September 27, 2017: Genvoya label update

FDA approved changes to the GENVOYA (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide) to update the package insert with Week 24 safety and efficacy data from Study GS-US-292-0106 (Cohort 2) in HIV-1 positive, virologically suppressed children 6 to < 12 years of age weighing at least 25 kilograms (kg). The specific changes are summarized below.

Section 1: INDICATIONS AND USAGE

GENVOYA is indicated as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 25 kg who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically-suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of GENVOYA

Section 2: DOSAGE AND ADMINISTRATION

Recommended Dosage

GENVOYA is a four-drug fixed dose combination product containing 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide (TAF). The recommended dosage of GENVOYA is one tablet taken orally once daily with 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

Section 6: ADVERSE REACTIONS

Clinical Trials in Pediatric Subjects:

Safety in Pediatric Patients

The safety of GENVOYA in HIV-1 infected pediatric subjects was evaluated in treatment-naïve subjects between the ages of 12 to less than 18 years and weighing at least 35 kg (N=50) throughWeek 48 (cohort 1), and in virologically-suppressed subjects between the ages of 6 to less than 12 years and weighing at least 25 kg (N=23) through Week 24 (cohort 2) in an open-label clinical trial (Study 106). With the exception of a decrease in the mean CD4+ cell count observed in cohort 2 of Study 106, the safety profile in pediatric subjects who received treatment with GENVOYA 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.

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 GENVOYA, 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 GENVOYA 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 GENVOYA, 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 GENVOYA subjects had significant (at least 4%) lumbar spine BMD loss at Week 24.
- Cohort 2: Virologically-suppressed children (6 to less than 12 years; at least 25 kg)

Change from Baseline in CD4+ cell counts

- Cohort 2 of Study 106 evaluated pediatric subjects (N=23) who were virologically-suppressed and who switched from their antiretroviral regimen to GENVOYA. 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 5. All subjects maintained their CD4+ cell counts above 400 cells/mm^3.

Table 5:

Mean Change in CD4+ Count and Percentage from Baseline to Week 24 Virologically -Suppressed Pediatric Patients from 6 to <12 Years Who Switched to GENVOYA

	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

- The safety and effectiveness of GENVOYA for the treatment of HIV-1 infection was established in pediatric patients with body weight greater than or equal to 25 kg.
- Use of GENVOYA in pediatric patients between the ages of 12 to less than 18 years and weighing at least 35 kg is supported by studies in adults and by a study in antiretroviral treatment-naïve HIV-1 infected pediatric subjects ages 12 to less than 18 years and weighing at least 35 kg (cohort 1 of Study 106, N=50). The safety and efficacy of GENVOYA in these pediatric subjects was similar to that in adults.
- Use of GENVOYA in pediatric patients weighing at least 25 kg is supported by studies in adults and by an open-label trial in virologically-suppressed pediatric subjects ages 6 to less than 12 years and weighing at least 25 kg, in which subjects were switched from their antiretroviral regimen to GENVOYA (cohort 2 of Study 106, N=23). The safety in these subjects through 24 weeks was similar to that in antiretroviral treatment-naïve adults with the exception of a decrease in mean change from baseline in CD4+ cell count.
- Safety and effectiveness of GENVOYA in pediatric patients less than 25 kg have not been established.

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Section 12: CLINICAL PHARMACOLOGY

Pediatric Patients

- Mean exposures of elvitegravir, cobicistat, and TAF achieved in 24 pediatric subjects aged 12 to less than 18 years who received GENVOYA in Study 106 were decreased compared to exposures achieved in treatment-naïve adults following administration of GENVOYA, but were overall deemed acceptable based on exposure-response relationships; emtricitabine exposure in adolescents was similar to that in treatment-naïve adults (Table 10)

Table 10:
Multiple Dose Pharmacokinetic Parameters of Elvitegravir, Cobicistat, Emtricitabine, Tenofovir Alafenamide (TAF) and its Metabolite Tenofovir Following Oral Administration of GENVOYA in HIV-Infected Pediatric Subjects Aged 12 to less than 18 Years[a]

Parameter Mean (CV%)	Elvitegravir	Cobicistat	Emtricitabine	TAF	Tenofovir
C_{max} (microgram per mL)	2.2 (19.2)	1.2 (35.0)	2.3 (22.5)	0.17 (64.4)	0.02 (23.7)
AUC_{tau} (microgram•hour per mL)	23.8 (25.5)	8.2[b] (36.1)	14.4 (23.9)	0.20[b] (50.0)	0.29[b] (18.8)
C_{trough} (microgram per mL)	0.30 (81.0)	0.03[c] (180.0)	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, cohort 1 of Study 106 (N=24).
b. N=23
c. N=15

- Exposures of the components of GENVOYA achieved in 23 pediatric subjects between the ages of 6 to less than 12 years who received GENVOYA in Study 106 were higher (20 to 80% for AUC) than exposures achieved in adults following the administration of GENVOYA; however, the increase was not considered clinically significant (Table 11) *[see Use in Specific Populations (8.4)]*.

Table 11:
Multiple Dose Pharmacokinetic Parameters of Elvitegravir, Cobicistat, Emtricitabine, Tenofovir Alafenamide (TAF) and its Metabolite Tenofovir Following Oral Administration of GENVOYA in HIV-Infected Pediatric Subjects Aged 6 to less than 12 Years[a]

Parameter Mean (CV%)	Elvitegravir	Cobicistat	Emtricitabine	TAF	Tenofovir
C_{max} (microgram per mL)	3.1 (38.7)	2.1 (46.7)	3.4 (27.0)	0.31 (61.2)	0.03 (20.8)
AUC_{tau} (microgram•hour per mL)	33.8[b] (57.8)	15.9[c] (51.7)	20.6[b] (18.9)	0.33 (44.8)	0.44 (20.9)
C_{trough} (microgram per mL)	0.37 (118.5)	0.1 (168.7)	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, cohort 2 of Study 106 (N=23).
b. N=22
c. N=20

14.5 Clinical Trial Results in HIV-1 Infected Pediatric Subjects Between the Ages of 6 to Less than 18

In Study 106, an open-label, single arm trial the efficacy, safety, and pharmacokinetics of GENVOYA in HIV-1 infected pediatric subjects were evaluated in treatment-naïve adolescents between the ages of 12 to less than 18 years weighing at least 35 kg (N=50) and in virologically-suppressed children between the ages of 6 to less than 12 years weighing at least 25 kg (N=23).

Cohort 1: Treatment-naïve adolescents (12 to less than 18 years; at least 35 kg)
Subjects in cohort 1 treated with GENVOYA once daily had a mean age of 15 years (range 12-17); 44% were male, 12% were Asian, and 88% were Black. At baseline, mean plasma HIV-1 RNA was 4.6 $\log_{10}$ copies per mL (22% had baseline plasma HIV-1 RNA greater than 100,000 copies per mL), median CD4+ cell count was 456 cells per mm^3 (range: 95 to 1110), and median CD4+ percentage was 23% (range: 7% to 45%).

In subjects in cohort 1 treated with GENVOYA, 92% (46/50) achieved HIV-1 RNA less than 50 copies per mL at Week 48. The mean increase from baseline in CD4+ cell count at Week 48 was 224 cells per mm^3. Three of 50 subjects had virologic failure at Week 48; no emergent resistance to GENVOYA was detected through Week 48.

Cohort 2: Virologically-suppressed children (6 to less than 12 years; at least 25 kg)
Subjects in cohort 2 treated with GENVOYA once daily had a mean age of 10 years (range: 8-11), a mean baseline weight of 31.6 kg, 39% were male, 13% were Asian, and 78% were Black. At baseline, median CD4+ cell count was 969 cells/mm3 (range: 603 to 1421), and median CD4% was 39% (range: 30% to 51%).

After switching to GENVOYA, 100% (23/23) of subjects in cohort 2 remained suppressed (HIV-1 RNA < 50 copies/mL) 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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