CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210455Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 210455
Review #1

Drug Name/Dosage Form	SYMTUZA (Darunavir, Cobicistat, Emtricitabine, and Tenofovir Alafenamide) Tablets
Strength	800mg/150mg/200mg/10mg (Fixed Dose Combo)
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Janssen
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Orig NDA Submission	Sept 22, 2017	All
Amendment	Nov 14, 2017	Quality
Amendment	Dec 1, 2017	Quality
Amendment	Feb 2, 2018	Quality
Amendment	Mar 6, 2018	Quality
Amendment	May 10, 2018	Labeling
Amendment	May 15, 2018	Quality

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance & Drug Master Files	Mohd Shahjahan Kabir	Charles Jewell
Drug Product & Labeling	Andrei Ponta	Balajee Shanmugam
Process & Microbiology	Iwona Weidlich	Arwa El Hagrasy
Facility	Daniel DeCiero	Ying Zhang
Biopharmaceutics	Zhuojun (Joan) Zhao	Elsbeth Chikhale
Environmental Assessment	James Laurenson	Michael (Scott) Furness
Regulatory Business Process Manager	Luz Rivera	
Application Technical Lead	Stephen Miller	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
18825	Type II	See DS summary				
(b) (4)	Type II	See DS summary				
	Type III *(if applicable)*	See DP review				
	Type IV *(if applicable)*	See DP review				

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
	IND 113456	IND for this product

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH	NA			
Clinical	NA			
Other				

Executive Summary

I. Recommendations and Conclusion on Approvability

This NDA is recommended for **APPROVAL** from the product quality perspective.

II. Summary of Quality Assessments

A. Product Overview

This monolithic film-coated table containing 4 active ingredients and is indicated for HIV treatment. Cobicistat is a CYP3A inhibitor intended to increase the plasma levels of darunavir.

Proposed Indication(s) including Intended Patient Population	Treatment of HIV infection in patients 12 years and older (b) (4)
Duration of Treatment	Chronic, until resistance develops
Maximum Daily Dose	One tablet per day taken with food
Alternative Methods of Administration	Instructions for splitting into two pieces using a tablet-cutter, and immediately consuming the entire dose

B. Quality Assessment Overview

Drug Substances:

The CMC information of the drug substance, **darunavir ethanolate**, is cross-referenced to DMF 18825 (Janssen Pharmaceutica NV is the holder). This DMF was last reviewed by M. Kabir on Oct 17, 2017 and found adequate. NDA 210455 also cross-referenced the approved NDA 21976 sponsored by Janssen Products LP and the IND 62477 sponsored by Janssen Research and Development LLC. The specification provided in NDA 210455 is tighter than the specification provided in the DMF 18825, and includes (b) (4) particle size control as well as chemical attributes.

The CMC information of the drug substance, **cobicistat on silicon dioxide**, is cross-referenced to DMF (b) (4) is the holder). DMF # (b) (4) reviewed by M. Kabir on Apr 4, 2018 and found adequate. No further amendment is submitted to date. The applicant also cross-referenced these approved applications: NDA 207561 Genvoya, NDA 203094 Tybost, and NDA 205395 Prezcobix. The specifications for cobicistat on silicon dioxide provided in NDA 210455 is equivalent to the specifications provided for the approved reference NDA 203094 and comparable with the specification provided in DMF (b) (4) of the cobicistat on silicon dioxide.. The difference in the acceptance criterion (b) (4) between the NDA (none detected) and the DMF (NMT (b) (4) % (b) (4)). The applicant clarified in the NDA amendment of Mar 6, 2018 that Symtuza tablets will only be manufactured using

cobicistat on silicon dioxide that meets the acceptance criteria (b) (4) listed in the NDA.

The CMC information of the drug substance, **emtricitabine**, is cross-referenced to the approved NDA 21500 Emtriva, and these approved applications are also referenced: NDA 21752 Truvada, NDA 207561 Genvoya, and NDA 208215 Descovy. The specification for emtricitabine provided in this, NDA 210455, is equivalent to the specification provided for in the referenced NDA 21752, and includes (b) (4) particle size control as well as chemical attributes.

The CMC information of the drug substance, **tenofovir alafenamide fumarate (TAF)**, is cross-referenced to the approved NDA 207561 Genvoya, and NDA 208215 Decovy is also referenced. The specification for TAF provided in NDA 210455 is equivalent to the specification provided in these referenced NDAs, and includes (b) (4) particle size control and melting point, as well as chemical attributes.

Elemental analyses were conducted on six drug product batches as per ICH Q3D and the results are in line with the ICH Q3D guidelines. The applicant agreed (May 10, 2018 amendment) (b) (4) in the specifications for the drug substances. The revised specifications will be provided through the annual report submissions in early 2019, both for the NDAs and the DMFs.

For additional information, see Mohd Shahjahan Kabir's Drug Substance Review, below.

Drug Product:
Symtuza is a fixed dose, immediate release combination tablet containing (b) (4) darunavir ethanolate (b) (4) mg of cobicistat (b) (4) 200.0 mg of emtricitabine, and 11.2 mg of tenofovir alafenamide fumarate (equivalent to 10.0 mg tenofovir alafenamide).

Symtuza tablets are yellow, film-coated tablets (22 mm by 10 mm in size) that are debossed with "8121" on one side and "JG" on the other. Drug product specifications were based on release data from 16 drug product batches used in clinical and stability studies, plus stability results. (b) (4)

The label contains the following instructions, "For patients who are unable to swallow the whole tablet, SYMTUZA may be split into two pieces using a tablet-cutter, and the entire dose should be consumed immediately after splitting." Note that the drug product does not contain a functional score line. Splitting the tablets is only to facilitate administration, not to create another drug product dose. The impact of splitting tablets has been studied in the Phase 1 study TMC114FD2HTX1004, using the commercial drug product formulation. The PK data assessed as part of the study demonstrated that the relative bioavailability (C_{max}, AUC_{last}, and AUC_{∞}) of the different components (darunavir,

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