CLINICAL UPDATE

Brand Name	Descovy®
Generic Name	emtricitabine and tenofovir alafenamide
Drug Manufacturer	Gilead Sciences, Inc

Clinical Update

TYPE OF CLINICAL UPDATE

New Strength

FDA APPROVAL DATE

January 7, 2022

LAUNCH DATE

February 25, 2022

REVIEW DESIGNATION

Standard

TYPE OF REVIEW

Type 4 - New Combination; New Drug Application (NDA): 208215

DISPENSING RESTRICTIONS

N/A

Overview

INDICATION(S) FOR USE

HIV-1 Treatment:

Descovy® is a two-drug combination of emtricitabine (FTC) and tenofovir alafenamide (TAF), both HIV nucleoside analog reverse transcriptase inhibitors (NRTIs), and is indicated:

- in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 35 kg.
- in combination with other antiretroviral agents other than protease inhibitors that require a CYP3A inhibitor for the treatment of HIV-1 infection in pediatric patients weighing at least 14 kg and less than 35 kg.

HIV-1 PrEP:

Descovy® is indicated in at-risk adults and adolescents weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection from sexual acquisition, excluding individuals at risk from receptive vaginal sex. Individuals must have a negative HIV-1 test immediately prior to initiating Descovy® for HIV-1 PrEP.

Limitations of Use:

The indication does not include use of Descovy® in individuals at risk of HIV-1 from receptive vaginal sex because effectiveness in this population has not been evaluated.

CLINICAL UPDATE

MECHANISMS OF ACTION

Emtricitabine: FTC, a synthetic nucleoside analog of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of the HIV-1 reverse transcriptase by competing with the natural substrate deoxycytidine 5'-triphosphate and by being incorporated into nascent viral DNA which results in chain termination. Emtricitabine 5'-triphosphate is a weak inhibitor of mammalian DNA polymerases α, β, Ɛ, and mitochondrial DNA polymerase γ.

Tenofovir Alafenamide: TAF is a phosphonoamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analog). Plasma exposure to TAF allows for permeation into cells and then TAF is intracellularly converted to tenofovir through hydrolysis by cathepsin A. Tenofovir is subsequently phosphorylated by cellular kinases to the active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HIV-1 replication through incorporation into viral DNA by the HIV reverse transcriptase, which results in DNA chain-termination.

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

DOSAGE FORM(S) AND STRENGTH(S)

Tablets: 200 mg/25 mg and 120 mg/15 mg of FTC and TAF respectively.

DOSE & ADMINISTRATION

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

EFFICACY

The efficacy and safety of Descovy® have been evaluated in the trials summarized in below table.

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

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

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

The primary outcome was the incidence of documented HIV-1 infection per 100 person-years in participants randomized to Descovy® and Truvada (with a minimum follow-up of 48 weeks and at least 50% of participants having 96 weeks of follow-up). Descovy® was non-inferior to Truvada in reducing the risk of acquiring HIV-1

infection (Table 2). The results were similar across the subgroups of age, race, gender identity, and baseline Truvada for PrEP use.

Table 2: HIV-1 Infection Results in DISCOVER Trial – Full Analysis Set

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

CI = Confidence interval.

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