October 2, 2017: Approved Changes to the DESCOVY Label

FDA HIV Email Updates provide information about FDA HIV product approval, safety warnings, medical product labeling changes, notices of upcoming meetings, and notices about proposed regulatory guidances.

The DESCOVY (emtricitabine/tenofovir alafenamide) package insert was recently updated to include the Week 24 safety and efficacy data from Study GS-US-292-0106 (cohort 2) in HIV-1 positive, virologically suppressed children 6 to less than 12 years of age weighing at least 25 kg. The following revisions were made to the package insert.

Section 1: INDICATIONS AND USAGE was updated as follows:
DESCOVY 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.

DESCOVY is also indicated, 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 25 kg and less than 35 kg.

Section 2: DOSAGE AND ADMINISTRATION was updated to state:

Recommended Dosage

DESCOVY is a two-drug fixed dose combination product containing 200 mg of emtricitabine (FTC) and 25 mg of tenofovir alafenamide (TAF). The recommended dosage of DESCOVY is one tablet taken orally once daily with or without food in adults and pediatric patients with body weight at least 25 kg and 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. The safety and effectiveness of DESCOVY coadminstered with an HIV-1 protease inhibitor that is administered with either ritonavir or cobicistat have not been established in pediatric subjects weighing less than 35 kg.

Section 5 WARNINGS AND PRECAUTIONS subsection 5.5 Bone Loss and Mineralization Defects was deleted from the package insert. The bone mineral density effects are included in Section 6: ADVERSE REACTIONS along with other changes as follows:

<u>Adverse Reactions in Clinical Trials in Pediatric Subjects with HIV-1 Infection</u>
In an open-label trial of antiretroviral treatment-naïve HIV-1 infected pediatric subjects between the ages of 12 to less than 18 years weighing at least 35 kg through 48 weeks (N=50; cohort 1) and virologically-suppressed subjects between the ages of 6 to less than 12 years weighing at least 25 kg (N=23; cohort 2) who received FTC+TAF with EVG+COBI through 24 weeks, with the exception of a decrease in the mean CD4+ cell count observed in cohort 2, the safety of this combination was similar to that of adults.

Bone Mineral Density Effects

- *Cohort 1: Treatment-naïve adolescents (12 to less than 18 years; at least 35 kg)*

Among the subjects in cohort 1 receiving FTC+TAF with EVG+COBI, mean BMD increased from baseline to Week 48, +4.2% at the lumbar spine and +1.3% for the total body less head (TBLH). Mean changes from baseline BMD Z-scores were −0.07 for lumbar spine and −0.20 for TBLH at Week 48. One subject had significant (at least 4%) lumbar spine BMD loss at Week 48.

- *Cohort 2: Virologically-suppressed children (6 to less than 12 years; at least 25 kg)*

Among the subjects in cohort 2 receiving FTC+TAF with EVG+COBI, mean BMD increased from baseline to Week 24, +2.9% at the lumbar spine and +1.7% for TBLH. Mean changes from baseline BMD Z-scores were -0.06 for lumbar spine and -0.18 for TBLH at Week 24. Two subjects had significant (at least 4%) lumbar spine BMD loss at Week 24.

Change from Baseline in CD4+ cell counts

- *Cohort 2: Virologically-suppressed children (6 to less than 12 years; at least 25 kg)*

Cohort 2 evaluated pediatric subjects (N=23) who were virologically-suppressed and who switched from their antiretroviral regimen to FTC+TAF with EVG+COBI. Although all subjects had HIV-1 RNA < 50 copies/mL, there was a decrease from baseline in CD4+ cell count at Week 24. The mean baseline and mean change from baseline in CD4+ cell count and in CD4% from Week 2 to Week 24 are presented in Table 1. All subjects maintained their CD4+ cell counts above 400 cells/mm^3.

Table 1 - Mean Change in CD4+ Count and Percentage from Baseline to Week 24 in Virologically-Suppressed Pediatric Patients from 6 to <12 Years Who Switched to FTC+TAF with EVG+COBI

	Baseline	**Mean Change from Baseline**			
		Week 2	**Week 4**	**Week 12**	**Week 24**
CD4+ Cell Count (cells/mm^3)	966 (201.7)[a]	-162	-125	-162	-150
CD4%	40 (5.3)[a]	+0.5%	-0.1%	-0.8%	-1.5%

a. Mean (SD)

Section 8.4 Pediatric Use was updated as follows:

The safety and effectiveness of DESCOVY, in combination with other antiretroviral agents, for the treatment of HIV-1 infection was established in pediatric patients with body weight greater than or equal to 25 kg.

Use of DESCOVY in pediatric patients between the ages of 12 to less than 18 years weighing at least 35 kg is supported by adequate and well controlled studies of FTC+TAF with EVG+COBI in adults and by an open-label trial in antiretroviral treatment-naïve HIV-1 infected pediatric subjects ages 12 to less than 18 years and weighing at least 35 kg (N=50; cohort 1). The safety and efficacy of FTC+TAF with EVG+COBI in these pediatric subjects was similar to that of HIV-1 infected adults on this regimen.

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Use of DESCOVY in pediatric patients weighing at least 25 kg is supported by adequate and well controlled studies of FTC+TAF with EVG+COBI in adults and by an open-label trial in virologically-suppressed pediatric subjects between the ages of 6 to less than 12 years weighing at least 25 kg, in which subjects were switched from their antiretroviral regimen to FTC+TAF with EVG+COBI (N=23; cohort 2). The safety in these subjects through 24 weeks of FTC+TAF with EVG+COBI was similar to that of HIV-1 infected adults on this regimen, with the exception of a decrease in mean change from baseline in CD4+ cell count.

Safety and effectiveness of DESCOVY coadminstered with an HIV-1 protease inhibitor that is administered with either ritonavir or cobicistat have not been established in pediatric subjects weighing less than 35 kg.

Safety and effectiveness of DESCOVY in pediatric patients less than 25 kg have not been established.

Section 12 CLINICAL PHARMACOLOGY and Section 14 CLINICAL STUDIES was updated as follows

Pediatric Patients

Mean exposures of TAF in 24 pediatric subjects aged 12 to less than 18 years who received FTC+TAF with EVG+COBI were decreased (23% for AUC) and FTC exposures were similar compared to exposures achieved in treatment-naïve adults following administration of this dosage regimen. The TAF exposure differences are not thought to be clinically significant based on exposure-response relationships (Table 6).

Table 6 - ultiple Dose PK Parameters of Emtricitabine, Tenofovir Alafenamide and its Metabolite Tenofovir Following Oral Administration of FTC+TAF with EVG+COBI in HIV-Infected Pediatric Subjects Aged 12 to less than 18 Years[a]

Parameter Mean (CV%)	**Emtricitabine**	**Tenofovir Alafenamide**	**Tenofovir**
C_{max} (microgram per mL)	2.3 (22.5)	0.17 (64.4)	0.02 (23.7)
AUC_{tau} (microgram•hour per mL)	14.4 (23.9)	0.20[b] (50.0)	0.29[b] (18.8)
C_{trough} (microgram per mL)	0.10[b] (38.9)	NA	0.01 (21.4)

CV = Coefficient of Variation; NA = Not Applicable
a. From Intensive PK analysis in a trial in treatment-naïve pediatric subjects with HIV-1 infection (N=24).
b. N=23

Exposures of FTC and TAF achieved in 23 pediatric subjects between the ages of 6 to less than 12 years and weighing at least 25 kg (55 lbs) who received FTC+TAF with EVG+COBI were higher (20 to 80% for AUC) than exposures achieved in adults following the administration of this dosage regimen; however, the increase was not considered clinically significant (Table 7) *[see Use in Specific Populations (8.4)]*.

Table 7 - Multiple Dose PK Parameters of Emtricitabine, Tenofovir Alafenamide and its Metabolite Tenofovir Following Oral Administration of FTC+TAF with EVG+COBI in HIV-Infected Pediatric Subjects Aged 6 to less than 12 Years[a]

Parameter Mean (CV%)	Emtricitabine	Tenofovir Alafenamide	Tenofovir
C_{max} (microgram per mL)	3.4 (27.0)	0.31 (61.2)	0.03 (20.8)
AUC_{tau} (microgram•hour per mL)	20.6[b] (18.9)	0.33 (44.8)	0.44 (20.9)
C_{trough} (microgram per mL)	0.11 (24.1)	NA	0.02 (24.9)

CV = Coefficient of Variation; NA = Not Applicable

[a] From Intensive PK analysis in a trial in virologically-suppressed pediatric subjects with HIV-1 infection (N=23).
[b] N=22

CLINICAL STUDIES

An open-label, single arm trial of FTC+TAF with EVG+COBI enrolled 50 treatment-naïve HIV-1 infected adolescents aged 12 to less than 18 years weighing at least 35 kg (cohort 1) and 23 virologically suppressed children aged 6 to less than 12 years weighing at least 25 kg (cohort 2). In cohort 1, the virologic response rate (i.e., HIV-1 RNA less than 50 copies per mL) was 92% (46/50) and the mean increase from baseline in CD4+ cell count was 224 cells per mm^3 at Week 48. In cohort 2, 100% of subjects remained virologically suppressed at Week 24. From a mean (SD) baseline CD4+ cell count of 966 (201.7), the mean change from baseline in CD4+ cell count was -150 cells/mm^3 and the mean (SD) change in CD4% was -1.5% (3.7%) at Week 24. All subjects maintained CD4+ cell counts above 400 cells/mm^3.

The updated label will soon be available at drugs@fda or DailyMed

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