# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 215423Orig1s000

# PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

# RECOMMENDATION

| |
|---|
| ☒ Approval |
| ☐ Approval with Post-Marketing Commitment |
| ☐ Complete Response |
| ☐ Approval Pending Final Labeling |

# NDA 215423
# ENTADFI™ (finasteride and tadalafil) capsules
# Assessment #1

| | |
|---|---|
| **Drug Product Name** | ENTADFI™ (finasteride and tadalafil) capsules, for oral use |
| **Dosage Form** | Capsules |
| **Strength** | 5 mg / 5 mg |
| **Route of Administration** | Oral |
| **Rx/OTC Dispensed** | Rx |
| **Applicant** | Veru Inc. |
| **US agent, if applicable** | - |

| Submission(s) Assessed | Document Date | Discipline(s) Affected |
|---|---|---|
| Initial (0001) | 02/17/2021 | All |
| Quality/Response (0006) | 04/19/2021 | Biopharm. |
| Labeling (0007) | 05/21/2021 | Drug Product |
| Labeling (0008) | 06/17/2021 | Drug Product |
| Quality/Response (0009) | 07/14/2021 | Biopharm. |
| Quality/Response (0011) | 07/30/2021 | Drug Product / OPMA |
| Quality/Response (0012) | 07/30/2021 | Drug Product / OPMA |
| Labeling (0013) | 08/13/2021 | Drug Product |
| Quality/Response (0014) | 08/30/2021 | Biopharm. |
| Quality/Response (0015) | 10/08/2021 | Biopharm. |
| Quality/Response (0017) | 10/12/2021 | OPMA |
| Quality/Response (0018) | 10/15/2021 | Biopharm. |
| Quality/Response (0019) | 10/20/2021 | Drug Product |
| Quality/Response (0020) | 10/27/2021 | OPMA, Biopharm. |
| Labeling (0021) | 11/02/2021 | Drug Product |
| Quality Response (0022) | 11/08/2021 | Drug Product, Biopharm. |
| Labeling (0024) | 11/23/2021 | Drug Product |
| Labeling (0025) | 11/30/2021 | Drug Product |

| | | |
|---|---|---|
| Labeling (0026) | 12/02/2021 | Drug Product |
| Labeling (0027) | 12/06/2021 | Drug Product |
| Labeling (0028) | 12/08/2021 | Drug Product |

**QUALITY ASSESSMENT TEAM**

| Discipline | Primary Assessor | Secondary Assessor |
|---|---|---|
| **Drug Substance** | Sharon Kelly | Donna Christner |
| **Drug Product / Labeling** | Mark Seggel | Hong Cai |
| **Manufacturing / Microbiology** | Sachinkumar Patel | Yubing Tang |
| **Biopharmaceutics** | Leah Falade | Vidula Kolhatkar |
| **RBPM** | Marquita Burnett, Dahlia Walters | |
| **Application Technical Lead** | Mark Seggel | |
| **Laboratory (OTR)** | N/A | N/A |
| **Environmental** | Mark Seggel | Hong Cai |

**INFORMATION REQUESTS and OPQ COMMUNICATIONS**

| Request Date | Requested Response Date | Response Date | Discipline(s) |
|---|---|---|---|
| 04/05/2021 | 04/19/2021 | 04/19/2021 (0006) | Biopharmaceutics |
| 05/11/2021 | - | - | OPMA on Inspection of (b) (4) |
| 06/29/2021 | ~~07/07/2021~~ 07/14/2021 (per 07/07/2021 agreement) | 07/14/2021 (0009) | Biopharm. |
| 07/13/2021 | 07/30/2021 | 07/30/2021 (0011) | OPMA |
| 07/26/2021 | 07/30/2021 | 07/30/2021 (0012) | DP / OPMA |
| 07/30/2021 | 08/30/2021 | 08/30/2021 (0014) | Biopharm. |
| 10/04/2021 | 10/07/2021 | 10/15/2021 (0018) | Biopharm. |
| 10/04/2021 | 10/12/2021 | 10/12/2021 (0017) | OPMA |
| 10/06/2021 | 10/15/2021 | 10/15/2021 (0018) | DP / OPMA |
| 10/13/2021 | 10/20/2021 | 10/20/2021 (0019) | DP / Biopharm. |
| 10/19/2021 | 10/22/2021 | 10/27/2021 (0020) | Biopharm. |
| 10/22/2021 | 10/27/2021 | 10/27/2021 (0020) | OPMA / Biopharm. |
| 11/03/2021 | 11/04/2021 | 11/08/2021 (0022) | DP* |

* Request for updated drug product specification 3.2.P.5.1 and all other related documentation.

U.S. FOOD & DRUG ADMINISTRATION

# QUALITY ASSESSMENT DATA SHEET

For more details about the items in this template, please see the Quality Assessment Data Sheet chapter of the NDA IQA Guide

## 1. RELATED/SUPPORTING DOCUMENTS

### A. DMFs:

| DMF # | Type | Holder | Item Referenced | Status | Date Assessment Completed | Comments |
|---|---|---|---|---|---|---|
| (b) (4) | II | (b) (4) | | Adequate | D.Amspacher, 08/03/2021 | |
| | II | | | Adequate | D.Christner, 10/28/2021 | |
| | IV | | | | | Sufficient info in NDA |
| | IV | | | | | Sufficient info in NDA |
| | IV | | | | | Sufficient info in NDA |
| | IV | | | | | Sufficient info in NDA |
| | IV | | | | | See Note 1<br>LOA provided 10/22/2021<br>Sufficient info in NDA |
| | - | | | | | See Note 1<br>See Note 2 |
| | III | | | | | Sufficient info in NDA |
| | III | | | | | Sufficient info in NDA |
| | III | | | | | Sufficient info in NDA |
| | III | | | | | Sufficient info in NDA |
| | III | | | | | Sufficient info in NDA |
| | III | | | | | Sufficient info in NDA |
| | III | | | | | Sufficient info in NDA |

Note 1: Veru (SN 0001) inappropriately submitted copies of manufacturer's letters addressed to the Center for Drug Evaluation, (b) (4) The letters are of no relevance to the U.S. FDA.

Note 2: There is currently no DMF for (b) (4). An extensive Technical Information package prepared by (b) (4) was submitted 10/20/2021 (SN 0019)

## B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

| Document | Application Number | Description |
|---|---|---|
| Pre-IND / pre-NDA meeting background information packages, and Agency preliminary responses, meeting minutes / WRO (09/25/2017 – present) | pre-IND 136844 | Fixed-dose combination of finasteride 5 mg and tadalafil 5 mg designed to be bioequivalent to Proscar (finasteride) and Cialis (tadalafil); for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH) |
| Original NDA and S-022, labeling, and associated FDA assessments | NDA 021368 | Cialis (tadalafil) tablets; Eli Lilly, AP 11/21/2003 |
| Original NDA, labeling, and associated FDA assessments | NDA 020180 | Proscar (finasteride) tablets; Merck, AP 06/19/1992 |

## 2. CONSULTS

| Discipline | Status | Recommendation | Date | Assessor |
|---|---|---|---|---|
| Biostatistics | N/A | | | |
| Nonclinical | N/A | | | |
| CDRH | N/A | | | |
| Clinical | N/A | | | |
| Other | N/A | | | |

FDA U.S. FOOD & DRUG ADMINISTRATION

# EXECUTIVE SUMMARY

For more details about the items in this template, please see the Executive Summary chapter of the NDA IQA Guide

## I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Veru's 505(b)(2) New Drug Application 215423 for ENTADFI (finasteride and tadalafil) capsules, 5 mg / 5 mg, is recommended for APPROVAL from the OPQ perspective.

Sufficient chemistry, manufacturing and controls information and supporting data have been provided in accordance with 21 CFR 314.50 to ensure the identity, strength, quality, purity, and bioavailability of this fixed-dose combination drug product.

All drug substance and product-related manufacturing, packaging and testing facilities have acceptable drug CGMP status. An overall manufacturing inspection recommendation of APPROVE was issued on November 3, 2021, and remains current. A post-approval inspection of (b) (4), the drug product manufacturing facility, is recommended to cover the manufacture and release testing of validation batches.

The prescribing information as submitted December 8, 2021 and the bottle, case, and pallet labels as submitted on December 2, 2021 conform to the requirements under 21 CFR 201.

A 24-month expiration dating period for the drug product when stored in the 30-count and 90-count commercial packaging configurations at 20ºC to 25ºC is granted.

The claimed categorical exclusion from the environmental assessment requirements under 21 CFR Part 25.31(a) is acceptable.

## II. SUMMARY OF QUALITY ASSESSMENTS

### A. Product Overview

Veru Inc., has developed a once-daily fixed-dose combination product containing 5 mg tadalafil and 5 mg finasteride in an oral capsule formulation for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH). The proposed drug product is intended to provide a single-product alternative to the once-daily administration of a 5mg Cialis tablet and a 5 mg Proscar tablet.

E. Lilly's NDA 21368 for Cialis (tadalafil) tablets, a phosphodiesterase type 5 (PDE5) inhibitor indicated for the treatment of erectile dysfunction (ED) was approved on 11/21/2003. Cialis was subsequently approved for use in the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH) and for the treatment of ED and BPH. Supplement S-022, approved on 10/10/2013, provided for the addition of new information on the effects of Cialis co-administered with finasteride in the treatment of men with symptomatic benign prostatic hyperplasia (BPH).

Merck's (Organon) NDA 20180 for Proscar (finasteride) tablets, a 5α-reductase (5-ARI) inhibitor was approved 06/19/1992 for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate.

To support approval of the proposed fixed-dose combination product, Veru conducted a bioequivalence study versus co-administered 5 mg Cialis and 5 mg Proscar. No other clinical studies were conducted under pre-IND 136844. The registration batches, one of which was used in the pivotal bioequivalence study, are fully representative of the commercial product.

The proposed formulation consists (b) (4) capsule shell filled with a (b) (4) A battery of standard tests to assure the identity, purity, strength, quality and bioavailability of the immediate-release drug product have been developed. Because of the relatively low drug load of the two active ingredients (each (b) (4)% by weight of the capsule fill), assurance of continent uniformity ((b) (4)) is critical.

Both finasteride and tadalafil exist in multiple solid-state forms (polymorphs). Because the drug product manufacturing process involves (b) (4) a polymorph conversion risk assessment was requested. (b) (4) however, suggests that the potential for change in polymorph for either tadalafil or finasteride drug substance is very small and will not occur during normal processing activities.

Both finasteride and tadalafil exhibit good chemical stability in the formulation. A 24-month expiration dating period for drug product stored at 25°C is supported by 12-months long-term and 6-months accelerated stability from 3 registration/primary stability batches.

The DUOG clinical review team raised concerns about the potential leakage of finasteride from the capsules. Finasteride is a NIOSH Group 3 Hazardous Drug that may be absorbed through the skin. As noted in the PROSCAR (finasteride) Tablets USPI, [redacted] (b) (4) should not handle crushed or broken PROSCAR tablets when they are pregnant or may potentially be pregnant due to potential risk to a male fetus." The PROSCAR prescribing information further states that, "PROSCAR tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets have not been broken or crushed."

In the proposed product ENTADFI, [redacted] (b) (4) finasteride (and tadalafil) is encapsulated in a two-part (body and cap) hypromellose capsule shell. Exposure of pregnant females to finasteride from the capsules (due, for example, to handling of capsules with residual finasteride-containing powder on the exterior surface, or leakage from damaged capsules) presents a similar potential risk to a male fetus. Veru was therefore asked to, "provide a comprehensive risk assessment of factors associated with manufacturing and product quality that could result in exposure to finasteride and detail the strategy for mitigating those risks." Veru was also asked to describe measures to prevent exposure of personnel in the manufacturing and packaging facilities, and to prevent cross-contamination of other products manufactured in the same facilities.

The risk mitigation strategy includes suitable controls to ensure capsule shell quality, in-process tests [redacted] (b) (4) (b) (4) Overall, the applicant has taken adequate steps to minimize product quality defects that could result in inadvertent direct exposure to finasteride when the drug product is handled under normal conditions.

Finally, the firm has included reasonable controls to prevent cross-contamination and exposure of individuals to the finasteride in the manufacturing environment.

| | |
|---|---|
| **Proposed Indication(s) including Intended Patient Population** | ENTADFI is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH) in adult males for up to 26 weeks |
| **Duration of Treatment** | once daily, for up to 26 weeks |
| **Maximum Daily Dose** | finasteride 5 mg and tadalafil 5 mg |

| | |
|---|---|
| **Alternative Methods of Administration** | Not Applicable |

## B. Quality Assessment Overview

### Drug Substance: Adequate

Tadalafil drug substance CMC is documented in [redacted] Type II DMF [redacted]. Finasteride drug substance CMC is documented in [redacted] Type II DMF [redacted]. Both tadalafil and finasteride are the subjects of USP monographs. Relevant information for each active ingredient, including the specifications and characterization of impurity / degradation profiles is also provided in the associated section 3.2.S in the NDA.

DMF [redacted] for Tadalafil, USP was last reviewed 08/03/2021 and was found adequate (see DMF Review #7). DMF [redacted] for Finasteride, USP was last reviewed 10/28/2021 and was found adequate (see DMF Review #13).

See OPQ IQA Chapter I, Drug Substance, for a discussion of the physical and chemical properties of each active ingredient that are relevant to the manufacture and performance of the drug product. Impurity and degradation profiles of finasteride and tadalafil have been characterized. [redacted] finasteride and tadalafil were selected for drug product development in order to achieve drug product dissolution similar to the reference standard products (Cialis and Proscar).

Overall, the CMC information provided for the finasteride and tadalafil drug substances supplied by [redacted] respectively, is adequate to support the use of these active ingredients in the manufacture of ENTADFI.

### Drug Product: Adequate

ENTADFI a once-daily fixed-dose combination product containing 5 mg tadalafil and 5 mg finasteride in an oral capsule formulation for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH). The proposed drug product is intended to provide a single-product alternative to the once-daily administration of a 5 mg Cialis tablet and a 5 mg Proscar tablet. Formulation development was informed by the components identified in the Proscar and Cialis prescribing information. Further formulation optimization and process development followed with the goal of ensuring content uniformity and achieving dissolution comparable to the listed drugs.

To support approval of the proposed fixed-dose combination product, Veru conducted a bioequivalence study versus co-administered 5 mg Cialis and 5 mg Proscar. No clinical studies were conducted under pre-IND 136844. The registration stability batches, one of which was used in the pivotal BA/BE study, are fully representative of the commercial product.

The product consists of hypromellose capsule shells filled with a (b) (4) (b) (4) The capsules are packaged in 30-count and 90-count, 60 cc HDPE bottles with polyester coils (b) (4)

The overall product manufacturing process consists (b) (4) (b) (4)

The finished product specification includes tests for active ingredient identification and assay, tests for related substances (degradation products), content uniformity, (b) (4), appearance, microbial quality, and dissolution. Based on information submitted by the applicant, tests for residual solvents, elemental impurities, and solid state forms are deemed unnecessary.

Three registration batches of capsules were manufactured per the intended commercial process. Capsules were packaged in both 30-count and 90-count configurations. Samples were placed on stability at 25ºC/60% RH and 40ºC/75% RH. Data through 12-months long-term and 6-months accelerated were reported. No significant changes to product quality were observed. The results support a 24-month expiration dating period for the drug product when stored in the 30-count and 90-count commercial packaging configurations at 20ºC to 25ºC.

Overall, sufficient chemistry, manufacturing and controls information and supporting data have been provided in accordance with 21 CFR 314.50 to ensure the identity, strength, quality, purity, and bioavailability of this fixed-dose combination drug product.

See OPQ IQA Chapter II, Drug Product, for details.

**Environmental Assessment: Adequate**

Veru has claimed a categorical exclusion from the requirements for the preparation of an environmental assessment or an environmental impact statement in accordance with 21 CFR 25.31(a), which applies to an action

that does not increase the use of the active moiety. The intended dosing, duration of use, and indication of ENTADFI will be the same as described in the Cialis labeling: combination capsule 5 mg tadalafil and 5 mg finasteride. Approval of the NDA will not increase the use of the active moieties. Veru has confirmed that, pursuant to 21 CFR 25.15(d), to their knowledge no extraordinary circumstances exist. See OPQ IQA Chapter II, Drug Product, for further discussion.

**Labeling: Adequate**

The prescribing information as submitted December 8, 2021 and the bottle, case, and pallet labels as submitted on December 2, 2021 conform to the requirements under 21 CFR 201. See OPQ IQA Chapter IV, Labeling, for details.

**Manufacturing: Adequate**

Facility Assessment Recommendation: Adequate
Process Assessment Recommendation: Adequate

Process:

(b) (4)

Because the drug load of each active ingredient in the oral capsules is low (b) (4)% w/w of the capsule fill), particular attention was given to the process conditions and in-process controls necessary to ensure blend uniformity and content uniformity in the finished product.

Facilities:
The drug substances manufacturing facilities were found acceptable based on previous history. An associated laboratory site was also found acceptable based on previous history. The drug product manufacturer, (b) (4) was found acceptable based on recent on-site inspection while the packaging and labeling site, (b) (4) , was found acceptable following a 704(a)(4) inspection. An associated drug product testing facility was also

found acceptable based on previous history. An overall manufacturing inspection recommendation of Approve was issued on November 3, 2021.

A post-approval inspection (PoAI) of the (b) (4) drug product manufacturing facility is recommended to cover the manufacture and release testing of validation batches.

See OPQ IQA Chapter V, Manufacturing Integrated Assessment, for a detailed assessment and discussion of manufacturing equipment qualification, unit operations, and in-process controls necessary to ensure that the drug product consistently manufactured with the requisite quality.

**Biopharmaceutics: Adequate**

The initially proposed dissolution methods and acceptance criteria were based on the USP monographs for the Listed Drug (LD) tablet formulations (i.e., finasteride tablets and tadalafil tablets). However, as noted in the Biopharmaceutics 07/30/2021 Information Request, "the dissolution method for [the] test product should be product-specific and properly developed using [the] proposed drug product and not the LD." After evaluating additional dissolution data obtained in different medium, the following dissolution test parameters and acceptance criteria were recommended and ultimately adopted by Veru (10/27/2021 (SN 0020):

**FDA-Approved Dissolution Methods and Acceptance Criteria:**

**Tadalafil**

| Apparatus | Agitation Speed | Medium Volume | Temp. | Medium | Acceptance Criterion |
|---|---|---|---|---|---|
| 2 (paddle) | 50 rpm | 1000 mL | 37°C | 0.1% SDS in water | Q= (b) (4)% in 60 min |

**Finasteride**

| Apparatus | Agitation Speed | Medium Volume | Temp. | Medium | Acceptance Criterion |
|---|---|---|---|---|---|
| 2 (paddle) | 50 rpm | 900 mL | 37°C | Water | Q= (b) (4)% in 20 min |

Because no changes have been made to the formulation or manufacturing site, bridging of the registration batch product used in the pivotal BE/BA study to the commercial product is not necessary.

See OPQ IQA Chapter VI, Biopharmaceutics, for details.

**Microbiology (if applicable): Adequate**

Because the proposed manufacturing process for the drug product involves (b) (4) there is a potential for microbial growth. The control strategy for ensuring the microbiological quality (i.e.,

low bioburden) of the finished product, a nonsterile solid oral dosage form, includes use of inactive ingredients (including [redacted] (b) (4)) with suitable microbiological quality and appropriate finished product testing. The finished product specification includes tests for Microbial Limits and Specified Microorganisms performed in accordance with USP<61> and USP<62>, respectively. The USP<62> test for specified microorganisms is performed to ensure the absence of *E. coli*, *S. aureus*, *P. aeruginosa*, and *Salmonella* sp. The limits for TAMC and TYMC follow USP <1111> recommendations for oral capsule dosage forms. Microbial control tests will be performed for batch release and every 12 months for stability. The registration stability batches met the microbial control requirements at release and at the 12-month timepoint.

Refer to OPQ IQA Chapter V, Manufacturing Integrated Assessment.

## C. Risk Assessment

| From Initial Risk Identification* | | | Assessment | | |
|---|---|---|---|---|---|
| **Attribute/ CQA** | **Factors that can impact the CQA** | **Initial Risk Ranking** | **Risk Mitigation Approach** | **Final Risk Evaluation** | **Lifecycle Considerations/ Comments** |
| Appearance | • Mfg. and packaging<br>• Container/closure system (CCS) | L | (b) (4) | Acceptable | |
| Identity | • CGMP | L | | Acceptable | |
| Assay / Stability | • Formulation<br>• Raw materials<br>• Process parameters<br>• Scale/equipment<br>• Site<br>• CCS | L | | Acceptable | |
| Related Substances Impurities / Degradants | • Process parameters<br>• CCS | L | | Acceptable | |
| Physical stability (solid state) | • Raw material<br>• Formulation<br>• Process | L | | Acceptable | |
| (b) (4) | • API<br>• Raw materials<br>• Process<br>• CCS | L | | Acceptable | |
| Uniformity of Dosage Units | • Raw materials<br>• Formulation<br>• Process parameters<br>• Scale/equipment<br>• Site | (b) (4) | | Acceptable | |
| Microbial Limits | • Raw materials<br>• Equipment and handling<br>• Moisture content | L | | Acceptable | |
| Dissolution | • Formulation<br>• Raw materials<br>• Process parameters<br>• Scale/equipment<br>• Site | L | | Acceptable | |

* See OPQ Filing Review dated 04/06/2021

## D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies *(Deficiencies that affect multiple sub-disciplines)*

| |
|---|
| Not applicable |

2. Drug Substance Deficiencies

| |
|---|
| Not applicable |

3. Drug Product Deficiencies

| |
|---|
| Not applicable |

4. Labeling Deficiencies

| |
|---|
| Not applicable |

5. Manufacturing Deficiencies

| |
|---|
| Not applicable |

6. Biopharmaceutics Deficiencies

| |
|---|
| Not applicable |

7. Microbiology Deficiencies

| |
|---|
| Not applicable |

8. Other Deficiencies *(Specify discipline, such as Environmental)*

| |
|---|
| Not applicable |

***Application Technical Lead Name and Date:***

Mark R. Seggel, Ph.D.
Chemist
OPQ/ONDP/DNDPII/Br4

Mark Seggel

Digitally signed by Mark Seggel
Date: 12/11/2021 03:54:34PM
GUID: 507572b5000036176969356148025bae

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# CHAPTER IV: LABELING

| Labeling Submissions Assessed | Document Date |
|---|---|
| Original Submission (SN 0001) Draft Labeling Text | 02/17/2021 |
| SN 0007 Draft Labeling Text Word version/Redline | 05/21/2021 |
| SN 0008 Container / Carton | 06/17/2021 |
| SN 0013 Container /Carton Labels | 08/13/2021 |
| SN 0021 Patient Information (PPI), Container /Carton Labels | 11/02/2021 |
| SN 0024 PI, Container /Carton Labels | 11/23/2021 |
| SN 0025 PI | 11/30/2021 |
| SN 0026 Container / Carton Labels | 12/02/2021 |
| SN 0027 PI | 12/06/2021 |
| SN 0028 PI+PPI | 12/08/2021 |

| Associated Labeling Reviews / Communications | Document Date |
|---|---|
| DMEPA Labeling Review (D. Baugh) | 07/21/2021 |
| Labeling Comments | 08/02/2021 |
| DDMAC (OPDP) Labeling Review | 10/07/2021 |
| DMEPA Labeling Review (D. Baugh) | 10/27/2021 |
| Labeling Comments | 10/28/2021 |
| Labeling Comments | 11/12/2021 |
| DMEPA Labeling Review (D. Baugh) | 11/23/2021 |
| Labeling Comments | 11/30/2021 |
| Labeling Comments | 12/08/2021 |
| Labeling Comments | 12/09/2021 |

## 1.0 PRESCRIBING INFORMATION

**Assessment of Product Quality Related Aspects of the Prescribing Information: *ADEQUATE***

ENTADFI™ is a fixed-dose combination product consisting of immediate-release capsules containing finasteride 5 mg and tadalafil 5 mg. The product will be supplied in 30-count and 90-count HDPE bottles (b) (4)
Much of the PI, including drug substance information in Section 11 Description, appears to be taken directly from the labeling of the two RLD, PROSCAR (finasteride) tablets and CIALIS (tadalafil) tablets. In several places the text taken from the RLD is used without making the necessary adjustments for the fact that ENTADFI fixed-dose combination product is a capsule.

The Applicant's originally proposed presentation of the product title and established name(s) is inconsistent with current labeling recommendations and requirements. (b) (4)

[redacted]. The format has been revised accordingly. The active ingredients are now presented in alphabetical order and separated by "and," and [redacted] have been removed.

Section 11 of the Prescribing Information (PI) follows the Proscar and Cialis labeling with regard to the information provided about the active ingredients, finasteride and tadalafil.

The list of inactive ingredients in Section 11 Description has been revised to include the components of the capsule shell. Inactive ingredients are arranged alphabetically.

The storage statement in Section 16, How Supplied and Storage, has been revised to include the names of the active ingredients, the strengths of each, a product description with identifying characteristics, and NDCs for the two different packaging configurations. The storage statement has been revised to include temperature ranges.

Additional recommendations were provided by Denise Baugh, OSE/DMEPA (see reviews dated 07/21/2021, 10/27/2021, and 11/23/2021) and Aisha Johnson, ADL in DUOG.

The Prescribing Information and Patient Information (i.e., the patient package insert or PPI) will be provided as single document. Inclusion of the manufacturer / distributor name and address at the end of the combined document is acceptable. The Patient Information also includes a list of the inactive ingredients in the drug product as well as a storage statement.

The CMC sections of the latest version of the PI+PPI document, submitted December 8, 2021 (SN 0028), meet the requirements under 21 CFR 201.

Note: The initially proposed proprietary name, [redacted], was found unacceptable by DMEPA because of potential confusion with another product currently under review. The alternative proprietary name, ENTADFI, was found conditionally acceptable on October 7, 2021, and was accepted by the Applicant on October 20, 2021.

## 1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

| Item | Information Provided in the NDA | Assessor's Comments |
|---|---|---|
| **Product Title in Highlights** | | |
| Proposed (SN 0001): [redacted] **capsule for oral use** | | |

| | | |
|---|---|---|
| Product Title | Inadequate | Presentation inconsistent with Product Title guidance. Inclusion of strengths not appropriate. Established names of active ingredients in the fixed dose combination product should be separated by “and” rather than (b) (4) Listing of active ingredients in alphabetical order preferred.<br><br>Recommended format: Proprietary name (finasteride and tadalafil) capsules, for oral use |
| Proprietary name | | Per DMEPA, the proposed proprietary name, (b) (4) is unacceptable. The Alternative, ENTADFI, was found acceptable. |
| Established name(s) | Inadequate | DS: finasteride and tadalafil are both USAN<br>DP: finasteride and tadalafil capsules |
| Route(s) of administration | Adequate | Oral |
| **Dosage and Administration in Highlights** | | |
| Proposed (SN 0001):<br>The recommended dose of (b) (4) is 1 capsule (b) (4) taken once daily at approximately the same time every day for up to 26 weeks (b) (4)).<br>(b) (4) (b) (4) | | |
| Dosage | Adequate | |
| Special Instructions | Adequate | |
| **Dosage Forms and Strengths Heading in Highlights** | | |
| Proposed (SN 0001):<br>Capsule containing 5 mg tadalafil and 5 mg finasteride (3) | | |
| Summary of the dosage form(s) and strength(s) in metric system. | Adequate | |

| | | |
|---|---|---|
| For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package. | N/A | - |

Latest Version (SN 0028):

**ENTADFI™ (finasteride and tadalafil) capsules, for oral use**
**Initial U.S. Approval:** *TBD*
**INDICATIONS AND USAGE**
ENTADFI is a combination of finasteride, a 5α-reductase inhibitor, and tadalafil, a phosphodiesterase 5 (PDE5) inhibitor, and, indicated to initiate treatment of the signs and symptoms of benign prostatic hyperplasia (BPH) in men with an enlarged prostate for up to 26 weeks. (1)
**DOSAGE AND ADMINISTRATION**
One capsule orally once daily at approximately the same time every day for up to 26 weeks. Take without food. (2)
**DOSAGE FORMS AND STRENGTHS**
Capsules: fixed dose combination containing finasteride 5 mg and tadalafil 5 mg. (3)

## 1.2 FULL PRESCRIBING INFORMATION
### 1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

| Item | Information Provided in the NDA | Assessor's Comments |
|---|---|---|
| **2 DOSAGE AND ADMINISTRATION section** | | |
| Proposed (SN 0001):<br>(b) (4)<br>The recommended dose of (b) (4) is 1 capsule (containing 5 mg tadalafil and 5 mg finasteride), (b) (4) once daily at approximately the same time every day for up to 26 weeks.<br><br>Take (b) (4) on an empty stomach. | | |
| Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product) | N/A | |
| Latest Version (SN 0028):<br>**2 DOSAGE AND ADMINISTRATION**<br>The recommended dosage of ENTADFI is one capsule (containing finasteride 5 mg and tadalafil 5 mg) orally once daily at approximately the same time every day for up to 26 weeks.<br>Take ENTADFI on an empty stomach [see Clinical Pharmacology (12.3)]. | | |

### 1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

| Item | Information Provided in the NDA | Assessor's Comments |
|---|---|---|
| **3 DOSAGE FORMS AND STRENGTHS section** | | |
| Proposed (SN 0001):<br><br>(b) (4) a white opaque cap (b) (4) (b) (4) with black two line bar printed on cap and body. | | |
| Available dosage form(s) | Adequate | Capsules with fixed-dose combination of finasteride and tadalafil |
| Strength(s) in metric system | Adequate | 5 mg / 5 mg |
| If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance | Adequate | Neither active ingredient is present as a salt. |
| A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting | Adequate | |
| For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package. | N/A | |
| Latest Version (SN 0028):<br>Capsules: finasteride 5 mg and tadalafil 5 mg, in a size 3 capsule with a white opaque cap and body with black two line bars printed on the cap and on the body. | | |

### 1.2.3 Section 11 (DESCRIPTION)

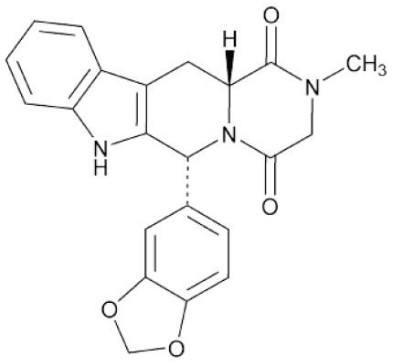
| Item | Information Provided in the NDA | Assessor's Comments |
|---|---|---|
| **11 DESCRIPTION section** | | |

Proposed (SN 0001):

**11 DESCRIPTION**

Tadalafil:

Tadalafil is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). Tadalafil has the empirical formula $C_{22}H_{19}N_3O_4$ representing a molecular weight of 389.41. The structural formula is:

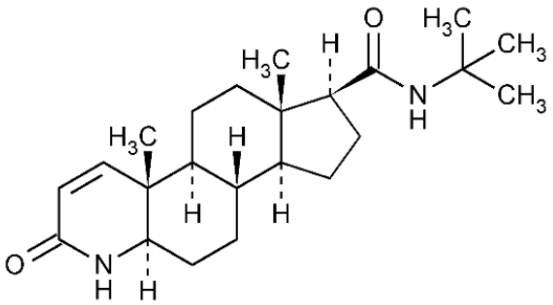


The chemical designation of tadalafil is pyrazino[1′,2′:1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)-. It is a crystalline solid that is practically insoluble in water and very slightly soluble in ethanol.

Finasteride:

Finasteride, a synthetic 4-azasteroid compound, is a specific inhibitor of steroid Type II 5α-reductase, an intracellular enzyme that converts the androgen testosterone into 5α-dihydrotestosterone (DHT).

The chemical designation of finasteride is 4-azaandrost-1-ene-17-carboxamide, N-(1,1-dimethylethyl)-3-oxo-,(5α,17β)-. The empirical formula of finasteride is $C_{23}H_{36}N_2O_2$ and its molecular weight is 372.55. Its structural formula is:



Finasteride is a white crystalline powder with a melting point near 250°C. It is freely soluble in chloroform and in lower alcohol solvents, but is practically insoluble in water.

(b) (4) is available as size 3, white opaque capsules for oral administration. Each capsule contains 5 mg of tadalafil and 5 mg of finasteride and the following inactive ingredients: lactose monohydrate, sodium starch glycolate, sodium lauryl sulfate, silicified microcrystalline cellulose, colloidal silicon dioxide and magnesium stearate.

| | | |
|---|---|---|
| Proprietary and established name(s) | Adequate | |
| Dosage form(s) and route(s) of administration | Adequate | |
| If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance. | N/A | |
| List names of all inactive ingredients. Use USP/NF names. Avoid Brand names. | Inadequate | Inactive ingredients should be listed in alphabetical order. Capsule shell components, including edible black printing ink, not listed. (Individual components of the printing ink do not need to be listed.) |
| For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. | N/A | |
| If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol | N/A | |
| Statement of being sterile (if applicable) | Adequate | |
| Pharmacological/ therapeutic class | Adequate | |
| Chemical name, structural formula, molecular weight | Adequate | |
| If radioactive, statement of important nuclear characteristics. | N/A | |
| Other important chemical or physical properties (such as pKa or pH) | Adequate | |
| For oral prescription drug products, include gluten statement if applicable | N/A | |

| | | |
|---|---|---|
| Remove statements that may be misleading or promotional (e.g., “synthesized and developed by Drug Company X,” “structurally unique molecular entity” | N/A | |

Latest Version (SN 0028):

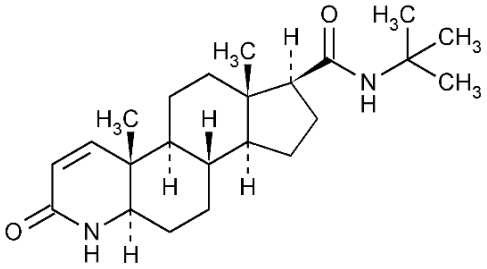
**11 DESCRIPTION**

ENTADFI (finasteride and tadalafil) capsules are a combination of finasteride and tadalafil for oral administration.

Finasteride:

Finasteride, a synthetic 4-azasteroid compound, is a specific inhibitor of steroid Type II 5α-reductase, an intracellular enzyme that converts the androgen testosterone into 5α-dihydrotestosterone (DHT).

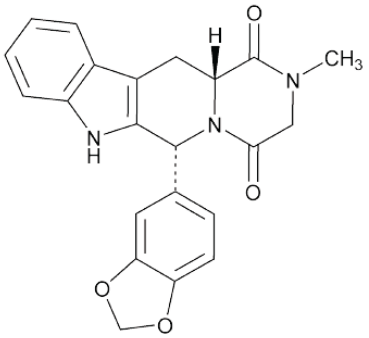
The chemical designation of finasteride is 4-azaandrost-1-ene-17-carboxamide, N-(1,1-dimethylethyl)-3-oxo-,(5α,17β)-. The empirical formula of finasteride is $C_{23}H_{36}N_2O_2$ and its molecular weight is 372.55. Its structural formula is:



Finasteride is a white crystalline powder with a melting point near 250°C. It is freely soluble in chloroform and in lower alcohol solvents but is practically insoluble in water.

Tadalafil:

Tadalafil is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). Tadalafil has the empirical formula $C_{22}H_{19}N_3O_4$ representing a molecular weight of 389.41. The structural formula is:



The chemical designation of tadalafil is pyrazino[1′,2′:1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)-. It is a crystalline solid that is practically insoluble in water and very slightly soluble in ethanol.

ENTADFI is available as size 3, white opaque capsules for oral administration. Each ENTADFI capsule contains finasteride 5 mg and tadalafil 5 mg and the following

inactive ingredients: colloidal silicon dioxide, lactose monohydrate, magnesium stearate, silicified microcrystalline cellulose, sodium lauryl sulfate, and sodium starch glycolate. The capsule shell is composed of carrageenan, hypromellose, potassium chloride, titanium dioxide, and is printed with an edible black printing ink.

### 1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

| Item | Information Provided in the NDA | Assessor's Comments |
|---|---|---|
| **HOW SUPPLIED/STORAGE AND HANDLING section** | | |
| Proposed (SN 0001):<br><br>**16 HOW SUPPLIED/STORAGE AND HANDLING**<br>(b) (4) | | |
| Product name | Inadequate | Does not include established name |
| Available dosage form(s) | Inadequate | The dosage form is not identified |
| Strength(s) in metric system | Inadequate | Even though there is only one strength, 5 mg / 5mg, it is not identified. |
| Available units (e.g., bottles of 100 tablets) | Adequate | 30-count and 90-count bottles |
| Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number | Inadequate | No description of the capsules is provided.<br><br>No placeholders for the NDCs for the 30-count and 90-count configurations are not provided. |
| Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored" | N/A | |

| | | |
|---|---|---|
| For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package. | N/A | |
| Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.) | Adequate | A recommendation to "Dispense in original container" to minimize handling and risk for exposure of women to finasteride may be warranted. |
| If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat." | N/A | |
| Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. | Inadequate | Revise to include temperature ranges, i.e., Store at 20ºC to 25°C (68ºF to 77°F); excursions permitted to 15ºC to 30°C (59ºF to 86°F) [see USP Controlled Room Temperature]. |
| Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free." | N/A | |
| Include information about (b) (4) | Adequate | (b) (4) |

Latest Version (SN 0028):

**16 HOW SUPPLIED/STORAGE AND HANDLING**
ENTADFI is a combination of finasteride and tadalafil.
*How Supplied*
ENTADFI capsules contain finasteride 5 mg and tadalafil 5 mg. The size 3 capsules have an opaque white cap and body with a black two-line bar printed on the cap and body.
ENTADFI is supplied as follows: HDPE bottles with a low moisture polyester coil and sealed with a heat-sealed foil HDPE cap as 30-count per bottle (NDC 69681-125-30) or 90-count per bottle (NDC 69681-125-90).
*Storage and Handling*
Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

### 1.2.5 Other Sections of Labeling

N/A

### 1.2.6 Manufacturing Information After Section 17 (for drug products)

| Item | Information Provided in the NDA | Assessor's Comments |
|---|---|---|
| **Manufacturing Information After Section 17** | | |
| Proposed (SN 0001):<br>--- | | |
| Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer | Inadequate – Information is missing | |
| Latest Version (SN 0028):<br><br>Manufacturer / distributor information is provided at the end of the combined PI and PPI:<br>**Marketed by: Veru Inc.**<br>**Miami, FL 33127, USA** | | |

## 2.0 PATIENT LABELING

**Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): *ADEQUATE***
Patient Labeling (PPI) will be incorporated in a single document with the PI. It will follow immediately after Section 17 of the PI. The ENTADFI PPI is patterned after the Patient Information for PROSCAR and CIALIS.

The CMC-related information in the PPI includes the product title, list of active ingredients, list of inactive ingredients, and a storage statement.

Apparently previous recommendations for revision of the list of inactive ingredients to include the capsule shell components, including edible black printing ink, were not communicated to the Applicant. Veru was advised on 12/07/2021 to update the list of inactive ingredients in the Section 11 of the PI and in the PPI to include the components of the capsule shell. Both PI and PPI were revised accordingly.

While not ideal, the proposed storage statement, "Store (b) (4) 59° and 86°F (15° and 30°C)," acceptable. Further, it is consistent with the storage statement in the CIALIS PPI.

Inclusion of the required manufacturer / distributor information at the end of the combined PI and PPI, rather than immediately after Section 17, is acceptable.

**PATIENT LABELING (Patient Package Insert (PPI))**
*Veru has confirmed that the Patient Information (PPI) will be distributed as a single document with the PI (SN 0028)*

Latest Version (SN 0028):

**Patient Information**

**ENTADFI™ (en-TAD-fee)**
**(finasteride and tadalafil) capsules for oral use**

**How Should I Store ENTADFI?**
Store ENTADFI at room temperature between 59° and 86°F (15° and 30°C).

**What Are The Ingredients In ENTADFI?**
Active Ingredients: finasteride and tadalafil
Inactive Ingredients: carrageenan, hypromellose, lactose monohydrate, potassium chloride, sodium starch glycolate, sodium lauryl sulfate, silicified microcrystalline cellulose, colloidal silicon dioxide, titanium dioxide, and magnesium stearate.

**Marketed by: Veru Inc.**
**Miami, FL 33127, USA**

## 3.0 CARTON AND CONTAINER LABELING

**Assessment of Carton and Container Labeling: *ADEQUATE***
The drug product is packaged in 30-count and 90-count bottles. No cartons for individual bottles are proposed at this time. However, mock-ups of labels for cases of bottles as well as for pallets, were included in the initial submission. Labels for cases and/or pallets of drug product are typically not submitted, nor are they routinely requested.

Many of the same deficiencies identified in the draft prescribing information and in the draft bottle labels can also be found in the proposed bottle label. In addition to the CMC-related deficiencies, Denise Baugh, in OSE's DMEPA, provided several other recommended revisions to the labels (see her reviews dated 07/21/2021, 10/27/2021, and 11/23/2021).

The labels as submitted on 12/02/2021 (SN 0026) incorporate all recommendations, and are now consistent with the prescribing information and conform to the labeling requirements under 21 CFR 201.

### 3.1 Container Label

| Item | Items in Proposed Labeling | Assessor's Comments |
|---|---|---|
| | (b) (4) | |

| | | |
|---|---|---|
| Proprietary name, established name, and dosage form (font size and prominence | Inadequate | Product established name and strength presentation are incorrect. |
| Dosage strength | Inadequate | Presentation of strength is incorrect |
| Route of administration | Oral | |
| If the active ingredient is a salt, include the equivalency statement per FDA Guidance | N/A | |
| Net contents (e.g., tablet count, volume of liquid) | Adequate<br>30-count and 90-count | |
| “Rx only” displayed | Adequate | |
| NDC number | NDC TBD | DMEPA has requested revisions to NDC location and format |
| Lot number and expiration date | Adequate | DMEPA has requested revisions to presentation of lot number and expiration date. |
| Storage conditions. If applicable, include a space on the labeling for the user to write the new BUD. | Adequate | Inclusion of temperature range is recommended. Revise for consistency with recommended revisions to the storage statement in the PI. |
| For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use) | N/A | |
| Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement. | N/A | |
| If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol | N/A | |
| Linear Bar Code | Adequate | |
| Name of manufacturer / distributor | Adequate | |
| No text on Ferrule and Cap overseal | N/A | |

| | | |
|---|---|---|
| When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label. | N/A | |
| And others, if space is available | N/A | |
| (b) (4) | | |

### 3.2 Carton Labeling

**Carton Labels**
Bottles will not be packaged in single-unit cartons. Accordingly, there are no carton labels.

**Case and Pallet Labels**
Labels for cases of bottles and for pallets (of multiple cases) were, however, proposed in SN 0001 and are discussed below. Note: Case and pallet labels are typical not submitted to NDAs, nor are the routinely requested. However, they will be assessed following the same requirements as would apply to labels for cartons of individual bottles.

| Item | Items in Proposed Labeling | Assessor's Comments about Carton Labeling |
|---|---|---|

Proposed Case Label (SN 0001):


The 90-count bottle case label is comparable.

Proposed Pallet Label (SN 0001):


The 90-count bottle pallet label is comparable.

| | | |
|---|---|---|
| Proprietary name, established name, and dosage form (font size and prominence) | Inadequate | See comments under Prescribing Information |
| Dosage strength | Inadequate | “ |
| Route of administration | Identified as (b) (4) but format is Inadequate | “ |
| If the active ingredient is a salt, include the equivalency statement per FDA Guidance | N/A | |
| Net contents (e.g., tablet count, volume of liquid) | Bottle capsule count (30- or 90-) indicated on the labels. However, the number of bottles per case or pallet is not specified. | |
| “Rx only” displayed on the principal display | Absent on case and pallet labels | All labels to include “Rx only” |
| NDC number | NDC TBD | |
| Lot number and expiration date | Adequate | |
| Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD. | Inadequate. | A storage statement is present on the case label but not on the pallet label. Revise to include the recommended storage statement on the PI. |
| For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use) | N/A | |
| Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement. | N/A | |
| If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol | N/A | |
| Linear Bar Code | Adequate | |
| Name of manufacturer/distributor | Adequate | |

| | | |
|---|---|---|
| Medication Guide (if applicable) | N/A | |
| No text on Ferrule and Cap overseal | N/A | |
| When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label. | N/A | |

| Case Label 30-count bottles (SN 0026): | Case Label 90-cont bottles (SN 0026): |
|---|---|
|  (b) (4) | |

| Pallet Label 30-count bottle (SN 0026): | Pallet Label 90-count bottle (SN 0026): |
| --- | --- |
|  (b) (4) | |

**ITEMS FOR ADDITIONAL ASSESSMENT**

N/A

***Overall Assessment and Recommendation: ADEQUATE***

All of the deficiencies noted above have been satisfactorily resolved. The combined prescribing information, with attached patient information, (PI+PPI) submitted on 12/08/2021 (SN 0028) complies with the labeling requirements under 21 CFR 201. The bottle labels as submitted on 12/02/2021 (SN 0026) are consistent with the revised PI and comply with the requirements under 21 CFR 201. The case and pallet labels as submitted 12/02/2021 (SN 0026) are also acceptable. There are currently no plans for individual single-bottle cartons. From the CMC labeling perspective, the application is deemed ready for approval.

*Primary Labeling Assessor Name and Date:*

Mark R. Seggel, Ph.D.
Chemist / Application Technical Lead
OPQ/ONDP/DNDPII/Br4

*Secondary Assessor Name and Date (and Secondary Summary, as needed):*

Hong Cai, Ph.D.
Branch Chief
OPQ/ONDP/DNDPII/Br4

Mark Seggel

Digitally signed by Mark Seggel
Date: 12/10/2021 10:33:33AM
GUID: 507572b5000036176969356148025bae

Hong Cai

Digitally signed by Hong Cai
Date: 12/10/2021 10:47:29AM
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# CHAPTER VI: BIOPHARMACEUTICS

| | |
|---|---|
| **NDA Number** | NDA-215423-ORIG-1 |
| **Drug Product Name/ Strength** | ENTADFI™ (tadalafil and finasteride) Capsules, 5 mg/5 mg |
| **Route of Administration** | Oral |
| **Applicant Name** | Veru Inc. |
| **Therapeutic Classification/ OND Division** | Benign Prostate Disease/Division of Urology, Obstetrics, and Gynecology (DUOG) |
| **RLD/RS Number** | N021368-Cialis (tadalafil) Tablets, 5 mg<br>N020180-Proscar (finasteride) Tablets, 5 mg |
| **Proposed Indication** | For the treatment of the signs and symptoms of benign prostatic hyperplasia |
| **Primary Reviewer** | Leah W. Falade, Ph.D. |
| **Secondary Reviewer** | Vidula Kolhatkar, Ph.D. |

## REVIEW SUMMARY

The Applicant seeks approval under the 505(b)(2) pathway for ENTADFI™ (tadalafil and finasteride) Capsules, 5 mg/5 mg using Cialis® (tadalafil) Tablets, 5 mg (NDA 021368) and Proscar® (finasteride) Tablets, 5 mg (NDA 020180) as the Listed drugs (LDs) relying on previous established safety and efficacy findings. The clinical package in support of this NDA includes one Phase 1 comparative bioavailability/bioequivalence study.

This review focuses on the Biopharmaceutics evaluation and acceptability of 1) the proposed dissolution methods and acceptance criteria and 2) formulation bridging, with key findings summarized below:

1) **In Vitro Drug Release Method and Acceptance Criteria:**

The Applicant proposed 2 dissolution methods (one for each API). Both methods use USP Apparatus 2 (Paddle) at 50 rpm at 37°C. Tadalafil uses 1000 mL 0.1% SDS in water and finasteride uses 900 mL of water. Tadalafil is considered a BCS Class 2 drug substance with low solubility. The proposed dissolution method for tadalafil was shown to have discriminating ability toward changes in (b) (4). However, the method was not shown to be discriminating towards changes in excipients SLS or (b) (4)

The acceptance criteria were proposed based on the mean dissolution profile data of the pivotal clinical batch and registration batches at release. The proposed acceptance criteria for tadalafil (Q= (b) (4)% in 60 min) and finasteride (Q= (b) (4)% in 20 min) are data-driven and deemed acceptable.

The Applicant's proposed dissolution methods and acceptance criteria are deemed acceptable for batch release and stability testing of the proposed drug product.

**2) Bridging Throughout Product Development:**

The pivotal BA/BE study used the to-be-marketed (TBM) formulation which was manufactured at the same site where the commercial batches will be manufactured. Therefore, additional formulation bridging is not needed.

**RECOMMENDATION:**

From the Biopharmaceutics perspective, NDA-215423-ORIG-1 for ENTADFI™ (tadalafil and finasteride) Capsules, 5 mg/5 mg is **adequate**.

**FDA-Approved Dissolution Methods and Acceptance Criteria:**

**Tadalafil**

| Apparatus | Agitation Speed | Medium Volume | Temp. | Medium | Acceptance Criterion |
|---|---|---|---|---|---|
| 2 (paddle) | 50 rpm | 1000 mL | 37°C | 0.1% SDS in water | Q= (b) (4)% in 60 min |

**Finasteride**

| Apparatus | Agitation Speed | Medium Volume | Temp. | Medium | Acceptance Criterion |
|---|---|---|---|---|---|
| 2 (paddle) | 50 rpm | 900 mL | 37°C | Water | Q= (b) (4)% in 20 min |

## BIOPHARMACEUTICS ASSESSMENT

### LIST of SUBMISSIONS BEING REVIEWED

| eCTD # (SD #) | Received date | Document |
|---|---|---|
| 0001 (SD 1) | 02/17/2021 | Original |
| 0006 (SD 6) | 04/19/2021 | Quality Response to IR |
| 0009 (SD 9) | 07/14/2021 | Quality Response to IR |
| 0014 (SD 14) | 08/30/2021 | Quality Response to IR |
| 0020 (SD 20) | 10/27/2021 | Quality Response to IR |

### BIOPHARMACEUTICS RELATED INFORMATION

| | Tadalafil | Finasteride |
|---|---|---|
| **BCS Class Designation** | BCS Class 2 | BCS Class 2* |
| **Solubility** | Buffer solution (pH:1.20): 0.001 mg/mL<br>Buffer solution (pH:4.01): 0.003 mg/mL<br>Buffer solution (pH:6.86): 0.002 mg/mL<br>Buffer solution (pH:9.18): 0.002 mg/mL<br>Water: 0.010 mg/mL | Water (pH 6.5): 0.18 mg/mL<br>0.01N Hydrochloric Acid (pH 2.0): 0.08 mg/mL<br>0.1N Hydrochloric acid (pH 1.2): 0.07 mg/mL<br>Acetate buffer (pH 4.5): 1.50 mg/mL<br>Phosphate buffer (pH 6.8): 0.07 mg/mL<br>Phosphate buffer(pH 7.2): 0.07 mg/mL |
| **Permeability** | Not provided | Not provided |
| **In Vitro Drug Release** | Rapidly dissolving in 0.5% SLS | Rapidly dissolving in water and 0.1% SLS |
| **Particle Size (Drug substance)** | The drug substance is (b) (4). The particle size distribution of tadalafil is controlled by the DS supplier. PSD (b) (4) | The drug substance is (b) (4) The particle size distribution of finasteride is controlled by (b) (4) PSD (b) (4) . |
| **Polymorphic form** | The obtained consistent crystalline form conforms to (b) (4). | Two different polymorphisms exist. The DS supplier's product is polymorph (b) (4) |
| **Particle Size** (b) (4) | $D_{90}$= (b) (4) µm | $D_{10}$= (b) (4) µm<br>$D_{50}$= µm<br>$D_{90}$= µm |
| **Formulation** | The drug product is a combination oral capsule filled with (b) (4) containing 5 mg tadalafil and 5 mg finasteride. | |
| **Dosing** | The drug product is intended to be taken orally, once daily. (b) (4) should be administered without food. | |

| | | |
|---|---|---|
| **Absorption** | Administration of [redacted] with a high fat meal has similar extent of absorption, but a reduced Cmax compared to [redacted] administered fasted. | |
| **Dose Proportionality** | N/A | |
| **BE** | Under fasted conditions, [redacted] has shown bioequivalence (for Cmax, AUCt, and AUC∞) to 5 mg tadalafil and 5 mg finasteride administered together. Refer to clinical pharmacology review for details. | |
| **Tmax** | 3 hours (1 to 4 hours range) | 2 hours (1 to 4 hours range) |
| **Food Effect** | [redacted] under fed conditions has a lower Cmax and longer Tmax in comparison to fasting conditions. | |

* The Applicant states that finasteride is a BCS Class 2 substance. However, the highest dosage amount (5 mg)/250 mL=0.02 mg/mL. Therefore, finasteride can be considered highly soluble. The FDA Dissolution Database was updated in July 2020 to refer to FDA's Dissolution Guidance, 2018 for the dissolution method, which is for high solubility drug substances.

## DISSOLUTION

### Applicant's Proposed Dissolution Method and Acceptance Criteria:

### Tadalafil

| Strengths/sample per vessel | Apparatus | Agitation Speed | Medium Volume | Temp. | Medium | Acceptance Criteria |
|---|---|---|---|---|---|---|
| 5 mg | 2 (paddle) | 50 rpm | 1000 mL | 37°C | 0.1% SDS in water | [redacted] Q [redacted]% in 60 min |

### Finasteride

| Strengths/sample per vessel | Apparatus | Agitation Speed | Medium Volume | Temp. | Medium | Acceptance Criterion |
|---|---|---|---|---|---|---|
| 5 mg | 2 (paddle) | 50 rpm | 900 mL | 37°C | Water | Q [redacted]% in [redacted]min |



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***Discriminating Capability of the Dissolution Method:***
During the filing review, the Applicant was asked to submit data supporting the discriminating ability of the dissolution method. The Applicant submitted the response on 04/19/2021 (Seq 0006[1]). This Reviewer only presents the tadalafil drug substance since finasteride is considered highly soluble and no changes in dissolution profiles were observed. The developmental method used 0.1% SLS for both API's; however, the USP method for finasteride was still adopted for the QC method (water) for finasteride. Considering high solubility of the API this is acceptable.

**Excipient:**
Capsules were prepared to evaluate the effect of modifying the amount of (b) (4) (b) (4) and type of (b) (4) (b) (4). The aberrant formulations and the LD's all had similar dissolution profiles. Therefore, the dissolution method is not discriminating to (b) (4) or (b) (4).

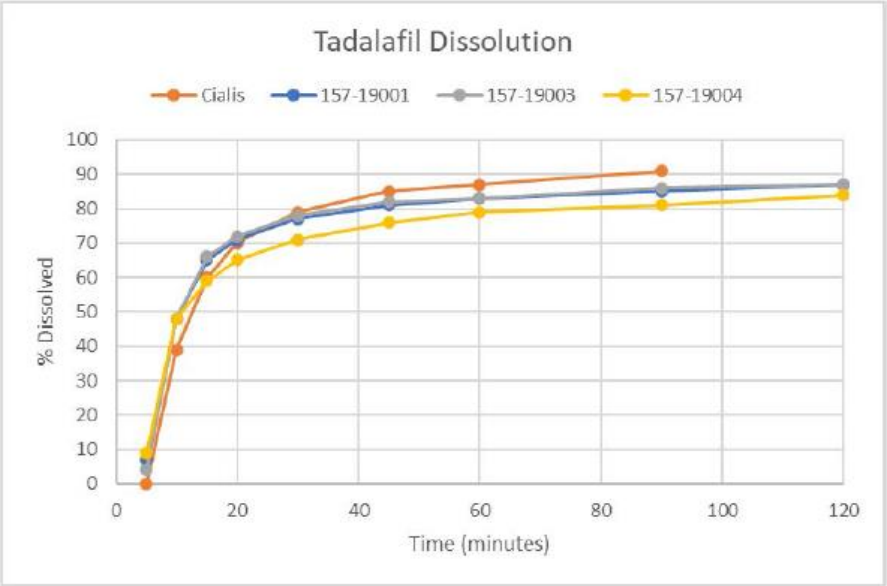


**Figure 3.** Tadalafil Dissolution Profiles for 157-19001, 157-19003, and 157-19004

(b) (4)

[1] \\CDSESUB1\evsprod\nda215423\0006\m1\us\quality-info-amend.pdf

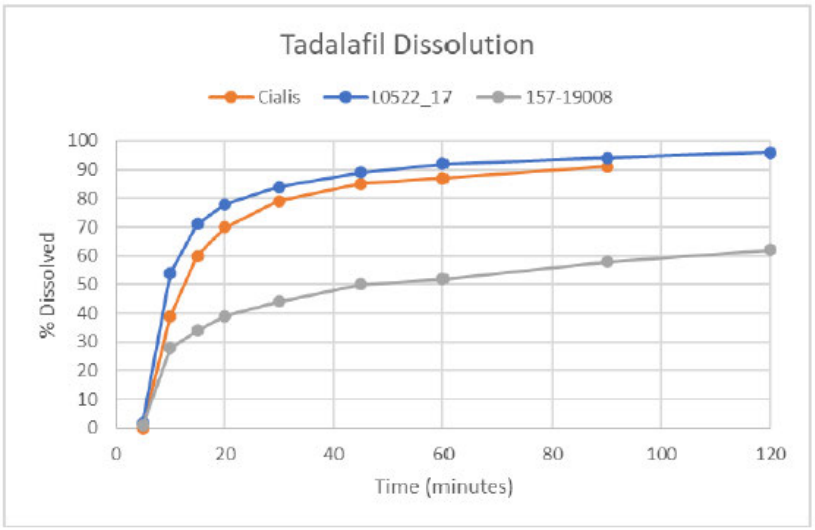


**Figure 4.** Tadalafil Dissolution Profiles for L0522_17 and 157-19008

(b) (4)

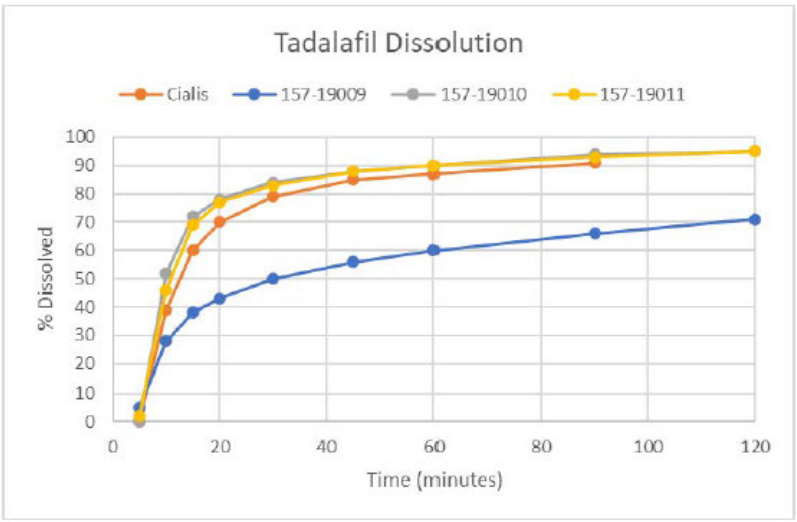


**Figure 5.** Tadalafil Dissolution Profiles for 157-19009 through 157-19011

The developmental dissolution method is discriminating to changes in (b) (4) . The Applicant submitted data on its proposed capsule formulation using 3 different methods:

(b) (4)

2) USP Method for finasteride tablets (900 mL of water)
3) Developmental Dissolution Method (1000 mL of 0.1% SDS in water)

In the original submission, the Applicant proposed to use the (b) (4) . In response to the IR, the Applicant only submitted discriminating ability of the developmental dissolution method. Based on the submitted data for the discriminatory ability of the dissolution method, the developmental dissolution method was recommended for QC at release and on stability for tadalafil. The applicant accepted Agency's recommendation in response to the IR.

**Table 2. Recommended Dissolution Testing Method**

**Finasteride**

| Apparatus | Agitation Speed | Medium Volume | Temp. | Medium |
|---|---|---|---|---|
| 2 (paddle) | 50 rpm | 900 mL | 37°C | Water |

**Tadalafil**

| Apparatus | Agitation Speed | Medium Volume | Temp. | Medium |
|---|---|---|---|---|
| 2 (paddle) | 50 rpm | 1000 mL | 37°C | 0.1% SDS in water |

***Dissolution Acceptance Criteria:***

There was a discrepancy in the individual unit dissolution data for the finasteride component submitted in Seq 006 and Seq 009 and data for only 3 registration batches was submitted in Seq 009. In a response to an IR, the Applicant stated that they inadvertently entered the wrong data in the spreadsheet. The correct data for all registration baches was submitted in Seq 0014. The dissolution data using the proposed method on the clinical and registration batches is summarized below:

**Table 3. Mean Dissolution Data for Finasteride for Pivotal Clinical/Registration Batches, n=12**

| Time (min) / Lot # | 10 | 20 | 30 | 45 |
|---|---|---|---|---|
| 19363 | (b) (4) | | | |
| 19364 | | | | |
| 19352 | | | | |
| 19358 | | | | |
| 19359 | | | | |
| 19353* | | | | |
| Mean | 78 | 96 | 98 | 99 |
| Min | (b) (4) | | | |
| Max | | | | |

* Pivotal Clinical Biobatch

**Table 4. Mean Dissolution Data for Tadalafil for Pivotal Clinical/Registration Batches, n=12**

| Time (min) / Lot # | 5 | 10 | 15 | 20 | 30 | 45 | 60 | 90 | 120 |
|---|---|---|---|---|---|---|---|---|---|
| 19352 | (b) (4) | | | | | | | | |
| 19353* | | | | | | | | | |
| 19358 | | | | | | | | | |
| 19359 | | | | | | | | | |
| 19363 | | | | | | | | | |
| 19364 | | | | | | | | | |
| Mean | 2 | 49 | 66 | 73 | 78 | 83 | 85 | 89 | 90 |
| Min | (b) (4) | | | | | | | | |
| Max | | | | | | | | | |

* Pivotal Clinical Biobatch

The Applicant proposed the following acceptance criteria (finasteride original method and tadalafil new method):

| | |
|---|---|
| Finasteride | (b) (4) |
| Tadalafil | |

The Applicant's proposed acceptance criteria for finasteride and tadalafil are permissive. Based on the submitted data, the following acceptance criteria were recommended:

| | |
|---|---|
| Finasteride | 20 min: Q= (b) (4)% |
| Tadalafil | 60 min: Q= (b) (4)% |

The Applicant agreed to the acceptance criteria on 10/27/2021 (Seq 0020).

***BRIDGING THROUGHOUT PRODUCT DEVELOPMENT***

The pivotal BA/BE study used the to-be-marketed (TBM) formulation which was manufactured at the same site where the commercial batches will be manufactured (b) (4) Therefore, additional formulation bridging is not needed.

**APPENDIX: LISTING OF BIOPHARMACEUTICS DEFICIENCIES**

**Quality Response to IR (Seq 0020) 10/27/2021**

**FDA Request:**

We do not accept your proposal to pursue option #3 due to the following reasons:

1. You have not provided adequate justification for slower release of batches 19358 and 19363 compared to the other batches including clinical/biobatch.

2. If you propose [redacted] (b) (4) then data supporting the discriminating ability of the dissolution method should be submitted as we requested on 04/05/2021.

3. For Tadalafil, when testing is conducted using 0.1% SDS all batches meet the recommended acceptance criterion at [redacted] (b) (4)

4. The following dissolution methods are acceptable for your proposed product (Tadalafil and Finasteride Capsules, 5 mg/5 mg):

**Tadalafil**

| Apparatus | Agitation Speed | Medium Volume | Temp. | Medium |
|---|---|---|---|---|
| 2 (paddle) | 50 rpm | 1000 mL | 37°C | 0.1% SDS in water |

**Finasteride**

| Apparatus | Agitation Speed | Medium Volume | Temp. | Medium |
|---|---|---|---|---|
| 2 (paddle) | 50 rpm | 900 mL | 37°C | Water |

Your proposed acceptance criteria for tadalafil and finasteride are permissive. Based on the submitted in vitro dissolution profile data for the biobatch/registration batches, the following acceptance criteria are recommended for finasteride and tadalafil:

| | |
|---|---|
| **Finasteride** | 20 min: Q= (b) (4)% |
| **Tadalafil** | 60 min: Q= (b) (4)% |

**Applicant's Response:**

The Applicant acknowledged and accepted the recommendations detailed above with respect to the specified dissolution media/conditions and the acceptance criteria for both Finasteride and Tadalafil.

With respect to the lower dissolution rate of batches 19358 and 19363 compared to the other batches including the clinical/biobatch, the Applicant is continuing to work with (b) (4) to better understand the root cause of the variation. the applicant re-assessed the results to determine why there was a lower dissolution rate for the two batches, 19358 and 19363. While still within the specification, the Applicant noted that these batches are on the lower end of the assay against label content for all six of the lots. Coupled with the inherently low solubility of the Tadalafil in the 0.1% SLS, it is feasible that the variation observed in the assay is reflected in the dissolution study.

**Reviewer's note:**
During the internal mid-cycle review meeting, the DP and OPMA teams did not express any concerns for the two batches 19358 and 19363.

Leah Falade

Digitally signed by Leah Falade
Date: 11/08/2021 01:54:37PM
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Vidula Kolhatkar

Digitally signed by Vidula Kolhatkar
Date: 11/08/2021 02:15:04PM
GUID: 5424aeae00c3274f93e50573f7ca407e

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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MARK R SEGGEL
12/11/2021 04:16:55 PM