CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215423Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 23, 2021
Requesting Office or Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Application Type and Number:	NDA 215423
Product Name and Strength:	Entadfi[a] (finasteride and tadalafil capsules) 5 mg/5 mg
Applicant/Sponsor Name:	Veru, Inc.
OSE RCM #:	2021-330-2
DMEPA 2 Safety Evaluator:	Denise V. Baugh, PharmD, BCPS
DMEPA 2 Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton (case and pallet) labeling received on November 2, 2021 for Entadfi (finasteride and tadalafil) capsules. The Division of Urology, Obstetrics, and Gynecology (DUOG) requested that we review the revised container labels and carton (case and pallet) labeling for Entadfi (finasteride and tadalafil) capsules (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[b]

2 CONCLUSION

The Applicant implemented all of our previous recommendations. However, we note that the format for the expiration date, NDC number, and temperature range on the container labels differ from that of the case and the pallet.

[a] Kalonia, J. Proprietary Name Review for Entadfi (NDA 215423). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 OCT 04. RCM No.: 2021-1044724080.
[b] Baugh, D. Label and Labeling Review for Entadfi (NDA 215423). Silver Spring (MD): FDA, CDER, OSE, DMEPA (DMEPA 2) (US); 2021 OCT 27. RCM No.: 2021-330-1.

3 RECOMMENDATIONS FOR VERU, INC.

We recommend the following be implemented prior to approval of this NDA:

A. Container Labels

1. We note that the temperature statement on the container labels is not presented as a range and is inconsistent with Section 16 (How Supplied/Handling) of the Prescribing Information (PI). We recommend revising the statement (b) (4) to read '20˚C to 25˚C (68˚F to 77˚F)'.

B. Case and Pallet Labeling

1. We note that presentation of the expiration date on the case and pallet labeling is different from that on the container label. To improve consistency, consider changing the expiration date on the case and pallet labeling to reflect the same format expressed on the container labels.

2. We note that the location and format for the NDC number on the case and pallet labeling is not the same as on the container labels. To improve consistency, consider revising this information to appear in the same location and to have the same format as that which is on the container label.

3. We note that storage information is absent on the pallet labeling. Consider adding the same temperature range statement to the pallet labeling that is in Section 16 (How Supplied/Handling) of the PI and is present on the case labeling for consistency and to avoid medication errors resulting from improper storage.

4. We note that a total quantity statement (i.e., number of bottles) is absent from the case and pallet labeling. Consider adding this statement so that users can identify how much product is contained in each case/pallet. For example, "## x 30 count bottles" or "## x 90 count bottles".

5. We note that the 'Rx only' statement is absent from the pallet and case labeling. Consider adding this statement for consistency with the container labels.

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/s/

DENISE V BAUGH
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STEPHANIE L DEGRAW
11/23/2021 11:03:13 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

TO: Sydney Tran, Regulatory Project Manager
Urology, Obstetrics and Gynecology (DUOG)

FROM: Tinya Sensie, MHA, Senior Regulatory Project Manager
Pediatric and Maternal Health (DPMH)

SUBJECT: New NDA with PLLR

NDA: 215423

DRUG: ENTADFI (tadalafil & finasteride)

On September 17, 2021, DPMH received a consult from DUOG for a new NDA with PLLR and pediatric questions on subsections 8.1 and 8.4.

DPMH pediatric and maternal health teams both attended the labeling meeting on September 24, 2021 and agreed with the final proposed labeling language in subsections 8.1 and 8.4.

The action date for ENTADFI is December 10, 2021.

This memorandum will close out the consult request.

DPMH RPM- Tinya Sensie
DPMH RPM Team Leader- George Greeley
DPMH Pediatric Reviewer/Team Leader- Shetarra Walker
DPMH Maternal Reviewer/Team Leader- Tamara Johnson
DPMH Division Director- Lynne P. Yao
DPMH Deputy Division Director- John J. Alexander

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/s/

TINYA J SENSIE
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 27, 2021
Requesting Office or Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Application Type and Number:	NDA 215423
Product Name and Strength:	Entadfi[a] (finasteride and tadalafil capsules) 5 mg/5 mg
Applicant/Sponsor Name:	Veru, Inc.
OSE RCM #:	2021-330-1
DMEPA 2 Safety Evaluator:	Denise V. Baugh, PharmD, BCPS
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton (case and pallet) labeling received on August 13, 2021 for Entadfi (finasteride and tadalafil) capsules. The Division of Urology, Obstetrics, and Gynecology (DUOG) requested that we review the revised container labels and carton (case and pallet) labeling for Entadfi (finasteride and tadalafil) capsules (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[b]

2 CONCLUSION

The Applicant implemented all of our recommendations. However, we note the use of "TRADENAME" on the container labels and carton labeling as a placeholder for the proprietary name. Given that the proposed proprietary name Entadfi was found conditionally acceptable[c],

[a] Kalonia, J. Proprietary Name Review for Entadfi (NDA 215423). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 OCT 04. RCM No.: 2021-1044724080.
[b] Baugh, D. Label and Labeling Review for tadalafil and finasteride (NDA 215423). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 JUL 21. RCM No.: 2021-330.
[c] Kalonia, J. Proprietary Name Review for Entadfi (NDA 215423). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 OCT 04. RCM No.: 2021-1044724080.

revised labels and labeling with the proprietary name “Entadfi” should be submitted for our review and comment.

3 RECOMMENDATIONS FOR VERU, INC.

We recommend the following be implemented prior to approval of this NDA:

A. Container Labels and Carton Labeling

1. We refer to the Proprietary Name Decision Letter dated October 7, 2021 finding the proposed proprietary name, Entadfi, conditionally acceptable. Therefore, replace the “TRADENAME” placeholder with the conditionally acceptable proprietary name “Entadfi” wherever it appears on the container labels and labeling and submit the revised labels and labeling for our review and comment.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON AUGUST 13, 2021

Container label – 30 count

(b) (4)

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DENISE V BAUGH
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STEPHANIE L DEGRAW
10/27/2021 07:08:13 PM

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

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

Memorandum

Date: October 7, 2021

To: Martin E. Kaufman, M.D.
Division of Urology, Obstetrics and Gynecology (DUOG)

Jennifer L. Dodson, M.D., DUOG

Sydney T. Tran, Regulatory Project Manager, DUOG

From: Elvy Varghese, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, Team Leader, OPDP

Subject: OPDP Labeling Comments for (b) (4) (tadalafil and finasteride) capsules, for oral use

NDA: 215423

In response to DUOG's consult request dated March 15, 2921, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for (b) (4) (b) (4) and finasteride) capsules, for oral use (b) (4) Please note that the PI contains a Patient Information section.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DUOG (Sydney Tran) on October 4, 2021, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Patient Information will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on August 8, 2021, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Elvy Varghese at (240) 402-0080 or Elvy.Varghese@fda.hhs.gov.

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/s/

ELVY M VARGHESE
10/07/2021 03:33:30 PM

LABEL, LABELING AND PACKAGING 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:	July 21, 2021
Requesting Office or Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Application Type and Number:	NDA 215423
Product Name and Strength:	tadalafil and finasteride capsules, 5 mg/5 mg
Product Type:	Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Veru Inc.
FDA Received Date:	February 17, 2021 May 21, 2021 June 17, 2021
OSE RCM #:	2021-330
DMEPA Safety Evaluator:	Denise V. Baugh, PharmD, BCPS
DMEPA Acting Team Leader:	Celeste Karpow, PharmD, MPH

1 REASON FOR REVIEW

As part of the approval process for tadalafil and finasteride capsules, the Division of Urology, Obstetrics, and Gynecology (DUOG) requested that we review the proposed tadalafil and finasteride container label, labeling and prescribing information (PI) for areas of vulnerability that may lead to medication errors.

In response to our April 23, 2021 Communication the Applicant indicated that they do not intend to have a carton for this product.

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
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 or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine post-market safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

The proposed tadalafil and finasteride container label and prescribing information (PI) may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and the proposed recommendation to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Veru Inc.

4 RECOMMEDATIONS FOR DIVISION OF UROLOGY, OBSTETRICS, AND GYNECOLOGY (DUOG)

Table 2. Identified Issues and Recommendations for Division of Urology, Obstetrics, and Gynecology (DUOG)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 2 Dosage and Administration			
1.	The route of administration is not stated in Section 2 Dosage and Administration.	The inclusion of the route of administration may minimize misinterpretation.	We recommend adding the route of administration (oral) to the dosage and administration section. Consider the following: 'The recommended dose of 'TRADENAME is one capsule orally taken once daily at approximately the same time every day up to 26 weeks.'
2.	The dosage regimen includes (b) (4) .	The addition of the (b) (4) is not part of the dosage regimen.	We recommend revising 'The recommended dose of (b) (4) is one capsule (containing (b) (4) once daily at approximately the same time every day for up to 26 weeks' to read 'The recommended dose of TRADENAME is one capsule taken orally once daily at approximately the same time every day for up to 26 weeks'
3.	(b) (4)	Reference to th (b) (4) may cause confusion.	We defer to DUOG to address this discrepancy.

Table 2. Identified Issues and Recommendations for Division of Urology, Obstetrics, and Gynecology (DUOG)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
4.	Units of measurement and symbols are not consistently used.	Appropriate units of measurement and symbols should be consistently stated to avoid confusion and misinterpretation.	Revise the Creatinine clearance in Section (b) (4) (Use in Specific Populations, Renal Impairment) (b) (4) (b) (4) Additionally, revise the temperature statement in Section 16 (How Supplied/Storage and Handling) from '15-30˚C (59-86˚F)' to read '15˚C to 30˚C (59˚F to 86˚F)'
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	Appropriate information to facilitate identification of the dosage forms, such as shape, color, coating, scoring, imprinting, and National Drug Code number is not listed in the How Supplied Section.	The information provided does not comply with 21 CFR 201.57(c)(17).	We recommend appropriate information to facilitate identification of the dosage forms, such as shape, color, coating, scoring, imprinting, and National Drug Code number is be listed in the How Supplied Section.

5 RECOMMENDATIONS FOR VERU INC.

Table 3. Identified Issues and Recommendations for Veru Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s)			
1.	The proposed proprietary name, (b) (4) appears on the container label.	The proposed proprietary name, (b) (4) was denied.	Denote the proprietary name placeholder as "Tradename" until a proprietary name has been granted conditional approval. We recommend you present "Tradename" in your intended design.

Table 3. Identified Issues and Recommendations for Veru Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
2.	The established name lacks prominence commensurate with the proprietary name and is not at least half the size of the proprietary name.	Important drug information may be overlooked and not in accordance with 21 CFR 201.10(g)(2).	Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
3.	The format for the expiration date, MMM/YYYY, can be improved.	Clearly defining the expiration date will minimize confusion and decrease the risk for 'deteriorated drug' medication errors.	FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date. Ensure that the intended expiration date is included on the container label for the pallets and for the cases.

Table 3. Identified Issues and Recommendations for Veru Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
4.	The net quantity statement includes the (b) (4).	Inclusion of the (b) (4) in the net quantity statement is redundant and clutters the label.	Revise the net quantity statement from '30 capsules (b) (4) to read '30 capsules'.
5.	The side panel includes unnecessary information and contributes to clutter. Specifically, the statement (b) (4) on the side panel is unnecessary.	We are concerned that this statement detracts from other important information such as the recommended dosage statement and storage information.	We recommend deleting the statement (b) (4)
6.	The storage statement on the side panel does not consistently include the units of measurement, degree symbol and includes hyphens.	The presentation of the storage statement should be clearly stated to avoid storage errors.	Revise '15-30C (59-86F) to read '15˚C to 30˚C (59˚F to 86˚F)'.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for tadalafil and finasteride that Veru Inc submitted on May 21, 2021.

Table 4. Relevant Product Information for tadalafil and finasteride	
Initial Approval Date	N/A
Active Ingredient	Tadalafil and finasteride
Indication	Treatment of the signs and symptoms of benign prostatic hyperplasia (BPH)
Route of Administration	oral
Dosage Form	capsule
Strength	5 mg/5 mg
Dose and Frequency	One capsule once daily on an empty stomach for up to 26 weeks
How Supplied	30 count and 90 count bottle
Storage	25C (77F); excursions permitted to 15C to 30 C (59F to 86F); [see USP Controlled Room Temperature].
Container Closure	HDPE bottles with a low moisture polyester coil and sealed with a heat sealed HDPE cap

APPENDIX B. PREVIOUS DMEPA REVIEWS

On June 7, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, ‘tadalafil and finasteride’ and ‘215423’. Our search identified no previous reviews.

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 post-market medication error data, we reviewed the following tadalafil and finasteride labels and labeling submitted by Veru Inc.

- Container label(s) received on May 21, 2021 and June 17, 2021
- Prescribing Information (Image not shown) received on May 21, 2021, available from \\CDSESUB1\evsprod\nda215423\0007\m1\us\draft-labeling-text.docx

F.2 Label and Labeling Images

Container label – 30 count (submitted May 21, 2021 and June 17, 2021 respectively)

(b) (4)

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

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 6/21/2021

TO: Division of Urology, Obstetrics, and Gynecology (DUOG)
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 215423

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that inspections are not warranted at this time for the sites listed below. The rationale for this decision is noted below.

Rationale

The Office of Regulatory Affairs (ORA) inspected the clinical site in June 2019, which falls within the surveillance interval. The inspection was conducted under the following submission: Non-responsive Non-responsive

OSIS inspected the analytical site in (b) (4), which falls within the surveillance interval. The inspection was conducted under the following submissions: Non-responsive

The final classification for the inspections was No Action Indicated (NAI).

Therefore, based on the rationale described above, inspections are not warranted at this time.

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	Altasciences	1200 Beaumont Avenue, Mount-Royal, Quebec, Canada
Analytical	(b) (4)	(b) (4)

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