NEW DRUG APPROVAL

Brand Name	Entadfi™
Generic Name	finasteride and tadalafil
Drug Manufacturer	Veru Inc.

New Drug Approval

FDA approval date: December 9, 2021

Review designation: Standard

Type of review: Type 4 - New Combination; NDA 215423

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Benign prostatic hyperplasia (BPH) refers to the non-malignant growth or hyperplasia of prostate tissue and is a common cause of lower urinary tract symptoms in men. Disease prevalence has been shown to increase with advancing age. Indeed, the histological prevalence of BPH at autopsy is as high as 50% to 60% for males in their 60's, increasing to 80% to 90% of those over 70 years of age. These include bladder outlet obstruction (BOO), lower urinary tract symptoms (LUTS), and benign prostatic enlargement (BPE). BPH describes the histological changes, benign prostatic enlargement (BPE) describes the increased size of the gland (usually secondary to BPH), and bladder outlet obstruction (BOO) describes the obstruction to flow. Those with BPE who present with BOO are termed benign prostatic obstruction. Lower urinary tract symptoms (LUTS) simply describe urinary symptoms shared by disorders affecting the bladder and prostate. The development of benign prostatic hyperplasia is characterized by stromal and epithelial cell proliferation in the prostate transition zone (surrounding the urethra), this leads to compression of the urethra and development of bladder outflow obstruction (BOO) which can result in clinical manifestations of lower urinary tract symptoms (LUTS), urinary retention or infections due to incomplete bladder emptying. Long-term, untreated disease can lead to the development of chronic high-pressure retention (a potentially life-threatening emergency) and long-term changes to the bladder detrusor (both overactivity and reduced contractility).

The prevalence of BPH rises markedly with increased age. Autopsy studies have observed a histological prevalence of 8%, 50%, and 80% in the 4th, 6th, and 9th decades of life, respectively. Observational studies from Europe, US, and Asia have also demonstrated older age to be a risk factor for clinical BPH onset and progression. Furthermore, the prostate volume increases with age based on data from the Krimpen and Baltimore Longitudinal Study of Aging suggesting a prostate growth rate of 2.0%–2.5% per year in older men. Continued prostate growth is a risk factor for LUTS progression and larger prostates are associated with benign prostatic enlargement (BPE) and increased risks of clinical BPH progression, urinary retention and need for prostate surgery. No clear patterns have emerged with respect to BPH risk and race. Evidence suggests a strong genetic component to BPH. A case control analysis, in which men below 64 years underwent surgery for BPH, noted that male relatives and brothers had a 4-fold and 6-fold increase, respectively of age-specific risks for BPH surgery. These investigators further estimated that 50% of men below 60 years undergoing surgery for BPH had a heritable form of disease. moderate alcohol intake also appears to be protective against multiple outcomes related to BPH. A meta-analysis of 19 published studies (*n* = 120 091) observed up to a 35% decreased likelihood of BPH among men who drank daily.

Efficacy

The efficacy of Entadfi™ is based on an adequate and well-controlled study of tadalafil co-administered with finasteride. A double-blinded, parallel-design study of 26 weeks duration randomized 696 men to initiate either tadalafil 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. Tadalafil and finasteride administered together demonstrated statistically significant improvement in the signs and symptoms of BPH compared to placebo with finasteride, as measured by the total symptom score (IPSS) at 12 weeks, the primary study endpoint. Key secondary endpoints demonstrated improvement in total IPSS starting at the first scheduled observation at week 4 (tadalafil -4.0, placebo -2.3: p< .001) and the score remained decreased through 26 weeks (tadalafil -5.5, placebo -4.5; p=.022). However, the magnitude of the treatment difference between placebo/finasteride and tadalafil/finasteride decreased from 1.7 points at Week 4 to 1.0 point at Week 26. The incremental benefit of Entadfi™ beyond 26 weeks is unknown.

Table 1: Mean Total IPSS Changes in BPH Patients in a Tadalafil Study Together with Finasteride

		Placebo and Finasteride 5 mg		Tadalafil 5 mg and Finasteride 5 mg	Treatment Difference	
	n	(N=350)[a]	n	(N=345)[a]		p-value[b]
Total Symptom Score (IPSS)						
Baseline[c]	349	17.4	344	17.1		
Change from Baseline to Week 4[b]	340	-2.3	330	-4.0	-1.7	<0.001
Change from Baseline to Week 12[b]	318	-3.8	317	-5.2	-1.4	0.001
Change from Baseline to Week 26[b]	295	-4.5	308	-5.5	-1.0	0.022

[a] Overall ITT population.
[b] Mixed model for repeated measurements.
[c] Unadjusted mean.

Safety

ADVERSE EVENTS

The safety of Entadfi™ is based on the following:

- Placebo controlled trials in which tadalafil was administered as monotherapy for the treatment of either BPH alone or BPH and a condition for which Entadfi™ is not approved.
- Placebo controlled trials in which finasteride was administered as monotherapy for the treatment of BPH.

Finasteride: 4-Year Placebo-Controlled Study (PLESS)-

In PLESS, 1524 patients treated with finasteride 5 mg once daily and 1516 patients treated with placebo were evaluated for safety over a period of 4 years. The most frequently reported adverse reactions were related to sexual function. 3.7% (57 patients) treated with finasteride and 2.1% (32 patients) treated with placebo discontinued therapy as a result of adverse reactions related to sexual function, which are the most frequently reported adverse reactions.

Table 2: Drug-Related Adverse Reactions				
	Year 1 (%)		Years 2, 3 and 4* (%)	
	Finasteride	Placebo	Finasteride	Placebo
Impotence	8.1	3.7	5.1	5.1
Decreased Libido	6.4	3.4	2.6	2.6
Decreased Volume of Ejaculate	3.7	0.8	1.5	0.5
Ejaculation Disorder	0.8	0.1	0.2	0.1
Breast Enlargement	0.5	0.1	1.8	1.1
Breast Tenderness	0.4	0.1	0.7	0.3
Rash	0.5	0.2	0.5	0.1

*Combined Years 2-4

N = 1524 and 1516, finasteride vs placebo, respectively

Phase III Studies and 5-Year Open Extensions-

The adverse experience profile in the 1-year, placebo-controlled, Phase III studies, the 5-year open extensions, and PLESS were similar.

Medical Therapy of Prostatic Symptoms (MTOPS) Study-

In the MTOPS study, 3047 men with symptomatic BPH were randomized to receive finasteride 5 mg once daily (n=768), doxazosin 4 or 8 mg once daily (n=756), the combination of finasteride 5 mg once daily and doxazosin 4 or 8 mg once daily (n=786), or placebo (n=737) for 4 to 6 years.

Table 3: Incidence ≥2% in One or More Treatment Groups Drug-Related Clinical Adverse Reactions in MTOPS				
Adverse Reaction	Placebo (N=737) (%)	Doxazosin 4 mg or 8 mg* (N=756) (%)	Finasteride (N=768) (%)	Combination (N=786) (%)
Body as a whole				
Asthenia Headache	7.1 2.3	15.7 4.1	5.3 2.0	16.8 2.3
Cardiovascular				
Hypotension Postural Hypotension	0.7 8.0	3.4 16.7	1.2 9.1	1.5 17.8
Metabolic and Nutritional				
Peripheral Edema	0.9	2.6	1.3	3.3
Nervous				
Dizziness Libido Decreased Somnolence	8.1 5.7 1.5	17.7 7.0 3.7	7.4 10.0 1.7	23.2 11.6 3.1
Respiratory				
Dyspnea Rhinitis	0.7 0.5	2.1 1.3	0.7 1.0	1.9 2.4
Urogenital				

Abnormal Ejaculation	2.3	4.5	7.2	14.1
Gynecomastia	0.7	1.1	2.2	1.5
Impotence	12.2	14.4	18.5	22.6
Sexual Function Abnormal	0.9	2.0	2.5	3.1

*Doxazosin dose was achieved by weekly titration (1 to 2 to 4 to 8 mg). The final tolerated dose (4 mg or 8 mg) was administered at end-Week 4. Only those patients tolerating at least 4 mg were kept on doxazosin. The majority of patients received the 8-mg dose over the duration of the study.

Long-Term Data-

High-Grade Prostate Cancer:
The PCPT trial was a 7-year randomized, double-blind, placebo-controlled trial that enrolled 18,882 men ≥55 years of age with a normal digital rectal examination and a PSA ≤3.0 ng/mL. Men received either finasteride 5 mg or placebo daily. Patients were evaluated annually with PSA and digital rectal exams. Biopsies were performed for elevated PSA, an abnormal digital rectal exam, or the end of study. The incidence of Gleason score 8-10 prostate cancer was higher in men treated with finasteride (1.8%) than in those treated with placebo (1.1%). In a 4-year placebo-controlled clinical trial with another 5α-reductase inhibitor, similar results for Gleason score 8-10 prostate cancer were observed (1% vs 0.5% placebo). No clinical benefit has been demonstrated in patients with prostate cancer treated with finasteride 5 mg.

Breast Cancer:
During the 4- to 6-year placebo- and comparator-controlled MTOPS study that enrolled 3047 men, there were 4 cases of breast cancer in men treated with finasteride but no cases in men not treated with finasteride. During the 4-year, placebo-controlled PLESS study that enrolled 3040 men, there were 2 cases of breast cancer in placebo-treated men but no cases in men treated with finasteride. During the 7-year placebo-controlled Prostate Cancer Prevention Trial (PCPT) that enrolled 18,882 men, there was 1 case of breast cancer in men treated with finasteride, and 1 case of breast cancer in men treated with placebo. The relationship between long-term use of finasteride and male breast neoplasia is currently unknown.

Sexual Function:
There is no evidence of increased sexual adverse reactions with increased duration of treatment with finasteride 5 mg. New reports of drug-related sexual adverse reactions decreased with duration of therapy.

Tadalafil:
The safety of tadalafil was evaluated in three placebo-controlled clinical trials of 12 weeks duration, in which tadalafil was administered as monotherapy at a dose of 5 mg orally once daily for the treatment of either BPH alone or BPH and a condition for which Entadfi™ is not approved. The mean age of the patients was 63 years (range 44 to 93) and the discontinuation rate due to adverse reactions in patients treated with tadalafil was 3.6% compared to 1.6% in placebo-treated patients. Adverse reactions leading to discontinuation reported by at least 2 patients treated with tadalafil included headache, upper abdominal pain, and myalgia. Additional, less frequent adverse reactions.

Table 4: Adverse Reactions Reported by ≥1% of Patients Treated with Tadalafil for Once Daily Use (5 mg) and More Frequent on Drug than Placebo in Three Placebo-Controlled Clinical Studies of 12 Weeks Treatment Duration

Adverse Reaction	Tadalafil 5 mg (N=581)	Placebo (N=576)
Headache	4.1%	2.3%
Dyspepsia	2.4%	0.2%
Back pain	2.4%	1.4%
Nasopharyngitis	2.1%	1.6%

Diarrhea	1.4%	1.0%
Pain in extremity	1.4%	0.0%
Myalgia	1.2%	0.3%
Dizziness	1.0%	0.5%

Postmarketing Experience-

Finasteride monotherapy:

- Hypersensitivity reactions, such as pruritus, urticaria, and angioedema (including swelling of the lips, tongue, throat, and face).
- Testicular pain.
- Hematospermia.
- Sexual dysfunction that continued after discontinuation of treatment, including erectile dysfunction, decreased libido and ejaculation disorders (e.g., reduced ejaculate volume).
- Male infertility and/or poor seminal quality.
- Depression.
- Male breast cancer.

Tadalafil:

- Cardiovascular and Cerebrovascular — Serious cardiovascular events, including myocardial infarction, sudden cardiac death, stroke, chest pain, palpitations, and tachycardia.
- Body as a Whole — hypersensitivity reactions including urticaria, Stevens-Johnson syndrome, and exfoliative dermatitis.
- Nervous — migraine, seizure and seizure recurrence, transient global amnesia.
- Ophthalmologic — visual field defect, retinal vein occlusion, retinal artery occlusion Non-arteritic anterior ischemic optic neuropathy (NAION).
- Otologic — Sudden decrease or loss of hearing.

Urogenital — priapism.

WARNINGS & PRECAUTIONS

Cardiovascular Risk-

Entadfi™ is contraindicated in patients taking any form of organic nitrate, either regularly and/or intermittently. Discuss with patients the appropriate action in the event that they experience anginal chest pain requiring nitroglycerin following intake of Entadfi™. In such a patient, who has taken Entadfi™, where nitrate administration is deemed medically necessary for a life-threatening situation, at least 48 hours should have elapsed after the last dose of Entadfi™ before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring. Therefore, advise patients who experience anginal chest pain after taking Entadfi™ to seek immediate medical attention. Patients with left ventricular outflow obstruction, (e.g., aortic stenosis and idiopathic hypertrophic subaortic stenosis) can be sensitive to the action of vasodilators, including PDE5 inhibitors. As with other PDE5 inhibitors, tadalafil, a component of Entadfi™, has mild systemic vasodilatory properties that may result in transient decreases in blood pressure. Prior to prescribing Entadfi™, carefully consider whether patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects. Patients with severely impaired autonomic control of blood pressure may be particularly sensitive to the actions of vasodilators, including PDE5 inhibitors.

Potential for Drug Interactions when Taking Entadfi™ -

Entadfi™ provides continuous plasma tadalafil levels. Consider this when evaluating the potential for Entadfi™ interactions with medications (e.g., nitrates, alpha-blockers, antihypertensives and strong inhibitors of CYP3A4) and with substantial consumption of alcohol.

Concomitant Use with Alpha-blockers or Antihypertensives-
Discuss with patients the potential for Entadfi™ to augment the blood-pressure-lowering effect of alpha-blockers and antihypertensive medications. Caution is advised when PDE5 inhibitors are coadministered with alpha-blockers. PDE5 inhibitors, including Entadfi™, and alpha-adrenergic blocking agents are both vasodilators with blood-pressure-lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. In some patients, concomitant use of these two drug classes can lower blood pressure significantly which may lead to symptomatic hypotension (e.g., fainting).

Consideration of Other Urological Conditions Prior to Initiating Treatment for BPH-
Prior to initiating treatment with Entadfi™ for BPH, consider whether the patient has other urological conditions that may cause similar symptoms. In addition, prostate cancer and BPH may coexist. Carefully monitor patients with large residual urinary volume and/or severely diminished urinary flow for obstructive uropathy. These patients may not be candidates for Entadfi™ therapy.

Effects on Prostate Specific Antigen (PSA) and the Use of PSA in Prostate Cancer Detection-
In clinical studies, finasteride, a component of Entadfi™, reduced serum PSA concentration by approximately 50% within six months of treatment. This decrease is predictable over the entire range of PSA values in patients with symptomatic BPH, although it may vary in individuals. Entadfi™ may also cause decreases in serum PSA in the presence of prostate cancer.

Increased Risk of High-Grade Prostate Cancer-
Use of 5α-reductase inhibitors, including Entadfi™, may increase the risk of development of high-grade prostate cancer. Men aged 55 years and over with a normal digital rectal examination and PSA less than or equal to 3.0 ng/mL at baseline taking finasteride, a component of Entadfi™ (5 mg daily) in the 7-year Prostate Cancer Prevention Trial (PCPT) had an increased risk of Gleason score 8 to 10 prostate cancer (finasteride 1.8% vs placebo 1.1%).

Risk to Male Fetus from Topical Entadfi™ Exposure to Pregnant Females-
Entadfi™ is contraindicated in pregnant females and is not indicated for use in females.

Hypersensitivity Reactions-
Entadfi™ is contraindicated in patients with a history of hypersensitivity reactions to finasteride, tadalafil, or to any component of Entadfi™. Hypersensitivity reactions have included Stevens-Johnson syndrome, exfoliative dermatitis, pruritis, urticaria, and angioedema.

Prolonged Erection and Priapism-
Use Entadfi™ with caution in patients who have conditions that might predispose them to priapism (such as sickle cell anemia, multiple myeloma, or leukemia), or in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis, or Peyronie's disease).

Ocular Adverse Reactions-
Advise patients to stop use of all phosphodiesterase type 5 (PDE5) inhibitors, including Entadfi™, and seek medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a rare condition and a cause of decreased vision, including permanent loss of vision, that has been reported rarely postmarketing in temporal association with the use of all PDE5 inhibitors.

Sudden Hearing Loss-

Advise patients to stop taking Entadfi™ and seek prompt medical attention in the event of sudden decrease or loss of hearing. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors, including Entadfi™.

Concomitant Use with Alcohol-
Inform patients that both alcohol and tadalafil, a PDE5 inhibitor and a component of Entadfi™, act as mild vasodilators. When mild vasodilators are taken in combination, blood-pressure lowering effects of each individual compound may be increased. Inform patients that substantial consumption of alcohol (e.g., 5 units or greater) in combination with Entadfi™ can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache.

Concomitant Use with Strong Inhibitors of Cytochrome P450 3A4 (CYP3A4)-
Tadalafil, a component of Entadfi™, is metabolized predominantly by CYP3A4 in the liver. Entadfi™ is not recommended in patients taking strong inhibitors of CYP3A4.

Effects on Bleeding-
Studies in vitro have demonstrated that tadalafil, a component of Entadfi™, is a selective inhibitor of PDE5. PDE5 is found in platelets. When administered in combination with aspirin, tadalafil 20 mg did not prolong bleeding time, relative to aspirin alone. Entadfi™ has not been administered to patients with bleeding disorders or significant active peptic ulceration.

CONTRAINDICATIONS

- Concomitant use of any form of organic nitrate, either regularly and/or intermittently. Entadfi™ can potentiate the hypotensive effect of nitrates.
- Patients with known hypersensitivity to finasteride, tadalafil, or to any of the components of Entadfi™. Hypersensitivity reactions have included Stevens-Johnson syndrome, exfoliative dermatitis, pruritis, urticaria, and angioedema.
- Pregnancy.
- Concomitant use with a guanylate cyclase (GC) stimulator. Entadfi™ may potentiate the hypotensive effects of GC stimulators.

Clinical Pharmacology

MECHANISMS OF ACTION

Finasteride: Finasteride competitively inhibits type II 5-alpha reductase, resulting in inhibition of the conversion of testosterone to dihydrotestosterone and markedly suppresses serum dihydrotestosterone levels.

Tadalafil: The exact mechanism for treating benign prostatic hyperplasia is unknown; effects are likely due to phosphodiesterase-5-mediated reduction in smooth muscle and endothelial cell proliferation, decreased nerve activity, and increased smooth muscle relaxation and tissue perfusion of the prostate and bladder.

Dose & Administration

ADULTS

Finasteride 5 mg/tadalafil 5 mg once daily for up to 26 weeks.

PEDIATRICS

Not applicable

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

CrCl ≥50 mL/minute: No dosage adjustment necessary.

CrCl <50 mL/minute: Not recommended.

Hemodialysis: Not recommended.

HEPATIC IMPAIRMENT

Use is not recommended in patients with severe hepatic impairment (Child-Pugh class C); use with caution in patients with mild to moderate hepatic impairment (Child-Pugh Class A or B).

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Capsules: fixed dose combination containing finasteride 5 mg and tadalafil 5 mg.