CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215423Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	505 (b)(2)
Application Number(s)	215423
Priority or Standard	Standard
Submit Date(s)	February 17, 2021
Received Date(s)	February 17, 2021
PDUFA Goal Date	December 17, 2021
Division/Office	Division of Urology, Obstetrics, and Gynecology (DUOG) Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Review Completion Date	December 7, 2021
Established/Proper Name	Finasteride and tadalafil
(Proposed) Trade Name	Entadfi
Pharmacologic Class	5-alpha reductase inhibitor and Phosphodiesterase (PDE) inhibitor
Code name	N/A
Applicant	Veru Inc.
Dosage form	Oral Capsule
Applicant proposed Dosing Regimen	Fixed combination oral capsule 5 mg finasteride and 5 mg tadalafil once a day without food, taken at approximately the same time each day, for up to 26 weeks
Applicant Proposed Indication(s)/Population(s)	Treatment of signs and symptoms of BPH
Recommendation on Regulatory Action	Approval (AP) action
Recommended Indication(s)/Population(s) (if applicable)	To initiate treatment of signs and symptoms of benign prostatic hyperplasia (BPH) in men with enlarged prostate for up to 26 weeks.

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OPQ = Office of Pharmaceutical Quality
OPDP = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
DEPI = Division of Epidemiology
DMEPA = Division of Medication Error Prevention and Analysis
DRISK = Division of Risk Management

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[**Is my review a streamlined review?**

Under Section 3031 of the 21st Century Cures Act, supplementary BLAs and supplementary NDAs for "qualified indications" may be eligible for streamlined review. In a streamlined review, reviewers rely on "qualified data summaries" and do not review the full datasets. For more information and eligibility criteria for streamlined reviews, see pages 5 and 6 of the instructions for completing the Unireview template and the instructional video on conducting streamlined reviews.]

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science

OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Entadfi is a fixed-dose combination oral (b) (4) capsule filled with (b) (4) to deliver 5 mg finasteride and 5 mg tadalafil drug substance. The Applicant submitted this NDA under section 505(b)(2) of the Federal Food Drug and Cosmetic Act and substantially relies on the Agency's findings of safety and efficacy for Proscar (finasteride, NDA 020180) and Cialis (tadalafil, NDA 021368), the referenced listed drugs (RLDs). In 2013, the co-administration of tadalafil 5 mg and finasteride 5 mg once daily was approved under NDA 021368/Supplement 022 to initiate the treatment of signs and symptoms of BPH for up to 26 weeks. Entadfi and the co-administration of tadalafil and finasteride contain the same active ingredients (finasteride and tadalafil), in the same strength (finasteride 5 mg and tadalafil 5 mg), and are administered by the same route of administration (oral). The Applicant seeks approval of Entadfi for the treatment of symptomatic BPH for up to 26 weeks.

Proscar (finasteride 5 mg) oral tablets once daily has been approved since 1992 for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate and has a well-established clinical profile. Finasteride is a competitive and specific inhibitor of Type II 5α-reductase. Type II 5α-reductase metabolizes testosterone to 5α-dihydrotestosterone (DHT). Because enlargement of the prostate gland is dependent on the androgen DHT, a reduction of DHT decreases the size of the prostate gland.

Cialis (tadalafil 5 mg) oral tablets once daily is approved for the treatment of signs and symptoms of BPH and has a well-established clinical profile. Tadalafil is a phosphodiesterase type 5 (PDE5) inhibitor that increases cyclic GMP and causes smooth muscle relaxation and increased blood flow into the corpus cavernosum, thereby enhancing erectile function. The effect of PDE5 inhibition on cGMP levels is also observed in the smooth muscle of the prostate, the bladder, and the vascular supply to these organs; however, the mechanism of action responsible for reduction of BPH symptoms is not known. In 2013, tadalafil 5 mg co-administered with finasteride 5 mg once daily was approved to initiate treatment of symptomatic BPH in men with an enlarged prostate for up to 26 weeks.

1.2. Conclusions on the Substantial Evidence of Effectiveness

This 505(b)2 NDA substantially relies on the Agency's finding of efficacy and safety for Proscar (finasteride 5 mg) and Cialis (tadalafil 5 mg) co-administered for the initiation of treatment of symptomatic BPH in men with an enlarged prostate for up to 26 weeks. The Applicant conducted the pivotal comparative BA/BE study (V0112502) to provide data to support therapeutic equivalence of Entadfi to the coadministration of tadalafil 5 mg and finasteride 5 mg. Study V0112502 was an open-label, randomized, single-center, single-dose, 3-period, crossover study in healthy subjects (≥45 years and ≤60 years of age) that compared BA under fasted condition between Entadfi oral capsule (fixed dose combination of 5 mg finasteride and 5 mg tadalafil) and reference drug products (Proscar® [finasteride] 5 mg tablet and Cialis®

[tadalafil] 5 mg tablet administered together). Study results indicated that the ratio of geometric least square means (LSmeans) and the 90% confidence interval (CI) for maximum observed concentration (C_{max}) and area under the concentration-time curve (AUC_t and AUC_∞) values for tadalafil and finasteride were within the specified bioequivalence range of 80% to 125%.

The observed PK results demonstrated that Entadfi oral capsule is bioequivalent to Proscar® (5 mg finasteride) and Cialis® (5 mg tadalafil) tablets administered together under fasted condition. Food did not affect the AUC but reduced the C_{max} of tadalafil and finasteride by 23% and 29%, respectively. Therefore, the labeling for Entadfi will specify that the drug should be taken without food.

Therefore, substantial evidence of effectiveness has been established for Entadfi, based on the demonstration of bioequivalence from study V0112502 between Entadfi and the reference listed drugs Proscar (5α-reductase inhibitor) and Cialis (phosphodiesterase 5 inhibitor), taken together and previously approved for the initiation of the treatment of symptomatic BPH in men with an enlarged prostate.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The benefit of Entadfi outweighs its risks because substantial evidence of effectiveness and acceptable safety for Entadfi has been established based on its bioequivalence to co-administered tablets of finasteride 5 mg and tadalafil 5 mg.

NDA 215423 was submitted as a 505(b)(2) application relying on the Agency's previous finding of safety and efficacy for the coadministration of Proscar and Cialis, the listed drugs (LDs). The Applicant conducted a bioavailability/bioequivalence study (Study V0112502) to establish a scientific bridge and demonstrate bioequivalence between Entadfi and the coadministration of Proscar and Cialis. The study was a single-dose, open-label, randomized, 3-period, crossover, bioavailability/bioequivalence study conducted under fasting and fed conditions. The study compared the bioavailability of finasteride and tadalafil from the Entadfi fixed dose combination (FDC) capsule to that of co-administered tablets of Proscar (5 mg finasteride) and Cialis (5 mg tadalafil). In addition, the study assessed the effect of food on the bioavailability of finasteride and tadalafil from Entadfi FDC. The study showed that the 90% confidence intervals around the ratio of Entadfi's geometric LS means to Proscar and Cialis geometric LS means were within the 80% to 125% limits for C_{max}, AUC_t, and AUC_∞. However, a food effect was seen for Entadfi; the C_{max} for finasteride and tadalafil was reduced by 29% and 23% respectively in the presence of food, which will be addressed in labeling. The review teams determined Entadfi was bioequivalent to tadalafil 5 mg coadministered with finasteride 5 mg, ensuring therapeutic equivalence.

In summary, the Applicant provides substantial evidence to conclude that Entadfi is safe and effective for the initiation of treatment of the signs and symptoms of benign prostatic hyperplasia (BPH) in men with an enlarged prostate for up to 26 weeks.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Benign prostatic hyperplasia (BPH) is a histologic diagnosis that is defined as an increase in the number of stromal and glandular epithelial cells in the transition zone of the prostate gland in men.[1] BPH may cause enlargement of the prostate, and resultant bladder outlet obstruction, leading to lower urinary tract symptoms (LUTS).[2] [3] The prevalence of BPH increases with age, and it is estimated that almost 70% of men ages 60-69 years and approximately 80% of men greater than 70 years of age have BPH.[1] The etiology of symptomatic BPH is not fully understood, and is related both to enlargement of the gland itself (static component) and increased smooth muscle tone (dynamic component).[1] Bladder outlet obstruction may also cause bladder detrusor muscle instability (overactive bladder), worsening LUTS. Several mechanisms have been identified as possible causes of BPH, including androgen activity and systemic and local inflammation.[1] Patients typically present with LUTS which may be categorized into symptoms related to urinary storage, voiding, and post-voiding.[1,3] Potential serious complications include acute urinary retention, urinary tract infection, bladder stones, bladder diverticula, and decreased renal function.[3]	BPH affects a substantial proportion of men as they age. Men with BPH may experience LUTS including storage symptoms (urinary frequency, urgency, nocturia and incontinence) and voiding symptoms (slow urinary stream, straining to void, intermittent urinary stream and hesitancy, splitting of the urinary stream, and terminal dribbling).[1] Potential serious complications of BPH include acute urinary retention and chronic obstruction that can lead to urinary tract infection, bladder stones, bladder diverticula, hydronephrosis, and renal insufficiency.[3]

[1] McVary KT. Epidemiology and pathophysiology of benign prostatic hyperplasia, UpToDate, 01/19/2021.
[2] Wei JT, Calhoun E, Jacobsen SJ. Urologic diseases in America project: benign prostatic hyperplasia. J Urol. 2005;173(4):1256.
[3] McVary KT. Clinical manifestations and diagnostic evaluation of benign prostatic hyperplasia. UpToDate, 11/18/2021.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• There are multiple approved therapeutic options for BPH. These include alpha-adrenergic receptor blockers such as terazosin, doxazosin, tamsulosin, alfuzosin, and silodosin. However, this class of drugs may cause postural hypotension, rhinitis, abnormal ejaculation, and intraoperative floppy iris syndrome. Another drug class, 5-alpha reductase inhibitors (5ARIs), including finasteride (5 mg) and dutasteride (0.5 mg), are available to treat symptomatic BPH in men with an enlarged prostate and are associated with possible increased risk of high-grade prostate cancer and sexual dysfunction. The phosphodiesterase type 5 (PDE5) inhibitor tadalafil (5 mg) is also indicated to treat BPH and is associated with risks including hypotension, non-arteritic ischemic optic neuropathy (NAION), prolonged erection, and hearing impairment. In addition, combinations of a 5ARI and alpha-blocker and coadministration of finasteride and tadalafil are approved to treat symptomatic BPH in men with an enlarged prostate.	There are three drug classes available to treat BPH. These include alpha-adrenergic receptor blockers, 5-alpha reductase inhibitors, and a phosphodiesterase type 5 inhibitor. In addition, the combination of 5ARIs with alpha-blockers and a 5ARI with a PDE5-inhibitor are approved for BPH treatment.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The efficacy of Entadfi was established by the demonstration of bioequivalence between the two components of fixed-dose combination, finasteride 5 mg and tadalafil 5 mg, and a finasteride 5 mg tablet coadministered with a tadalafil 5 mg tablet, in the fasted state. Coadministration of Cialis (tadalafil 5 mg) and Proscar (finasteride 5 mg) is approved to treat symptomatic BPH in men with an enlarged prostate. Cialis (tadalafil 5 mg) taken with finasteride 5 mg was shown to be effective as initial treatment of symptomatic BPH in men with an enlarged prostate for up to 26 weeks in an active controlled study of 696 adult males.	Based on the data submitted by the Applicant, this study provides an acceptable evidence of bioequivalence for Entadfi and Proscar with Cialis administered at the same time, in the fasted state. Entadfi fixed dose combination capsule may provide increased convenience to patients over the individual tablets taken together.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• No new safety signals were identified from the data for Study V0112502, the search of published literature, or the search of the FAERS database for adverse events reported with coadministration of finasteride and tadalafil. • The results of Study V0112502 demonstrated that the Entadfi fixed dose combination is bioequivalent to co-administered Proscar 5 mg and Cialis 5 mg under fasted conditions. • This finding of bioequivalence established a scientifically justified bridge to the listed drugs – Proscar and Cialis. Therefore, reliance on safety information in the labeling for the listed drugs is appropriate for Entadfi.	• It is appropriate for this NDA to rely on the safety data for the listed drugs (Proscar and Cialis) based on the bioequivalence results of Study V0112502. • Based on the long marketing histories of the listed drugs, the risks of these drugs are well characterized and quantified. • These risks have been successfully managed with labeling for the listed drugs and will be managed with labeling for Entadfi. • However, because bioequivalence was only established in the fasted condition, Entadi will be labeled for administration without food. • If Entadfi is inadvertently taken with food, it will not pose a safety risk.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
X	**Patient experience data was not submitted as part of this application.**			

2. Therapeutic Context

2.1. Analysis of Condition

Benign prostatic hyperplasia (BPH) is a histologic diagnosis that is defined as an increase in the number of stromal and glandular epithelial cells in the transition zone of the prostate gland in men.[4] BPH may cause enlargement of the prostate, and resultant bladder outlet obstruction, leading to lower urinary tract symptoms (LUTS).[5][6] The prevalence of BPH increases with age, and it is estimated that almost 70% of men ages 60-69 years and approximately 80% of men greater than 70 years of age have BPH.[4] The etiology of symptomatic BPH is not fully understood, and is related both to enlargement of the gland itself (static component) and increased smooth muscle tone (dynamic component).[4] Bladder outlet obstruction may also cause bladder detrusor muscle instability (overactive bladder), worsening LUTS. Several mechanisms have been identified as possible causes of BPH, including androgen activity and systemic and local inflammation.[4] Patients typically present with LUTS which may be categorized into symptoms related to urinary storage, voiding, and post-voiding.[4,6] Potential serious complications include acute urinary retention, urinary tract infection, bladder stones, bladder diverticula, and decreased renal function.[6]

In summary, BPH affects a substantial proportion of men as they age. Men with BPH may experience LUTS including storage symptoms (urinary frequency, urgency, nocturia and incontinence) and voiding symptoms (slow urinary stream, straining to void, intermittent urinary stream and hesitancy, splitting of the urinary stream, and terminal dribbling).[4] Potential serious complications of BPH include acute urinary retention and chronic obstruction that can lead to urinary tract infection, bladder stones, bladder diverticula, hydronephrosis, and renal insufficiency.[6]

2.2. Analysis of Current Treatment Options

Currently, there are many pharmacologic therapies available to treat BPH. These include alpha-adrenergic receptor blockers such as terazosin, doxazosin, tamsulosin, alfuzosin, and silodosin. However, this class of drugs may cause postural hypotension, rhinitis, abnormal ejaculation, and intraoperative floppy iris syndrome. 5-alpha reductase inhibitors including finasteride (5 mg) and dutasteride (0.5 mg) are available to treat symptomatic BPH in men with an enlarged prostate and are associated with possible increased risk of high-grade prostate cancer and sexual dysfunction. The phosphodiesterase type 5 (PDE5) inhibitor tadalafil (5 mg) is also indicated to treat BPH and is associated with risks including hypotension, non-arteritic ischemic

[4] McVary KT., Epidemiology and pathophysiology of benign prostatic hyperplasia, UpToDate, 01/19/2021.
[5] Wei JT, Calhoun E, Jacobsen SJ. Urologic diseases in America project: benign prostatic hyperplasia. J Urol. 2005;173(4):1256.
[6] McVary KT. Clinical manifestations and diagnostic evaluation of benign prostatic hyperplasia. UpToDate, 11/18/2021.

optic neuropathy (NAION), prolonged erection, and hearing impairment. In addition, there is an available fixed dose combination product that contains dutasteride and tamsulosin, the coadministration of dutasteride + tamsulosin, coadministration of finasteride + doxazosin, and coadministration of finasteride and tadalafil. Entadfi fixed dose combination capsule may provide an increased convenience to patients over the individual tablets of finasteride and tadalafil taken together.

Table 1. Currently Available Products for the Treatment of Benign Prostatic Hyperplasia

Route of Administration	Trade/ Generic Name	Dose	NDA	ANDA
Oral	**Alpha-adrenergic receptor antagonists**			
	Flomax/ tamsulosin hydrochloride	0.4 mg capsule daily (can be increased to 0.8 mg once daily)	020579	
	tamsulosin hydrochloride	0.4 mg capsule daily (can be increased to 0.8 mg once daily)		077630 078015 078225 078801 078938 090377 090931 202433 204645 207405 211885
	Cardura/ doxazosin mesylate	1 mg, 2 mg, 4 mg, or 8 mg tablet daily	019668	
	Cardura XL/ doxazosin mesylate	4 mg or 8 mg extended release tablet daily	021269	
	Doxazosin mesylate	1 mg, 2 mg, 4 mg, or 8 mg tablet daily		075536 075580 075750 202824 205210 208719 209013
	Rapaflo/ silodosin	4 mg or 8 mg capsule daily	022206	
	Silodosin	4 mg or 8 mg capsule daily		204726 204793 206541 209745 210626 210687 211060 211166
	Uroxatral/ alfuzosin hydrochloride	10 mg extended release tablet daily	021287	
	Alfuzosin hydrochloride	10 mg extended release tablet daily		079013 079057 079060 090284 203192

Route of Administration	Trade/ Generic Name	Dose	NDA	ANDA
	Terazosin hydrochloride	1 mg, 2 mg, 5 mg, or 10 mg capsule daily		074823
				075317
				075614
	Phosphodiesterase 5 (PDE5) inhibitors			
	Cialis/ tadalafil	5 mg tablet daily	021368	
	Tadalafil	5 mg tablet daily		090141
				204809
				206285
				206693
				207244
				208824
				208934
				209167
				209250
				209539
				209654
				209744
				209908
				210069
				210420
				210567
				211298
				211335
				211839
				215556
	5 alpha-reductase inhibitors			
	Avodart/ dutasteride	0.5 mg capsule daily	021319	
	Dutasteride	0.5 mg capsule daily		090095
				200899
				202421
				202660
				203118
				204262
				204373
				204376
				206373
				206574
				209909
	Proscar/ finasteride	5 mg tablet daily	020180	
	Finasteride	5 mg tablet daily		076437
				076511
				078341
				078900
				090061
				090121
				090507
				204304

Route of Administration	Trade/ Generic Name	Dose	NDA	ANDA
	Combination product(s)			
	Jalyn/ dutasteride and tamsulosin hydrochloride	0.5 mg dutasteride and 0.4 mg tamsulosin capsule daily	022460	
	Dutasteride and tamsulosin	0.5 mg dutasteride and 0.4 mg tamsulosin capsule daily		202509 207769
	Finasteride and doxazosin tablets (coadministered)	5 mg finasteride and 4 or 8 mg doxazosin daily	See above	
	Finasteride and tadalafil tablets (coadministered)	5 mg finasteride and 5 mg tadalafil	See above	

Source: Reviewer designed table using:
Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book), electronic version accessed November 22, 2021.
Product labeling accessed at the DailyMed website on November 22, 2021.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

This is an original application for NDA 215423, therefore, there are no prior U.S. Regulatory Actions or Marketing History.

3.2. Summary of Presubmission/Submission Regulatory Activity

During the development program for the proposed product, the Applicant had 2 meetings with the Division of Urology, Obstetrics and Gynecology. In addition, the Division reviewed and provided comments on the Initial Pediatric Study Plan.

- **Type B, Pre-IND 136844 Meeting; Final Written Responses on November 21, 2017**: The objective of this meeting was to discuss the Applicant's development plan for a finasteride/tadalafil fixed-dose combination oral capsule for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH) pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. In the Written Response, the Division asked that the proposed relative bioavailability and food effect study be conducted in subjects aged ≥45 years old to determine the pharmacokinetics of the drug product in the target age range of men with BPH. The Division also asked that the analysis of postmarketing safety information include a search of the FAERS database including the time since approval of the finasteride/tadalafil concomitant administration in October 2014 until 3 months prior to submission of the NDA and a separate section on adverse events reported in patients who took the combination of finasteride and tadalafil. The Division provided comments about drug product specification criteria.
- **Type B, Pre-NDA Meeting on May 23, 2019**: The objective of this meeting was to discuss the submission of the proposed finasteride/tadalafil combination (b) (4) via the 505(b)(2) pathway. The Division explained that the submitted comparative bioavailability study did not establish a clinical bridge necessary to file a 505(b)(2) NDA

and asked that the Applicant design a new formulation and conduct a new comparative bioavailability study to establish bioequivalence between the proposed product and the listed drugs or, alternatively, establish that the 27% lower C_{max} of tadalafil has no clinically meaningful impact on the efficacy of the proposed combination product. The Division stated that the effect of food on the bioavailability of the drug product should be considered in determining whether the safety can be supported. The Applicant stated that they would conduct a new comparative bioavailability study as requested, data from which are now submitted in the current NDA. The Division asked that the Applicant submit an ISE and ISS with the NDA submission. Also, the Division asked that additional drug specification testing should be submitted, and that the NDA should include at least 12 months of long-term stability data and 6 months of accelerated stability data from three registration batches.

- **Initial Pediatric Study Plan – Written Response, on April 29, 2020:** The Division provided comments pertaining to the Initial Pediatric Study Plan.
- **Agreed Initial Pediatric Study Plan – Agreement, on August 04, 2020:** The Division reviewed and agreed to the Agreed Initial Pediatric Study Plan for a full waiver based on the claim that the necessary studies are impossible or highly impracticable due to the small number of pediatric patients with BPH, pursuant to Section 505B(a)(4)(A)(i) of the Federal Food, Drug, and Cosmetic (FD&C) Act.

Reviewer's Comment*: The Applicant originally submitted the comparative BA/BE study of a* (b) (4) *formulation of the fixed dose combination finasteride/tadalafil drug product. However, that study showed a 27% lower C_{max} of tadalafil of the test product compared to the listed drug. The Applicant agreed to conduct a new comparative bioavailability study as recommended by FDA. Data from the new BA/BE study (V0112502) using a reformulated test product in a capsule are now submitted with this current NDA.*

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Study Integrity and Surveillance (OSIS)

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that inspections of the clinical site and the analytical site are not warranted for this NDA.

The Office of Regulatory Affairs (ORA) inspected the clinical site in June 2019, which falls within the surveillance interval. OSIS inspected the analytical site in (b) (4) which falls within the surveillance interval.

The final classification for the inspections was No Action Indicated (NAI). Therefore, OSIS concludes that inspections are not warranted at this time.

4.2. Product Quality

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, and purity 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 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.

Finasteride is a NIOSH Group 3 Hazardous Drug that may be absorbed through the skin. As noted in the PROSCAR (finasteride) Tablets USPI, "females 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 Entadfi, a (b) (4) of 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 (b) (4)) performed during (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.

4.3. Clinical Microbiology

No microbiology supporting information was submitted or requested.

4.4. Devices and Companion Diagnostic Issues

The product does not include a device or companion diagnostic.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

There were no nonclinical data submitted to support this application. Veru is relying on the safety and efficacy of two listed drugs (LDs), PROSCAR® (finasteride 5 mg tablet, NDA 20180 approved 1992) and CIALIS® (tadalafil 5 mg tablet, NDA 21368 approved 2003). Nonclinical information relied upon is in the approved product labeling of Cialis and Proscar.

Reliance on the LDs is based on a scientifically justified bridge established in a comparative bioavailability/bioequivalence study (Study V0112502), in which Entadfi (5 mg tadalafil/5 mg finasteride) oral capsule was determined to be bioequivalent to Cialis (tadalafil 5 mg) and Proscar (finasteride 5 mg) tablets administered together.

According to the guidance on Nonclinical Safety Evaluation of Drug or Biologic Combinations, there was no need for further nonclinical testing of this combination product.

There are no new excipients in the proposed drug product. All excipients are used at approved amounts and did not require qualification.

Per the nonclinical review submitted in the Document Archiving, Reporting, and Regulatory Tracking System (DARRTS) dated November 19, 2021, the nonclinical review team concludes that this application is approvable.

6. Clinical Pharmacology

6.1. Executive Summary

Tadalafil is an FDA approved drug as Cialis® (tadalafil 5 mg tablet, NDA 021368, Eli Lily and Co.). One of the approved indications for Cialis® is for the treatment of signs and symptoms of benign prostatic hyperplasia (BPH). Finasteride is an FDA approved drug as Proscar® (finasteride 5 mg tablet, NDA 020180, Merck and Co., Inc) which is also indicated for treatment of BPH. In addition, Cialis® is approved for use with finasteride to initiate BPH treatment and such use is recommended for up to 26 weeks. Veru Inc. has developed Entadfi, a fixed dose combination oral capsule containing 5 mg of finasteride and 5 mg of tadalafil. The Applicant is seeking

approval via 505(b)(2) pathway using Cialis® and Proscar® as the listed drugs for the same indication and dosage regimen approved for the co-administered therapy of Cialis® and finasteride. The Applicant proposed to rely on the Agency's safety and efficacy findings of the listed drugs and conducted a relative bioavailability/bioequivalence study V0112502 to establish a scientific bridge to the listed drugs in support of this NDA. The study also assessed food effect on the pharmacokinetics of Entadfi.

The Office of Clinical Pharmacology, Division of Cardiometabolic and Endocrine Pharmacology (DCEP) has reviewed the clinical pharmacology information submitted for NDA 215423 (a fixed dose combination oral capsule containing 5 mg tadalafil and 5 mg finasteride). We find that the application is acceptable for approval from a clinical pharmacology standpoint.

The key clinical pharmacology review assessments are summarized below (Table 2).

Table 2. The Key Clinical Pharmacology Review Issue and Assessments

Review issue	Key assessments
Pharmacokinetics (PK) bioavailability (BA)/ bioequivalence (BE)	The Applicant conducted a single phase-1 comparative BA/BE study (study number V0112502). This study was an open-label, randomized, single-center, single-dose, 3-period, crossover study in healthy subjects (≥45 years and ≤60 years of age) to compare the BA under fasted condition between test (Entadfi oral capsule, a combination of 5 mg tadalafil and 5 mg finasteride) and reference (Cialis® [tadalafil] 5 mg tablet, manufactured by Lilly USA, and Proscar® [finasteride] 5 mg tablet, manufactured by AIAC International Pharm, LLC, USA for Merck and Co., Inc., administered together) products. Study results indicated that the test/reference ratio of geometric least square means (LS means) and the 90% confidence interval (CI) for maximum observed concentration (C_{max}) and area under the concentration-time curve (AUC_t and AUC_∞) values for tadalafil and finasteride were within the specified no-effect boundary of 80% to 125%. This finding demonstrated that Entadfi oral capsule is bioequivalent to Cialis® and Proscar® tablets administered together under fasted conditions.
Food effect assessment	Food effect on Entadfi was evaluated in the same phase-1 comparative BA/BE study (study number V0112502). For both tadalafil and finasteride from the Entadfi oral capsule, the 90% CI limits for the ratios of geometric LSmean for AUC_t and AUC_∞ were within the specified no-effect boundary of 80% to 125%. However, C_{max} values of tadalafil and finasteride were 23% and 29% lower and the 90% CI for the ratios of geometric LSmean were not within the 80% to 125% limits.

In conclusion, observed PK results demonstrated that Entadfi oral capsule is bioequivalent to Cialis® (5 mg tadalafil) and Proscar® (5 mg finasteride) tablets administered together under fasted condition. Food did not affect the AUC but reduced the C_{max} of tadalafil and finasteride by 23% and 29%, respectively.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

6.2.1.1. Relative bioavailability/bioequivalence determination

Results from the study V0112502 demonstrated that Entadfi is bioequivalent to Cialis® and Proscar® tablets administered together under fasted conditions. The geometric LSmean ratios of C_{max}, AUC_t, and AUC_∞ were 93.28%, 103.48%, and 103.75% for tadalafil and 99.84%, 108.26%, and 108.19% for finasteride, respectively. The 90% CI limits for C_{max}, AUC_t, and AUC_∞ were all within the 80% to 125% (Table 3 and Table 4).

Table 3. Study V0112502: PK Parameter Comparison for Tadalafil Between Entadfi (Treatment-1) and Cialis® 5 mg and Proscar® 5 mg Administered Together (Treatment-3) Under Fasted Conditions

Parameter	Intra-Subject C.V. (%)	Geometric LSmeans[a]		Ratio (%)	90% Confidence Limits (%)	
		Treatment-1 (n=30)	Treatment-3 (n=30)		Lower	Upper
C_{max}	13.1	104.193	111.698	93.28	87.97	98.92
AUC_t	11.6	2328.277	2249.994	103.48	98.21	109.03
AUC_∞	12.1	2452.432	2363.822	103.75	98.26	109.54

[a] units are ng/mL for C_{max} and ng·h/mL for AUC_t and AUC_∞

Table 4. Study V0112502: PK Parameter Comparison for Finasteride Between Entadfi (Treatment-1) and Cialis® 5 mg and Proscar® 5 mg Administered Together (Treatment-3) Under Fasted Conditions

Parameter	Intra-Subject C.V. (%)	Geometric LSmeans[a]		Ratio (%)	90% Confidence Limits (%)	
		Treatment-1 (n=30)	Treatment-3 (n=30)		Lower	Upper
C_{max}	11.7	41.319	41.386	99.84	94.48	105.50
AUC_t	8.7	310.078	286.431	108.26	104.11	112.57
AUC_∞	8.8	313.212	289.497	108.19	104.01	112.54

[a] units are ng/mL for C_{max} and ng·h/mL for AUC_t and AUC_∞

6.2.1.2. Food effect determination

Results from the study V0112502 demonstrated that a high fat meal did not affect the extent of absorption (i.e., AUC_t and AUC_∞) of tadalafil and finasteride from Entadfi. However, food reduced the rate of absorption (i.e., C_{max}) of tadalafil and finasteride from Entadfi. The geometric LSmeans for C_{max}, AUC_t, and AUC_∞ are provided in Table 5 for tadalafil and in Table 6 for finasteride. The geometric LSmean ratios of C_{max}, AUC_t, and AUC_∞ were 77.32%, 102.65%, and 104.52% for tadalafil and 71.07%, 105.59%, and 106.04% for finasteride, respectively. For both tadalafil and finasteride, the 90% CI limits for AUC_t and AUC_∞ were within the specified no-effect boundary of 80% to 125%. The 90% CI limits for C_{max} for both tadalafil and finasteride were not contained within the 80% to 125% limits.

Table 5. Study V0112502: PK Parameter Comparison for Tadalafil From Entadfi under Fed (Treatment-2) and Fasted (Treatment-1) Conditions

Parameter	Intra-Subject C.V. (%)	Geometric LSmeans[a]		Ratio (%)	90% Confidence Limits (%)	
		Treatment-2 (n=34)	Treatment-1 (n=34)		Lower	Upper
C_{max}	18.4	81.187	104.997	77.32	71.61	83.49
AUC_t	9.8	2431.760	2368.922	102.65	98.52	106.96
AUC_∞	10.8	2623.620	2510.156	104.52	99.90	109.35

[a] units are ng/mL for C_{max} and ng·h/mL for AUC_t and AUC_∞

Table 6. Study V0112502: PK Parameter Comparison for Finasteride From Entadfi Under Fed (Treatment-2) and Fasted (Treatment-1) Conditions

Parameter	Intra-Subject C.V. (%)	Geometric LSmeans[a]		Ratio (%)	90% Confidence Limits (%)	
		Treatment-2 (n=34)	Treatment-1 (n=34)		Lower	Upper
C_{max}	21.1	29.616	41.669	71.07	65.11	77.59
AUC_t	10.1	333.787	316.117	105.59	101.22	110.15
AUC_∞	10.1	338.816	319.518	106.04	101.62	110.65

[a] units are ng/mL for C_{max} and ng·h/mL for AUC_t and AUC_∞

These results demonstrated that food did not affect the extent of absorption (i.e., AUC_t and AUC_∞) but reduced the rate of absorption (i.e., C_{max}) of tadalafil and finasteride by 23% and 29%, respectively.

According to the approved labeling of Cialis® and Proscar®, rate and extent of absorption of tadalafil and bioavailability of finasteride are not affected by food, respectively. Thus, both listed drugs (Cialis® and Proscar®) can be taken with or without food. However, in study V0112502, food reduced the rate of absorption for both tadalafil and finasteride after administration of Entadfi oral capsule. The Applicant proposed that Entadfi be administered without food, which has been deemed justified by the review team due to the findings of the C_{max} reduction by food. Therefore, Office of Clinical Pharmacology review team has recommended adding "Effect of Food" section in the section 12.3 of the proposed labeling as per the "Guidance for Industry: Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format."

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The Applicant proposed a dosing regimen of one Entadfi capsule (containing 5 mg tadalafil and 5 mg finasteride) taken orally at approximately the same time everyday for up to 26 weeks. This dosing regimen is the same as the listed drug Cialis®'s approved dosing regimen for the same indication when used with finasteride. The Applicant proposed that Entadfi be administered without food. The proposed dosing regimen is supported by the study results from phase-1 comparative BA/BE study (Study number V0112502).

Therapeutic Individualization

No studies were conducted for the assessment of the effect of various intrinsic (e.g., organ impairment, genotype) factors. The Applicant proposed to rely on the Agency's previous findings of the listed drugs. However, one of the extrinsic factors, food effect, was assessed. Food did not affect the AUC but reduced the C_{max} of tadalafil and finasteride by 23% and 29%, respectively. While the listed drugs, Cialis® and Proscar® can be administered with or without food, due to the findings of the C_{max} reduction by food, Entadfi is to be taken without food. (see section 6.3.2 for detail).

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

6.3.1.1. General pharmacology and pharmacokinetic characteristics of finasteride

Finasteride (PROSCAR®) is 4-azaandrost-1-ene-17-carboxamide, N-(1,1-dimethylethyl)-3-oxo-(5α,17β)- compound. The development and enlargement of the prostate gland is dependent on the potent androgen 5α-dihydrotestosterone (DHT). Type II 5α-reductase, an intracellular enzyme, metabolizes testosterone to DHT in the prostate gland. Finasteride is a competitive and specific inhibitor of Type II 5α-reductase with which it slowly forms a stable enzyme complex. Finasteride has no affinity for the androgen receptor (PROSCAR, prescribing information).

After a single dose administration of Entadfi, following (see Table 7) pharmacokinetic parameters of finasteride were observed.

Table 7. Summary Pharmacokinetic Parameters of Finasteride After a Single Dose Administration of Entadfi Under Fasted Condition

Parameter	Mean	CV (%)
C_{max} (ng/mL)	43.224	24.1
T_{max} (hours)[a]	2.00	1.00-4.07
AUC_t (ng*h/mL)	335.811	28.0
AUC_∞ (ng*h/mL)	339.832	28.5
$t_{1/2}$ (hours)	6.63	24.5
Cl/F (L/h)	15.962	30
V_d/F (L)	146.017	22.7

[a] Median and range are presented
Abbreviations: CV, coefficient of variation

6.3.1.2. General pharmacology and pharmacokinetic characteristics of tadalafil

Tadalafil (CIALIS®) is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PED5). The inhibition of PDE5 enhances erectile function by increasing the amount of cGMP. Tadalafil inhibits PDE5. Because sexual stimulation is required to initiate the local release of nitric oxide, the inhibition of PDE5 by tadalafil has no effect in the absence of sexual stimulation. The effect of PDE5 inhibition on cGMP concentration in the corpus cavernosum and pulmonary arteries is also observed in the smooth muscle of the prostate, the bladder and their vascular supply. The mechanism for reducing benign prostate hyperplasia (BPH) symptoms has not been established (CIALIS®, prescribing information).

After a single dose administration of Entadfi, the following (see Table 8) pharmacokinetic parameters of tadalafil were observed.

Table 8. Summary Pharmacokinetic Parameters of Tadalafil After a Single Dose Administration of Entadfi Under Fasted Condition

Parameter	Mean	CV (%)
C_{max} (ng/mL)	106.751	23.6
T_{max} (hours)[a]	3.00	1.00 – 4.05
AUC_t (ng*h/mL)	2507.502	31.9
AUC_∞ (ng*h/mL)	2682.645	35.3
$t_{1/2}$ (hours)	22.33	24.9
Cl/F (L/h)	2.080	35.8
V_d/F (L)	62.922	21.4

[a] Median and range are presented
Abbreviations: CV = Coefficient of variation

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. The clinical pharmacology program provides supportive evidence of effectiveness.

The Applicant performed the Phase 1 comparative BA/BE study (study number V0112502) to establish a clinical bridge via BE between the proposed drug, Entadfi (Treatment-1, fasted) and the listed drugs (Treatment-3, Cialis® and Proscar® administered together, fasted), and thus established the scientific bridge for reliance on the Agency's previous findings of safety and efficacy for the use of tadalafil and finasteride combination in treating BPH.

The pharmacokinetic parameters of tadalafil and finasteride from Entadfi were similar to that from the co-administered Cialis® (Table 9) and Proscar® (Table 10). The values of C_{max}, AUC_t and AUC_∞ were not significantly different as the geometric LSmeans ratios and associated 90% CIs were within the acceptable BE range of 80% to 125% (Table 3 and Table 4).

Table 9. Summary of Plasma Tadalafil Pharmacokinetic Parameters From Entadfi (Treatment-1) and Co-administered Cialis® and Proscar® (Treatment-3)

Parameter	Treatment-1 (n=30)		Treatment-3 (n=30)	
	Mean	CV (%)	Mean	CV (%)
C_{max} (ng/mL)	106.751	(23.6)	113.431	(21.1)
T_{max} (hours)[a]	3.00	(1.00-4.05)	2.00	(1.00-4.22)
AUC_t (ng*h/mL)	2507.502	(31.9)	2428.806	(32.6)
AUC_∞ (ng*h/mL)	2682.645	(35.3)	2592.292	(35.9)
$AUC_{t/\infty}$ (%)	94.32	(3.9)	94.66	(4.0)
λ_Z (hours^{-1})	0.0331	(27.3)	0.0334	(25.9)
$t_{1/2}$ (hours)	22.33	(24.9)	22.12	(26.5)
Cl/F (L/h)	2.080	(35.8)	2.172	(35.6)
V_d/F (L)	62.922	(21.4)	64.819	(22.3)

Abbreviations: CV = coefficient of variation.
a. Median and range are presented.

Table 10. Summary of Plasma Finasteride Pharmacokinetic Parameters From Entadfi (Treatment-1) and Co-administered Cialis® and Proscar® (Treatment-3)

Parameter	Treatment-1 (n=30)		Treatment-3 (n=30)	
	Mean	CV (%)	Mean	CV (%)
C_{max} (ng/mL)	43.224	(24.1)	42.591	(21.1)
T_{max} (hours)[a]	2.00	(1.00-4.07)	1.50	(1.00-4.22)
AUC_t (ng*h/mL)	335.811	(28.0)	309.818	(27.4)
AUC_∞ (ng*h/mL)	339.832	(28.5)	313.418	(27.7)
$AUC_{t/\infty}$ (%)	98.93	(0.8)	98.88	(0.6)
λ_Z (hours^{-1})	0.1105	(24.0)	0.1148	(25.9)
$t_{1/2}$ (hours)	6.63	(24.5)	6.41	(24.1)
Cl/F (L/h)	15.962	(30.0)	17.157	(27.9)
V_d/F (L)	146.017	(22.7)	152.155	(22.0)

Abbreviations: CV = coefficient of variation.
a. Median and range are presented.

In the study, all the samples were adequately analyzed with validated bioanalytical method (see section 13.4.1. Summary of bioanalytical method validation and performance) with acceptable accuracy, precision, and no carryover effect.

The above findings demonstrated that the proposed drug Entadfi and the listed drugs (Cialis® and Proscar®, administered at the same time) are bioequivalent and therefore established the scientific bridge for reliance on the Agency's previous findings of safety and efficacy for Cialis® and Proscar® in treating the signs and symptoms of BPH.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed dosing regimen is appropriate for the general patient population for which the indication is being sought.

Cialis® (tadalafil) tablet 5 mg for oral use (NDA 021368, Eli Lilly and Company) is approved by the FDA for the treatment of the signs and symptoms of BPH alone and in combination with finasteride to initiate BPH treatment for up to 26 weeks. Proscar® (finasteride) tablet (5 mg; NDA 020180, Merck and Co. Inc.) is also an FDA approved drug for the treatment of symptomatic BPH in men with an enlarged prostate to improve symptoms, reduce the risk of acute urinary retention, and reduce the risk of the need for surgery, including transurethral resection of the prostate (TURP) and prostatectomy. The Applicant developed Entadfi which is a fixed dose combination of tadalafil (5 mg) and finasteride (5 mg) indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH) in men with an enlarged prostate for up to 26 weeks. The Applicant's proposed indication and dosing regimen for Entadfi are the same as that for the approved use of the reference listed drug, Cialis® 5 mg, in combination of finasteride 5 mg.

The Applicant performed the Phase 1 pivotal study (study number V0112502) which demonstrated BE between the proposed drug, Entadfi, and the co-administered listed drugs (Cialis® 5 mg and Proscar® 5 mg), and thus established the scientific bridge for reliance on the Agency's previous findings of safety and efficacy for the use of tadalafil and finasteride for the treatment of the signs and symptoms of BPH.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Yes. The Applicant did not assess any intrinsic factor in the current NDA. However, the Applicant proposed to rely on the Agency's previous findings of clinical pharmacology information of the listed drugs, Cialis® and Proscar®, related to any alternative dosing regimen or management strategy for subpopulation based on intrinsic patient factors. Because the Applicant's completed BA/BE study demonstrated that after single dose administration under fasted conditions, Entadfi and the co-administered listed drugs (Cialis® and Proscar®) were bioequivalent, the Applicant's proposal is acceptable.

Below is a summary of the recommendation for subpopulations based on the labels of the listed drugs.

Hepatic Impairment:
The effect of hepatic impairment on finasteride pharmacokinetics has not been studied. However, finasteride is extensively metabolized in the liver. Cautions should be exercised in the administration of Entadfi in those patients with mild to moderate hepatic impairment (Child Pugh Class A or B). Insufficient tadalafil data are available for patients with severe hepatic impairment (Child Pugh Class C). Therefore, Entadfi use is not recommended in these patients.

Renal Impairment:
Due to increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to influence clearance by dialysis, Entadfi is not recommended in patients with creatinine clearance less than 50 mL/min or on hemodialysis.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Food-drug interaction:

In study V0112502, the Applicant tested the food effect on the pharmacokinetics of Entadfi by comparing two treatment arms (Treatment 1 (Entadfi fasted) and Treatment 2 (Entadfi fed)). The results of the food effect analysis demonstrated that when Entadfi was administered with food (Treatment 2), the pharmacokinetics parameters AUC_t and AUC_∞ of tadalafil and finasteride were comparable to that under fasted conditions (Table 11 and Table 12). For both tadalafil and finasteride, the 90% CI limits for AUC_t, and AUC_∞ for tadalafil were within the specified no-effect boundary of 80% to 125% (Table 5 and Table 6). However, the pharmacokinetic parameter C_{max} of tadalafil and finasteride were reduced when Entadfi was administered with food (Treatment 2) compared to that under fasted conditions (Table 11 and Table 12). The 90% CI limits for C_{max} for both tadalafil and finasteride were not contained within the 80% to 125% limits (Table 5 and Table 6). The results of the food effect analysis demonstrated that C_{max} of Entadfi was reduced in the presence of food. Therefore, in the proposed Entadfi's label, it is recommended that Entadfi oral capsule be taken without food.

Table 11. Summary of Plasma Tadalafil Pharmacokinetics Parameters From Treatment 2 and Treatment 1

Parameter	Treatment-2 (n=34)		Treatment-1 (n=34)	
	Mean	CV (%)	Mean	CV (%)
C_{max} (ng/mL)	86.346	(36.7)	107.823	(22.5)
T_{max} (hours)[a]	6.00	(2.00-12.00)	3.00	(1.00-4.05)
AUC_t (ng*h/mL)	2627.572	(33.2)	2538.212	(31.9)
AUC_∞ (ng*h/mL)	2874.265	(37.0)	2725.450	(35.8)
$AUC_{t/\infty}$ (%)	92.56	(4.8)	94.11	(4.1)
λ_Z (hours^{-1})	0.0312	(28.3)	0.0326	(27.4)
$t_{1/2}$ (hours)	23.90	(27.1)	22.68	(25.1)
Cl/F (L/h)	1.974	(38.6)	2.048	(34.8)
V_d/F (L)	63.029	(21.9)	62.832	(20.4)

Abbreviations: CV = coefficient of variation.
a. Median and range are presented.

Table 12. Summary of Plasma Finasteride Pharmacokinetic Parameter From Treatment 2 and Treatment 1

Parameter	Treatment-2 (n=34)		Treatment-1 (n=34)	
	Mean	CV (%)	Mean	CV (%)
C_{max} (ng/mL)	31.175	(33.3)	43.091	(23.2)
T_{max} (hours)[a]	6.00	(2.00-12.15)	2.00	(1.00-4.07)
AUC_t (ng*h/mL)	355.072	(25.7)	336.925	(25.9)
AUC_∞ (ng*h/mL)	361.162	(26.5)	340.874	(26.3)
$AUC_{t/\infty}$ (%)	98.50	(1.2)	98.94	(0.8)
λ_Z (hours^{-1})	0.1070	(23.3)	0.1097	(22.9)
$t_{1/2}$ (hours)	6.82	(23.2)	6.65	(23.4)
Cl/F (L/h)	14.818	(27.3)	15.699	(27.2)
V_d/F (L)	139.578	(18.1)	145.078	(21.6)

Abbreviations: CV = coefficient of variation.
a. Median and range are presented.

Drug-drug interaction:

The Applicant proposed to rely on the drug-drug interactions (DDIs) information contained in the labels for the approved listed products Cialis® and Proscar®.

Tadalafil can potentiate the hypotensive effects of nitrates, alpha-blocker, antihypertensives or alcohol. Strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir) increase tadalafil exposure requiring dose adjustment. On the other hand, CYP3A4 inducers (e.g., rifampin) decrease tadalafil exposure (Cialis® prescribing information).

No DDI of clinical importance has been identified for finasteride (Proscar® prescribing information).

Considering the DDI potential mentioned in the Cialis® and Proscar® labeling information, Entadfi has potential to work as a perpetrator or victim drug. The Applicant did not assess the DDI potential, however, based on the scientific bridge via BE established in the Applicant's comparative BA/BE study V0112502, the proposal of relying on the Agency's previous findings of DDI information of listed drugs is acceptable.

Question on clinically relevant specifications (TBD)?

N/A

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

This 505(b)(2) application is supported by one clinical study: a bioequivalence study (Study V0112502). The study is summarized in Table 13.

Table 13. Study Submitted to Support the Application

Type of Study	Study Number	Study Objective	Study Design	Test Product	N	Type of Subjects
Bioequivalence	V0112502	To evaluate the bioequivalence of Entadfi versus finasteride and tadalafil	Single-dose, open-label, randomized, 3-period, crossover	Entadfi	36	Healthy male volunteers

7.2. Review Strategy

This 505(b)(2) application relies on FDA's finding of safety and efficacy for Proscar (finasteride), and Cialis (tadalafil), the LDs. The Applicant conducted Study V0112502 to demonstrate the bioequivalence of Entadfi to Proscar and Cialis, taken together. This study will be reviewed to determine whether the test product, Entadfi, and the two LDs taken together, are bioequivalent. If bioequivalence is established between Entadfi and the LDs, it will be considered adequate evidence that Entadfi is effective. In addition, a food effect study of Entadfi was also conducted.

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study V0112502

Trial Design

Study V0112502, a randomized, open-label, single-center, single-dose, 3-period, crossover, bioavailability, and food effect study, was conducted by the Applicant. The objectives of the study were to compare the bioavailability of finasteride from the Entadfi Combination Capsule to that of Proscar, and the bioavailability of tadalafil from the Entadfi Combination Capsule to that of Cialis, in addition to assessing the effect of food on the bioavailability of finasteride and tadalafil from the Entadfi Combination Capsule.

This was a single center, single-dose, open-label, randomized, 3-period, crossover bioequivalence study in healthy adult male subjects. The study compared the bioavailability of finasteride from the Entadfi Combination Capsule containing 5 mg finasteride and 5 mg tadalafil

(test product) to that of Proscar 5 mg (reference) by AIAC International Pharma, LLC, U.S.A. The study also compared the bioavailability of tadalafil from the Entadfi Combination Capsule containing 5 mg finasteride and 5 mg tadalafil (test product) to that of Cialis 5 mg (reference) by Lilly, LLC, U.S.A. In addition, the study assessed the effect of food on the bioavailability of finasteride and tadalafil from the Entadfi Combination Capsule.

In each period, blood samples were obtained predose, and at 0.25, 0.5, 1, 1.5 (for finasteride only), 2, 3 (for tadalafil only), 4, 6, 8, 12, 16, 24, 36, 48, 72 (for tadalafil only), and 96 hours (for tadalafil only) after the study drug administration. The screening and clinical facility for the study was located at the Altasciences facility in Mount-Royal, Quebec, Canada. The doses were separated by a washout period of 14 days.

Table 14. Treatment Groups

Treatment Number	Study Drug	Fasted/Fed
Treatment 1	Entadfi	Fasted
Treatment 2	Entadfi	Fed
Treatment 3	Cialis and Proscar	Fasted

Inclusion Criteria

Subjects who met the following criteria were included in the study:

1. Healthy adult male volunteer between 45 and 60 years of age (inclusive)
2. Able to understand and provide signed informed consent
3. Willing to comply with the requirements of the study
4. A male volunteer meeting one of the following criteria: able to procreate and agreed to use one of the accepted contraceptive regimens (abstinence from heterosexual intercourse or male condom with spermicide or male condom with a vaginal spermicide) and not donate sperm from the first study drug administration to at least 90 days after the last drug administration; or unable to procreate, defined as surgically sterile (i.e., had undergone a vasectomy at least 180 days prior to the first study drug administration)
5. Seated blood pressure between 100 and 140 mmHg systolic and between 60 and 90 mmHg diastolic (inclusive) at Screening and prior to the first study drug administration unless deemed not CS (clinically significant) by the Investigator
6. Seated pulse rate between 45 and 100 beats/minute (inclusive) at Screening and prior to the first study drug administration
7. Normally active and otherwise judged to be in good health on the basis of medical history and physical examination
8. Body mass index ≥18.5 and ≤30.0 kg/m^2
9. Body weight ≥55 kg

Exclusion Criteria

Subjects who met any of the following criteria were excluded from the study:

1. History of any CS cardiovascular, hepatic, renal, pulmonary, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, or neurologic disease
2. Any use of prescription medications within 28 days prior to check-in for Period 1
3. Any use of over the counter (OTC) medicines within 7 days prior to check-in for Period 1
4. History of significant hypersensitivity to tadalafil, finasteride, PDE5, other 5α-reductase or any related products (including excipients of the formulations) as well as severe hypersensitivity reactions (like angioedema) to any drugs
5. Abnormal and clinically relevant (as determined by the Investigator)electrocardiogram (ECG) tracing at Screening
6. Clinically significant illness or surgery within 28 days prior to dosing (including flu, flu-like symptoms, diarrhea, vomiting) or acute illness at the time of either the prestudy medical evaluation or dosing
7. Use of any medication known to alter hepatic enzyme activity within 28 days prior to the initial dose of study medication (e.g., omeprazole or other proton pump inhibitors [PPIs])
8. Positive test for hepatitis B, hepatitis C, or HIV at Screening
9. Any CS abnormal laboratory test results found prior to the first drug administration as determined by the Investigator. The definition of CS was related to the normal levels of each test at the local laboratory conducting the test. NOTE: A test value above or below the normal range did not necessarily indicate that the value was “CS.” The determination was made at the discretion of the Investigator with consultation, when necessary, with the Medical Monitor.
10. A positive drug or alcohol screen at Screening or check-in for Period 1
11. History of use of any nicotine products in the 3 months preceding the study start (first dose) and/or a positive cotinine test at Screening
12. History of major mental illness that, in the opinion of the Investigator, may have affected the ability of the subject to participate in the study. Institutionalized subjects were not eligible for participation
13. Exposure to any investigational agent within 30 days prior to study start (first dose)
14. Exposure to tadalafil or finasteride within 30 days prior to study start (first dose)
15. Subject made a donation (standard donation amount or more) of blood or blood products (with the exception of plasma as noted below) within 56 days prior to the study start (first dose)
16. Subject made a plasma donation within 7 days prior to the study start (first dose)
17. Subject had a condition the Investigator believed would interfere with the ability to provide informed consent or comply with study instructions, or that might confound the interpretation of the study results or put the subject at undue risk

Study Drugs

The investigational products used in the study were identified in the study report as:

A. CoreRx, Inc., U.S.A., Entadfi Combination Capsule (finasteride, tadalafil) 5 mg/5 mg: oral capsule. (Batch No.: 19353; Manufacturing date: November 20, 2019).
B. Merck & Co., Inc., Proscar® (finasteride) 5 mg tablets: oral tablets. (Batch No.: S041205; Manufacturing date: not available; Expiry date: September 25, 2022)
C. Lilly U.S.A., LLC, U.S.A., Cialis® (tadalafil) 5 mg tablets: oral tablets. (Batch No.: C998985A; Manufacturing date: not available; Expiry date: October 2021).

Study Endpoints

This study compared the relative bioavailability (rate and extent of absorption) of finasteride from the Entadfi Combination Capsule to that of Proscar, each containing 5 mg finasteride. This study also compared the relative bioavailability (rate and extent of absorption) of tadalafil from the Entadfi Combination Capsule to that of Cialis containing 5 mg tadalafil. The study also assessed the effect of food on the bioavailability of finasteride and tadalafil from the Entadfi Combination Capsule. The study drugs were administered as a single oral dose in healthy adult male volunteers.

The hypothesis of bioequivalence of the formulations was accepted if the ratio of geometric least-squares means (LSmeans) with corresponding 90% CI calculated from the exponential of the difference between test to reference product for the ln-transformed parameters C_{max}, AUC_t, and AUC_∞ were within the 80to 125% bioequivalence range.

The hypothesis of an absence of food effect on the PK profile of finasteride and tadalafil for the Entadfi Combination Capsule product was indicated when the ratio of geometric LSmeans with corresponding 90% CI calculated from the exponential of the difference between the Entadfi Combination Capsule product administered under fed conditions and administered under fasting conditions for the ln-transformed parameters C_{max}, AUC_t, and AUC_∞ were within the 80 to 125% range.

Statistical Analysis Plan

Pharmacokinetic parameters were analyzed using an analysis of variance (ANOVA) model. The 90% confidence interval (CI) for the exponential of the difference in least-square means (LSmeans) between each comparison of interest (Treatment-1 versus Treatment-3 and Treatment-2 versus Treatment-1) were calculated.

Statistical inference regarding tadalafil (comparison 1) and finasteride (comparison 2) was based on a bioequivalence approach. The ratio of geometric LSmeans with corresponding 90% CI calculated from the exponential of the difference between the Treatment-1 and the Treatment-3 products for the ln-transformed parameters C_{max}, AUC_t and AUC_∞ should all be within the 80.00 to 125.00% bioequivalence range.

Statistical inference regarding the presence or absence of a food effect was determined by comparing the C_{max}, AUC_t, AUC_∞, and T_{max} obtained during fasted and fed conditions after administration of Entadfi Combination Capsule. An absence of food effect on the PK profile of tadalafil (comparison 3) and finasteride (comparison 4) for the Entadfi Combination Capsule was defined as the following. The ratio of geometric LSmeans with corresponding 90% CI calculated from the exponential of the difference between the Entadfi Combination Capsule administered under fed conditions (Treatment-2) and administered under fasting condition (Treatment-1) for the ln-transformed parameters C_{max}, AUC_t, AUC_∞ should be within the 80.00 to 125.00% range.

Protocol Amendments

Protocol Amendment 1:

Protocol Amendment 1 was completed on February 26, 2020. A summary of the protocol changes is shown in Table 15.

Table 15. Protocol Amendment 1: Summary of Changes

Description of Change Made	Section/Location	Rationale
Removed return visits on Days 6, 7, 20, 21, 34 and 35	Section 2. Study Procedures and Assessments	To correct a discrepancy given that there are no scheduled tests or PK blood draws on those days.
Updated day of Study Exit/ Exit Procedures from Day 35 to 33	Throughout the protocol	To correct a typographical error
Updated the total duration of the study from 36 days to 34 days	Throughout the protocol	To correct a typographical error
Modified drug screening of hallucinogens to phencyclidine	Section 6.3. Pre-Study Procedures	To specify the type of hallucinogen to be tested, requested by the Altasciences clinic

Source: Applicant's submission, NDA 215423, 1611-prot-amend, page 49/135

Protocol Amendment 2:

Protocol Amendment 2 was completed on August 6, 2020. A summary of the protocol changes is shown in Table 16.

Table 16. Protocol Amendment 2: Summary of Changes

Description of Change Made	Section/Location	Rationale
Added the option of performing urine alcohol screen instead of alcohol breathalyzer screen	Throughout the protocol	Option added to limit physical contact in response to the ongoing COVID-19 pandemic.
Updated the description of Treatment-1 and Treatment-2 in Sequence 2 and Sequence 5 of the treatment scheme	Synopsis, Study Design Section 6.1. Overall Design and Plan of the Study	To correct a discrepancy
Clarified the hematology tests in the study	Synopsis, Study Procedures Section 6.4.2. Study Periods 1, 2, & 3 Section 8.9.3. Laboratory Testing	To correct a discrepancy
Added subsection 9.1. Bioanalytical Methods	Section 9. Data Analysis	To allow the start of bioanalysis of samples from a group that completed the study, requested by the Sponsor
Added subsection 10.5. COVID-19 Response Plan	Section 10. Study Administration	Response plan added for the ongoing COVID-19 pandemic

Source: Applicant's Submission, NDA 215423, 1611-prot-amend, page 4/135

Reviewer's Comment: *The listed protocol amendments would not be expected to change the study results.*

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant has indicated that the study was conducted in compliance with Good Clinical Practice Rules (GCP).

Financial Disclosure

The Applicant provided financial certification and disclosure forms for all investigators that participated in the single Phase 1 comparative bioavailability/bioequivalence study V0112502. The Applicant stated that all of the investigators certified that no financial arrangements with an investigator have been made where study outcome could affect compensation; the investigator does not have a proprietary interest in the tested product; the investigator does not have a significant equity interest in Veru Inc.; and the investigator has not received significant payments of other sorts. Therefore, no disclosure statements were submitted for any of the investigators.

Patient Disposition

Thirty-six (36) male subjects were randomized into the study, with 35 subjects receiving Entadfi (fasting), 35 subjects receiving Entadfi (fed) and 31 subjects receiving Proscar and Cialis administered at the same time (fasting). Of those 36, 5 subjects were discontinued from the study prior to the end of the study. Two subjects were withdrawn due to a positive COVID-19 test result (Subjects (b) (6) and (b) (6) and three were withdrawn for adverse events. The disposition of subjects in the study is summarized in Table 17.

Table 17. Summary of Subject Disposition (Study V0112502)

Category		Overall
Subjects included (N)		36
Subjects completed the study (n[%])	Yes	31 (86.1)
	No	5 (13.9)
If no, reason of study discontinuation (n[%])	Adverse Event	3 (8.3)
	Withdrawal By Subject	0
	Study Terminated By Sponsor	0
	Physician Decision	2 (5.6)
	Protocol Deviation	0
	Death	0
	Lost To Follow-Up	0
	Other	0
Number of subjects included in each analysis population (n[%])	Safety Population	36 (100.0)
	Pharmacokinetic Population	35 (97.2)

Source: Applicant's submission, NDA 215423, Module 5.3.1.2, Study Report V0112502, Table 10.1, p.28.

Subject (b) (6) was withdrawn due to a high serum creatinine result (175 µmol/L; reference range 60-110 µmol/L) at check-in for Period 3. The subject's creatinine value returned to a normal value of 108 µmol/L 4 days later.

Subject (b) (6) was withdrawn due to an elevated prostate specific antigen (PSA) result (6.80 µg/L; reference rage <2.51 µg/L) at check-in for Period 3. The subject's PSA 4 days later was 4.34 µg/L. The subject's PSA at screening and on Day 14 were 0.73 µg/L and 0.75 µg/L, respectively.

Subject (b) (6) was withdrawn due to a high serum creatinine level of 135 µmol/L (reference range: 60 to 110 µmol/L) on Day 28 at check-in of Period 3. A repeat of serum creatinine 15 hours later was within the normal range (94 µmol/L). The subject's serum creatinine at screening and on Day 14 were 80 µmol/L and 91 µmol/L, respectively.

Reviewer's Comment*: It is not possible to determine causality to the study drug from the limited information provided in the study report, but it cannot be ruled out either.*

Protocol Violations/Deviations

There were twelve protocol deviations reported during the study. In addition, there were several blood sampling time deviations noted during the study. There were no documented protocol deviations in the inclusion/exclusion criteria during the study. The reported protocol deviations are listed below.

1. Vital signs not performed as required (n=3)
    a. Vital signs were to be obtained after the subject had been seated for at least 3 minutes. However, the following occurred: For Subject (b) (6) in Period 3 on Day 29 for the pre-dose assessment, the Vital Signs were obtained after only 2 minutes of the subject being seated.
    b. Vital signs were to be performed within 15 minutes of the scheduled time. However, the following occurred: For Subject (b) (6) in Period 3 on Day 30 for the 24.00hr assessment, the Vital Signs were performed 1 minute outside of the allotted time.
    c. Vital signs were to be performed within 15 minutes of the scheduled time. However, the following occurred: For Subject (b) (6) in Period 3 on Day 30 for the 24.00hr assessment, the Vital Signs were performed 3 minutes outside of the allotted time.
2. Fasting time not respected before laboratory safety test (n=3)
    a. Prior to screening, subjects were to be fasted at least 8 hours for blood draw of laboratory samples. However, subject (b) (6) was not fasted for their retest blood draws.
    b. Prior to screening, subjects were to be fasted at least 8 hours for blood draw of laboratory samples. However, subject (b) (6) was not fasted for their retest blood draws.
    c. Prior to screening, subjects were to be fasted at least 8 hours for blood draw of laboratory samples. However, subject (b) (6) was not fasted for their retest blood draws.
3. Housing requirements not respected (n=4)
    a. Subjects were to be admitted to the clinical research unit at least 15 hours prior to drug administration. However, the following occurred for Subject (b) (6): In Period 3, Subject checked in approximately 14 hours and 40 minutes before dosing due to non-compliance.
    b. Subjects were to be admitted to the clinical research unit at least 15 hours prior to drug administration. However, the following occurred for Subject (b) (6): In Period 2, Subject checked in approximately 14 hours and 16 minutes before dosing due to non-compliance. In Period 3, Subject checked in approximately 14 hours and 19 minutes before dosing due to non-compliance.
    c. Subjects were to be admitted to the clinical research unit at least 15 hours prior to drug administration. However, the following occurred for Subject (b) (6): In Period 2, Subject checked in approximately 14 hours and 41 minutes before dosing due to non-compliance. In Period 3, Subject checked in approximately 14 hours and 43 minutes before dosing due to non-compliance.
    d. Subjects were to be admitted to the clinical research unit at least 15 hours prior to drug

administration. However, the following occurred for Subject (b) (6): In Period 3, checked in approximately 13 hours and 51 minutes before dosing due to non-compliance.

4. Concomitant medication restriction not followed (n=2)
    a. Subjects were prohibited from taking any over-the-counter (OTC) products for 7 days prior to Period 1 check-in and throughout the study. However, the following medication intake occurred due to Adverse Event: Subject (b) (6) was given 2 X 500 mg Acetaminophen at 14:06 on (b) (6) (6hr 4mins post-dose), 18:56 on (b) (6) (10 hrs 54 mins post-dose), 22:37 on (b) (6) (14hrs 35mins post-dose), 03:16 on (b) (6) (19hrs 14 mins post-dose).
    b. Subjects were prohibited from taking any over-the-counter (OTC) products for 7 days prior to Period 1 check-in and throughout the study. However, the following medication intake occurred due to Adverse Event: Subject (b) (6) was given 2 X 500 mg Acetaminophen at 01:24 on (b) (6) (6hr 41 mins prior to first dose).

Table of Demographic Characteristics

The demographics of the study subjects are presented in Table 18.

Table 18. Summary of Subject Demographics (PK Population [n =35], Study V0112502)

Parameter	Mean (SD)	Range	Median
Age (years)	54.3 (3.98)	47, 60	56.0
Weight (kg)	78.67 (10.173)	57.5, 98.0	77.0
Height (cm)	174.05 (6.890)	162.1, 191.6	172.70
BMI (kg/m^2)	25.92 (2.427)	20.2, 29.3	26.70

Source: NDA 215423, Module 5.3.1.2, Study Report V0112502, Table 14.1.2.2, p. 52.

***Reviewer's Comment**: The subjects studied were representative of the patient population expected to use Entadfi.*

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Other baseline characteristics such as smoking status, alcohol use and baseline medical history are not expected to have a significant effect on the outcome of the study.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

During the study, the investigational products were administered according to protocol for all subjects. One subject received concomitant medication during the study. The subject received acetaminophen for back pain after administration of Treatment-3 in Period 1. Applicant assessed the impact of the administration of this medication and concluded that it had no impact on the PK evaluation of the study. No rescue medications were used during this study.

Efficacy Results – See Section 6

Bioequivalence was established between Entadfi and finasteride 5 mg tablet co-administered with tadalafil 5 mg tablet in the fasted state.

Data Quality and Integrity

The submission is of acceptable quality and no concerns have been raised about the integrity of the processes that were used by the Applicant to generate this submission.

Efficacy Results – Secondary and other relevant endpoints

There were no secondary efficacy endpoints in this Phase 1 study.

Dose/Dose Response

No dose response analysis was conducted during this study.

Durability of Response

Durability of response was not assessed during this study.

Persistence of Effect

Persistence of effect was not assessed during this study.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Secondary or exploratory COA (PRO) endpoints were not assessed during this study.

Additional Analyses Conducted on the Individual Trial

There were no additional analyses on this trial.

8.1.3. Assessment of Efficacy Across Trials

This application included one study (Study V0112502).

Primary Endpoints

Not applicable to this application.

Secondary and Other Endpoints

Not applicable to this application.

Subpopulations

Not applicable to this application.

Additional Efficacy Considerations

Not applicable to this application.

8.1.4. Integrated Assessment of Effectiveness

There was only one study (Study V0112502) and no integrated assessment of effectiveness is warranted.

8.2. Review of Safety

8.2.1. Safety Review Approach

Entadfi is a fixed dose combination drug product consisting of tadalafil 5 mg and finasteride 5 mg. The safety of Entadfi was not evaluated in a clinical trial. Instead, the safety of the drug product was established by demonstrating its bioequivalence to coadministration of separate tablets of the listed drugs, Cialis (5 mg tadalafil) and Proscar (5 mg finasteride), in the comparative bioavailability (BA)/bioequivalence (BE) study V0112502.

Co-administration of Cialis (tadalafil) 5 mg and finasteride 5 mg for the initiation of treatment of BPH was approved in October 2013 under NDA 021368/Supplement 022. Co-administration of the drugs was evaluated in a double-blind, parallel-design, 26 week study that randomized 696 men with an enlarged prostate to initiate either Cialis 5 mg with finasteride 5 mg or placebo with finasteride 5 mg. The study population had a mean age of 64 years (range 46-86). Patients with multiple co-morbid conditions such as erectile dysfunction, diabetes mellitus, hypertension, and other cardiovascular disease were included in the study.

A study showing that Entadfi is bioequivalent to coadministration of Cialis (tadalafil) 5 mg and Proscar 5 mg provides reasonable support for the conclusion that Entadfi is safe for the initiation of treatment of men with BPH for 26 weeks.

8.2.2. Review of the Safety Database

Overall Exposure

Exposure to Entadfi
The Applicant conducted a single Phase 1 comparative BA/BE study (Study V0112502) to support marketing approval of Entadfi. The study enrolled 36 healthy male subjects (mean age 54.4 years [range: 47 to 60 years]). The safety database included all 36 subjects.

In Study V0112502, 35 subjects were exposed to Entadfi in the fasted state, 35 subjects were exposed to Entadfi in the fed state, and 31 subjects were exposed to Cialis 5 mg and Proscar 5 mg administered together. Subjects were exposed to a single dose of investigational product or control product in each period.

Adequacy of the safety database:

Exposure to Entadfi is limited to the 36 subjects in the comparative BA/BE study (Study V0112502). However, because this study demonstrated that Entadfi taken when fasted was BE to coadministration of Proscar 5 mg and Cialis 5 mg (the listed drugs), it established a scientific bridge to both of these drugs. Therefore, reliance on safety information for the LDs is appropriate and the safety database is considered adequate.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The submission is of acceptable quality and no concerns have been raised about the integrity of the processes that were used by the Applicant to generate this submission.

Categorization of Adverse Events

Adverse events were coded using the MedDRA version 23.1 and summarized for the number of subjects reporting the adverse event. A by-subject adverse event data listing including verbatim term, coded term, and severity were provided.

Routine Clinical Tests

Table 19. Routine Clinical Tests

Chemistry	Endocrinology	Hematology	Serology
Alanine aminotransferase	Prostate specific	Basophils	Hepatitis B virus
Albumin	Antigen	Eosinophils	Surface antigen
Alkaline phosphatase		Ery. Mean	Hepatitis C virus
Bilirubin		Corpuscular Vol	Antibody
Chloride		Erythrocytes	HIV-1/2
Creatinine		Hematocrit	Antigen/Antibody
Glucose		Hemoglobin	
Potassium		Leukocytes	
Sodium		Lymphocytes	
		Monocytes	
		Neutrophils	
		Platelets	

Clinical laboratory testing: Clinical chemistry (blood chemistry), endocrinology, and hematology analyses were conducted at Screening, at check-in of Period 2 (Day 14) and Period 3 (Day 28) and study exit (Day 33). Serology was conducted at Screening.

In addition to the above tests, routine urinalysis was conducted at Screening and study exit (Day 33) and drug screen was performed during Screening. Subjects were also tested for COVID-19 and their test had to be negative in order to participate in the study.

The routine clinical testing in this study is considered adequate.

8.2.4. Safety Results

Deaths

No deaths were reported during this study.

Serious Adverse Events

No serious adverse events were reported during this study.

Dropouts and/or Discontinuations Due to Adverse Effects

Three subjects were discontinued from the study due to an adverse events. Two additional subjects were discontinued from the study due to a positive test for COVID-19.

Subject (b) (6) is a 57 year old white, not Hispanic or Latino male with no relevant medical history disclosed at Screening. No concomitant medications were taken by the subject at study entry. On Day 28, at check-in of Period 3, the subject showed a high creatinine result (175 µmol/L; reference range: 60 to 110 µmol/L) that was considered clinically significant (CS) by the Investigator and led to subject's withdrawal from the study. This CS result was reported as a TEAE of blood creatinine increased, deemed moderate in intensity and possibly related to drug administration using a worst-case scenario approach. The event was resolved approximately 4 days and 14 hours from onset, when a repeat test showed a creatinine value within normal range (108 µmol/L). The subject's creatinine values at Screening and on Day 14 were 102 µmol/L and 113 µmol/L (deemed abnormal-not CS), respectively. The subject received Treatment-1 in Period 1 and Treatment-2 in Period 2. No other TEAEs were experienced by the subject on-study. No concomitant medication was given to the subject during the study.

Reviewer comment*: This subject's increase in creatinine occurred 13 days and 8 hours after his last dose of the drug and resolved 4 days and 14 hours after onset when the test was repeated. Based on the time course of exposure to the drug and resolution of the event, it is unlikely that this event was drug related.*

Subject (b) (6) is a 50 year old white Hispanic or Latino male with no medical history disclosed at Screening. No concomitant medications were taken by the subject at study entry. On Day 28, at check-in of Period 3, the subject showed a high prostate specific antigen (PSA) result (6.80 µg/L; reference range: <2.51 µg/L) that was considered CS by the Investigator and led to subject's withdrawal from the study. This CS result was reported as a TEAE of PSA increased, deemed mild in intensity and possibly related to drug administration using a worst-case scenario approach. The event was resolved approximately 4 days and 16 hours from onset, when a repeat test showed a lower PSA value that was deemed not CS (4.34 µg/L). The subject's PSA values at Screening and on Day 14 were 0.73 µg/L and 0.75 µg/L, respectively. The subject received Treatment-1 in Period 1 and Treatment-2 in Period 2. No other TEAEs were experienced by the subject on-study. No concomitant medication was given to the subject during the study.

Reviewer comment: *This subject's increase in PSA occurred 13 days and 8 hours after his last dose of the drug and resolved 4 days and 16 hours after onset when the test was repeated. Based on the subjects exposure to only two doses of the drug, the time to resolution of the event, and that finasteride is known to decrease PSA, this event was not drug-related.*

Subject (b) (6) is a 60 year old white not Hispanic or Latino male with no relevant medical history disclosed at Screening. No concomitant medications were taken by the subject at study entry. On Day 28, at check-in of Period 3, the subject showed a high creatinine result (135 µmol/L; reference range: 60 to 110 µmol/L) that was considered CS by the Investigator and led to subject's withdrawal from the study. This CS result was reported as a TEAE of blood creatinine increased, deemed mild in intensity and unrelated to drug administration. This TEAE was reviewed by the Principal Investigator following database lock and it was concluded that its causality assessment was not consistent with the clinical research unit's standards for causality assessment; the TEAE should have been assessed as possibly related to study drug using the standard worst-case scenario approach. This update in causality was made to the subject's source documents; however, the database was not unlocked to reflect this change as this clarification was judged sufficient for the purposes of this study. The event was resolved approximately 15 hours from onset, when a repeat test showed a creatinine value within normal range (94 µmol/L). The subject's creatinine values at Screening and on Day 14 were 80 µmol/L and 91 µmol/L, respectively. The subject received Treatment-1 in Period 1 and Treatment-2 in Period 2. No other TEAEs were experienced by the subject on-study. No concomitant medication was given to the subject during the study.

Reviewer comment*: This subject's increase in creatinine occurred 13 days and 8 hours after his last dose of the drug and resolved 15 days after onset when the test was repeated. Based on the time course of exposure to the drug and resolution of the event, it is unlikely that this event was drug related.*

Significant Adverse Events

No significant adverse events were reported during this study.

Treatment Emergent Adverse Events and Adverse Reactions

Ten subjects (27.8%) reported a total of 20 TEAEs over the course of the study. Subjects reported AEs with incidences of 5.7%, 20.0%, and 9.7% after administration of Treatment-1, Treatment-2, and Treatment-3, respectively. Drug-related TEAEs were reported with incidences of 2.9%, 17.1%, and 9.7% for subjects dosed with Treatment-1, Treatment-2, and Treatment-3, respectively.

The TEAEs experienced during the study were deemed mild (13/20; 65.0%) and moderate (7/20; 35.0%) in intensity. None of the subjects experienced a severe TEAE during the study.

Table 20 provides an overview of TEAEs by the treatment received.

Table 20. Overview of Treatment Emergent Adverse Events

Parameter	Treatment-1 (N=35)	Treatment-2 (N=35)	Treatment-3 (N=31)	Overall (N=36)
AEs reported (n)				22
TEAEs reported (n)	2	14	4	20
Subjects with at least one TEAE (n [%])[a]	2 (5.7)	7 (20.0)	3 (9.7)	10 (27.8)
Subjects with at least one drug-related TEAE (n [%])[a, c]	1 (2.9)	6 (17.1)	3 (9.7)	8 (22.2)
TEAEs relationship[b]				
Related (n [%])[c]	1 (50.0)	12 (85.7)	4 (100.0)	17 (85.0)
Unrelated (n [%])	1 (50.0)	2 (14.3)	0	3 (15.0)
TEAEs intensity[b]				
Mild (n [%])	2 (100.0)	8 (57.1)	3 (75.0)	13 (65.0)
Moderate (n [%])	0	6 (42.9)	1 (25.0)	7 (35.0)
Severe (n [%])	0	0	0	0
SAEs reported (n)[b]	0	0	0	0
Subjects with at least one SAE (n [%])[a]	0	0	0	0
Subjects with at least one drug-related SAE (n [%])[a, c]	0	0	0	0
Subjects with any TEAE leading to study investigational product withdrawal (n [%])[a]	1 (2.9)	4 (11.4)	0	5 (13.9)
Deaths (n [%])[a]	0	0	0	0

Abbreviations: AE =adverse event; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
N = number of subjects who received the specified treatment
Treatment-1 = Tadfin Combination Capsule (fasting); Treatment-2 = Tadfin Combination Capsule (fed);
Treatment-3 = Cialis and Proscar administered at the same time (fasting)
a. Percentages are based on the number of subjects in the safety population in each treatment group.
b. Percentages are based on the total number of TEAEs reported in each treatment group.
c. TEAE was reported as: definitely related, probably related, or possibly related.
Source: NDA 215423 (SDN 001), Module 5.3.1.2, Table 14.3.1.1.

The TEAEs reported in this study were most commonly from the Musculoskeletal and Connective Tissue Disorders system organ class (SOC) (8.6% for Treatment-2 and 9.7% for Treatment-3).

The TEAEs reported most commonly in this study were back pain and headache, each reported by 2 subjects (5.7%) after administration of Treatment-2 and 1 subject (3.2%) after administration of Treatment-3. Other TEAEs reported less frequently includ blood creatinine increased, reported by 2 subjects (5.7%) after administration of Treatment-2; arthralgia, reported by 1 subject (2.9%) after administration of Treatment-2 and 1 subject (3.2%) after administration of Treatment-3; COVID-19, reported by 1 subject (2.9%) after administration of Treatment-1 and 1 subject (2.9%) after administration of Treatment-2. The remaining TEAEs were experienced by 1 subject (3.2 or 2.9%) in either one of the treatment groups. A total of 20

TEAEs were experienced by 10 of the 36 subjects (27.8%) who participated in this study. Of these TEAEs, 2 occurred after administration of Treatment-1, 14 after administration of Treatment-2, and 4 after administration of Treatment-3. Most of the TEAEs experienced during the study were considered drug-related by the investigator (17/20; 85.0%). All TEAEs experienced during the study were resolved by the end of the study.

Two of the 35 subjects (5.7%) who received Treatment-1 reported 2 TEAEs: COVID-19 and constipation. Constipation was considered possibly related to drug administration while COVID-19 was considered unrelated. Both TEAEs were deemed mild in intensity.

Seven of the 35 subjects (20.0%) who received Treatment-2 reported 14 TEAEs, the most common of which were back pain, blood creatinine increased, and headache (2 subjects each; 5.7%). Most of these TEAEs were considered related to drug administration (12/14; 85.7%). The TEAEs were deemed mild (8/14; 57.1%) and moderate (6/14; 42.9%) in intensity.

Three of the 31 subjects (9.7%) who received Treatment-3 reported 4 TEAEs: back pain, arthralgia, muscular weakness, and headache (1 subject each; 3.2%). All TEAEs were considered related to drug administration. All TEAEs were deemed mild in intensity, with the exception of back pain that was deemed of moderate intensity.

Table 21 summarizes the TEAEs reported in the study.

Table 21. Summary of Treatment-Emergent Adverse Events by SOC and Preferred Term

SOC, n(%) MedDRA PT, n(%)	Treatment-1 (N=35)	Treatment-2 (N=35)	Treatment-3 (N=31)
Musculoskeletal and connective tissue disorders	**0**	**3 (8.6)**	**3 (9.7)**
Back pain	0	2 (5.7)	1 (3.2)
Arthralgia	0	1 (2.9)	1 (3.2)
Muscular weakness	0	0	1 (3.2)
Myalgia	0	1 (2.9)	0
Pain in extremity	0	1 (2.9)	0
Investigations	**0**	**3 (8.6)**	**0**
Blood creatinine increased	0	2 (5.7)	0
Prostatic specific antigen increased	0	1 (2.9)	0
Nervous system disorders	**0**	**2 (5.7)**	**1 (3.2)**
Headache	0	2 (5.7)	1 (3.2)
Dizziness	0	1 (2.9)	0
Infections and infestations	**1 (2.9)**	**1 (2.9)**	**0**
COVID-19	1 (2.9)	1 (2.9)	0
Gastrointestinal disorders	**1 (2.9)**	**0**	**0**
Constipation	1 (2.9)	0	0
General disorders and administration site conditions	**0**	**1 (2.9)**	**0**
Fatigue	0	1 (2.9)	0
Psychiatric disorders	**0**	**1 (2.9)**	**0**
Insomnia	0	1 (2.9)	0

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class; TEAE =treatment-emergent adverse event.
Note: Each TEAE was counted only once for each subject within each SOC and MedDRA PT.
Treatment-1 = Tadfin Combination Capsule (fasting); Treatment-2 = Tadfin Combination Capsule (fed);
Treatment-3 = Cialis and Proscar administered at the same time (fasting)
Source: NDA 215423 (SDN 001), Module 5.3.1.2, Table 14.3.1.2.

Laboratory Findings

Except for the three subjects who had abnormal values for creatinine (2 subjects) and PSA that were considered clinically significant (see *Dropouts and/or Discontinuations Due to Adverse Effects*), no other abnormal laboratory values reported during the study were considered clinically significant.

Vital Signs

No clinically significant abnormal findings in vital signs were reported during the study.

Electrocardiograms (ECGs)

ECGs were assessed at Screening, check-in for Period 2 (Day 14), check-in for Period 3 (Day 28), and the End of Study Visit. No abnormal ECG recordings were reported during the study.

QT

No studies to evaluate Entadfi's effect on QT were submitted to support this application.

Immunogenicity

No immunogenicity studies were submitted to support this application.

8.2.5. Analysis of Submission-Specific Safety Issues

Entadfi demonstrated bioequivalence to coadministered Cialis (5 mg tadalafil) and Proscar (5 mg finasteride) tablets under the fasted condition only. When Entadfi was administered with food, the C_{max} of tadalafil and finasteride was reduced by 23% and 29%, respectively. Therefore, Entadfi will be labeled for administration without food.

Because both Cialis and Proscar are labeled for administration without regard to food and Entadfi is to be administered without food it raises the possibility of inadvertent administration of Entadfi with food. However, since the C_{max} for the component drugs is reduced when Entadfi is administered with food, taking Entadfi with food would not pose a safety risk.

Therefore, no new safety concerns were identified during Study V0112502.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Clinical Outcome Assessment (COA) analyses informing safety or tolerability were not conducted for this application.

8.2.7. Safety Analyses by Demographic Subgroups

The Applicant did not conduct any safety analyses by demographic subgroups.

8.2.8. Specific Safety Studies/Clinical Trials

Specific safety studies or clinical trials were not submitted to support this application.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No information on human carcinogenicity or tumor development was submitted with this application.

Human Reproduction and Pregnancy

Entadfi is not indicated for females, therefore, no reproduction or pregnancy data were submitted with this application. Because finasteride may cause fetal harm, product labeling will contraindicate Entadfi in females who are pregnant and warn that pregnant females should not handle crushed or broken Entadfi capsules.

Pediatrics and Assessment of Effects on Growth

Entadfi is indicated for adult males and has not been evaluated in males less than 18 years of age.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No information on overdose, drug abuse potential, withdrawal, and rebound was submitted with this application.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Entadfi is a new product, therefore, there is no postmarketing experience with the product. However, the Applicant conducted a search of the FAERS database to identify safety information on the combination of tadalafil and finasteride. The search focused on the 7.25-year period of 2014 to 31 March 2021 to capture safety events that occurred after the Cialis labeling was updated to include coadministration of tadalafil and finasteride.

Few adverse events were reported between 2014 and 2021 for the combination of tadalafil and finasteride. Among the 11 cases reported, six were serious and there were three deaths. Among the 3 subjects who died, one male in Britain used the combination for BPH, LUTS and prostatomegaly, and two males in Israel used the combination for alopecia or an unknown indication.

No new safety signals were identified from this postmarketing database search.

Expectations on Safety in the Postmarket Setting

Safety in the postmarket setting is expected to be similar to that of coadministered tadalafil 5 mg and finasteride 5 mg.

8.2.11. Integrated Assessment of Safety

This ISS includes safety information from the single Applicant-conducted Phase 1 comparative BA/BE study (Study V0112502), published literature, the FDA's Adverse Event Reporting System (FAERS), and the approved product labeling of Cialis and Proscar (the LDs). No new safety findings were noted.

Study V0112502

A detailed discussion of this study is provided in Section 8.1.1. The safety data for this study do not raise any new safety concerns for Entadfi. Detailed safety results for this study are presented in Section 8.2.4.

Published Literature

The Applicant conducted a PubMed search using the terms “tadalafil,” “finasteride,” and “BPH” with limits “humans” to identify published studies with efficacy and safety information related to the proposed indication (BPH) for the tadalafil/finasteride combination. The date range limits of 01 January 2016 to 14 May 2021 for tadalafil and 01 January 2013 to 14 May 2021 for finasteride were used. The most recent updates to the LD approved labeling are February 2018 for tadalafil and April 2021 for finasteride.

In the 16 studies identified in the search, 345 patients were exposed to 5 mg tadalafil/5 mg finasteride in combination, 3049 patients were exposed to 5 mg or 20 mg tadalafil, and 13171 patients were exposed to 0.01 mg to 5 mg finasteride (or an unknown amount of finasteride). In general, the AEs reported in the studies in the published literature were similar to those reported in the Cialis (tadalafil) and Proscar (finasteride) approved labeling. Adverse events for tadalafil/finasteride in combination were mild to moderate in severity and included ED, decreased libido, and ejaculation disorders. Patients treated with tadalafil reported back pain, dizziness, headache, nasopharyngitis, insomnia, diarrhea, myalgia and patients treated with finasteride reported sexual dysfunction, blurred vision, and osteoporosis. Safety findings from this literature search are summarized below in Table 22.

The safety findings from the published literature do not raise any new safety concerns for coadministration of finasteride and tadalafil.

Table 22. Exposure and Safety Data for Tadalafil and Finasteride in Patients With BPH From the Published Literature

Reference	Treated Population	Dose	Treatment Duration	Safety Findings
Tadalafil/Finasteride in Combination				
(Casabé et al., 2014; Glina et al., 2015; Roehrborn et al., 2015) RCT	Men 45 years old or older with BPH-LUTS for more than 6 months	• Finasteride 5 mg qd, 26 weeks (n = 350) • Tadalafil 5 mg/finasteride 5 mg, qd, 26 weeks (n = 345)	Up to 26 weeks	A total of 108 patients on tadalafil/finasteride (31.3%) and 95 on finasteride + placebo (27.1%) reported 1 or more TEAEs. Most TEAEs were mild to moderate in severity. In addition, the incidences of SAEs and discontinuations due to AEs were low, and were not significantly different between treatment groups. Overall 5 patients on finasteride + placebo reported ED as an adverse event compared to 1 patient on tadalafil/finasteride. Five patients on finasteride + placebo also reported decreased or lost libido while no patients on tadalafil/finasteride reported this event. Two patients on tadalafil/finasteride experienced ejaculation delay/failure while no patients on finasteride + placebo reported adverse ejaculation issues. No clinically meaningful AEs were observed in vital signs or clinical laboratory measures. The incidence of sexual AEs was low: A total of 12 patients (1.7%) reported AEs related to sexual dysfunction in the study. Five tadalafil/finasteride patients and seven placebo/finasteride patients reported sexual AEs, including ED, decreased/lost libido, and ejaculation disorders.
Tadalafil				
(Oelke et al., 2017) (International) RCT	Men aged < or ≥75 years with LUTS/BPH and additional safety in men aged ≥75 years with erectile dysfunction (ED). <75 years: n = 1662 ≥75 years: n = 154	• 5 mg tadalafil, qd	• short-term (12–26 weeks) • longer-term (42–52 weeks)	• Summary: for men <75 and ≥ 75 include: TEAEs (52 [33.8%] vs 503 [30.1%]), AEs leading to discontinuation (3 [1.9%] vs 50 [3.0%]), SAEs (4 [2.6%] vs 15 [0.9%]) and cardiovascular AEs (4 [2.6%] vs 30 [1.8%]). Long-term tadalafil safety data did not reveal clinically relevant differences between age groups • **Summary Week 0-12**: Among men aged ≥75 years, five (3.2%) in the tadalafil group reported dizziness as a TEAE. One tadalafil-treated man had treatment emergent orthostasis. At least 1 cardiovascular TEAE in tadalafil-treated men was reported for 4 men (2.6%) aged ≥75 years and 30 men (1.8%) aged <75 years. For men aged ≥75 years, 4 (2.6%) SAEs occurred in tadalafil-treated men. SAEs reported were myocardial infarction, coronary artery disease, renal cancer, and femur fracture. Small mean decreases in diastolic and systolic blood pressure were observed for tadalafil-treated men in both age groups. • **Summary Week 12-42/52:** The most common TEAEs (≥3%) in men aged ≥75 years were insomnia, diarrhea, nasopharyngitis and osteoarthritis. For the ≥75-year age group, osteoarthritis (n = 2) and one each of atrial fibrillation, back pain, benign lung neoplasm, congestive heart failure, acute cholecystitis, colonic polyps, fibula fracture, hip arthroplasty, cholestatic jaundice, myocardial infarction, pancreatic carcinoma, renal cancer and urinary retention were all reported. • **Individual TEAE:** n, (%) **<75 years** Out of 1662: Diarrhea: 17 (1%), Nasopharyngitis 43 (2.6), Dizziness 11 (0.7), Cough 9 (0.5), Headache 75 (4.5), Back pain 40 (2.4), Dyspepsia 52 (3.1), Dyspnoea 3 (0.2), Fall 2 (0.1), Micturition urgency 1 (0.1), Nocturia 1 (0.1), Pain extremity 21 (1.3), PSA increased 1 (0.1), Vomiting 5 (0.3), Abdominal pain 3 (0.2), Abdominal pain upper 11 (0.7), Acute myocardial infarction 0 (0), Angina pectoris 0 (0).

Reference	Treated Population	Dose	Treatment Duration	Safety Findings
				>/-75 years Out of 154: Diarrhea: 7 (4.5%), Nasopharyngitis 7 (4.5), Dizziness 5 (3.2), Cough 3 (1.9), Headache 3 (1.9), Back pain 2 (1.3), Dyspepsia 2 (1.3), Dyspnoea 2 (1.3), Fall 2 (1.3), Micturition urgency 2 (1.3), Nocturia 2 (1.3), Pain extremity 2 (1.3), PSA increased 2 (1.3), Vomiting 2 (0.3), Abdominal pain 1 (0.6), Abdominal pain upper 1 (0.6), Acute myocardial infarction 1 (0.6), Angina pectoris 1 (0.6). • Discontinuation due to AE: n (%) <75 years: 50 (3) >/-75 years: 3 (1.9) • **SAE n (%)** <75 years: 15 (0.9) >/-75 years: 4 (2.6)
(Karami et al., 2016) (Iran) RCT	Men with BPH and ED	• Tadalafil 20 mg, qd (n = 60) • Tadalafil 20 mg/tamsulosin 0.4 mg, qd (n = 58)	3 months	The most frequent complications in all of participants were back pain (4.5%) and myalgia, headache, and discontinuation because of AEs (3.9% for each). Despite of higher complication rate in tadalafil/tamsulosin group, there was no significant difference between the three groups in this regard. Drug related complications among the groups were: • Mylagia, N(%): tadalafil 3(5); tadalafil/tamsulosin 4(6.7) • Headache, N(%): tadalafil 3(5); tadalafil/tamsulosin 3(5) • Back pain, N(%) tadalafil 4(6.6); tadalafil/tamsulosin 3(5) • Nasopharyngitis, N (%): tadalafil 2(3.3); tadalafil/tamsulosin 3(5) • Dizziness, N(%): tadalafil 1(1.6); tadalafil/tamsulosin 2(3.3) • Discontinuation due to AE, N(%) tadalafil 1(1.6); tadalafil/tamsulosin 3(5)
(Roehrborn et al., 2016) (USA) RCT	Men aged ≥45 years randomized to tadalafil 5 mg once daily or placebo enrolled in one of four randomized, placebo-controlled LUTS/BPH clinical trials (n=467)	• 5 mg tadalafil, qd	12 weeks	Adverse effects related to tadalafil were not reported in this study that analyzes combined improvement in symptoms.
(Matsukawa et al., 2018; Matsukawa et al., 2019) (Japan) Open-label Trial	Men between 51 to 83 years with complaints of storage and voiding LUTS received tadalafil 5 mg once daily (n = 105)	• 5 mg tadalafil, qd	12 weeks	Of 105 patients, five patients (4.8%) discontinued treatment due to adverse reactions: headache (n = 2), problem on erection (n = 2), dizziness (n = 1). Two patients developed urinary retention during the study period.
(Takahashi et al., 2018)	Men ≥45 years who had not	• 5 mg tadalafil, qd	12 weeks	There were no clinically severe AEs in this study. Of 35 patients, four patients discontinued due to AEs (reasons:

Reference	Treated Population	Dose	Treatment Duration	Safety Findings
(Japan) Open-label Trial	been treated with alpha blockers for BPH and had a total IPSS ≥8, IPSS-QoL ≥2 and prostate volume ≥20mL (n = 35)			headache, dizziness, dyspepsia, and erectile enhancement at night). The most common AEs were headache (n = 3) and/or back pain (n = 3), dizziness (n =1), and dyspepsia (n = 2).
(Zhang et al., 2019) (China, Taiwan, Korea) RCT	Men 45 to 81 years with LUTS associated with BPH and ED (n = 362)	• 5 mg tadalafil, qd • Placebo, qd • 0.2 mg tamsulosin, qd	12 weeks	The only TEAE reported in ≥2% of patients in the tadalafil 5 mg group was nasopharyngitis (n=8, 2.2%). Other TEAEs were dizziness (n=3, 0.8%), and back pain (n=6, 1.7%). Overall, 65 patients receiving tadalafil experienced a TEAE, which was not statistically significant from the placebo group. The majority of reported TEAEs were mild or moderate severity and the safety results for tadalafil were consistent with the known tadalafil safety profile.
(Matsumoto et al., 2019) (Japan) RCT, Open-label	Men with BPH/LUTS, mean age 77 years (n = 34)	• 5 mg tadalafil, qd	12 weeks	No harmful effects were observed in patients switching from dutasteride to tadalafil.
(Yamanishi et al., 2020) (Japan) RCT	Male patients with LUTS, aged from 50 to 89 years (n = 87)	• 5 mg tadalafil, qd • 5 mg/50 mg tadalafil/mirabegron, qd	12 weeks	One moderate adverse event (1.1%; 1/87) was noted in the tadalafil group: pain in the left hip joint due to pseudogout, presumably hardly related to study treatment.
(Sebastianelli et al., 2021) (Multiple countries) Prospective, Observational	Male patients with ED and LUTS aged from 48 to 77 years (n=50 for combination therapy, 25 for monotherapy)	• 5 mg tadalafil/0.4 mg tamsulosin, qd for 12 weeks, THEN • 5 mg tadalafil, qd • 0.4 mg tamsulosin, qd	12 weeks of combination therapy, 12 weeks of monotherapy	The proportion of patients reporting at least one treatment-emergent AE (TEAE) was similar between groups (tadalafil: 16% vs tamsulosin: 20%). TEAEs were mild to moderate in severity, with the most common being headache and back pain. There were no clinically significant changes in laboratory measurements or vital signs. No urinary retention was reported. None of the patients discontinued therapy because of a TEAE. For tadalafil monotherapy, 2 patients (8%) had headache, 1 patient (4%) had back pain, and 1 patient (4%) had dyspepsia.
Finasteride				
(Unger et al., 2016) (USA) Retrospective analysis	Men age ≥55 years, with normal digital rectal examination and prostate-specific antigen (PSA) of ≤3.0 ng/mL. (n = 6941)	• Finasteride, qd • Placebo, qd	7 years	• Finasteride patients had a 10% higher risk of new claims for depression and a 6% lower risk of procedures for BPH-related events (primarily lower urinary tract symptoms; HR=0.94, 95% CI=0.89 to 1.00, P=0.03). • Most common adverse effects were sexual dysfunction and gynecomastia. • Commonly recorded events were endocrine (76.4%), especially hypercholesterolemia (67.3%), BPH-related events (36.5%), and diabetes (28.4%). • Bone-related events were also common, with 10.7% of men diagnosed with osteoporosis and 11.6% having a fracture. • 21.7% of men experienced ischemic or thrombotic events over the follow-up period, including 9.1% identified as having ischemic heart disease.

Reference	Treated Population	Dose	Treatment Duration	Safety Findings
(Liu et al., 2016) Meta-analysis	Men with BPH or AGA treated with 5α-reductase inhibitors	• finasteride 0.01, 0.05, 0.2, 1, or 5 mg/day	1.4–24 months	Evidence from the randomized controlled trials suggested that 5ARIs were associated with increased adverse effects on sexual function in men (erectile dysfunction, decreased libido) with BPH compared with placebo.
(Khwaja et al., 2016) (Pakistan) RCT	Patients with BPH planned for TURP having prostate size of >40 grams ranging from 48 to 86 years (n = 40)	• 5 mg oral finasteride, qd	2 weeks	No adverse effects or side effects were reported in this article.
(Gupta et al., 2016) (India) Case Report	Case report of a 33-year-old male	• 1 mg finasteride, qd	Treatment started in Oct 2014, but there is no clear indication as to when it was stopped.	• Adverse effects such as itching, burning micturition, abdominal discomfort, skin rash, and seborrhea was observed as soon as he was prescribed finasteride. The symptoms did not subside with exercise and were irreversible. The patient was hence labeled as "Atypical postfinasteride syndrome (PFS)". • Although hemogram tests were all normal, semen analysis had pus cells and semen culture showed moderate growth of *Enterococcus faecalis*.
(Nguyen et al., 2021) (153 countries) Pharmacovigilance Case-Noncase Design	Users of finasteride for any indication (n = 3282, of which 141 took finasteride for BPH)	• Not stated	Not stated	• In this pharmacovigilance case-noncase study, significant reporting odds ratio (ROR) of suicidality and psychological adverse events were associated with finasteride use in patients younger than 45 years who used finasteride for alopecia. • These signals for suicidality and psychological adverse events were not detected in older patients with BPH.
(Zhu et al., 2021) (New York, USA) Retrospective Analysis	Men with BPH, mean age 70 years (n = 5698)	• Not stated	Not stated	• Men who took finasteride had a lower risk of developing bladder cancer (BCa) compared to men who did not. • When the results are stratified by race and ethnicity, it was found that Caucasian and Hispanic men who took finasteride had a lower risk of developing BCa compared to finasteride non-users. • However, African American men who took finasteride did not experience a lower risk of developing BCa compared to finasteride non-users. • There were also reductions in the risk of high grade BCa and non-muscle invasive BCa among finasteride users compared to non-users.
Total Exposed to Tadalafil/Finasteride in Combination				345
Total Exposed to Tadalafil				3049
Total Exposed to Finasteride				13171

5ARI = 5α –reductase inhibitor; AE = adverse events; AGA = androgenetic alopecia; BCa = bladder cancer; BPH = benign prostatic hyperplasia;CI = confidence interval; ED = erectile dysfunction; LUTS = lower urinary tract symptoms; ns= not specified; HR = hazard ratio; PFS = postfinasteride syndrome; PSA = prostate-specific antigen; qd = once daily; RAPD = relative afferent pupillary defect; RCT = randomized controlled trial; ROR = reporting odds ratio; SAE = serious adverse event; TEAE = treatment emergent adverse event.

Source: NDA 215423 (SDN 008), Module 5.3.5.3, ISS Table 8.

Adverse Events Reported to FAERS for Coadministration of Finasteride and Tadalafil

The Applicant conducted a search of the FAERS database to identify safety information on coadministration of finasteride and tadalafil. The results of this search are presented in Section 8.2.10.

8.3. Statistical Issues

None identified.

8.4. Conclusions and Recommendations

Entadfi (finasteride 5 mg/ tadalafil 5 mg), fixed dose combination capsule is bioequivalent to the coadministration of tadalafil 5 mg and finasteride 5 mg in the fasted state. As such, therapeutic equivalence and safety between Entadfi and the coadministration of the two drugs have been established for the initiation of treatment of symptomatic BPH in men with an enlarged prostate for up to 26 weeks. There were no unexpected safety findings in the single clinical study (V0112502) supporting this NDA.

The review team recommends approval of NDA 215423.

9. Advisory Committee Meeting and Other External Consultations

This product was not discussed at an Advisory Committee meeting. There were no issues that required external expert input.

10. Pediatrics

This product is granted a full PREA waiver for all pediatric subgroups because BPH does not occur in these subgroups.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information

Indication
ENTADFI is indicated to initiate the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH) in men with an enlarged prostate for up to 26 weeks.

Limitations of Use
ENTADFI is not recommended for more than 26 weeks because the incremental benefit of tadalafil decreases from 4 weeks until 26 weeks, and the incremental benefit beyond 26 weeks is unknown

Dosage Administration
Take Entadfi (b) (4).

In general the label for Entadfi will mirror the labels of Cialis and Proscar.

12. Risk Evaluation and Mitigation Strategies (REMS)

No Risk Evaluation and Mitigation Strategies were needed for this application.

13. Postmarketing Requirements and Commitment

No postmarketing requirements or commitments are recommended for this application.

14. Division Director (DHOT) Comments

15. Division Director (OCP) Comments

16. Division Director (OB) Comments

17. Division Director (Clinical) Comments

18. Office Director (or Designated Signatory Authority) Comments

19. Appendices

19.1. References

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19.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): Study V0112502

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 13		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Applicant of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

19.3. Nonclinical Pharmacology/Toxicology

N/A

19.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

19.4.1. Summary of Bioanalytical Method Validation and Performance

The office of Clinical Pharmacology review team has assessed the adequacy and acceptability of the bioanalytical methods used to measure the plasma concentration of tadalafil and finasteride in the clinical study V0112502. The concentrations of tadalafil and finasteride in the huma plasma were determined by a validated HPLC method using MS/MS detection.

The validation and performance results of the bioanalytical method for finasteride and tadalafil are summarized in table 1 and 2, respectively.

Table 23. Summary of Performance of the Bioanalytical Method Used to Measure the Concentration of Finasteride in Human Plasma

Bioanalytical validation method summary	The validation for finasteride included an assessment of specificity, sensitivity, precision, accuracy, matrix effect, linearity, percent extraction yields, dilution integrity, carry over effect, and stability (long-term at -20^{0}C and -80^{0}C, freeze-thaw stability, processed reconstituted stability, shot-term stability at 22^{0}C, solution stability for short and long-term). Thirty-nine validation batches were performed using 4 quality control (QC) concentrations (0.100 ng/mL, 0.300 ng/mL, 12.000 ng/mL, and 60.000 ng/mL).
Method description	Liquid-liquid reversed-phase HPLC with MS/MS detection (detector: MS/MS API3000)
Reference standard	Finasteride (99.7% purity)
Internal Standard (IS)	Finasteride-D9 (98-99.4% purity)
Validation assay range	0.100 ng/mL (LLOQ) – 75.00 ng/mL (ULOQ) in human plasma as biological matrix
Anticoagulant	K2 EDTA
Regression type	The linearity of the calibration curve was determined using a weighted ($1/x^2$) linear regression (y = mx+b) least squares regression analysis for finasteride

Validation parameters	Method validation summary		Acceptability
Specificity	No significant interference observed in the 11 blank matrix lots screened (Blank Lot No.: 0002323752A, 0002323828A, 0002323842A, 0002324462A, 0002323764A, 0002323754A, 0002324488A, 0005528591A, 0002323607A, 0002323594A, 0002323845A) as we as in lipemic (Blank Lot No.: BRH1288682) and hemolyzed (Blank Lot No.: (R2)FNDV0664-02) lots. Assay specificity in the presence of concomitantly administered compounds, such as acetaminophen, acetylsalicylic acid, caffeine, ibuprofen etc., was assessed by adding the compounds to lot of blank matrix. No significant interference at the retention times and mass transitions of finasteride and IS was observed in the blank matrix screened. Assay specificity in the presence of tadalafil was also assessed and found no significant inference.		Acceptable
Carryover	A carryover evaluation was performed by injecting a ULOQ sample followed by the injection of 3 analyte-free samples without IS. This sequence was injected 3 times serially. The presence of interference was verified and compared to an LLOQ sample at the retention times and mass transitions of finasteride. In addition, the interference at the retention time and mass transition of the IS was compared to the mean IS response of evaluable QC samples and non-zero calibrants used to define the curve. No significant interference was observed in all injections of analyte-free samples.		Acceptable
Precision and accuracy	Between-run accuracy	99.9% to 101.3%	Acceptable
	Within-run accuracy	97.7% to 103.9%	Acceptable
	Between-run precision	1.9% to 5.2%	Acceptable
	Within-run precision	1.3% to 5.9%	Acceptable
Matrix effect	Accuracy (% nominal): 104.0% for Low QC and 103.1% for High QC. Precision: 6.2% for Low QC and 2.8% for High QC.		Acceptable
Calibration curve performance among validation batches/ linearity	Cumulative precision (% CV) from LLOQ to ULOQ	≤4.5%	Acceptable
	Cumulative accuracy (% nominal) from LLOQ to ULOQ	98.6% to 103.2%	Acceptable
	Number of standard calibrator	11	Acceptable
Dilution integrity/ Dilution factor	150.000 ng/mL diluted 5-fold. Accuracy (% nominal): 103.9% Precision (%CV): 1.2%		Acceptable
Recovery	Difference between lowest (low QC) and highest (high QC) percent extraction yields for finasteride	77.6% - 88.8% (%CV ≤5.3)	Acceptable
	Percent extraction yields for IS	90.8% (%CV ≤5)	Acceptable

Short-term stability of the stock solution and working solutions	Confirmed up to 25.2 hours for finasteride in MeOH:H_2O 50:50% v/v at 100.00 µg/mL at 22°C nominal. % deviation: 1.4%. Confirmed up to 25.2 hours for finasteride in MeOH:H_2O 50:50% v/v at 0.10 µg/mL at 22°C nominal. % deviation: -0.6%. Confirmed up to 25.2 hours for finasteride-D9 in MeOH:H**2**O 50:50% v/v at 100.00 µg/mL at 22°C nominal. % deviation: -2.1%.	Acceptable
Long-term stability of the stock solution and working solutions	Confirmed up to 63 days for finasteride in MeOH:H_2O 50:50% v/v at 100.00 µg/mL at 4°C nominal. % deviation: 0.2%. Confirmed up to 63 days for finasteride in MeOH:H_2O 50:50% at 0.10 µg/mL at 4°C nominal. % deviation: 0.4%. Confirmed up to 77 days for finasteride-D9 in MeOH:H**2**O 50:50% at 100.00 µg/mL at 4°C nominal. % deviation: -2.1%.	Acceptable
Short-term stability in biological matrix at room temperature or at sample processing temperature	Confirmed up to 24.7 hours at 22°C nominal. Accuracy (% nominal): 99.1% for Low Stability QC and 97.5% for High Stability QC.	Acceptable
Long-term stability in biological matrix	Confirmed up to 686 days at -20°C nominal. Accuracy (%bias): 0.0% for Low Stability QC and -6.1% for High Stability QC. Confirmed up to 9 days at -80°C nominal. Accuracy(% nominal): 102.8% for Low Stability QC and 98.5% for High Stability QC.	Acceptable
Freeze and thaw stability	Four (4) cycles Accuracy (% nominal): 97.9% for Low Stability QC and 98.2% for High Stability QC.	Acceptable

Method performance in bioanalytical study number VRU-P9-797(FND)		
Method Summary		
Reference standard	Finasteride (Purity: 99.7%)	
Internal Standard	Finasteride-d_9 (Purity: 99.1%)	
Stock solution	Stock solutions of finasteride and finasteride-D9 were prepared on 2020/09/25 and stored at 4°C nominal. The stock solution used for standards had a different lot number than the stock solution used for QC samples.	
Standard and quality (QC) samples	In addition to blank and zero standards, 11 non-zero standards and 5 levels of QC samples containing finasteride were prepared on 2020/10/07 with analyte-free human plasma, using K_2EDTA as anticoagulant. Standards and QC samples were stored at -20°C nominal from their preparation until the end of analysis for a maximum of 103 days. The long-term stabilities of 686 days at -20°C nominal, without and in the presence of tadalafil, covered the sample storage duration. Standard concentrations ranged from 0.100 ng/mL (LLOQ) to 75.000 ng/mL (ULOQ). QC sample concentrations were 0.300 ng/mL, 12.000 ng/mL, 22.000 ng/mL, 37.500 ng/mL, and 60.000 ng/mL. In order that QC samples better represent study samples, QC samples also contained the co-administered compound tadalafil, at a concentration of 200.000 ng/mL.	
Method Performance		
Assay passing rate	A total of 26 runs performed. Out of 26 runs, 24 runs (except run number 6 and 20) met the acceptance criteria. Run number 13 was the repeat run for run number 6 (for subjects (b) (6) and (b) (6)) and met acceptance criteria. Run number 20 was not counted for evaluation.	Acceptable
Standard curve performance	Cumulative bias range: -1.7% to 3.1% Cumulative precision: 1.6%-4%	Acceptable
Quality control samples performance	Cumulative bias range: -2.4% to 5% Cumulative precision: 2.4% to 5.7%	Acceptable
Study samples stability	The total duration of the study sample storage was 135 days (2020/09/05 – 2021/01/08), which is covered by the established long-term stability period of 686 days at -20^{0}C in the presence of tadalafil in human plasma.	
Incurred sample reanalysis	At least 10% of the first 1000 analyzable study samples and 5% of the remaining samples were re-assayed and compared to their original values. Cumulative bias range: -13.9% to 10.1% 100% of the samples met the acceptable specifications.	Acceptable

Carryover	The presence or absence of carryover was evaluated prior to the injection of every run using the injection of a high concentration sample (equivalent to the ULOQ concentration) followed by an analyte-free sample, as well as the injection of an LLOQ sample. Furthermore, carryover was continuously monitored within every run, when applicable, using the results of the analyte-free samples in each run, which were always injected following a ULOQ standard, both at the beginning and end of the injection sequence. The analyte response of the analyte-free sample was ≤20.0% of the analyte response of the LLOQ, and/or the IS response was ≤5% of the IS response of the LLOQ for all accepted runs except two runs (run 5 and 7). In run 5, no quantifiable study sample was affected by the carryover. In run 7, two quantifiable pre-dose (time zero) study samples were affected by carryover and subsequently they were repeated in duplicate and found acceptable limit.

Table 24. Summary of Performance of the Bioanalytical Method Used to Measure the Concentration of Tadalafil in Human Plasma

Bioanalytical validation method summary	The bioanalytical method validation study for the determination of tadalafil included an assessment of specificity, sensitivity, precision, accuracy, matrix effect, linearity, percent extraction yields, dilution integrity, carry over effect and stability (long-term at -20^{0}C and -80^{0}C, freeze-thaw stability, processed reconstituted stability, shot-term stability at 22^{0}C, solution stability for short and long-term). Twenty-three validation batches were performed using 5 quality control (QC) concentrations (0.500 ng/mL, 1.500 ng/mL, 30.000 ng/mL, 100.000 ng/mL, and 150.000 ng/mL).
Method description	Protein precipitation Reversed-phase HPLC with MS/MS detection (detector: MS/MS API5000)
Reference standard	Tadalafil (99.9% purity)
Internal Standard (IS)	Tadalafil-d_3-^{13}C2 (100% purity)
Validation assay range	0.5 ng/mL (LLOQ) – 200.00 ng/mL (ULOQ) in human plasma as biological matrix
Anticoagulant	K_2EDTA
Regression type	The linearity of the calibration curve was determined using a weighted ($1/x^2$) linear regression (y = mx+b) least squares regression analysis for tadalafil.

Validation parameters	Method validation summary		Acceptability
Specificity	No significant interference observed in the 10 regular blank matrix lots screened (Blank Lot No.: LS1149253A, LS1149256A, LS2365027A, LS2365684A, LS2365698A, LS2365706A, LS5545231A, LS8813987A, LS8813999A, LS8814392A) as well as in lipemic (Blank Lot No.: BRH1372801, BRH1337917, BRH1595229, BRH1595227) and hemolyzed (Blank Lot No.: (R2)TDIV4553-01) lots. Assay specificity in the presence of concomitantly administered compounds, such as acetaminophen, acetylsalicylic acid, caffeine, ibuprofen etc., was assessed by adding the compounds to lot of blank matrix (with or without IS). No significant interference at the retention times and mass transitions of tadalafil and IS was observed in the blank matrix screened. Assay specificity in the presence of tadalafil was also assessed and found no significant inference.		Acceptable
Carryover	The presence or absence of carryover was evaluated prior to the injection of every batch using the injection of a high concentration sample (equivalent to the ULOQ concentration) followed by an analyte-free sample, as well as the injection of a LLOQ sample. In addition, carryover was continuously monitored within every batch when applicable, using the results of the analyte-free samples in each batch, which were always injected following a ULOQ calibrant, both at the beginning and end of the injection sequence. The acceptance criteria were: % interference for IS ≤5.0% of the IS response of the LLOQ, and % interference for analyte ≤20.0% of the analyte response of the LLOQ. No significant interference was observed in all injections of analyte-free samples.		Acceptable
Precision and accuracy	Between-run accuracy	96.3% - 103.7%	Acceptable
	Within-run accuracy	95.3% - 107.1%	Acceptable
	Between-run precision	2.6% - 5.0%	Acceptable
	Within-run precision	1.9% - 5.6%	Acceptable
Matrix effect	Accuracy (% nominal): 105.2% for Low QC and 103.5% for High QC. Precision: 3.7% for Low QC and 2.2% for High QC.		Acceptable
Calibration curve performance among validation batches / linearity	Cumulative precision (% CV) from LLOQ to ULOQ	≤5.3%	Acceptable
	Cumulative accuracy (% nominal) from LLOQ to ULOQ	97.9% to 102.5%	Acceptable
	Number of standard calibrator	10	Acceptable
Dilution integrity/ Dilution factor	400.000 ng/mL diluted 5-fold. Accuracy 93.6% Precision 2.7%		Acceptable
Recovery	Difference between lowest (low QC) and highest (high QC) percent extraction yields for tadalafil	98.3% - 104.7% (%CV ≤3.5)	Acceptable
	Percent extraction yields for IS	103.9% (%CV ≤3.4)	Acceptable

Short-term stability of the stock solution and working solutions	Confirmed up to 48.9 hours for tadalafil in ACN at 500.00 µg/mL at 22°C nominal. % deviation: 0.5%. Confirmed up to 45.5 hours for tadalafil in ACN at 50.00 ng/mL at 22°C nominal. % deviation: 0.5%. Confirmed up to 65.7 hours for tadalafil-D3-13C2 in ACN at 250.00 µg/mL at 22°C nominal. % deviation: -6.4%.	Acceptable
Long-term stability of the stock solution and working solutions	Confirmed up to 203 days for tadalafil in ACN at 500.00 µg/mL at 4°C nominal. % deviation: -1.1%. Confirmed up to 203 days for tadalafil in ACN at 0.50 µg/mL at 4°C nominal. % deviation: 2.3%. Confirmed up to 10 days for tadalafil in ACN at 50.00 ng/mL at 4°C nominal. % deviation: 0.5%. Confirmed up to 203 days for tadalafil-D3-13C2 in CAN at 250.00 µg/mL at 4°C nominal. % deviation: 0.2%.	Acceptable
Short-term stability in biological matrix at room temperature or at sample processing temperature	Confirmed up to 27.8 hours at 22°C nominal. Accuracy (% nominal): 95.5% for Low Stability QC and 91.0% for High Stability QC. Confirmed up to 22.4 hours at 22°C nominal using 3 QC sample tubes subjected to stability conditions. Accuracy (% nominal): 101.0% for Low Stability QC and 102.9% for High Stability QC.	Acceptable
Long-term stability in biological matrix	Confirmed up to 510 days at -80°C nominal. Accuracy (% nominal): 109.9% for Low Stability QC and 102.6% for High Stability QC	Acceptable
Freeze and thaw stability	4 cycles. Accuracy (% nominal): 101.3% for Low Stability QC and 103.9% for High Stability QC.	Acceptable

Method performance in bioanalytical study number VRU-P9-797(FND)		
Method Summary		
Reference standard	Tadalafil (Purity: 99.9%)	
Internal Standard	Tadalafil-d_3-$^{13}C_2$ (Purity: 100%)	
Stock solution	Stock solutions of tadalafil and tadalafil-D_3-$^{13}C_2$ were prepared on 2020/10/01 and stored at 4°C nominal. The stock solution used for standards had a different lot number than the stock solution used for QC samples.	
Standard and quality (QC) samples	In addition to blank and zero standards, 10 non-zero standards and 6 levels of QC samples containing tadalafil were prepared on 2020/10/06 with analyte-free human plasma, using K_2EDTA as anticoagulant. Standards and QC samples were stored at -80°C nominal from their preparation until the end of analysis for a maximum of 105 days. The long-term stabilities of 510 days (without finasteride) and 679 days (in the presence of finasteride) at -80°C nominal, covered the sample storage duration. Standard concentrations ranged from 0.500 ng/mL (LLOQ) to 200.00 ng/mL (ULOQ). QC sample concentrations were 1.500 ng/mL, 10.000 ng/mL, 30.000 ng/mL, 60.00 ng/mL and 100.000 ng/mL and 150 ng/mL. In order that QC samples better represent study samples, QC samples also contained the co-administered compound finasteride, at a concentration of 200.000 ng/mL.	
Method Performance		
Assay passing rate	A total of 14 runs performed. All bioanalytical runs were accepted.	Acceptable
Standard curve performance	Cumulative bias range: -3.6% to 3.0% Cumulative precision: 1.4%-3.9%	Acceptable
Quality control samples performance	Cumulative bias range: 0.0% to 0.8% Cumulative precision: 2.4% to 3.4%	Acceptable
Study samples stability	The total duration of the sample storage was 136 days (2020/09/05 – 2021/01/19), which was covered by the long-term stability period of 679 days at -80^{0}C in the presence of finasteride in human plasma.	
Incurred sample reanalysis	At least 10% of the first 1000 analyzable study samples and 5% of the remaining samples were re-assayed and compared to their original values. Cumulative bias range: -70.9% to 10.0% Out of all incurred samples analyzed, one sample (subject (b) (6) period 3, hour 96) was out of acceptable limit (≥20%). At least 2/3 of the total quantifiable samples selected for incurred sample reanalysis met the acceptable specifications.	Acceptable

Carryover	The presence or absence of carryover was evaluated prior to the injection of every run using the injection of a high concentration sample (equivalent to the ULOQ concentration) followed by an analyte-free sample, as well as the injection of an LLOQ sample. Furthermore, carryover was continuously monitored within every run, when applicable, using the results of the analyte-free samples in each run, which were always injected following a ULOQ standard, both at the beginning and end of the injection sequence. The analyte response of the analyte-free sample was ≤20.0% of the analyte response of the LLOQ, and/or the IS response was ≤5% of the IS response of the LLOQ for all runs. No carryover effect was observed in all accepted runs.

The method validation and performance of analytical runs for finasteride and tadalafil are acceptable to support the clinical study V0112502.

The review team requested inspections of the analytical and clinical sites to Division of New Drug Study Integrity (DNDSI), Office of Study Integrity and Surveillance (OSIS). DNDSI declined to conduct an on-site inspection and determined that an inspection was not warranted. OSIS inspected the analytical site in (b) (4) and clinical site in June 2019 and recommended that no further action was needed.

19.4.2. Individual Clinical Pharmacology Summary

Study number: V0112502

Title:
A single-dose, randomized, crossover study to assess the bioequivalence of a Entadfi™ (tadalafil and finasteride) combination capsule to the listed drug tablet formulations of tadalafil and finasteride and effect of food on Entadfi® in healthy male subjects

Objective:
The primary objectives were:

- To establish the relative bioavailability of tadalafil from the Entadfi combination capsule to that of Cialis® and the relative bioavailability of finasteride from the Entadfi combination capsule to that of Proscar® under fasted conditions.
- To assess the effect of food on the bioavailability of tadalafil and finasteride from the Entadfi combination capsule.

The secondary objectives were:

- To assess the PK of tadalafil and finasteride from a single dose of the Entadfi Combination Capsule administered under fasted and fed conditions.
- To assess the safety and tolerability of a single dose of Entadfi Combination Capsule formulation administered under fasted and fed conditions.

Study design:

- The study was open-label, randomized, single-center, single-dose, 3-period, crossover, BA and food effect study.
- A total of 36 healthy adult male subjects between 45 and 60 years of age were enrolled. Subjects were randomized in a 1:1:1:1:1:1: fashion to 6 different sequence groups.
- Treatment administered:
  Subjects received each of the following treatments in a randomized sequence:
  - Treatment-1 (Test): Entadfi Combination Capsule, containing 5 mg tadalafil and 5 mg finasteride, fasted
  - Treatment-2 (Test): Entadfi Combination Capsule, containing 5 mg tadalafil and 5 mg finasteride, fed
  - Treatment-3 (Reference): Cialis® (tadalafil) 5 mg tablet and Proscar® (finasteride) 5 mg tablet administered at the same time, fasted

  There was a 14-day washout period between doses and subjects received the study drugs with approximately 240 mL of ambient-temperature water on dosing day for each study period.
- PK samples:
  - Blood samples for PK measurements were collected for finasteride at predose (within 120 minutes prior to dose), and at 0.25, 0.50, 1.00, 1.50, 2.00, 4.00, 6.00, 8.00, 12.00, 16.00, 24.00, 36.00, and 48.00 hours postdose.
  - Blood sample for PK measurements were collected for tadalafil at predose (within 120 minutes prior to dose) and at 0.25, 0.50, 1.00, 2.00, 3.00, 4.00, 6.00, 8.00, 12.00, 16.00, 24.00, 36.00, 48.00, 72.00, and 96.00 hours postdose.
- The primary PK parameter for BA/BE and food effect analysis: C_{max}, AUC_t, AUC_∞ and T_{max}
- Key parameters to assess the PK of tadalafil and finasteride from a single dose of the Entadfi: C_{max}, AUC_t, AUC_∞, T_{max}, $AUC_{t/\infty}$, $t_{1/2}$, λ_z, Cl/F, and Vd/F.
- Bioanalytical assay: The validated LC/MS methods for the estimation of tadalafil and finasteride concentrations in human K_2EDTA plasma were used (refer to section 13.4.1)
- Safety: Adverse events (AEs), vital signs, physical exam, electrocardiogram, concomitant medications, clinical evaluations (general biochemistry, endocrinology, hematology, and urine analysis) and medical history were considered.

Study results:

- Bioequivalence determination and PK results from the study: refer to section 6.2.1.1 (BE determination, table 6 and 7), 6.3.1.1 (Finasteride PK characterization from a single oral administration of Entadfi capsule, table 10 and 11), and 6.3.1.2 (Tadalafil PK characterization from a single oral administration of Entadfi capsule).
- Food effect determination: refer to section 6.2.1.2 (Table 8 and 9).

Study conclusion:

The Applicant concluded as follows:

- Based on the study results, the test formulation (Entadfi combination capsule [finasteride, tadalafil] 5 mg/5 mg) is BE to the two reference products taken concomitantly (Cialis® [tadalafil] 5 mg tablet, and Proscar® [finasteride] 5 mg tablet) following a single oral dose administration under fasting condition, however, the absence of food effect could not be statistically demonstrated for the test product.
- Overall, the drugs tested were generally well tolerated by the subjects included in this study.

Reviewer comments:

- *The study was comparative BA/BE study between the test product (Entadfi) and reference products administered together (Cialis® [tadalafil] 5 mg tablet, and Proscar® [finasteride] 5 mg tablet) to determine whether there were significant differences in the PK of finasteride and tadalafil between test and reference products. The study design (e.g., the sample size, PK sampling points, and statistical analysis) appears reasonable to assess the BE of Entadfi to the reference products.*

- *A total of thirty-six (36) subjects were enrolled into the study. One subject (Subject ID (b) (6) was excluded (based on physician's decision) from the study due to lack of evaluable samples from treatment-1 (Entadfi Combination Capsule, containing 5 mg tadalafil and 5 mg finasteride, fasted). The remaining 35 subjects were included for PK analysis. A total of 30 and 34 subjects were included in the statistical analyses of Treatment-1 vs Treatment-3 (Subjects (b) (6) and Treatment-2 vs Treatment-1 (Subjects (b) (6)) comparisons, respectively. However, Subjects (b) (6) in Period 3 and Subjects (b) (6) in Period 2 were not included in the PK and statistical analyses. Subject (b) (6) were discontinued due to adverse events, however, the Applicant reported that none of the adverse events were related to any serious adverse events.*

- *Protocol violations were reported. No violation was reported during drug administration and follow up period. In case of Subjects (b) (6), fasting time was not respected at screening period before laboratory safety test. Prior to screening subjects were to be fasted at least 8 hours for blood draw of laboratory samples. However, they were not fasted for their retest blood draws.*

- *All deviations from the nominal PK sampling times were considered for PK samples evaluation. Actual sample collecting times were considered for PK analysis.*

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/s/

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	215423
Supporting document/s:	SDN 1
Applicant's letter date:	2-17-21
CDER stamp date:	2-17-21
Product:	combination oral capsule containing 5 mg tadalafil and 5 mg finasteride
Indication:	treatment of the signs and symptoms of benign prostatic hyperplasia (BPH)
Applicant:	Veru, Inc.
Review Division:	Division of Urology, Obstetrics and Gynecology
Reviewer:	Leslie McKinney, PhD
Supervisor:	Mukesh Summan, PhD, DABT
Team Leader:	Kim Hatfield, PhD
Division Director:	Christine Nguyen, MD
Project Manager:	Sydney Tran

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of 215423 are owned by Veru, Inc., or are data for which Veru, Inc., has obtained a written right of reference. Any information or data necessary for approval of 215423 that Veru, Inc., does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Veru, Inc. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of 215423.

1 Executive Summary

1.1 Introduction

The product submitted under this NDA has a proposed tradename of ENTADFI. ENTADFI is a combination oral capsule containing 5 mg tadalafil and 5 mg finasteride indicated for the treatment of benign prostatic hyperplasia (BPH). Each component is approved singly for the treatment of BPH. ENTADFI is intended to be taken orally, once daily (at approximately the same time each day) for up to 26 weeks. The purpose of this NDA is to gain approval for combination therapy in a single capsule.

1.2 Brief Discussion of Nonclinical Findings

There were no nonclinical data submitted to support this application. Veru is relying on the safety and efficacy of two listed drugs (LDs), CIALIS® (tadalafil) tablets (5 mg; NDA 21368 approved 2003) and PROSCAR® (finasteride) tablets (5 mg; NDA 20180 approved 1992). Nonclinical information relied upon is in the approved product labeling of CIALIS and PROSCAR.

Reliance on the LDs is based on a scientifically justified bridge established in a comparative bioavailability/bioequivalence study (Study V0112502, see Section 2.7.1), in which the ENTADFI (5 mg tadalafil/5 mg finasteride) oral capsule was determined to be bioequivalent to Cialis (5 mg tadalafil) and Proscar (5 mg finasteride) tablets administered together.

According to the guidance on Nonclinical Safety Evaluation of Drug or Biologic Combinations, there was no need for further nonclinical testing of this combination product.

There are no new excipients in the proposed drug product. All excipients are used at approved amounts and did not require qualification.

1.3 Recommendations

None

1.3.1 Approvability

The application is approvable from a pharmacology/toxicology perspective.

1.3.2 Additional Nonclinical Recommendations

None

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2 Drug Information

2.1 Drug

The proposed drug product is a combination of finasteride and sildenafil, filled in a single oral capsule. At the time of review, the proposed tradename is ENTADFI. Earlier reviews and submissions may reference a previously proposed tradename of (b) (4)

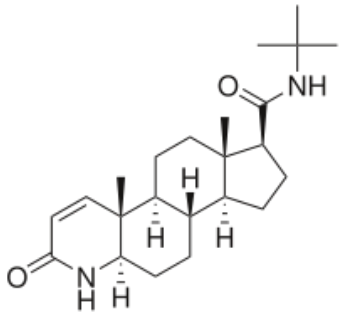
2.1.1 Finasteride

CAS Registry Number 98319-26-7

Chemical Name: N-tert-Butyl)-3-oxo-4-aza-5α -androst-1-ene-17β-carboxamide

Molecular Formula / Molecular Weight: $C_{23}H_{36}N_2O_2$ / 372.55 g/mol

Structure:



Pharmacologic class: 5α-reductase inhibitor

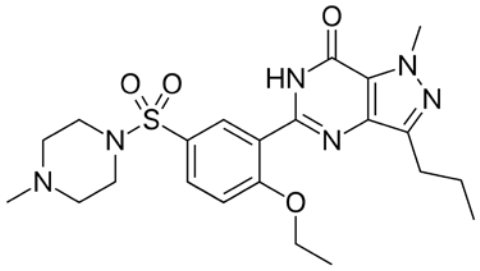
2.1.2 Sildenafil

CAS Registry Number: 171596-29-5

Chemical Name: 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)-;(6R, 12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-[3,4-(methylenedioxy)phenyl] pyrazino-[1´,2´:1,6]pyrido[3,4-b]indole-1,4-dione

Molecular Formula / Molecular Weight: $C_{22}H_{19}N_3O_4$ / 389.40 g/mol

Structure



Pharmacologic class: phosphodiesterase-5 inhibitor

2.2 Relevant IND: 136844 opened in 2017

2.3 Clinical Formulation

Oral capsule

2.3.1 Drug Formulation

Component	Amount per Capsule (mg)	Concentration % w/w	Function	Quality Standard
[redacted]				
Tadalafil USP [redacted]	5.0	[redacted]	[redacted]	USP
Finasteride USP [redacted]	5.0			USP
Sodium Lauryl Sulfate, NF [redacted]	[redacted]			NF
Lactose (Monohydrate), NF [redacted]				NF
Sodium Starch Glycolate, [redacted] NF [redacted]				NF
[redacted]				USP
[redacted]				
Silicified Microcrystalline Cellulose, NF [redacted]				NF
Colloidal Silicon Dioxide, NF [redacted]				NF
Magnesium Stearate, NF [redacted]				NF
[redacted] Capsule Shells [redacted]			Capsule Shell	NF

[1] N/A = not applicable as the ingredient is removed during the manufacturing process

2.3.2 Comments on Novel Excipients

None. All excipients are within approved amounts.

Component	Amount per [redacted] capsule (Total Daily Dose)	IID Oral Capsule Limit
Sodium Lauryl Sulfate	[redacted]	[redacted]
Lactose Monohydrate		
Sodium Starch Glycolate [redacted]		
Silicified Microcrystalline Cellulose		
Colloidal Silicon Dioxide		
Magnesium Stearate		

[1] Total Daily Dose for [redacted] is 1 capsule per day.
[2] Maximum Daily Exposure (MDE)
[3] Maximum Potency per unit dose

1.3.3 Labeling

The following represents the most recent updated text for Sections 8 and 13 of the product labeling as of November 1, 2021. The final label will reflect any additional edits that have been agreed to by the nonclinical team.

8 Use in Specific Populations

8.1 Pregnancy

Risk Summary

TRADENAME is contraindicated in pregnancy and not indicated for use in females *[see Contraindications (4)]*. Based on animal studies and its mechanism of action, finasteride, a component of TRADENAME, may cause abnormal development of external genitalia in a male fetus if administered to a pregnant female *[see Clinical Pharmacology (12.1)]*. In animal reproduction studies, oral administration of finasteride to pregnant rats during the period of major organogenesis resulted in a dose-dependent increase in hypospadias that occurred in 3.6 to 100% of male offspring at maternal doses approximately 0.1 to 86 times the maximum recommended human dose (MRHD) of 5 mg/day; decreased prostatic and seminal vesicular weights, delayed preputial separation and transient nipple development in male offspring at maternal doses approximately 0.03 times the MRHD and decreased anogenital distance in male offspring at maternal doses approximately 0.003 times the MRHD *(see Data).* Finasteride is a Type II 5α-reductase inhibitor that prevents conversion of testosterone to 5α-dihydrotestosterone (DHT), a hormone necessary for normal development of male genitalia. Abnormal male genital development is an expected consequence when conversion of testosterone to 5α-dihydrotestosterone (DHT) is inhibited by 5α-reductase inhibitors. These outcomes are similar to those reported in male infants with genetic 5α-reductase deficiency.

In animal reproduction studies, no adverse developmental effects were observed with oral administration of tadalafil to pregnant rats or mice during organogenesis at exposures up to 44 times the maximum recommended human dose (MRHD) of 5 mg/day (*See Data*).

Females of reproductive potential, including pregnant females, should not handle crushed or open TRADENAME capsules because of possible exposure of a male fetus *[see Warnings and Precautions (5.X)]*.

Data

Animal Data

Finasteride:

In an embryo-fetal development study, pregnant rats received finasteride during the period of major organogenesis (gestation days 6 to 17). At maternal doses of oral finasteride approximately 0.1 to 86 times the maximum recommended human dose (MRHD) of 5 mg/day (based on AUC at animal doses of 0.1 to 100 mg/kg/day) there was a dose-dependent increase in hypospadias that occurred in 3.6 to 100% of male offspring. Exposure multiples were estimated using data from nonpregnant rats. Days 16 to 17 of gestation is a critical

period in male fetal rats for differentiation of the external genitalia. At oral maternal doses approximately 0.03 times the MRHD (based on AUC at animal dose of 0.03 mg/kg/day), male offspring had decreased prostatic and seminal vesicular weights, delayed preputial separation and transient nipple development. Decreased anogenital distance occurred in male offspring of pregnant rats that received approximately 0.003 times the MRHD (based on AUC at animal dose of 0.003 mg/kg/day). No abnormalities were observed in female offspring at any maternal dose of finasteride.

Slightly decreased fertility was observed in male offspring after administration of about 3 times the MRHD (based on AUC at animal dose of 3 mg/kg/day) to female rats during late gestation and lactation. No effects on fertility were seen in female offspring under these conditions.

No evidence of male external genital malformations or other abnormalities were observed in rabbit fetuses exposed to finasteride during the period of major organogenesis (gestation days 6-18) at maternal oral doses up to 100 mg/kg/day, (finasteride exposure levels were not measured in rabbits). However, this study may not have included the critical period for finasteride effects on development of male external genitalia in the rabbit.

The fetal effects of maternal finasteride exposure were evaluated during the period of embryonic and fetal development from gestation day 20-100 in the rhesus monkey. Intravenous administration of finasteride to pregnant monkeys at doses as high as 800 ng/day (estimated maximal blood concentration of 1.86 ng/mL or about 143 times the highest estimated exposure of pregnant women to finasteride from semen of men taking 5 mg/day) resulted in no abnormalities in male fetuses. However, oral administration of finasteride (2 mg/kg/day or approximately 18,000 times the highest estimated blood levels of finasteride from semen of men taking 5 mg/day) to pregnant monkeys resulted in external genital abnormalities in male fetuses. No other abnormalities were observed in male fetuses and no finasteride-related abnormalities were observed in female fetuses at any dose.

Tadalafil:

Animal reproduction studies showed no evidence of teratogenicity, embryotoxicity, or fetotoxicity when tadalafil was given orally to pregnant rats or mice at exposures up to 44 times the indicated dose of 5 mg/day during organogenesis. In a prenatal/postnatal developmental study in rats, postnatal pup survival decreased following maternal exposure to tadalafil doses greater than 40 times the indicated dose based on AUC. Signs of maternal toxicity occurred at doses greater than 64 times the indicated dose based on AUC. Surviving offspring had normal development and reproductive performance.

In another rat prenatal and postnatal development study at doses of 60, 200, and 1000 mg/kg, a reduction in postnatal survival of pups was observed. The no observed effect level (NOEL) for maternal toxicity was 200 mg/kg/day and for developmental toxicity was 30 mg/kg/day. This gives approximately 64- and 40-fold exposure multiples, respectively, of the human AUC for the indicated dose of 5 mg.

Tadalafil and/or its metabolites cross the placenta, resulting in fetal exposure in rats.

8.2 Lactation

Risk Summary

TRADENAME is not indicated for use in females.

8.3 Females and Males of Reproductive Potential

Infertility

Males

Tadalafil:

There have been no studies evaluating the effect of TRADENAME, including tadalafil, on fertility in men *[see Clinical Pharmacology (12.2)]*.

Based on studies in animals, a decrease in spermatogenesis was observed in dogs, but not in rats. *[see Nonclinical Toxicology (13.1)]*.

Fertility Effects

Finasteride:
Treatment with finasteride for 24 weeks to evaluate semen parameters in healthy male volunteers revealed no clinically meaningful effects on sperm concentration, mobility, morphology, or pH. A 0.6 mL (22.1%) median decrease in ejaculate volume with a concomitant reduction in total sperm per ejaculate was observed. These parameters remained within the normal range and were reversible upon discontinuation of therapy with an average time to return to baseline of 84 weeks.

Tadalafil:

Based on the data from 3 studies in adult males, tadalafil decreased sperm concentrations in the study of 10 mg tadalafil for 6 months and the study of 20 mg tadalafil for 9 months. This effect was not seen in the study of 20 mg tadalafil taken for 6 months. There was no adverse effect of tadalafil 10 mg or 20 mg on mean concentrations of testosterone, luteinizing hormone or follicle stimulating hormone. The clinical significance of the decreased sperm concentrations in the two studies is unknown.

13 Nonclinical Toxicology

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Finasteride:

No evidence of a tumorigenic effect was observed in a 24-month study in Sprague-Dawley rats receiving doses of finasteride up to 160 mg/kg/day in males and 320 mg/kg/day in females. These doses produced respective systemic exposure in rats of 111 and 274 times

those observed in man receiving the recommended human dose of 5 mg/day. All exposure calculations were based on calculated $AUC_{(0\text{-}24\ hr)}$ for animals and mean $AUC_{(0\text{-}24\ hr)}$ for man (0.4 μg•hr/mL).

In a 19-month carcinogenicity study in CD-1 mice, a statistically significant ($p \leq 0.05$) increase in the incidence of testicular Leydig cell adenomas was observed at 228 times the human exposure (250 mg/kg/day). In mice at 23 times the human exposure (25 mg/kg/day) and in rats at 39 times the human exposure (40 mg/kg/day) an increase in the incidence of Leydig cell hyperplasia was observed. A positive correlation between the proliferative changes in the Leydig cells and an increase in serum LH levels (2- to 3-fold above control) has been demonstrated in both rodent species treated with high doses of finasteride. No drug-related Leydig cell changes were seen in either rats or dogs treated with finasteride for 1 year at 30 and 350 times (20 mg/kg/day and 45 mg/kg/day, respectively) or in mice treated for 19 months at 2.3 times the human exposure, estimated (2.5 mg/kg/day).

Tadalafil:

Tadalafil was not carcinogenic to rats or mice when administered daily for 2 years at doses up to 400 mg/kg/day. Systemic drug exposures, as measured by AUC of unbound tadalafil, were approximately 40-fold for mice, and 56-and 104-fold for male and female rats, respectively, the exposures in human males given the indicated dose of 5 mg.

Mutagenesis —

Finasteride:

No evidence of mutagenicity was observed in an in vitro bacterial mutagenesis assay, a mammalian cell mutagenesis assay, or in an in vitro alkaline elution assay. In an in vitro chromosome aberration assay, using Chinese hamster ovary cells, there was a slight increase in chromosome aberrations. These concentrations correspond to 4000-5000 times the peak plasma levels in man given a total dose of 5 mg. In an in vivo chromosome aberration assay in mice, no treatment-related increase in chromosome aberration was observed with finasteride at the maximum tolerated dose of 250 mg/kg/day (228 times the human exposure) as determined in the carcinogenicity studies.

Tadalafil:

Tadalafil was not mutagenic in the in vitro bacterial Ames assays or the forward mutation test in mouse lymphoma cells. Tadalafil was not clastogenic in the in vitro chromosomal aberration test in human lymphocytes or the in vivo rat micronucleus assays.

Impairment of Fertility

Finasteride:

In sexually mature male rabbits treated with finasteride at 543 times the human exposure (80 mg/kg/day) for up to 12 weeks, no effect on fertility, sperm count, or ejaculate volume was seen. In sexually mature male rats treated with 61 times the human exposure (80 mg/kg/day), there were no significant effects on fertility after 6 or 12 weeks of treatment; however, when treatment was continued for up to 24 or 30 weeks, there was an apparent decrease in fertility, fecundity and an associated significant decrease in the weights of the seminal vesicles and

prostate. All these effects were reversible within 6 weeks of discontinuation of treatment. No drug-related effect on testes or on mating performance has been seen in rats or rabbits. This decrease in fertility in finasteride-treated rats is secondary to its effect on accessory sex organs (prostate and seminal vesicles) resulting in failure to form a seminal plug. The seminal plug is essential for normal fertility in rats and is not relevant in man.

Tadalafil:

There were no effects on fertility, reproductive performance or reproductive organ morphology in male or female rats given oral doses of tadalafil up to 400 mg/kg/day, a dose producing AUCs for unbound tadalafil of 56-fold for males or 104-fold for females the exposures observed in human males given the indicated dose of 5 mg. In beagle dogs given tadalafil daily for 3 to 12 months, there was treatment-related non-reversible degeneration and atrophy of the seminiferous tubular epithelium in the testes in 20-100% of the dogs that resulted in a decrease in spermatogenesis in 40-75% of the dogs at doses of ≥10 mg/kg/day. Systemic exposure (based on AUC) at no-observed-adverse-effect level (NOAEL) (10 mg/kg/day) for unbound tadalafil was similar to that expected in humans at a dose of 20 mg. There were no treatment-related testicular findings in rats or mice treated with doses up to 400 mg/kg/day for 2 years.

13.2 Animal Toxicology and/or Pharmacology

Animal studies showed vascular inflammation in tadalafil-treated mice, rats, and dogs. In mice and rats, lymphoid necrosis and hemorrhage were seen in the spleen, thymus, and mesenteric lymph nodes at unbound tadalafil exposure of 8-to 132-fold above the human exposure (AUCs) at the indicated dose of 5 mg. In dogs, an increased incidence of disseminated arteritis was observed in 1-and 6-month studies at unbound tadalafil exposure of 4-to 216-fold above the human exposure (AUC) at the indicated dose of 5 mg. In a 12-month dog study, no disseminated arteritis was observed, but 2 dogs exhibited marked decreases in white blood cells (neutrophils) and moderate decreases in platelets with inflammatory signs at unbound tadalafil exposures of approximately 56-to 72-fold the human exposure at the indicated dose of 5 mg. The abnormal blood-cell findings were reversible within 2 weeks after stopping treatment.

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/s/

LESLIE C MCKINNEY
11/18/2021 10:54:17 PM

KIMBERLY P HATFIELD
11/19/2021 08:57:26 AM
I concur with the review and recommendations of Dr. McKinney.