CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210455Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: May 31, 2018

To: Myung-Joo Patricia Hong, Regulatory Project Manager
Division of Antiviral Products (DAVP)

From: Wendy Lubarsky, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for SYMTUZA™ (darunavir, emtricitabine, and tenofovir alafenamide) tablets, for oral use

NDA: 210455

In response to DAVP consult request dated September 25, 2017, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for SYMTUZA™ (darunavir, emtricitabine, and tenofovir alafenamide) tablets, for oral use (Symtuza).

PI and PPI: OPDP's comments on the proposed labeling are based on the draft PI and PPI received by electronic mail from DAVP (Myung-Joo Patricia Hong) on May 17, 2018, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover on May 31, 2018.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DAVP (Myung-Joo Patricia Hong) on May 30, 2018, and we have no comments at this time.

Thank you for your consult. If you have any questions, please contact Wendy Lubarsky at (240) 402-7721 or wendy.lubarsky@fda.hhs.gov .

49 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

----

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WENDY R LUBARSKY
05/31/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	May 30, 2018
To:	Debra Birnkrant, MD Director **Division of Antiviral Products (DAVP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Morgan Walker, PharmD, MBA, CPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Wendy Lubarsky, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	SYMTUZA (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	210455
Applicant:	Jassen Products, LP

1 INTRODUCTION

On September 22, 2017, Jassen Products, LP submitted for the Agency's review an original New Drug Application (NDA) 210455 for SYMTUZA (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide) tablets. The proposed indication is for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Antiviral Products (DAVP) on September 25, 2017 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for SYMTUZA (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide) tablets.

2 MATERIAL REVIEWED

- Draft SYMTUZA (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide) tablets PPI received on September 22, 2017, and received by DMPP and OPDP on May 17, 2018.
- Draft SYMTUZA (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide) tablets Prescribing Information (PI) received on September 22, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 17, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

----

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MORGAN A WALKER
05/30/2018

WENDY R LUBARSKY
05/31/2018

LASHAWN M GRIFFITHS
05/31/2018

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	March 5, 2018
Requesting Office or Division:	Division of Antiviral Products (DAVP)
Application Type and Number:	NDA 210455
Product Name and Strength:	Symtuza (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide) Tablet, 800 mg/150 mg/200 mg/10 mg
Product Type:	Multi-ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Janssen Research & Development, LLC.
Submission Date:	September 22, 2017 and October 23, 2017
OSE RCM #:	2017-1955
DMEPA Safety Evaluator:	Valerie S. Wilson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF REVIEW

As part of the approval process for Symtuza (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide) 800mg/150 mg/200 mg/10 mg tablet, the Division of Antiviral Products (DAVP) requested that we review the proposed labels and labeling for areas that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B (N/A)
ISMP Newsletters	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Other	E (N/A)
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Table 2 below includes identified medication error issues with the submitted Prescribing Information, DMEPA's rationale for concern, and the proposed recommendations to minimize the risk for medication error for DAVP's consideration. Table 3 includes an identified medication error issue with the submitted container label, along with a general comment about the container label, DMEPA's rationale for concern, and recommendations to the Applicant to minimize the risk for medication error.

Table 2: Identified Issues and Recommendations for Division of Antiviral Products

Prescribing Information			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Full Prescribing Information (FPI)			
1.	We note the unit of measurement of temperature (i.e. °C and °F) does not follow each numerical expression within the storage statement in Section 16 of the FPI. The format also does not align with the format used in the Patient Package Insert or container label.	The acceptable storage temperature could be misinterpreted and pose a risk for improper storage, which could affect the integrity of the tablets.	To mitigate possible storage errors and to promote alignment across the label and labeling, we recommend the storage statement is revised to read: "Store at 20°C-25°C (68°F-77°F); with excursions permitted to 15°C-30°C (59°F-86°F)."
2.	We note important storage information such as, "Keep Symtuza in the original container" and "Keep the bottle tightly closed" is missing from the Patient Package Insert (PPI).	This missing information poses a risk for improper storage of Symtuza by patients, which could affect the integrity of the tablet.	We recommend additional storage instructions, for example, "Keep Symtuza in the original container" and "Keep the bottle tightly closed" be included in the PPI. We defer to the Patient Labeling Team to determine the appropriate language to use to convey the additional storage instructions.

Table 3: Identified Issues and Recommendations for Janssen Research & Development, LLC (*entire table to be conveyed to Applicant***)**

Container Labels			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
1.	The storage statement includes instruction to [redacted] (b) (4) " which does not align with the storage statement, *"Dispense only in original container,"* located in the Full Prescribing Information.	Discrepancy between the storage statements could result in dispensing or storage errors which may affect the quality of the product.	For consistency and to mitigate possible dispensing or storage errors, we recommend you ensure the storage statement on the container label aligns with the storage statement in the Prescribing Information.
2.	We note the inclusion of [redacted] (b) (4)	[redacted] (b) (4)	We recommend you revise the establish name to read: *"Symtuza (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide) tablets 800 mg/ 150 mg/ 200 mg/ 10 mg"*

4 CONCLUSION

DMEPA's evaluation of the proposed label and labeling identified areas of vulnerability that may lead to medication errors. We have provided recommendations in Table 3 above and ask that the Division conveys the entire table to the Applicant so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Symtuza that Janssen Research & Development, LLC submitted on October 23, 2017.

Table 4. Relevant Product Information for Symtuza	
Initial Approval Date	N/A
Active Ingredient	Darunavir, cobicistat, emtricitabine, and tenofovir alafenamide
Indication	A complete regimen for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older (b) (4)
Route of Administration	Oral
Dosage Form	Tablet
Strength	800 mg/150 mg/200 mg/10 mg
Dose and Frequency	1 tablet once daily with food
How Supplied	Bottles of 30 tablets
Storage	Store at 20-25°C (between 68-77°F); with excursions permitted to 15-30°C (59-86°F). Keep container tightly closed. Dispense only in original container.
Container Closure System	Bottle with child-resistant closure.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Symtuza labels and labeling submitted by Janssen Research & Development, LLC on September 22, 2017.

- Container label
- Professional Sample Container Label
- Prescribing Information (Image not shown)

F.2 Label and Labeling Images

(b) (4)

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.


(b) (4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VALERIE S WILSON
03/05/2018

OTTO L TOWNSEND
03/05/2018