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,

cobicistat, emtricitabine, and tenofovir alafenamide) was not impacted, except for an 11% decrease in tenofovir alafenamide C_{max}, which is not considered clinically relevant. The labeling instruction for splitting the table and consuming the entire dose immediately is acceptable from the product quality perspective.

Symtuza tablets are packaged in a high-density polyethylene bottle, with (b) (4) child-resistant closure, foil induction seal, and a desiccant pouch. Each bottle contains 30 tablets. Release and stability data were provided on 3 primary stability batches produced at the commercial drug product manufacturing facility (b) (4). The three batches were produced at approximately 42% of the intended commercial batch size. A 36-month expiration dating period is granted based on acceptable stability data of 24 months at 25 °C /60% RH and 30 °C /75%, and 6 months at 40 °C /75% when Symtuza is stored at USP Controlled Room Temperature in the commercial 120-cc HDPE bottles. In-use stability data also indicates that the drug product remains stable for 6 weeks at 25 °C/60% RH and 30 °C/75% RH.
For additional information, see Andrei Ponta's Drug Product Review, below.

Biopharmaceutics:
The following acceptance criteria and dissolution methods are acceptable, based on evaluation of dissolution data provided in the application:

Acceptable Dissolution Method and Acceptance Criteria					
Component	USP Apparatus	Speed (RPMs)	Medium	Volume	Cumulative % of Drug Dissolved (Label Claim)
Darunavir	II (Paddle)	75	2% Tween in 0.05 M Phosphate Buffer, pH 3.0	900 mL	Q= (b) (4) % at 30 minutes
Cobicistat			Citrate Phosphate Buffer, pH 4.2		Q= % at 20 minutes
Emtricitabine/Tenofovir Alafenamide					Q= % at 15 minutes

No bridging study is needed as the proposed commercial formulation, presentation and drug product manufacturing site is the same as that of the drug product used in the Phase III studies.
For additional information, see Zhuojun (Joan) Zhao's Biopharmaceutics Review, below.

Process:

(b) (4)

(b) (4)

Facilities:

(b) (4)

Environmental Assessment:

The applicant provided an environmental assessment (EA) for darunavir, and claims for categorical exclusions from EAs for cobicistat, emtricitabine, and tenofovir alafenamide (TAF). FDA determined that darunavir qualifies for an exclusion in accordance with 21

CFR 25.31(a), which is for actions that do not increase the use of active moiety. For the other three substances, the applicant claimed exclusions in accordance with 21 CFR 25.31(b), which is for actions that increase the use of the active moiety, but for which the estimated concentration of the substance at the point of entry into the aquatic environment—the expected introduction concentration (EIC)—will be below 1 part per billion (1 ppb). The required statement of no extraordinary circumstances was included for the latter three substances, and was inferred for the darunavir. The claims for an exclusion from an EA are acceptable.
For additional information, see James Laurenson's EA Review, below.

C. Special Product Quality Labeling Recommendations (NDA only)

Product quality recommendations for labeling have been conveyed to the OND PM for consideration as the labeling is finalized. See Andrei Ponta's Labeling Review, below.

D. Final Risk Assessment (see Attachment)

Stephen Miller

Digitally signed by Stephen Miller
Date: 6/13/2018 02:25:07PM
GUID: 508da7210002a000609476bbecd040f0
Comments: ATL for NDA 210455

BIOPHARMACEUTICS

Product Background:

NDA: 210455 (505(b)(1)).

Drug Product Name / Strength: SYMTUZA (Darunavir, Cobicistat, Emtricitabine and Tenofovir Alafenamide) IR Tablets, 800 mg/150 mg/200 mg/10 mg

Route of Administration: Oral

Applicant Name: Janssen Products, LP

Review Summary:

The proposed fixed dose combination (FDC) SYMTUZA tablet is indicated as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older.

This 505(b)(1) New Drug Application does not contain a new chemical entity (NCE). The proposed FDC drug product contains the following four drug substances:

- Darunavir (D), an inhibitor of the human immunodeficiency virus (HIV-1) protease.
- Cobicistat (C), a PK enhancer of Darunavir.
- Emtricitabine (F), a nucleoside analog HIV-1 reverse transcriptase inhibitor (NRTI).
- Tenofovir Alafenamide (TAF), a nucleoside analog HIV-1 reverse transcriptase inhibitor.

The Biopharmaceutics review is focused on the evaluation and acceptability of the proposed dissolution methods and acceptance criteria and the evaluation of the need for bridging.

Based on the provided dissolution data, the following dissolution methods and acceptance criteria are acceptable:

Acceptable Dissolution Method and Acceptance Criteria					
Component	USP Apparatus	Speed (RPMs)	Medium	Volume	Cumulative % of Drug Dissolved (Label Claim)
Darunavir	II (Paddle)	75	2% Tween in 0.05 M Phosphate Buffer, pH 3.0	900 mL	Q (b)(4) at 30 minutes
Cobicistat			Citrate Phosphate Buffer, pH 4.2		Q at 20 minutes
Emtricitabine/Tenofovir Alafenamide					Q at 15 minutes

No bridging study is needed as the proposed commercial formulation, presentation and drug product manufacturing site is the same as that of the drug product used in the Phase III studies.

List Submissions being reviewed (table):

Submission(s) Reviewed	Document Date
Original Submission	9/22/2017

Recommendation:

From the Biopharmaceutics perspective, NDA 210455 for SYMTUZA (Darunavir, Cobicistat, Emtricitabine and Tenofovir Alafenamide) IR Tablets, 800 mg/150 mg/200 mg/10 mg is recommended for **APPROVAL**.

REVIEW

This 505(b)(1) New Drug Application does not contain a new chemical entity (NCE). The proposed FDC drug product contains the following four drug substances:

- Darunavir (D), an inhibitor of the human immunodeficiency virus (HIV-1) protease developed by the Applicant and approved in NDA 21976 Prezista® (Darunavir ethanolate) tablets.
- Cobicistat (C), a PK enhancer of Darunavir, approved in NDA 203094 Tybost® (Cobicistat) tablets, NDA 206353 Evotaz® (Atazanavir Sulfate and Cobicistat) Tablets, NDA 207561 Genvoya® (Cobicistat; Elvitegravir; Emtricitabine; Tenofovir Alafenamide Fumarate) Tablets, NDA 205395 Prezocobix® (Cobicistat and Darunavir Ethanolate) tablets and NDA 203100 Stribild® (Cobicistat; Elvitegravir; Emtricitabine and Tenofovir Disoproxil Fumarate) Tablets.
- Emtricitabine (F), a nucleoside analog HIV-1 reverse transcriptase inhibitor, approved in NDA 21500 Emtriva® (emtricitabine) Capsules and NDA 21896 Emtriva® (emtricitabine) solution.
- Tenofovir Alafenamide (TAF), a nucleoside analog HIV-1 reverse transcriptase inhibitor, approved in NDA 208215 Descovy® (Emtricitabine and Tenofovir Alafenamide) tablets,

BCS Designation

The Applicant did not request an official BCS designation.

Drug Substance Solubility:

Solubility of the drug substances are provided as shown below:

Table 1 Solubility Profiles of Drug Substance

Cobicistat at 20°C

Solvent	pH of Solution	Solubility (mg/mL)[a]	USP/Ph. Eur. Solubility Desscription
0.1 N HCl	1.9	> 40	Soluble
50 mM acetic acid	4.5	16	Sparingly soluble
50 mM sodium phosphate buffer	6.8	0.08	Practically insoluble
50 mM sodium phosphate buffer	7.5	0.04	Practically insoluble
50 mM sodium phosphate buffer	8.2	0.04	Practically insoluble
Water	7.0	0.1	Practically insoluble

a Determined using reference standard lot RS-C-9350-4 at 20 ± 5 °C.

Cobicistat on silicon dioxide at 20°C

Solvent	Solubility (mg/mL)[a]	USP/Ph. Eur. Solubility Description
0.1 N HCl	14	Sparingly soluble
0.01 N HCl	5	Slightly soluble
50 mM sodium acetate buffer, pH 4.5	3	Slightly soluble
50 mM sodium phosphate buffer, pH 6.8	0.1	Practically insoluble

a Solubility of cobicistat measured from a suspension of cobicistat on silicon dioxide, determined from lot PP-1001-0002 at 20 ± 5 °C. The pH of the final solution was not determined.

Darunavir at 20°C

Solvent	Solubility in g/100 mL Solution	pH of Solution	Ph. Eur./USP Definition
Water	0.015	7.6	Very slightly soluble
0.1 N HCl	0.096	1.0	Very slightly soluble
0.01 N HCl	0.025	2.1	Very slightly soluble
Citrate-HCl Buffer pH 2	0.025	2.0	Very slightly soluble
Citrate-NaOH Buffer pH 5	0.013	5.0	Very slightly soluble
Phosphate Buffer pH 7	0.014	7.0	Very slightly soluble
Borate-KCl-NaOH Buffer pH 9	0.016	9.0	Very slightly soluble
Phosphate-NaOH Buffer pH 12	0.014	12.0	Very slightly soluble
Simulated Gastric Fluid	0.083	1.1	Very slightly soluble
Simulated Intestinal Fluid	0.016	7.4	Very slightly soluble

Emtricitabine at RT

Solvent	Solubility (mg/mL)	USP/Ph. Eur. Solubility Description
0.1 N HCl	170	Freely soluble
0.1 N NaOH	115	Freely soluble
Methanol	113	Freely soluble
Water	112	Freely soluble
Acetonitrile	4	Slightly soluble
Isopropyl acetate	0.3	Very slightly soluble

Tenofovir Alafenamide (TAF) Fumarate at 20°C

Aqueous Media	Solubility[a] (mg/mL)	USP/Ph. Eur. Solubility Description
Water, pH 2.0 (HCl)	85.4	Soluble
Water, final pH 3.8	21.7	Sparingly soluble
Water, pH 4.5 (20 mM acetate buffer)	8.73	Slightly soluble
Water, pH 6.8 (50 mM phosphate buffer)	4.70	Slightly soluble
Water, pH 8.0 (50 mM phosphate buffer)	4.86	Slightly soluble

Permeability:

No data are provided.

Drug Substances:

Darunavir

(b) (4)

Cobicistat

(b) (4)

Emtricitabine

(b) (4)

Tenofovir Alafenamide (TAF) Fumarate

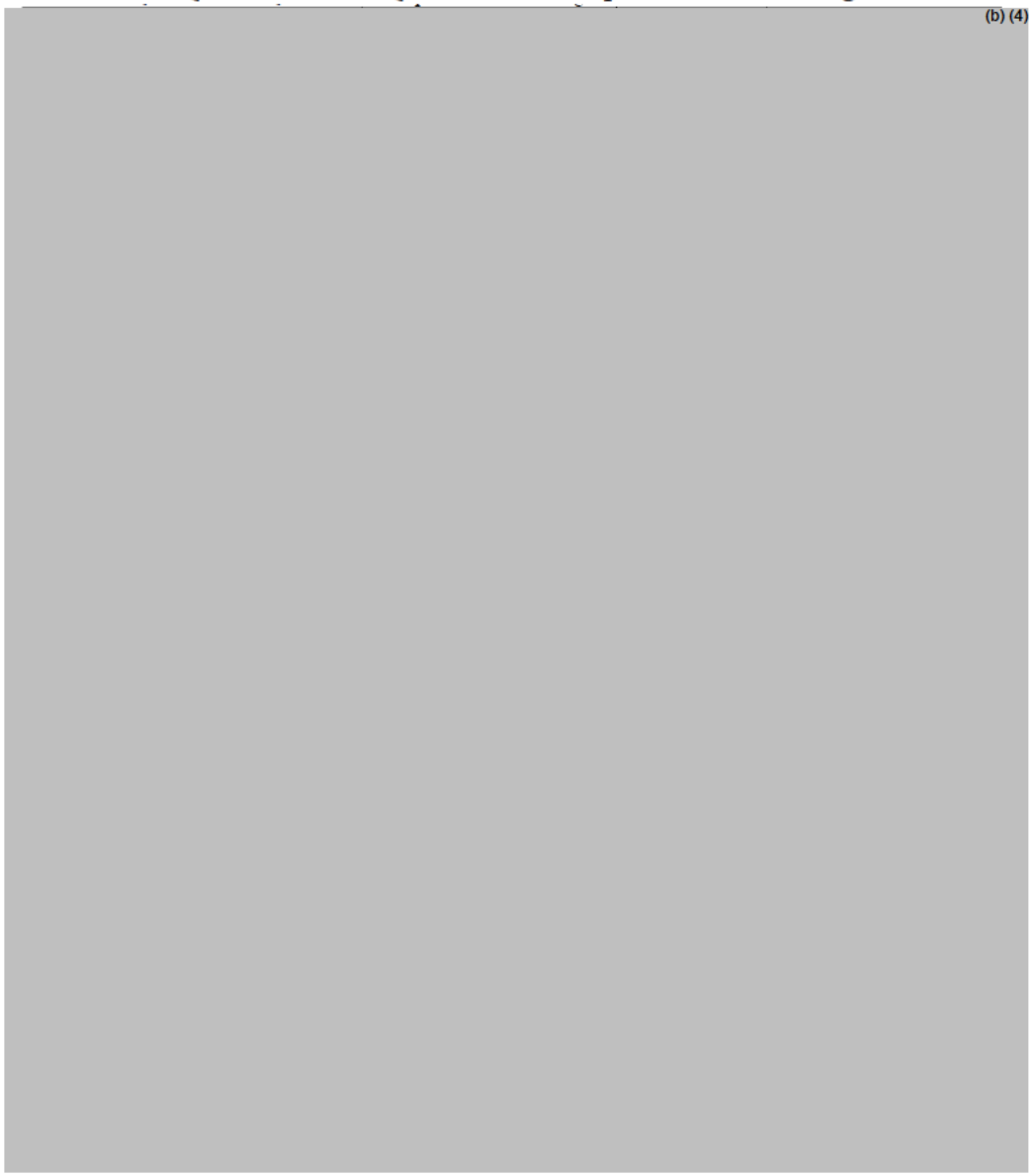
(b) (4)

Formulation:

The proposed drug product is a yellow-brown, capsule-shaped, immediate release D/C/F/TAF FDC film-coated (b) (4) tablet debossed with "8121" on one side and "JG" on the other.

Table 2: Qualitative and Quantitative Composition of the Drug Product

(b) (4)



Dissolution Method and Acceptance Criteria

The Applicant proposes two dissolution methods (Table 4), based on the difference in dose and solubility of the 4 drug substances in the proposed FDC drug product.

- The proposed dissolution method for Darunavir is the same as the approved method in the Applicant's NDA 21976 Prezista® (Darunavir) Tablets, 600 mg [1] and method for Darunavir in the Applicant's NDA 205395 Prezocobix® (Cobicistat and Darunavir Ethanolate) tablets[2].

[1] DARRTS: NDA 21976, REV-QUALBIOPHARM-21 (Primary Review), final date 12/18/2017

[2] \\cdsesub1\evsprod\nda205395\0045\m3\32-body-data\32p-drug-prod\active-all-presentations\32p5-contr-drug-prod\32p52-analyt-proc\analytical-procedure-dar-ds-tm-12983.pdf

- The proposed dissolution method for Cobicistat, Emtricitabine and Tenofovir Alafenamide is the same as the approved method for Cobicistat in the Applicant's NDA 205395 Prezocobix® (Cobicistat and Darunavir Ethanolate) tablets [3].

Table 4: Proposed Dissolution Methods

Component	Darunavir	Cobicistat	Tenofovir Alafenamide	Emtricitabine
Solubility	Limited	pH dependent		High
Apparatus	II (Paddle)			
Volume	900 mL			
Medium	2% Tween in 0.05 M phosphate Buffer, pH 3.0	Citrate Phosphate Buffer, pH 4.2		
Speed	75 RPM			

The Applicant provided justification for the choice of dissolution apparatus, dissolution medium, and agitation speed for each method in the Pharmaceutical Development Report (Module 3.2.P.2).

Dissolution Method for Darunavir (DS-TMD-17520)

(b) (4)

[redacted]

[3] \\cdsesub1\evsprod\nda205395\0000\m3\32-body-data\32p-drug-prod\active-all-presentations\32p5-contr-drug-prod\32p52-analyt-proc\analytical-procedure-cob-di-007396.pdf

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Reviewer's Assessment: Acceptable.

Based on the provided information, the proposed dissolution method (DS-TMD-17522) for Cobicistat/Emtricitabine/Tenofovir Alafenamide is acceptable as QC method for the proposed FDC drug product. The proposed dissolution method (b) (4) but not towards any other tested material attributes or process parameters.

Dissolution Acceptance Criteria: Acceptable

The Applicant proposed the following dissolution acceptance criteria based on the dissolution results obtained on the phase III clinical batches (SBCH, SXVC, TNYC and TNYF)[5] and registration batches (STKF, STKG and STKH).

Proposed Dissolution Acceptance Criteria				
Component	**Darunavir**	**Cobicistat**	**Tenofovir Alafenamide**	**Emtricitabine**
Cumulative % of Drug Dissolved (Label Claim)	(b) (4) % (Q) at 30 min	(b) (4) % (Q) at 20 min	(b) (4) % (Q) at 15 min	

Darunavir

The Applicant proposed an acceptance criterion of Q = (b) (4) % at 30 minutes based on the average dissolution profiles (Figure 7) and the amount of S2 and S3 testing required.

Figure 7 Dissolution Profiles of Darunavir for Representative Batches

(b) (4)

Cobicistat

The Applicant proposed an acceptance criterion of Q = (b) (4) % at 20 minutes based on the average dissolution profiles (Figure 8) and the amount of S2 and S3 testing required.

[5] Appendix I

Figure 8 Dissolution Profiles of Cobicistat for Representative Batches

Emtricitabine

The Applicant states that Emtricitabine is a highly soluble compound, which is dissolved within 15 minutes in media covering the physiological pH range (1-6.8) and thus the Applicant proposed an acceptance criterion of Q = (b) (4) % at 15 minutes.

Figure 9 Dissolution Profiles of Emtricitabine for Representative Batches

Tenofovir Alafenamide

The Applicant states that Emtricitabine is a highly soluble compound, which is dissolved within 15 minutes in media covering the physiological pH range (1-6.8) and thus the Applicant proposed an acceptance criterion of Q = (b) (4) % at 15 minutes.

Figure 10 Dissolution Profiles of Tenofovir Alafenamide for Representative Batches

Reviewer's Assessment:
The Applicant's proposed dissolution acceptance criteria are acceptable based on the provided data (Figures 7-10 and Appendix II).

Bridging of Formulations: N/A
No bridging is needed as the proposed commercial formulation G001 (including the debossing, yellow film-coat and manufacturing site) was used in the D/C/F/TAF pivotal Phase 3 studies TMC114IFD3013 and TMC114FD2HTX3001, and in a bioequivalence study (TMC114FD2HTX1001) that compared the intended commercial D/C/F/TAF FDC G001 formulation to the combination of the separate agents (DRV + COBI + F/TAF).

R Regional Information

Comparability Protocols: None

Post-Approval Commitments: None

Lifecycle Management Considerations: None

List of Deficiencies: None

Recommendations:
From the Biopharmaceutics perspective, NDA 210455 for SYMTUZA (Darunavir, Cobicistat, Emtricitabine and Tenofovir Alafenamide) IR Tablets, 800 mg/150 mg/200 mg/10 mg is recommended for **APPROVAL**.

Primary Biopharmaceutics Reviewer Name and Date: Zhuojun Joan Zhao, Ph.D. 2/22/2018

Secondary Reviewer Name and Date: Elsbeth Chikhale, Ph.D. 3/4/2018

APPENDIX I: Drug Product Batches Employed in Clinical Studies

Drug Substance Lot	Manufacturing			Formulation	Batch Size (kg)	Clinical Study Identification/Stability Use
	Packaged Batch Identification (Bulk)	Site	Date			
Darunavir: A15CC1164[a] (Janssen Cork) Cobicistat: PP-1001-4018[b] (b) (4) Emtricitabine: 10571420048[c] (b) (4) Tenofovir Alafenamide: 5477-P56/15-003[e] (b) (4)	VSKM (WDBK)	Patheon[f]	24 Apr 2016	G001	(b) (4)	TMC114FD2HTX3001
Darunavir: A15CC1160[a] (Janssen Cork), A15CC1163[a] (Janssen Cork) Cobicistat: PP-1001-4018[b] (b) (4) PP-1001-3026[b] (b) (4) Emtricitabine: PP-0066-4011[b] (b) (4), PP-0066-4056[b] (b) (4) PP-0066-4043[b] (b) (4) Tenofovir Alafenamide: 5477-P56-13-401[e] (b) (4)	WDGS (VFMK)	Patheon[f]	19 November 2015	G001		TMC114IFD3013
Darunavir: A15DC1261[a] (Janssen Cork) Cobicistat: PP-1001-3026[b] (b) (4) Emtricitabine: 10571420048[c] (b) (4) Tenofovir Alafenamide: 7340-03-DC-7P[d] (Gilead Alberta)	VPVP, VPVS (VPVN)	Patheon[f]	6 October 2015	G001		TMC114FD2HTX3001 (VPVS) TMC114IFD3013 (VPVS) In-use Stability (VPVP)
Darunavir: A15DC1261[a] (Janssen Cork) Cobicistat: PP-1001-3026[b] (b) (4) Emtricitabine: 10571420048[c] (b) (4) Tenofovir Alafenamide: 7340-03-DC-7P[d] (Gilead Alberta)	TYYF, VFBS (TNYF)	Patheon[f]	16 Sept. 2015	G001		TMC114IFD3013 (TYYF) TMC114FD2HTX3001 (TYYF) Photostability (VFBS)
Darunavir: A15CC1163[a] (Janssen) Cobicistat: PP-1001-3026[b] (b) (4) Emtricitabine: PP-0066-4056[b] (b) (4) Tenofovir Alafenamide: 7340-03-DC-7P[d] (Gilead)	TTVG (TNYC)	Patheon[f]	25 June 2015	G001		TMC114IFD3013
Darunavir: A14GC1987[a](Janssen), A14GC1989[a] (Janssen) Cobicistat: PP-1001-2016[b] (b) (4) Emtricitabine: PP-0066-4011[b] (b) (4) Tenofovir Alafenamide: 5477-P56-13-401 (b) (4)	SXVF (SXVC)	Patheon[f]	13 February 2015	G001		TMC114FD2HTX3001

Drug Substance Lot	Manufacturing			Formulation	Batch Size (kg)	Clinical Study Identification/Stability Use
	Packaged Batch Identification (Bulk)	Site	Date			
		(Continued)			(b) (4)	
Darunavir: A14FC1863[a] (Janssen) Cobicistat: PP-1001-2016[b] (b) (4) Emtricitabine: PP-0066-4011 (b) (4) Tenofovir Alafenamide: 5477-P56-13-401 (b) (4)	SBCT (SBCH)	Patheon[f]	29 August 2014	G001		TMC114FD2HTX1002 TMC114IFD3013
Darunavir: ZR319064 EIA061[a] (Janssen) Cobicistat: 9350-CC-2P[d] (Gilead) Emtricitabine: FTC05-1100106[f] (b) (4) Tenofovir Alafenamide: 7340-03-AC[a] (Gilead)	DB1103B1, DB1103B2 (DB1103B)	Patheon[f]	12 October 2011	Phase 1		GS-US-299-0101 (DB1103B1) GS-US-299-0102 (DB1103B1, DB1103B2)
Darunavir: ZR319064 EIA061[a] (Janssen), ZR319064EID491[a] (Janssen) Cobicistat: PP-1001-1002[b] (b) (4) Emtricitabine: PP-0066-1001 (b) (4) Tenofovir Alafenamide: 7340-03-AC-1P[d] (Gilead)	DB1201B1 (DB1201B)	Patheon[f]	25 May 2012	Phase 2		GS-US-299-0102
Darunavir: A12FC2130[a] (Janssen) Cobicistat: 9350-CC-3P[d] (Gilead) Emtricitabine: FTC05-11012311[f], FTC05-11011261[f] (b) (4) Tenofovir Alafenamide: 7340-03-DC-2P[d] (Gilead)	DB1204B1 (DB1204B)	Patheon[f]	28 November 2012	Phase 2		GS-US-299-0102

[a] Janssen Pharmaceutical, Little Island, Co. Cork, Ireland (b) (4)

[d] Gilead Alberta ULC, Edmonton, Alberta, Canada (b) (4)

[f] Patheon, Inc., Mississauga, Ontario, Canada

APPENDIX II: Batch Overview of Release Dissolution Results[6]

1. Darunavir

Batch	Dissolution Mean Percent Dissolved (Minimum-Maximum)							
	5 min	10 min	15 min	20 min	30 min	45 min	60 min	90 min
STKF	36 (34-39)	63 (62-64)	77 (77-78)	86 (85-86)	95 (94-95)	101 (100-101)	103 (102-103)	104 (103-104)
STKG	36 (33-42)	66 (63-67)	78 (77-79)	87 (86-87)	95 (94-96)	101 (100-102)	104 (102-105)	105 (103-106)
STKH	29 (21-37)	61 (55-65)	79 (76-80)	87 (86-88)	95 (94-96)	101 (100-102)	103 (102-104)	104 (102-104)
SBCH[a]	46 (37-50)	64 (60-67)	75 (71-79)	82 (78-86)	90 (88-93)	97 (95-99)	98 (97-101)	99 (98-102)
SXVC[b]	14 (11-19)	46 (39-53)	68 (63-72)	80 (78-82)	91 (89-92)	98 (97-99)	99 (98-100)	100 (100-101)
TNYC	47 (36-54)	67 (36-71)	78 (71-82)	85 (80-88)	92 (88-95)	97 (95-98)	98 (94-99)	98 (95-100)
TNYF	46 (42-48)	69 (64-71)	79 (76-81)	86 (83-87)	91 (90-93)	97 (96-98)	98 (97-99)	99 (98-100)

[a] Results reported for stability samples from the 9 month time point at the 25 °C/60% RH storage (packaged batch SBCT) with commercial test method

[b] Results reported for stability samples from the 6 month time point at the 25 °C/60% RH storage (packaged batch SXVF) with commercial test method

2. Cobicistat

Batch	Dissolution Mean Percent Dissolved (Minimum-Maximum)							
	5 min	10 min	15 min	20 min	30 min	45 min	60 min	90 min
STKF	48 (43-53)	74 (71-75)	83 (80-85)	87 (85-88)	91 (89-92)	92 (91-93)	93 (92-94)	94 (92-96)
STKG	47 (44-51)	74 (72-75)	83 (82-85)	88 (86-89)	93 (91-94)	96 (94-98)	95 (94-97)	96 (94-97)
STKH	45 (40-52)	74 (70-77)	82 (81-83)	86 (86-87)	90 (88-92)	93 (92-95)	92 (90-94)	93 (92-94)
SBCH[a]	63 (55-71)	79 (73-85)	86 (82-89)	90 (87-94)	94 (91-97)	95 (93-97)	96 (95-98)	97 (95-98)
SXVC[b]	26 (15-36)	64 (49-67)	80 (73-82)	87 (84-89)	94 (92-95)	96 (94-97)	96 (95-97)	97 (95-99)
TNYC	66 (60-68)	81 (78-82)	89 (87-91)	91 (89-93)	94 (92-96)	96 (94-98)	96 (95-98)	96 (95-99)
TNYF	48 (36-57)	77 (74-81)	86 (82-88)	91 (88-94)	95 (93-96)	95 (94-97)	96 (95-97)	97 (96-98)

[a] Results reported for stability samples from the 9 month time point at the 25 °C/60% RH storage (packaged batch SBCT) with commercial test method

[b] Results reported for stability samples from the 6 month time point at the 25 °C/60% RH storage (packaged batch SXVF) with commercial test method

[6] \\cdsesub1\evsprod\nda210455\0000\m3\32-body-data\32p-drug-prod\active-film-coated-tablet\32p5-contr-drug-prod\32p56-justif-spec\justification-of-specifications.pdf

3. Emtricitabine

Batch	Dissolution Mean Percent Dissolved (Minimum-Maximum)							
	5 min	10 min	15 min	20 min	30 min	45 min	60 min	90 min
STKF	94 (92-96)	99 (98-99)	99 (98-99)	99 (99-100)	100 (99-100)	100 (99-100)	100 (100-100)	100 (99-101)
STKG	94 (92-95)	99 (98-100)	99 (98-100)	99 (98-100)	100 (99-100)	101 (98-109)	100 (98-101)	100 (99-101)
STKH	89 (84-95)	99 (97-101)	100 (98-101)	100 (99-101)	100 (99-101)	100 (99-101)	100 (99-101)	101 (99-101)
SBCH[a]	102 (100-103)	102 (101-103)	102 (101-103)	102 (100-103)	102 (100-103)	102 (100-103)	102 (101-104)	102 (101-103)
SXVC[b]	55 (30-73)	95 (80-99)	100 (98-101)	101 (99-103)	102 (100-104)	102 (100-103)	101 (100-103)	102 (100-104)
TNYC	100 (97-101)	100 (99-102)	100 (99-102)	100 (99-102)	100 (99-101)	100 (99-101)	100 (99-101)	100 (99-102)
TNYF	92 (78-100)	101 (100-102)	102 (101-103)	102 (101-103)	103 (102-105)	103 (102-104)	102 (102-103)	104 (102-104)

[a] Results reported for stability samples from the 9 month time point at the 25 °C/60% RH storage (packaged batch SBCT) with commercial test method

[b] Results reported for stability samples from the 6 month time point at the 25 °C/60% RH storage (packaged batch SXVF) with commercial test method

4. Tenofovir Alafenamide

Batch	Dissolution Mean Percent Dissolved (Minimum-Maximum)							
	5 min	10 min	15 min	20 min	30 min	45 min	60 min	90 min
STKF	82 (80-84)	94 (93-96)	96 (94-98)	96 (95-98)	95 (94-97)	95 (95-97)	96 (95-98)	96 (95-98)
STKG	79 (77-80)	90 (89-92)	92 (91-95)	93 (92-96)	94 (93-96)	95 (93-97)	95 (93-98)	95 (94-98)
STKH	75 (70-82)	92 (91-94)	95 (94-96)	96 (95-97)	97 (96-98)	97 (96-98)	98 (96-99)	98 (96-99)
SBCH[a]	95 (93-99)	97 (93-99)	98 (94-99)	98 (97-100)	98 (94-100)	98 (95-100)	99 (97-102)	100 (96-102)
SXVC[b]	45 (26-62)	85 (70-92)	94 (89-97)	95 (92-98)	97 (94-98)	97 (94-100)	98 (95-100)	99 (95-101)
TNYC	93 (91-96)	96 (94-98)	97 (95-99)	98 (96-100)	98 (96-100)	98 (97-101)	99 (96-101)	99 (96-101)
TNYF	80 (67-89)	95 (92-97)	96 (94-98)	97 (95-100)	98 (96-101)	98 (96-101)	98 (96-101)	99 (97-102)

[a] Results reported for stability samples from the 9 month time point at the 25 °C/60% RH storage (packaged batch SBCT) with commercial test method

[b] Results reported for stability samples from the 6 month time point at the 25 °C/60% RH storage (packaged batch SXVF) with commercial test method

Zhuojun Zhao

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Date: 3/07/2018 12:09:39PM
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Elsbeth Chikhale

Digitally signed by Elsbeth Chikhale
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ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment - NDA
   a) Drug Product

Final Risk Table for Darunavir, Cobicistat, Emtricitabine, and Tenofovir Alafenamide Tablets

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Eval.**	**Lifecycle Considerations/ Comments**
Assay, Stability	TAF is moderately stable in the tablet	L	(b) (4)	Acc	
Physical stability (solid state)	Based on cobicistat	M		Acc	
Content uniformity	Based on TAF loading	H		Acc	
Microbial limits		L		Acc	
Dissolution – BCS Class II & IV	Darunavir and cobicistat	M		Acc	

Stephen Miller

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Date: 6/13/2018 02:22:58PM
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Comments: ATL for NDA 210455

ENVIRONMENTAL

Summary: The applicant provided an environmental assessment (EA) for darunavir, and claims for categorical exclusions from EAs for cobicistat, emtricitabine, and tenofovir alafenamide (TAF). FDA determined that darunavir qualifies for an exclusion in accordance with 21 CFR 25.31(a), which is for actions that do not increase the use of active moiety. For the other three substances, the applicant claimed exclusions in accordance with 21 CFR 25.31(b), which is for actions that increase the use of the active moiety, but for which the estimated concentration of the substance at the point of entry into the aquatic environment—the expected introduction concentration (EIC)—will be below 1 part per billion (1 ppb). The required statement of no extraordinary circumstances was included for the latter three substances, and was inferred for darunavir. The claims for an exclusion from an EA are acceptable.

R Regional Information

Environmental

The applicant provided an environmental assessment (EA) for darunavir, and claims for categorical exclusions from EAs for cobicistat, emtricitabine, and tenofovir alafenamide (TAF). For darunavir, the applicant provided an EA with an EIC of (b) (4) ppb, claiming that the EA illustrated how this substance would not result in a significant environmental impact. Both the EA and EIC are the same as what was submitted for NDA 205395. Both EAs refer to the original EA for this substance, under NDA 021976. During the FDA reviews of the earlier EAs—under NDAs 205395 and 021976—FDA had determined that darunavir would not result in a significant impact on the environment. The FDA review for NDA 205395 also involved additional confirmatory analysis.

For the other three substances—cobicistat, emtricitabine, and TAF—the applicant submitted claims for categorical exclusions from EAs in accordance with 21 CFR 25.31(b), which is for actions that increase the use of the active moiety, but for which the estimated concentration of the substance at the point of entry into the aquatic environment—the expected introduction concentration (EIC)—will be below 1 part per billion (1 ppb). Exclusion claims for these substances also have been examined in some detail in previous NDAs, i.e., NDAs 205395 and 203100 for cobicistat, NDA 021752/S-055 for emtricitabine, and NDA 210251 for tenofovir (the active moiety of TAF). The required statement of no extraordinary circumstances was included for these substances.

Reviewer's Assessment: ***{Adequate/Inadequate}***

For darunavir, a categorical exclusion from an EA in accordance with 21 CFR 25.31(a), which is for actions that do not increase the use of active moiety, is more

appropriate than an EA because of the no increased use and the existing EA. The required statement of no extraordinary circumstances, per 21 CFR 25.15(a) and (c), is inferred due to the submission of an EA and the claim of no significant environmental impact. For cobicistat, emtricitabine, and TAF, no indication of potential for significant impact was identified. In addition, the required statement of no extraordinary circumstances was provided.

The submissions are adequate, and the claims for exclusions from an EA are acceptable.

Primary Environmental Reviewer Name and Date: James P. Laurenson, May 31, 2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed): M. Scott Furness, May 31, 2018

James Laurenson

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Date: 5/31/2018 08:19:13AM
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Michael Furness

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Date: 5/31/2018 09:21:40AM
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LABELING

I. Package Insert

(b) (4)

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	Symtuza (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide) tablets
Dosage form, route of administration	Tablets, oral
Controlled drug substance symbol (if applicable)	Not applicable
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Tablets: 800 mg of darunavir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide.

Is the information accurate? ☒ Yes ☐ No

2. ***Section 2 Dosage and Administration***

2.2 Recommended Dosage

SYMTUZA is a four-drug fixed dose combination product containing 800 mg of darunavir (DRV), 150 mg of cobicistat (COBI), 200 mg of emtricitabine (FTC), and 10 mg of tenofovir alafenamide (TAF). The recommended dosage of SYMTUZA is one tablet taken orally once daily with food in adults (b) (4) (b) (4) 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 *[Clinical Pharmacology (12.3)]*.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	The tablet is a once per day regimen. For patients who are unable to swallow the tablet whole, Symtuza may be split into two pieces using a tablet-cutter and the dose should be consumed immediately after splitting

Is the information accurate? ☒ Yes ☐ No

3. ***Section 3 Dosage Forms and Strengths***

3 DOSAGE FORMS AND STRENGTHS

Each SYMTUZA tablet contains darunavir ethanolate equivalent to 800 mg of darunavir, 150 mg of cobicistat, 200 mg of emtricitabine (FTC), and tenofovir alafenamide fumarate equivalent to 10 mg of tenofovir alafenamide (TAF). The yellow to yellowish-brown, capsule-shaped, film-coated tablet is debossed with "8121" on one side and "JG" on the other side.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Tablet
Strengths: in metric system	800 mg of darunavir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide.
Active moiety expression of strength with equivalence statement (if applicable)	(b) (4)
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Symtuza are 22 mm by 10 mm in size and are debossed with "8121" on one side and "JG" on the other. The Tablets are yellow and capsule shaped.

Is the information accurate? ☒ Yes ☐ No

4. ***Section 11 Description***

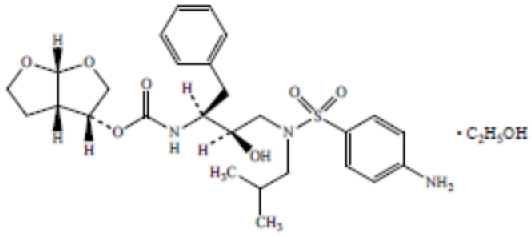
11 DESCRIPTION

SYMTUZA (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide) is a fixed-dose combination tablet.

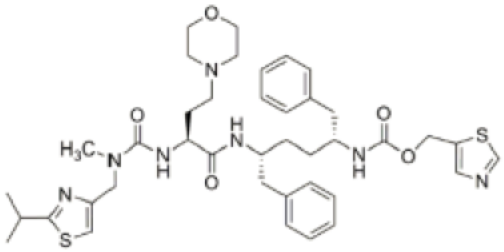
- Darunavir is an inhibitor of the HIV-1 protease.
- Cobicistat is a mechanism-based inhibitor of cytochrome P450 (CYP) enzymes of the CYP3A family.
- Emtricitabine, a synthetic nucleoside analog of cytidine, is an HIV nucleoside analog reverse transcriptase inhibitor (HIV NRTI).
- Tenofovir alafenamide, an HIV NRTI, is converted *in vivo* to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate.

SYMTUZA tablets are for oral administration. Each tablet contains darunavir ethanolate equivalent to 800mg of darunavir, 150 mg of cobicistat , 200 mg of emtricitabine, and tenofovir alafenamide fumarate equivalent to 10 mg of tenofovir alafenamide. The tablets include the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The tablets are film-coated with a coating material containing polyethylene glycol (macrogol), polyvinyl alcohol (partially hydrolyzed), talc, titanium dioxide, and yellow ferric oxide.

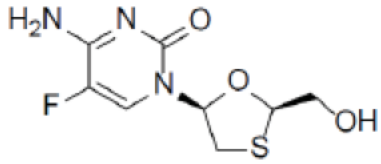
Darunavir: Darunavir, in the form of darunavir ethanolate, has the following chemical name: [(1*S*,2*R*)-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-carbamic acid (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-yl ester monoethanolate. Its molecular formula is $C_{27}H_{37}N_3O_7S \cdot C_2H_5OH$ and its molecular weight is 593.73. Darunavir ethanolate has the following structural formula:



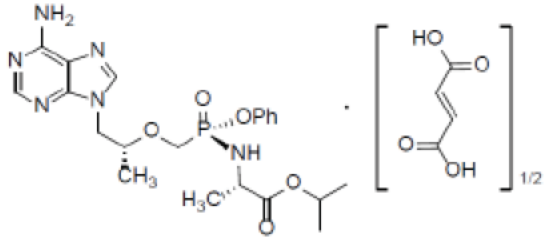
Cobicistat: Cobicistat is adsorbed onto silicon dioxide. The chemical name for cobicistat is 1,3-thiazol-5-ylmethyl[(2*R*,5*R*)-5-{[(2*S*)-2-[(methyl{[2-(propan-2-yl)-1,3-thiazol-4-yl]methyl}carbamoyl)amino]-4-(morpholin-4yl)butanoyl]amino}-1,6-diphenylhexan-2-yl]carbamate. It has a molecular formula of $C_{40}H_{53}N_7O_5S_2$ and a molecular weight of 776.02. It has the following structural formula:



Emtricitabine: The chemical name of emtricitabine is 4-amino-5-fluoro-1-(2*R*-hydroxymethyl-[1,3]-oxathiolan-5*S*-yl)-(1H)-pyrimidin-2-one. Emtricitabine is the (-)enantiomer of a thio analog of cytidine, which differs from other cytidine analogs in that it has a fluorine in the 5 position. Emtricitabine has a molecular formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.24. It has the following structural formula:



Tenofovir alafenamide: The chemical name of tenofovir alafenamide fumarate drug substance is L-alanine, (b) (4) *N*-[(*S*)-[[(1*R*)-2-(6-amino-9*H*-purin-9-yl)-1-methylethoxy]methyl]phenoxyphosphinyl]-, 1-methylethyl ester, (2*E*)-2-butenedioate (2:1). Tenofovir alafenamide fumarate has a molecular formula of $C_{21}H_{29}O_5N_6P \cdot ½(C_4H_4O_4)$ and a formula weight of 534.50. It has the following structural formula:



Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Symtuza (darunavir, covicistat, emtricitabine, and tenofovir alafenamide) tablets
Dosage form and route of administration	Tablet, oral
Active moiety expression of strength with equivalence statement (if applicable)	800 mg of darunavir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide equivalent to 11.2 mg of tenofovir alafenamide fumarate
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	The tablets include the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The tablets are film-coated with a coating material containing polyethylene glycol (macrogol), polyvinyl alcohol (partially hydrolyzed), talc, titanium dioxide, and yellow ferric oxide.
Statement of being sterile (if applicable)	Not applicable
Pharmacological/ therapeutic class	Darunavir is an inhibitor of the HIV-1 protease. Cobicistat is a mechanism-based

	inhibitor of cytochrome P450 (CYP) enzymes of the CYP3A family. Emtricitabine is an HIV nucleoside analog reverse transcriptase inhibitor (HIV NRTI). Tenofovir alafenamide, an HIV NRTI, is converted in vivo to tenofovir, an acyclicnucleoside phosphonate (nucleotide) analog of adenosine 5-monophosphate.
Chemical name, structural formula, molecular weight	Included and accurate
If radioactive, statement of important nuclear characteristics.	Not applicable
Other important chemical or physical properties (such as pKa or pH)	Not applicable

Is the information accurate? ☒ Yes ☐ No

5. ***Section 16 How Supplied/Storage and Handling***

16 HOW SUPPLIED/STORAGE AND HANDLING

SYMTUZA (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide) tablets are supplied as yellow to yellowish-brown, capsule-shaped, film-coated tablets debossed with "8121" on one side and "JG" on the other side.

SYMTUZA is packaged in bottles of 30 tablets (NDC 59676-800-30), with a silica gel desiccant and child-resistant closure.

Storage:

- Store at 20°C-25°C (between 68°F -77°F); with excursions permitted to 15°C-30°C (59°F-86°F).
- Keep container tightly closed with desiccant inside to protect from moisture.
- Dispense only in the original (b) (4) to protect from moisture

Product of Canada

Manufactured by:
Patheon Inc, Mississauga ON L5N 7K9, Canada

Manufactured for:
Janssen Therapeutics, Division of Janssen Products, LP, Titusville NJ 08560

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	Tablets: 800 mg of darunavir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide.

Available units (e.g., bottles of 100 tablets)	Bottles of 30 tablets.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Symtuza are (b) (4) debossed with "8121" on one side and "JG" on the other. The Tablets are yellow and capsule shaped.
Special handling (e.g., protect from light)	Keep container tightly closed. Dispense only in original container
Storage conditions	Store at 20-25°C (between 68-77°F); with excursions permitted to 15°-30°C (59°-86°F).
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Manufactured by Patheon Inc. Manufactured for Janssen

Reviewer's Assessment of Package Insert: ***Adequate***
Revisions identified and will be communicated to the Applicant as part of labeling negotiations. The PI is adequate assuming Applicant accepts edits.

II. Labels:

1. ***Container and Carton Labels***

(b) (4)

Item	Information provided in the container label
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Symtuza (darunavir, covicistat, emtricitabine, and tenofovir alafenamide) tablets
Dosage strength	800 mg of darunavir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide.
Net contents	30 Tablets
"Rx only" displayed prominently on the main panel	Complies
NDC number (21 CFR 207.35(b)(3)(i))	Complies
Lot number and expiration date (21 CFR 201.17)	Complies
Storage conditions	Store at 20-25°C (between 68-77°F); (b) (4) excursions permitted to 15°-30°C (59°-86°F).
Bar code (21CFR 201.25)	Complies
Name of manufacturer/distributor	Manufactured by Patheon Inc. Manufactured for Janssen
And others, if space is available	Not applicable.

Reviewer's Assessment of Labels: ***Adequate***
The container and carton label complies with all regulatory requirements from a CMC perspective.

List of Deficiencies: Not Applicable

Overall Assessment and Recommendation: Adequate

Andrei Ponta

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Balajee Shanmugam

Digitally signed by Balajee Shanmugam
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