CLINICAL PHARMACOLOGY REVIEW

NDA/SDN (Supplement #)	210455/198 (S-9)
Submission Type	Efficacy supplement
Applicant Name	Janssen
Submission Date	7/11/2019
Generic Name	Darunavir / cobicistat / emtricitabine / tenofovir alafenamide (D/C/F/TAF)
Brand Name	Symtuza
Dosage Form (Strength)	Tablet (800/150/200/10 mg)
Indication	Treatment of HIV-1 infection for patients weighing ≥40 kg
Review Team	Mario Sampson, PharmD, Vikram Arya, PhD, FCP

Based on approval in October 2019 of darunavir and cobicistat (DRV/c; brand name Tybost) for patients weighing at least 40 kg, this efficacy supplement revises Symtuza labeling to extend the indication from adults only to patients weighing at least 40 kg. Emtricitabine and tenofovir alafenamide (F/TAF) are contained in Genvoya (also contains elvitegravir and cobicistat), which is approved for patients weighing at least 25 kg.

No new trials of D/C/F/TAF were conducted to support approval of D/C/F/TAF for patients weighing at least 40 kg. Instead, the Applicant extrapolated results from two prior pediatric trials which enrolled HIV-infected subjects weighing at least 40 kg. The treatment regimen in trial GS-US-216-0128 (trial 1028) was DRV/c + background regimen and in trial GS-US-292-0106 (trial 0106) was elvitegravir/cobicistat/F/TAF (E/C/F/TAF). We previously reviewed PK results of adolescent trials 0128 and 0106 and concluded there was sufficient similarity of adolescent exposures in comparison to adults. This supported previous approval of Tybost and Genvoya for adolescents (NDA 203094 Clinical Pharmacology reviews dated 8/2/2019 and 10/1/2019, NDA 207561 Clinical Pharmacology reviews dated 7/10/2015 and 10/7/2015).

For the reference adult PK parameters of each component of Symtuza, the Applicant used intensive PK data from two trials (GS-US-299-0102 for the PK parameters of DRV and COBI and GS-US-292-0102 for the PK parameters of FTC and TAF). The reason for not using TAF PK parameters from GS-US-299-0102 as the reference is because of the effect of COBI and DRV/COBI on TAF (COBI alone increased mean TAF AUC 2.65-fold while DRV/c had no effect on mean TAF AUC). Because the exposures of FTC and TAF in patients weighing at least 40 kg were determined (in trial 0106) without DRV as part of the regimen, the reference adult comparator without DRV (from trial GS-US-292-0102) was used for comparison purposes. Underlying this approach to compare adolescent vs adult exposures of each component of D/C/F/TAF is the assumption that the magnitudes of the COBI-TAF and DRV/c-TAF drug interactions (measured in healthy adults) would be the same in HIV-infected adolescents.

In labeling, per our request, the Applicant included adolescent and adult intensive PK parameters for each component of Symtuza as well as geometric mean ratios and 90% confidence intervals of the PK parameters in adolescents vs adults. The intensive PK data for DRV and COBI were

taken directly from Tybost labeling and for FTC and TAF were taken from the publicly available Genvoya review at Drugs@FDA (NDA 207561, Clinical Pharmacology review page 109).

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/s/

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