University of Illinois at Chicago Mail - HIV/AIDS Update

U.S. Food & Drug Administration (FDA) <fda@service.govdelivery.com>Tue, Apr 5, 2016 at 10:58 AM
Reply-To: fda@service.govdelivery.com
To: matec@uic.edu

You are receiving this message as a subscriber to the FDA HIV/AIDS electronic list serve. The purpose of the list serve is to relay important information about HIV/AIDS-related products and issues, including product approvals, significant labeling changes, safety warnings, notices of upcoming public meetings and alerts to proposed regulatory guidances for comment.

Please do not reply to this message.

On April 4, 2016 FDA approved DESCOVY, a two-drug fixed dose combination tablet containing 2 HIV nucleoside analog reverse transcriptase inhibitors (NRTIs), emtricitabine (FTC) and tenofovir alafenamide (TAF). Each DESCOVY tablet contains 200 mg of FTC and 25 mg of TAF (equivalent to 28 mg of tenofovir alafenamide fumarate).

DESCOVY is not a complete regimen for the treatment of HIV-1 infection and must be combined with other antiretroviral agents to form a complete regimen.

The approval is based on a relative bioavailability trial demonstrating FTC and TAF exposures were similar between DESCOVY and GENVOYA (elvitegravir/cobicistat/FTC/TAF). A clinical trial to evaluate the efficacy and safety of DESCOVY was not required because the safety and efficacy of FTC and TAF was established previously in clinical trials with GENVOYA.

TAF 25 mg provides for TAF exposures that match or exceed those observed in patients receiving GENVOYA, ensuring adequate antiviral effect. With respect to safety, TAF exposures for FTC/TAF 200 mg/25 mg when used with some boosted protease inhibitors will be higher than that of GENVOYA. However, exposures of the metabolite, tenofovir, will remain substantially lower than that observed with previously approved tenofovir disoproxil fumarate (TDF) formulations such as, Viread (TDF), Truvada (FTC/TDF) and Stribild (Elvitegravir, COBI, FTC, TDF). Thus, the safety of DESCOVY is supported by formulations with substantially higher tenofovir exposures.

Below are more specific details included in the DESCOVY package insert.

INDICATIONS 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 Testing Prior to Initiation of DESCOVY

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

Recommended Dosage

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 with body weight at least 35 kg and creatinine clearance greater than or equal to 30 mL per minute

Not Recommended in Patients with Severe Renal Impairment

DESCOVY is not recommended in patients with estimated creatinine clearance below 30 mL per minute

The product labeling contains the following **WARNINGS and PRECAUTIONS**

WARNINGS AND PRECAUTIONS

- Lactic Acidosis/Severe Hepatomegaly with Steatosis
- Severe Acute Exacerbation of Hepatitis B in Patients Coinfected with HIV-1 and HBV
- Fat Redistribution
- Immune Reconstitution Syndrome
- New Onset or Worsening Renal Impairment
- Bone Loss and Mineralization Defects

Additionally, the DESCOVY label includes a boxed warning for lactic acidosis/severe hepatomegaly with steatosis and post treatment acute exacerbation of Hepatitis B.

DRUG INTERACTIONSPotential 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 1). 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 by a combination of glomerular filtration and active tubular secretion, coadministration of DESCOVY with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of FTC, tenofovir, and other renally eliminated drugs and this may increase the risk of adverse reactions. Some examples of drugs that are eliminated by active tubular secretion include, but are not limited to, acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs

Established and Other Potentially Significant Interactions

Table 1 provides a listing of established or potentially clinically significant drug interactions with recommended steps to prevent or manage the drug interaction (the table is not all inclusive). The drug interactions described are based on studies conducted with either DESCOVY, the components of DESCOVY (emtricitabine and tenofovir alafenamide) as individual agents, or are predicted drug interactions that may occur with DESCOVY.

Table 1 Established and Other Potentially Significant[a] Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Antiretroviral Agents: Protease Inhibitors (PI)		
tipranavir/ritonavir	TAF	Coadministration with DESCOVY is not recommended.
Other Agents		
Anticonvulsants: carbamazepine oxcarbazepine phenobarbital phenytoin	↓TAF	Consider alternative anticonvulsant.

Antimycobacterials: rifabutin rifampin rifapentine	↓TAF	Coadministration of DESCOVY with rifabutin, rifampin, or rifapentine is not recommended.
Herbal Products: St. John's wort *(Hypericum perforatum)*	↓TAF	Coadministration of DESCOVY with St. John's wort is not recommended.

[a] This table is not all inclusive.

[b] ↓=Decrease

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.

Drug Interaction Studies

The effects of coadministered drugs on the exposure of TAF are shown in Table 5 and the effects of DESCOVY or its components on the exposure of coadministered drugs are shown in Table 6 [these studies were conducted with DESCOVY or the components of DESCOVY (FTC or TAF) administered alone].

Table 5 Drug Interactions: Changes in TAF Pharmacokinetic Parameters in the Presence of Coadministered Drug(s)[a]

Coadministered Drug	**Coadministered Drug(s) Dosage (once daily) (mg)**	**Tenofovir Alafenamide Dosage (once daily) (mg)**	**N**	**Mean Ratio of TAF PK Parameters (90% CI); No effect = 1.00**		
				C_{max}	**AUC**	**C_{min}**

Atazanavir	300 (+100 ritonavir)	10	10	1.77 (1.28, 2.44)	1.91 (1.55, 2.35)	NC
Cobicistat	150	8	12	2.83 (2.20, 3.65)	2.65 (2.29, 3.07)	NC
Darunavir	800 (+150 cobicistat)	25[b]	11	0.93 (0.72, 1.21)	0.98 (0.80, 1.19)	NC
Darunavir	800 (+100 ritonavir)	10	10	1.42 (0.96, 2.09)	1.06 (0.84, 1.35)	NC
Dolutegravir	50	10	10	1.24 (0.88, 1.74)	1.19 (0.96, 1.48)	NC
Efavirenz	600	40[b]	11	0.78 (0.58,1.05)	0.86 (0.72, 1.02)	NC
Lopinavir	800 (+200 ritonavir)	10	10	2.19 (1.72, 2.79)	1.47 (1.17, 1.85)	NC
Rilpivirine	25	25	17	1.01 (0.84,	1.01 (0.94,	NC

				1.22)	1.09)	
Sertraline	50 (dosed as a single dose)	10[c]	19	1.00 (0.86, 1.16)	0.96 (0.89,1.03)	NC

NC=Not Calculated

[a] All interaction studies conducted in healthy volunteers.

[b] Study conducted with DESCOVY (FTC/TAF).

[c] Study conducted with FTC+TAF with EVG+COBI.

Table 6 Drug Interactions: Changes in PK Parameters for Coadministered Drug in the Presence of DESCOVY or the Individual Components[a]

Coadministered Drug	Coadministered Drug Dosage (once daily) (mg)	Tenofovir Alafenamide Dosage (once daily) (mg)	N	Mean Ratio of Coadministered Drug PK Parameters (90% CI); No effect = 1.00		
				C_{max}	AUC	C_{min}
Atazanavir	300 +100 ritonavir	10	10	0.98 (0.89, 1.07)	0.99 (0.96, 1.01)	1.00 (0.96, 1.04)
Cobicistat	150	8	14	1.06 (1.00, 1.12)	1.09 (1.03, 1.15)	1.11 (0.98, 1.25)
Darunavir	800 +150 cobicistat	25[b]	11	1.02 (0.96, 1.09)	0.99 (0.92, 1.07)	0.97 (0.82, 1.15)

Darunavir	800 +100 ritonavir	10	10	0.99 (0.91, 1.08)	1.01 (0.96, 1.06)	1.13 (0.95, 1.34)
Dolutegravir	50 mg	10	10	1.15 (1.04, 1.27)	1.02 (0.97, 1.08)	1.05 (0.97, 1.13)
Lopinavir	800 +200 ritonavir	10	10	1.00 (0.95, 1.06)	1.00 (0.92, 1.09)	0.98 (0.85, 1.12)
Midazolam[c]	2.5 (orally)	25	18	1.02 (0.92, 1.13)	1.12 (1.03, 1.22)	NC
	1 (intravenous)			0.99 (0.89, 1.11)	1.08 (1.04, 1.14)	NC
Rilpivirine	25	25	16	0.93 (0.87, 0.99)	1.01 (0.96, 1.06)	1.13 (1.04, 1.23)
Sertraline	50 (dosed as a single dose)	10[d]	19	1.14 (0.94, 1.38)	0.93 (0.77, 1.13)	NC

NC=Not Calculated

[a] All interaction studies conducted in healthy volunteers.

[b] Study conducted with DESCOVY (FTC/TAF).

[c] A sensitive CYP3A4 substrate.

[d] Study conducted with FTC+TAF with EVG+COBI.

The product labeling for DESCOVY will be made available through Drugs@FDA and DailyMed.

DESCOVY is a product of Gilead Sciences.

Richard Klein
Office of Health and Constituent Affairs
Food and Drug Administration

Kimberly Struble
Division of Antiviral Products
Food and Drug Administration

Steve Morin
Office of Health and Constituent Affairs
Food and Drug Administration

If you are interested in receiving information about a broader range of FDA topics, consider subscribing to the FDA Patient Network News, a twice monthly newsletter containing FDA-related information on a variety of topics, including new product approvals, significant labeling changes, safety warnings, notices of upcoming public meetings, proposed regulatory guidances and opportunity to comment, and other information of interest to patients and patient advocates.