SYMTUZA: Pediatric Labeling Updates

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FDA recently approved changes to the SYMTUZA (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide) label to provide for the use of SYMTUZA in pediatric patients weighing at least 40 kg. A summary of the key changes are as follows.

Section 1 INDICATIONS AND USAGE

SYMTUZA is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and pediatric patients weighing at least 40 kg:

- who have no prior antiretroviral treatment history or
- who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 6 months and have no known substitutions associated with resistance to darunavir or tenofovir

Section 2.2 Recommended Dosage

The recommended dosage of SYMTUZA is one tablet taken orally once daily with food in adults and pediatric patients weighing at least 40 kg.

Section 6.1 Clinical Trials Experience

Clinical Trials in Pediatric Patients

Adverse Reactions in Pediatric Patients Weighing At Least 40 kg

No clinical trials with SYMTUZA were performed in pediatric patients. However, the safety of the components of SYMTUZA was evaluated in pediatric subjects of 12 to less than 18 years of age through clinical trials GS-US-216-0128 (virologically-suppressed, N=7 with weight ≥40 kg) for darunavir co administered with cobicistat and other antiretroviral agents, and GS-US-292-0106 (treatment-naïve, N=50 with weight ≥35 kg) for a fixed-dose combination regimen containing cobicistat, emtricitabine, and tenofovir alafenamide together with elvitegravir. Safety analyses of the trials in these pediatric subjects did not identify new safety concerns compared to the known safety profile of SYMTUZA in adult subjects.

Section 8.4 Pediatric Use

The safety and effectiveness of SYMTUZA in pediatric patients less than 18 years of age have not been established. for the treatment of HIV-1 infection in pediatric patients weighing at least 40 kg was established through studies with components of SYMTUZA. Use of SYMTUZA in this group is supported by evidence from adequate and well-controlled studies of SYMTUZA in adults with additional pharmacokinetic, safety, and virologic data from studies of components of

SYMTUZA (Trials GS-US-216-0128 and GS US 292 0106) in pediatric subjects with HIV 1 infection aged 12 to less than 18 years.

The safety and effectiveness of SYMTUZA have not been established in pediatric patients weighing less than 40 kg.

Section 12.3 Pharmacokinetics

Specific Populations

Pediatric Patients Weighing at Least 40 kg

Available pharmacokinetic data for the different components of SYMTUZA indicate that there were no clinically relevant differences in exposure between adults and pediatric subjects weighing at least 40 kg.

Darunavir and cobicistat: In pediatric subjects aged 12 to less than 18 years, weighing at least 40 kg who received darunavir 800 mg co−administered with cobicistat 150 mg (N=7), geometric mean darunavir Cmax values were similar between adults and pediatric subjects. Geometric mean darunavir AUC24h and C24h values were 15% and 32% lower, with geometric mean ratios of 0.85 (90% CI: 0.64, 1.13) and 0.68 (90% CI: 0.30, 1.55) in pediatric subjects relative to adults, respectively. These differences were not considered clinically significant. Geometric mean cobicistat AUC24h, Cmax, and C24h values were comparable in pediatric subjects and adults (Table 7).

Table 7:	**Multiple-Dose PK Parameters of Darunavir and Cobicistat Following Administration of Darunavir with Cobicistat in HIV 1 Infected Adults and Pediatric Subjects Weighing at least 40 kg**	
Parameter Geometric mean (CV%)	**Darunavir**	**Cobicistat**
Pediatric Subjects[a]	N=7	N=7
AUC_{24h} (mcg.hr/mL)	77.22 (29.5)	8.33 (34.9)
C_{max} (mcg/mL)	7.32 (21.7)	1.10 (20.0)
C_{24h} (mcg/mL)	0.68 (91.6)	0.02 (123.9)[b]
Adults[c]	N=21	N=21
AUC_{24h} (mcg.hr/mL)	90.56 (45.3)	7.69 (43.9)
C_{max} (mcg/mL)	8.34 (33.3)	1.04 (35.3)
C_{24h} (mcg/mL)	1.00 (108.0)	0.02 (135.1)[d]

CV = Coefficient of Variation; mcg = microgram

[a] From intensive PK analysis of trial GS-US-216-0128, where HIV-infected subjects were administered darunavir 800 mg and cobicistat 150 mg once daily with 2 NRTIs

[b] N=5; Data from two subjects who had undetectable cobicistat C_{24h} concentrations were excluded from summary statistics

[c] From intensive PK analysis of trial GS-US-299-0102 where HIV-infected subjects were administered SYMTUZA once daily

[d] N=18

Emtricitabine and tenofovir alafenamide: In 24 pediatric subjects aged 12 to less than 18 years, who received emtricitabine + TAF with elvitegravir + cobicistat, geometric mean emtricitabine Cmax, and C24h values were comparable to adults, with geometric mean ratios of 1.10 (90% CI: 0.98, 1.23) and 1.07 (90% CI: 0.88, 1.29), respectively (Table 8). Geometric mean emtricitabine AUC24h was 21% higher, with a geometric mean ratio of 1.21 (90% CI: 1.09, 1.34) in pediatric subjects relative to adults. Geometric mean tenofovir alafenamide Cmax and AUClast values were 29% and 23% lower in pediatric subjects versus adults with geometric mean ratios of 0.71 (90% CI: 0.50, 1.00) and 0.77 (90% CI: 0.59, 1.02), respectively (Table 8). The observed differences were not considered clinically significant.

Table 8: Multiple-Dose PK Parameters of Emtricitabine and Tenofovir Alafenamide Following Oral Administration with Food in HIV 1 Infected Adults and Pediatric Subjects		
Parameter Geometric mean (CV%)	**Emtricitabine**	**Tenofovir alafenamide**
Pediatric Subjects[a]	N=24	N=24
AUC_{24h} (mcg.hr/mL)[b]	14.0 (23.9)	0.16 (55.8)
C_{max} (mcg/mL)	2.2 (22.5)	0.14 (64.4)
C_{24h} (mcg/mL)	0.10 (38.9)[c]	NA
Adults[d]	N=19	N=19
AUC_{24h} (mcg.hr/mL)[b]	11.6 (16.6)	0.21 (47.3)
C_{max} (mcg/mL)	2.0 (20.2)	0.19 (64.6)
C_{24h} (mcg/mL)	0.09 (46.7)	NA

CV = Coefficient of Variation; mcg = microgram; NA = not applicable

[a] From intensive PK analysis in trial GS-US-292-0106 in treatment-naïve pediatric subjects with HIV-1 infection

[b] AUC_{last} for tenofovir alafenamide

[c] N=23

[d] From intensive PK analysis in trial GS-US-292-0102 in HIV-infected adults treated with emtricitabine+tenofovir alafenamide and elvitegravir+cobicistat

Section 14.3 Clinical Trial Results in Pediatric Subjects with HIV-1 Infection

The pharmacokinetic profile, safety, and antiviral activity of the components of SYMTUZA were evaluated in open-label clinical trials in pediatric subjects with HIV-1 infection aged 12 to less than 18 years: GS-US-216-0128 (N=7) and GS US-292-0106 (N=50).

In the Phase 2/3 trial GS-US-216-0128 darunavir 800 mg and cobicistat 150 mg once daily with 2 NRTIs were evaluated in 7 virologically suppressed pediatric subjects aged 12 to less than 18 years and weighing at least 40 kg. Subjects had a median (range) age of 14 (12-16) years and a median (range) weight of 57 (45-78) kg. At baseline, plasma HIV-1 RNA was <50 copies/mL in all subjects, and the median (range) CD4+ cell count was 1,117 (658-2,416) cells/mm3. At Week 48, the proportion of subjects who maintained HIV-1 RNA <50 copies/mL was 86%, and the median change in CD4+ cell count from baseline was -342 cells/mm3 (range -1,389 to 210 cells/mm3). All 6 subjects with available data had CD4+ cell counts above 800 cells/mm3 at Week 48.

In the Phase 2/3 trial GS-US-292-0106, cobicistat 150 mg, emtricitabine 200 mg, and tenofovir alafenamide 10 mg, as part of a fixed-dose combination regimen together with elvitegravir 150 mg, were evaluated in 50 treatment-naïve pediatric subjects with HIV-1 aged 12 to less than 18 years and weighing at least 35 kg. Subjects had a median (range) age of 15 (12-17) years. At

baseline, median (range) plasma HIV-1 RNA was 4.7 (3.3-6.5) log10 copies/mL, median (range) CD4+ cell count was 456 (95 1,110) cells/mm3, and 22% had baseline plasma HIV-1 RNA >100,000 copies/mL). At Week 48, the proportion of subjects who had HIV-1 RNA <50 copies/mL was 92%, and the median increase in CD4+ cell count from baseline was 220 cells/mm3.

The use of SYMTUZA in pediatric patients weighing less than 40 kg has not been established.

The updated label will soon be available at Drugs@FDA or DailyMed.

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