of pathologic fracture or risk factors for bone loss. Mineralization defects, including osteomalacia associated with PRT, have been reported with the use of TDF-containing products.

# HIV DISEASE STATE OVERVIEW

## THE HIV PATIENT PROFILE

The Centers for Disease Control and Prevention (CDC) estimates that over 1.2 million adults and adolescents in the United States (US) are infected with HIV-1.<sup>4</sup> Since the beginning of the epidemic in the mid-1980s, the annual number of new HIV infections in the US has been reduced by more than two-thirds, from roughly 130,000 to approximately 50,000 annually—and has remained relatively stable for over a decade.<sup>4-6</sup>

While certain populations of Americans remain at high risk for HIV—specifically men who have sex with men (MSM) of all races and ethnicities<sup>4,5</sup>—the patient profile is changing:

- ◆ Nearly 25% of people living with HIV are women<sup>4</sup>
- ◆ Hispanics and African Americans account for an estimated 65% of those newly diagnosed and 61% of people living with HIV<sup>4</sup>
- ◆ New HIV infections are most common in MSM in the youngest cohort<sup>4,5</sup>
- ◆ Since 2010, the number of people living with diagnosed HIV infection has increased steadily in people 65 and older<sup>6</sup>

Additionally, because more than 50% of people living with HIV are aged 50 or older, they are at risk for diseases typically associated with aging.<sup>7,8</sup> These noninfectious comorbidities (non-acquired immunodeficiency syndrome [AIDS] related conditions) occur at a rate that is significantly higher in patients with HIV than in the general population.<sup>7</sup> As such, more time is spent managing the complexities of HIV-related comorbidities.<sup>8</sup>

Onset of age-related comorbidities in HIV+ patients can increase cost expenditures, including the associated costs of noninfectious comorbidities, outpatient visits, and pharmacy costs across commercial, Medicare, and Medicaid payer channels.<sup>10,11</sup>

## THE IMPORTANCE OF EARLY TREATMENT

Historically, since the early days of the HIV epidemic, HIV-infected individuals have had low CD4 counts at presentation to care. Yet, because of the toxicity associated with earlier antiretroviral therapies (ARTs), therapy was deferred until CD4 counts declined, putting an individual at risk of AIDS-defining conditions. Additionally, the magnitude of CD4 recovery was directly correlated with CD4 count at ART initiation. Consequently, many individuals who started treatment with CD4 counts  $<350$  cells/mm<sup>3</sup> never achieved counts  $>500$  cells/mm<sup>3</sup> after up to 6 years on ART. The management of HIV-infected patients has changed substantially since the early days of the HIV epidemic, and with the availability of newer, more potent, and less toxic antiretroviral agents, the Department of Health and Human Services (DHHS) guidelines now recommend ART for all HIV-infected patients regardless of their CD4 count.<sup>12</sup>

The global trend toward earlier initiation of treatment has gained momentum given the recent findings from the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) Strategic Timing of Antiretroviral Therapy (START) trial. Results from this trial revealed that HIV-infected individuals have a considerably lower risk of AIDS or other serious illnesses if they start taking antiretroviral drugs before their CD4+ T-cell count drops under 500 cells/mm<sup>3</sup>.<sup>13</sup>





# HIV DISEASE STATE OVERVIEW

## THE IMPORTANCE OF EARLY TREATMENT (cont.)

In response to the findings of the START study, the World Health Organization (WHO) now recommends initiating antiretroviral therapy early, effectively at the time of HIV diagnosis, as follows<sup>14</sup>:

- ◆ ART should be initiated among all adults with HIV, regardless of WHO clinical stage and at any CD4 cell count (strong recommendation, moderate-quality evidence)
- ◆ As a priority, ART should be initiated among all adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adults with CD4 count  $\leq 350$  cells/mm<sup>3</sup> (strong recommendation, moderate-quality evidence)

## TREATMENT OVERVIEW

Today, more than 25 antiretroviral drugs encompassing 6 classes are available for treating HIV infection.<sup>15</sup> Each class of antiretroviral therapy has a different mechanism of action, each interfering with a different step in the HIV replication cycle.<sup>15</sup>

Gilead Sciences currently offers more than 10 HIV single and combination products, including DESCOVY, and remains committed to transforming HIV care for the people living with this disease.

# DESCOVY SUMMARY OF PRODUCT INFORMATION

## BOXED WARNING

### **WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B**

**Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs in combination with other antiretrovirals.**

**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 coinfecting with human immunodeficiency virus-1 (HIV-1) and HBV. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfecting with HIV-1 and HBV and have discontinued products containing emtricitabine (FTC) and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of DESCOVY. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are coinfecting with HIV-1 and HBV and discontinue DESCOVY. If appropriate, initiation of anti-hepatitis B therapy may be warranted.**

## INDICATION AND USAGE

DESCOVY is indicated, in combination with other antiretroviral agents, for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older.

### Limitations of Use:

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

## DOSAGE AND ADMINISTRATION

Prior to initiation of DESCOVY, patients should be tested for hepatitis B infection.

Estimated creatinine clearance, urine glucose and urine protein should be assessed before initiating DESCOVY therapy and should be monitored during therapy in all patients.

The recommended dosage of DESCOVY is one tablet taken orally once daily, with or without food, in adult and pediatric patients 12 years of age and older weighing at least 35 kilograms and with creatinine clearance greater than or equal to 30 mL per minute. For specific dosing recommendations for coadministered third agents, refer to their respective prescribing information.

No dosage adjustment of DESCOVY is required in patients with estimated creatinine clearance greater than or equal to 30 mL per minute.

- ◆ DESCOVY is not recommended in patients with estimated creatinine clearance below 30 mL per minute, because data in this population are insufficient
- ◆ Please see page 11 for additional information on new onset or worsening of renal impairment and information on renal monitoring recommendations

# DESCOVY SUMMARY OF PRODUCT INFORMATION

## PRODUCT DESCRIPTION AND DOSAGE FORMS

Each DESCOVY tablet contains:

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Each bottle contains 30 tablets (NDC 61958-2002-1), a silica gel desiccant, polyester coil, and is closed with a child-resistant closure.

## WARNINGS AND PRECAUTIONS

### 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. Since TAF and FTC are nucleos(t)ide analogs, 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).

### Severe acute exacerbation of hepatitis B in patients coinfecting 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 antiretroviral therapy. DESCOVY is not approved for the treatment of chronic HBV infection, and the safety and efficacy of DESCOVY have not been established in patients coinfecting with HIV-1 and HBV.

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



Pill not actual size

# DESCOVY SUMMARY OF PRODUCT INFORMATION

## WARNINGS AND PRECAUTIONS (cont.)

### Fat redistribution

While no causal relationship has been established, redistribution or 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. The mechanism and long-term consequences of these events are currently unknown.

### Immune reconstitution syndrome

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

Autoimmune disorders (such as Graves' disease, polymyositis, 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.

### New onset or worsening renal impairment

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir prodrugs in both animal toxicology studies and human trials. In clinical trials of FTC+TAF with cobicistat (COBI) + elvitegravir (EVG), there have been no cases of Fanconi syndrome or proximal renal tubulopathy (PRT).

In clinical trials of FTC+TAF with EVG+COBI in treatment-naïve patients and in virally-suppressed adults switched to FTC+TAF with eGFRs greater than 50 mL per minute, renal serious adverse events or discontinuations due to renal adverse reactions were encountered in less than 1% of participants treated with FTC+TAF with EVG+COBI. In a study of virally-suppressed adults with baseline eGFRs between 30 and 69 mL per minute treated with FTC+TAF with EVG+COBI for a median duration of 43 weeks, FTC+TAF with EVG+COBI was permanently discontinued due to worsening renal function in 2 of 80 (3%) adults with a baseline eGFR between 30 and 50 mL per minute. DESCOVY is not recommended in patients with estimated creatinine clearance below 30 mL per minute because data in this population are insufficient.

Patients taking tenofovir prodrugs who have impaired renal function and those taking nephrotoxic agents including non-steroidal anti-inflammatory drugs are at increased risk of developing renal-related adverse reactions. Estimated creatinine clearance, urine glucose, and urine protein should be assessed before initiating DESCOVY therapy and should be monitored during therapy in all patients. Serum phosphorus should be monitored in patients with chronic kidney disease because these patients are at greater risk of developing Fanconi syndrome on tenofovir prodrugs. Discontinue DESCOVY in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

# DESCOVY SUMMARY OF PRODUCT INFORMATION

## WARNINGS AND PRECAUTIONS (cont.)

### Bone loss and mineralization defects

*Decrease in bone mineral density (BMD).* In animal toxicology studies and human clinical trials, TAF and tenofovir have been associated with decreases in BMD and increases in biochemical markers of bone metabolism suggestive of increased bone turnover. In clinical trials in HIV-1 infected treatment-naïve adults, a significant decline in bone mineral density was observed in 15% of adults treated with FTC+TAF with EVG+COBI. The long-term clinical significance of these changes has not been established.

Assessment of BMD should be considered for adults and pediatric patients treated with DESCOVY who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Calcium and vitamin D supplementation may be beneficial for all patients. If bone abnormalities are suspected, then appropriate consultation should be obtained.

*Mineralization defects.* Cases of osteomalacia associated with proximal renal tubulopathy, manifested as bone pain or pain in extremities and which may contribute to fractures, have been reported in association with the use of TDF-containing products. Hypophosphatemia and osteomalacia secondary to PRT have occurred in patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms while receiving products containing TDF. While not observed in clinical studies of DESCOVY, the risk of osteomalacia with DESCOVY is not known.

## ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug (or a drug given in various combinations with other concomitant therapy) cannot be directly compared to rates in the clinical trials of another drug (or drug given in the same or different combination therapy) and may not reflect the rates observed in practice.

### Adverse reactions in clinical trials of FTC+TAF with EVG+COBI in treatment-naïve adults with HIV-1 infection

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

# DESCOVY SUMMARY OF PRODUCT INFORMATION

## ADVERSE REACTIONS (cont.)

### Adverse reactions in clinical trials of FTC+TAF with EVG+COBI in treatment-naïve adults with HIV-1 infection (cont.)

#### Renal laboratory tests

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

#### Bone mineral density effects

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

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

### Adverse reactions in clinical trials in pediatric patients with HIV-1 infection

In a 24 week, open-label trial of 23 antiretroviral treatment-naïve HIV-1 infected pediatric patients aged 12 to less than 18 years old (weighing at least 35 kg) who received FTC+TAF with EVG+COBI, the safety of this combination was similar to that of adults. Among these pediatric patients, mean BMD increased from baseline to Week 24, +1.7% at the lumbar spine and +0.8% for the total body less head. Mean changes from baseline BMD Z-scores were -0.10 for lumbar spine and -0.11 for total body less head at Week 24. Two subjects had significant (greater than 4%) lumbar spine BMD loss at Week 24.

# DESCOVY SUMMARY OF PRODUCT INFORMATION

## DRUG INTERACTIONS

### Potential for other drugs to affect one or more components of DESCOVY

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

### Drugs affecting renal function

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

### Established and other potentially significant drug interactions

Important drug interaction information for DESCOVY is summarized in **Table 2**. The drug interactions described are based on studies conducted with DESCOVY, the components of DESCOVY (emtricitabine and tenofovir alafenamide) as individual agents, or are predicted drug interactions that may occur with DESCOVY.

**Table 2: Established and other potentially significant drug interactions<sup>a</sup>**

Alteration in dose or regimen may be recommended based on drug interaction studies or predicted interaction

Concomitant Drug Class: Drug Name	Effect on Concentration <sup>b</sup>	Clinical Comment
<b>Antiretroviral Agents: Protease Inhibitors (PIs)</b>		
Tipranavir/ritonavir	↓ TAF	Coadministration with DESCOVY is not recommended.
<b>Other Agents</b>		
<b>Anticonvulsants:</b> carbamazepine oxcarbazepine phenobarbital phenytoin	↓ TAF	Consider alternative anticonvulsant.
<b>Antimycobacterials:</b> rifabutin rifampin rifapentine	↓ TAF	Coadministration of DESCOVY with rifabutin, rifampin, or rifapentine is not recommended.
<b>Herbal Products:</b> St. John's wort ( <i>Hypericum perforatum</i> )	↓ TAF	Coadministration of DESCOVY with St. John's wort is not recommended.

a. This table is not all inclusive.

b. Decrease = ↓.

[Click here](#) for full Prescribing Information for DESCOVY, including **BOXED WARNING**.

# DESCOVY SUMMARY OF PRODUCT INFORMATION

## DRUG INTERACTIONS (cont.)

### Drugs without clinically significant interactions with DESCOVY

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

## USE IN SPECIFIC POPULATIONS

### Pregnancy

#### Pregnancy exposure registry

To monitor pregnancy outcomes of women exposed to DESCOVY, a pregnancy exposure registry has been established. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

#### Risk summary

There are insufficient human data on the use of DESCOVY during pregnancy to inform a drug-associated risk of birth defects and miscarriage. Tenofovir alafenamide (TAF) use in women during pregnancy has not been evaluated; however, emtricitabine (FTC) use during pregnancy has been evaluated in a limited number of women reported to the APR. Available data from the APR show no difference in the risk of overall major birth defects for FTC (2.4%) compared with the background rate for major birth defects of 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in the clinically recognized pregnancies in the U.S. general population is 15%–20%.

#### Human data

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



# DESCOVY SUMMARY OF PRODUCT INFORMATION

## USE IN SPECIFIC POPULATIONS (cont.)

### Lactation

#### Risk summary

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

While it is not known whether TAF is present in human breast milk, FTC has been shown to be present in human breast milk. Tenofovir has been shown to be present in the milk of lactating rats and rhesus monkeys after administration of TDF. It is not known if TAF can be present in animal milk.

It is not known if DESCOVY affects milk production or has effects on the breastfed child. Because of the potential for: 1) HIV transmission (in HIV-negative infants); 2) developing viral resistance (in HIV-positive infants); and 3) adverse reactions in a breastfed infant similar to those seen in adults, mothers should be instructed not to breastfeed if they are receiving DESCOVY.

#### Human data

*Emtricitabine:* Samples of breast milk obtained from 5 HIV-1-infected mothers show that emtricitabine is secreted in human milk. Breastfeeding infants whose mothers are being treated with emtricitabine may be at risk for developing viral resistance to emtricitabine. Other emtricitabine-associated risks in infants breastfed by mothers being treated with emtricitabine are unknown.

### Pediatric use

The efficacy and safety of DESCOVY, in combination with other antiretroviral agents, for the treatment of HIV-1 infection was established in pediatric patients aged 12 years old and older with body weight greater than or equal to 35 kg. Use of DESCOVY in this age group is supported by adequate and well controlled studies of FTC+TAF with EVG+COBI in adults and by a 24-week open-label trial of 23 antiretroviral treatment-naïve HIV-1 infected pediatric patients 12 to less than 18 years old (weighing at least 35 kg) treated with FTC+TAF with EVG+COBI. The safety and efficacy of FTC+TAF with EVG+COBI was similar to that of antiretroviral treatment-naïve HIV-1 infected adults on this regimen.

Safety and effectiveness of DESCOVY in pediatric patients less than 12 years of age or less than 35 kg have not been established.

### Geriatric use

In clinical trials, 80 of the 97 subjects enrolled aged 65 years and over received FTC+TAF and EVG+COBI. No differences in safety or efficacy have been observed between elderly subjects and those between 12 and less than 65 years of age.

# DESCOVY SUMMARY OF PRODUCT INFORMATION

## USE IN SPECIFIC POPULATIONS (cont.)

### Renal impairment

DESCOVY is not recommended in patients with severe renal impairment (estimated creatinine clearance below 30 mL per minute). No dosage adjustment of DESCOVY is recommended in patients with estimated creatinine clearance greater than or equal to 30 mL per min.

### Hepatic impairment

No dosage adjustment of DESCOVY is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. DESCOVY has not been studied in patients with severe hepatic impairment (Child-Pugh Class C).

## CLINICAL PHARMACOLOGY

### Pharmacodynamics

#### Cardiac electrophysiology

In a thorough QT/QTc study in 48 healthy subjects TAF, at the therapeutic dose or at a 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 of DESCOVY, FTC, or the combination of FTC and TAF on the QT interval is not known.

### Pharmacokinetics

#### Absorption, distribution, metabolism, and excretion

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

# DESCOVY SUMMARY OF PRODUCT INFORMATION

## CLINICAL PHARMACOLOGY (cont.)

### Pharmacokinetics (cont.)

#### Absorption, distribution, metabolism, and excretion (cont.)

**Table 3: Pharmacokinetic properties of the components of DESCOVY**

	Emtricitabine	Tenofovir Alafenamide
<b>Absorption</b>		
T <sub>max</sub> (h)	3	1
Effect of high-fat meal (relative to fasting) <sup>a</sup>	AUC Ratio = 0.91 (0.89,0.93) C <sub>max</sub> Ratio = 0.74 (0.69,0.78)	AUC Ratio = 1.75 (1.64,1.88) C <sub>max</sub> Ratio = 0.85 (0.75,0.95)
<b>Distribution</b>		
% Bound to human plasma proteins	<4	~80
Source of protein binding data	In vitro	Ex vivo
Blood-to-plasma ratio	0.6	1.0
<b>Metabolism</b>		
Metabolism	Not significantly metabolized	Cathepsin A <sup>b</sup> (PBMCs) CES1 (hepatocytes) CYP3A (minimal)
<b>Elimination</b>		
Major route of elimination	Glomerular filtration and active tubular secretion	Metabolism (>80% of oral dose)
t <sub>1/2</sub> (h) <sup>c</sup>	10	0.51
% Of dose excreted in urine <sup>d</sup>	70	<1
% Of dose excreted in feces <sup>d</sup>	13.7	31.7

PBMCs = peripheral blood mononuclear cells; CES1 = carboxylesterase 1.

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

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

c. t<sub>1/2</sub> values refer to median terminal plasma half-life. Note that the pharmacologically active metabolite, tenofovir diphosphate, has a half-life of 150-180 hours within PBMCs.

d. Dosing in mass balance studies: FTC (single dose administration of [<sup>14</sup>C] emtricitabine after multiple dosing of emtricitabine for ten days); TAF (single dose administration of [<sup>14</sup>C] tenofovir alafenamide).

# DESCOVY SUMMARY OF PRODUCT INFORMATION

## CLINICAL PHARMACOLOGY (cont.)

### Pharmacokinetics (cont.)

#### Absorption, distribution, metabolism, and excretion (cont.)

**Table 4: Multiple dose PK parameters of emtricitabine, tenofovir alafenamide and its metabolite tenofovir following oral administration with food in HIV-infected adults**

Parameter Mean (CV%)	Emtricitabine <sup>a</sup>	Tenofovir Alafenamide <sup>b</sup>	Tenofovir <sup>c</sup>
C <sub>max</sub> (microgram per mL)	2.1 (20.2)	0.16 (51.1)	0.02 (26.1)
AUC <sub>tau</sub> (microgram•hour per mL)	11.7 (16.6)	0.21 (71.8)	0.29 (27.4)
C <sub>trough</sub> (microgram per mL)	0.10 (46.7)	NA	0.01 (28.5)

CV = coefficient of variation; NA = not applicable.

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

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

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

## Microbiology

### Mechanism of action

The following describes the mechanism of action of each component of DESCOVY:

- ◆ Emtricitabine, a synthetic nucleoside analog of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of the HIV-1 reverse transcriptase by competing with the natural substrate deoxycytidine 5'-triphosphate and by being incorporated into nascent viral DNA, which results in chain termination. Emtricitabine 5'-triphosphate is a weak inhibitor of mammalian DNA polymerases  $\alpha$ ,  $\beta$ ,  $\epsilon$ , and mitochondrial DNA polymerase  $\gamma$
- ◆ Tenofovir alafenamide is a phosphonoamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analog). Plasma exposure to TAF allows for permeation into cells and then TAF is intracellularly converted to tenofovir through hydrolysis by cathepsin A. Tenofovir is subsequently phosphorylated by cellular kinases to the active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HIV replication through incorporation into viral DNA by the HIV reverse transcriptase, which results in DNA chain termination

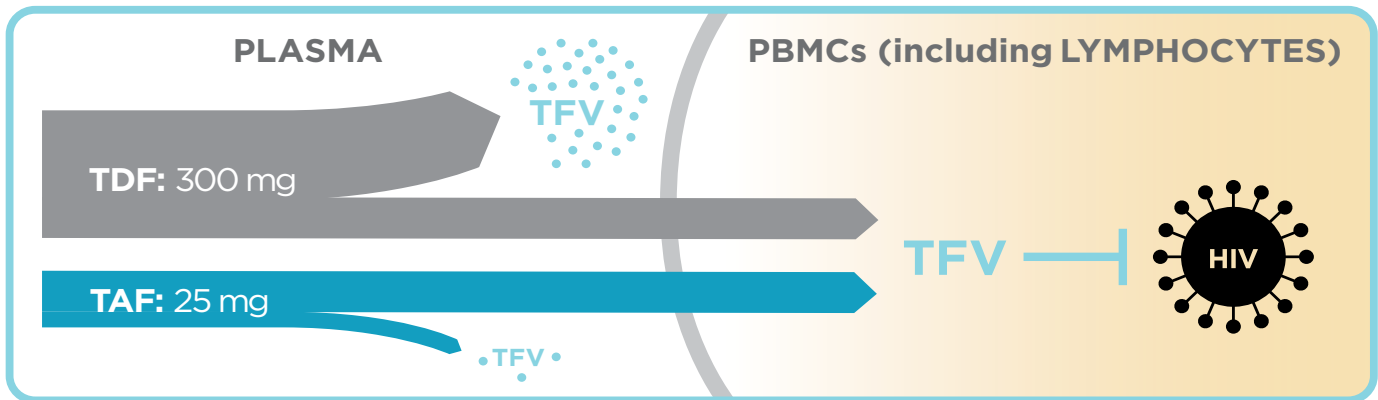
Tenofovir has activity against HIV-1. Cell culture studies have shown that both tenofovir and FTC can be fully phosphorylated when combined in cells. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase  $\gamma$  and there is no evidence of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

# DESCOVY SUMMARY OF PRODUCT INFORMATION

## CLINICAL PHARMACOLOGY (cont.)

### Microbiology (cont.)

**Figure 1: Mechanism of action and pharmacokinetics of TAF**



The TAF component of DESCOVY is expected to result in >90% lower concentration of tenofovir (TFV) in plasma vs a 300 mg dose of TDF.<sup>16</sup>

- ◆ In two trials of treatment-naïve adults with HIV-1 infection, a 10 mg oral dose of TAF in FTC/TAF + EVG/COBI resulted in >90% lower concentrations of TFV in plasma as compared to a 300 mg oral dose of TDF in EVG/COBI/FTC/TDF<sup>16</sup>
- ◆ In a PK study, the unboosted 25 mg of TAF in DESCOVY was demonstrated to be bioequivalent to the COBI-boosted 10 mg of TAF in FTC/TAF + EVG/COBI<sup>17</sup>

### Resistance

#### In cell culture

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

*Tenofovir alafenamide:* HIV-1 isolates with reduced susceptibility to TAF were selected in cell culture. HIV-1 isolates selected by TAF expressed a K65R substitution in HIV-1 RT, sometimes in the presence of S68N or L429I substitutions; in addition, a K70E substitution in HIV-1 RT was observed.

#### In clinical trials

The resistance profile of DESCOVY in combination with other antiretroviral agents for the treatment of HIV-1 infection is based on studies of FTC+TAF with EVG+COBI in the treatment of HIV-1 infection. In a pooled analysis of antiretroviral-naïve subjects, genotyping was performed on plasma HIV-1 isolates from all subjects with HIV-1 RNA greater than 400 copies per mL at confirmed virologic failure, at Week 48, or at time of early study drug discontinuation. Genotypic resistance developed in 7 of 14 evaluable subjects. The resistance-associated substitutions that emerged were M184V/I (N = 7) and K65R (N = 1). Three subjects had virus with emergent R, H, or E at the polymorphic Q207 residue in reverse transcriptase.

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

# DESCOVY SUMMARY OF PRODUCT INFORMATION

## CLINICAL PHARMACOLOGY (cont.)

### Microbiology (cont.)

#### Cross-resistance

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

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

*Tenofovir alafenamide:* Tenofovir resistance substitutions K65R and K70E result in reduced susceptibility to abacavir, didanosine, emtricitabine, lamivudine, and tenofovir. HIV-1 with multiple thymidine analog substitutions (M41L, D67N, K70R, L210W, T215F/Y, K219Q/E/N/R), or multinucleoside resistant HIV-1 with a T69S double insertion mutation or with a Q151M mutation complex including K65R, showed reduced susceptibility to TAF in cell culture.

## CLINICAL STUDIES

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

In a trial of FTC+TAF with EVG+COBI in 23 treatment-naïve HIV-1 infected pediatric patients aged 12 to less than 18 years old and greater than 35 kg, the virologic response rate (i.e., HIV-1 RNA less than 50 copies per mL) was 91% at 24 weeks.

In a trial in 248 HIV-1 infected adult patients with estimated creatinine clearances greater than 30 mL per minute but less than 70 mL/min, 95% (235/248) of the combined population of treatment-naïve subjects (N = 6) begun on FTC+TAF with EVG+COBI and those previously virologically-suppressed on other regimens (N = 242) and switched to FTC+TAF with EVG+COBI had HIV-1 RNA less than 50 copies per mL at Week 24.

# IMPORTANT SAFETY INFORMATION

## BOXED WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

- ◆ **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs in combination with other antiretrovirals.**
- ◆ **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 coinfecting with HIV-1 and HBV. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfecting with HIV-1 and HBV and have discontinued products containing emtricitabine and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of DESCOVY. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are coinfecting with HIV-1 and HBV and discontinue DESCOVY. If appropriate, initiation of anti-hepatitis B therapy may be warranted.**

### Warnings and precautions

- ◆ **Fat redistribution** or accumulation has been observed in patients receiving antiretroviral therapy.
- ◆ **Immune reconstitution syndrome**, including the occurrence of autoimmune disorders with variable time to onset, has been reported.
- ◆ **New onset or worsening renal impairment:** Cases of acute renal failure and Fanconi syndrome have been reported with the use of tenofovir prodrugs. In clinical trials of emtricitabine and tenofovir alafenamide with elvitegravir and cobicistat, there have been no cases of Fanconi syndrome or proximal renal tubulopathy (PRT). Do not initiate DESCOVY in patients with estimated creatinine clearance (CrCl) <30 mL/min. Patients with impaired renal function and/or taking nephrotoxic agents (including NSAIDs) are at increased risk of renal-related adverse reactions. Discontinue DESCOVY in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

*Renal monitoring:* In all patients, monitor CrCl, urine glucose, and urine protein prior to initiating and during therapy. In patients with chronic kidney disease, additionally monitor serum phosphorus.

- ◆ **Bone loss and mineralization defects:** Decreases in bone mineral density (BMD) have been reported with the use of tenofovir prodrugs. Consider monitoring BMD in patients with a history of pathologic fracture or risk factors for bone loss. Mineralization defects, including osteomalacia associated with PRT, have been reported with the use of TDF-containing products.

### Adverse reactions

- ◆ **Most common adverse reaction** (incidence  $\geq 10\%$ ; all grades) in clinical studies was nausea (10%).

### Drug interactions

- ◆ **Prescribing information:** Consult the full prescribing information for DESCOVY for more information on potentially significant drug interactions, including clinical comments.
- ◆ **Metabolism:** Drugs that inhibit P-gp can increase the concentrations of components of DESCOVY. Drugs that induce P-gp can decrease the concentrations of components of DESCOVY, which may lead to loss of efficacy and development of resistance.
- ◆ **Drugs affecting renal function:** Coadministration of DESCOVY with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of emtricitabine and tenofovir and the risk of adverse reactions.



# IMPORTANT SAFETY INFORMATION

## Dosage and administration

- ◆ **Dosage:** Patients 12 years and older ( $\geq 35$  kg): 1 tablet taken orally once daily with or without food.
- ◆ **Renal impairment:** Not recommended in patients with CrCl  $< 30$  mL/min.
- ◆ **Testing prior to initiation:** Test patients for HBV infection and assess CrCl, urine glucose and urine protein.

## Pregnancy and lactation

- ◆ **Pregnancy:** There are insufficient data on the use of DESCOVY during pregnancy. In animal studies, no adverse developmental effects were observed with the components of DESCOVY. An Antiretroviral Pregnancy Registry has been established.
- ◆ **Lactation:** Women infected with HIV-1 should be instructed not to breastfeed, due to the potential for HIV-1 transmission.



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