

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ENTADFI safely and effectively. See full prescribing information for ENTADFI.

ENTADFI™ (finasteride and tadalafil) capsules, for oral use  
Initial U.S. Approval: 2021

### INDICATIONS AND USAGE

ENTADFI is a combination of finasteride, a 5 $\alpha$ -reductase inhibitor, and tadalafil, a phosphodiesterase 5 (PDE5) inhibitor, and, indicated to initiate treatment of the signs and symptoms of benign prostatic hyperplasia (BPH) in men with an enlarged prostate for up to 26 weeks. (1)

### DOSAGE AND ADMINISTRATION

One capsule orally once daily at approximately the same time every day for up to 26 weeks. Take without food. (2)

### DOSAGE FORMS AND STRENGTHS

Capsules: fixed dose combination containing finasteride 5 mg and tadalafil 5 mg. (3)

### CONTRAINDICATIONS

- Concomitant use with any form of organic nitrate, either regularly and/or intermittently. ENTADFI can potentiate the hypotensive effect of nitrates. (4)
- Known hypersensitivity to ENTADFI or any of its components. (4)
- Pregnancy. (4)
- Concomitant use with guanylate cyclase (GC) stimulators. ENTADFI may potentiate the hypotensive effects of GC stimulators. (4)

### WARNINGS AND PRECAUTIONS

- Cardiovascular Risk:** Administer nitrates concomitantly only in life-threatening situations under close medical supervision. (5.1)
- Potential for Drug Interactions when taking ENTADFI:** Use alpha-blockers, antihypertensives, strong CYP3A4 inhibitors and alcohol with caution due to the potential for symptomatic hypotension. (5.2), (5.3), (5.12)
- Consideration of Other Urological Conditions Prior to Initiation of Treatment for BPH:** Carefully monitor patients with large residual urinary volume and/or severely diminished urinary flow for obstructive uropathy. Prostate cancer and BPH may coexist. (5.4)
- Effects of PSA and the Use of PSA in Prostate Cancer Detection:** PSA reduction by approximately 50% within six months of treatment can be seen which can affect interpretation of serial and isolated PSA values. Evaluate any confirmed increase in PSA as it may signal the presence of prostate cancer. (5.5)

- Increased Risk of High-Grade Prostate Cancer:** Increased incidence of high-grade prostate cancer has been observed. (5.6)
- Risk to Male Fetus from Topical ENTADFI Exposure to Pregnant Females:** Pregnant women should not handle crushed or open ENTADFI capsules. (5.7)
- Hypersensitivity Reactions:** Immediately discontinue if a hypersensitivity reaction occurs. (5.8)
- Prolonged Erection and Priapism:** Use with caution in patients predisposed to priapism. Advise patients to seek emergency treatment if an erection lasts more than 4 hours. (5.9)
- Ocular Adverse Reactions:** Stop use 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). Use with caution in patients at increased risk of NAION. (5.10)
- Sudden Hearing Loss:** Stop use and seek prompt medical attention. (5.11)

### ADVERSE REACTIONS

Most common adverse reactions associated with finasteride monotherapy ( $\geq 1\%$ ) in a 4-year study were impotence, decreased libido, decreased volume of ejaculate, breast enlargement, breast tenderness, and rash (6.1). Most common adverse reactions ( $\geq 2\%$ ) associated with tadalafil were headache, dyspepsia, back pain, myalgia, nasal congestion, flushing, and pain in limb (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Veru Inc. at 1-8XX-XXX-XXXX or [www.verupharma.com](http://www.verupharma.com) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

**CYP3A4 inducers:** Concomitant use may increase tadalafil exposure. Use is not recommended. (7.2)

### USE IN SPECIFIC POPULATIONS

#### Hepatic Impairment:

- Child's Pugh Class A and B: Use with caution. (8.6)
- Child's Pugh Class C: Use is not recommended. (8.6)

#### Renal Impairment:

- Creatinine clearance less than 50 mL/min or hemodialysis: Use is not recommended. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

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

#### 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 [see *Clinical Studies (14)*].

### 2 DOSAGE AND ADMINISTRATION

The recommended dosage of ENTADFI is one capsule (containing finasteride 5 mg and tadalafil 5 mg) orally once daily at approximately the same time every day for up to 26 weeks.

Take ENTADFI on an empty stomach [see *Clinical Pharmacology (12.3)*].

### 3 DOSAGE FORMS AND STRENGTHS

Capsules: finasteride 5 mg and tadalafil 5 mg, in a size 3 capsule with a white opaque cap and body with black two line bars printed on the cap and on the body.

### 4 CONTRAINDICATIONS

ENTADFI is contraindicated in the following situations:

- Concomitant use of any form of organic nitrate, either regularly and/or intermittently. ENTADFI can potentiate the hypotensive effect of nitrates [see *Warning and Precautions (5.1, 5.2) and Drug Interactions (7.1)*].
- 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 [see *Warnings and Precautions (5.8) and Adverse Reactions (6.2)*].
- Pregnancy [see *Warnings and Precautions (5.7) and Use in Specific Populations (8.1)*].
- Concomitant use with a guanylate cyclase (GC) stimulator. ENTADFI may potentiate the hypotensive effects of GC stimulators [see *Drug Interactions (7.1)*].

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Cardiovascular Risk

ENTADFI is contraindicated in patients taking any form of organic nitrate, either regularly and/or intermittently [see *Contraindications (4)*]. 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 [see *Contraindications (4)*].

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.

The following groups of patients with cardiovascular disease were not included in clinical safety and efficacy trials for tadalafil, and therefore until further information is available, ENTADFI is not recommended for the following groups of patients:

- myocardial infarction within the last 90 days
- unstable angina or angina occurring during sexual intercourse
- New York Heart Association Class 2 or greater heart failure in the last 6 months
- uncontrolled arrhythmias, hypotension (<90/50 mm Hg), or uncontrolled hypertension
- stroke within the last 6 months.

As with other PDE5 inhibitors, tadalafil, a component of ENTADFI, has mild systemic vasodilatory properties that may result in transient decreases in blood pressure. In a clinical pharmacology study, tadalafil 20 mg resulted in a mean maximal decrease in supine blood pressure, relative to placebo, of 1.6/0.8 mm Hg in healthy subjects [see *Clinical Pharmacology (12.2)*]. While this effect should not be of consequence in most patients, 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.

### 5.2 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, anti-hypertensives and strong inhibitors of CYP3A4) and with substantial consumption of alcohol [see *Drug Interactions (7)*].

### 5.3 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 [*see Drug Interactions (7.1) and Clinical Pharmacology (12.2)*].

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 [*see Drug Interactions (7.2) and Clinical Pharmacology (12.2)*], which may lead to symptomatic hypotension (e.g., fainting). Consider the following:

#### BPH

- The efficacy of the coadministration of an alpha-blocker and ENTADFI for the treatment of BPH has not been adequately studied, and due to the potential vasodilatory effects of combined use resulting in blood pressure lowering, the combination of ENTADFI and alpha-blockers is not recommended for the treatment of BPH [*see Drug Interactions (7.2), and Clinical Pharmacology (12.2)*].
- Discontinue alpha-blockers at least one day prior to starting ENTADFI for once daily use for the treatment of BPH.

### 5.4 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.

### 5.5 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.

For interpretation of serial PSAs in men taking ENTADFI, a new PSA baseline should be established at least six months after starting treatment and PSA monitored periodically thereafter. Any confirmed increase from the lowest PSA value while on ENTADFI may signal the presence of prostate cancer and should be evaluated, even if PSA levels are still within the normal range for men not taking a 5 $\alpha$ -reductase inhibitor. Non-compliance with ENTADFI therapy may also affect PSA test results. To interpret an isolated PSA value in patients treated with ENTADFI for six months or more, double the PSA values for comparison with normal ranges in untreated men. These adjustments preserve the utility of PSA to detect prostate cancer in men treated with ENTADFI.

ENTADFI may also cause decreases in serum PSA in the presence of prostate cancer.

The ratio of free to total PSA (percent free PSA) remains constant even under the influence of ENTADFI. If clinicians elect to use percent free PSA as an aid in the detection of prostate cancer in men undergoing ENTADFI therapy, no adjustment to its value appears necessary.

## **5.6 Increased Risk of High-Grade Prostate Cancer**

Use of 5 $\alpha$ -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%) [*See Adverse Reactions (6.1)*]. Similar results were observed in a 4-year placebo-controlled clinical trial with a different 5 $\alpha$ -reductase inhibitor. Whether the effect of 5 $\alpha$ -reductase inhibitors to reduce prostate volume, or study-related factors, impacted the results of these studies has not been established.

## **5.7 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. Based on animal studies and the mechanism of action of finasteride, ENTADFI may cause abnormal development of external genitalia in a male fetus if administered to a pregnant female. Pregnant females should not handle crushed or open ENTADFI capsules because of the possibility of absorption of finasteride and the subsequent potential risk to a male fetus. If a pregnant female comes in contact with crushed or broken ENTADFI capsules, the contact area should be washed immediately with soap and water [*see Contraindications (4), Use in Specific Populations (8.1)*].

## **5.8 Hypersensitivity Reactions**

ENTADFI is contraindicated in patients with a history of hypersensitivity reactions to finasteride, tadalafil, or to any component of ENTADFI [*see Contraindications (4)*]. Immediately discontinue ENTADFI if a hypersensitivity reaction occurs. Hypersensitivity reactions have included Stevens-Johnson syndrome, exfoliative dermatitis, pruritis, urticaria, and angioedema [*see Adverse Reactions (6.2)*].

## **5.9 Prolonged Erection and Priapism**

Instruct patients who have an erection lasting greater than 4 hours, whether painful or not, to seek emergency medical attention. 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).

There have been rare reports of prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) for this class of compounds. Priapism, if not treated promptly, can result in irreversible damage to the erectile tissue.

## 5.10 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. Based on published literature, the annual incidence of NAION is 2.5 to 11.8 cases per 100,000 in males aged 50 years and older.

Consider whether patients with underlying NAION risk factors could be adversely affected by use of PDE5 inhibitors. Individuals who have already experienced NAION are at increased risk of NAION recurrence. Therefore, use PDE5 inhibitors, including ENTADFI, with caution in these patients and only when the anticipated benefits outweigh the risks. Individuals with “crowded” optic disc are also considered at greater risk for NAION compared to the general population; however, evidence is insufficient to support screening of prospective users of PDE5 inhibitors, including ENTADFI, for this uncommon condition.

Patients with known hereditary degenerative retinal disorders, including retinitis pigmentosa, were not included in the clinical trials, and use of ENTADFI in these patients is not recommended.

An observational case-crossover study evaluated the risk of NAION when PDE5 inhibitor use, as a class, occurred immediately before NAION onset (within 5 half-lives), compared to PDE5 inhibitor use in a prior time period. The results suggest an approximate 2-fold increase in the risk of NAION, with a risk estimate of 2.15 (95% CI 1.06, 4.34). A similar study reported a consistent result, with a risk estimate of 2.27 (95% CI 0.99, 5.20). Other risk factors for NAION, such as the presence of “crowded” optic disc, may have contributed to the occurrence of NAION in these studies.

Neither the rare postmarketing reports, nor the association of PDE5 inhibitor use and NAION in the observational studies, substantiate a causal relationship between PDE5 inhibitor use and NAION [see *Adverse Reactions (6.2)*].

## 5.11 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. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, such as ENTADFI, or to other factors [see *Adverse Reactions (6.1, 6.2)*].

## 5.12 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 [see *Drug Interactions (7.3)*].

### **5.13 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 [see *Drug Interactions (7.1), Clinical Pharmacology (12.3)*].

### **5.14 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. Although tadalafil, a component of ENTADFI, has not been shown to increase bleeding times in healthy subjects, use ENTADFI with caution in patients with bleeding disorders or significant active peptic ulceration after a careful risk-benefit assessment.

## **6 ADVERSE REACTIONS**

### **6.1 Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

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 1 presents the only clinical adverse reactions considered possibly, probably or definitely drug related by the investigator, for which the incidence on finasteride was  $\geq 1\%$  and greater than placebo over the 4 years of the study. In years 2-4 of the study, there was no significant difference between treatment groups in the incidences of impotence, decreased libido and ejaculation disorder.

#### **Table 1: 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.

The incidence rates of drug-related adverse reactions reported by  $\geq 2\%$  of patients in any treatment group in the MTOPS Study are listed in Table 2.

The individual adverse reactions which occurred more frequently in the combination group compared to either drug alone were: asthenia, postural hypotension, peripheral edema, dizziness, decreased libido, rhinitis, abnormal ejaculation, impotence and abnormal sexual function (see Table 1). Of these, the incidence of abnormal ejaculation in patients receiving combination therapy was comparable to the sum of the incidences of this adverse experience reported for the two monotherapies.

Combination therapy with finasteride and doxazosin was associated with no new clinical adverse reactions.

Four patients in MTOPS reported the adverse reaction of breast cancer. Three of these patients were on finasteride only and one was on combination therapy. *See Long-Term Data.*

The MTOPS Study was not specifically designed to make statistical comparisons between groups for reported adverse reactions. In addition, direct comparisons of safety data between the MTOPS study and previous studies of the single agents may not be appropriate based upon differences in patient population, dosage or dose regimen, and other procedural and study design elements.

### Table 2: Incidence $\geq 2\%$ 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) (%)
<b>Body as a whole</b>				
Asthenia	7.1	15.7	5.3	16.8
Headache	2.3	4.1	2.0	2.3
<b>Cardiovascular</b>				
Hypotension	0.7	3.4	1.2	1.5
Postural Hypotension	8.0	16.7	9.1	17.8
<b>Metabolic and Nutritional</b>				
Peripheral Edema	0.9	2.6	1.3	3.3
<b>Nervous</b>				
Dizziness	8.1	17.7	7.4	23.2
Libido Decreased	5.7	7.0	10.0	11.6
Somnolence	1.5	3.7	1.7	3.1
<b>Respiratory</b>				
Dyspnea	0.7	2.1	0.7	1.9
Rhinitis	0.5	1.3	1.0	2.4
<b>Urogenital</b>				
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  $\geq 55$  years of age with a normal digital rectal examination and a PSA  $\leq 3.0$  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%) [*see and Precautions (5.2)*]. In a 4-year placebo-controlled clinical trial with another 5 $\alpha$ -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. The following adverse reactions were reported (see Table 3).

**Table 3: Adverse Reactions Reported by  $\geq 1\%$  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**

<b>Adverse Reaction</b>	<b>Tadalafil 5 mg (N=581)</b>	<b>Placebo (N=576)</b>
<b>Headache</b>	4.1%	2.3%
<b>Dyspepsia</b>	2.4%	0.2%
<b>Back pain</b>	2.4%	1.4%
<b>Nasopharyngitis</b>	2.1%	1.6%
<b>Diarrhea</b>	1.4%	1.0%
<b>Pain in extremity</b>	1.4%	0.0%
<b>Myalgia</b>	1.2%	0.3%
<b>Dizziness</b>	1.0%	0.5%

Additional, less frequent adverse reactions ( $<1\%$ ) reported in the controlled clinical trials of tadalafil for BPH or a different indication and BPH included: gastroesophageal reflux disease, upper abdominal pain, nausea, vomiting, arthralgia, and muscle spasm.

### *Back Pain*

Back pain or myalgia was reported at incidence rates described in Table 3. In tadalafil clinical pharmacology trials, back pain or myalgia generally occurred 12 to 24 hours after dosing and typically resolved within 48 hours. The back pain/myalgia associated with tadalafil treatment was characterized by diffuse bilateral lower lumbar, gluteal, thigh, or thoracolumbar muscular discomfort and was exacerbated by recumbency. In general, pain was reported as mild or moderate in severity and resolved without medical treatment, but severe back pain was reported

with a low frequency (<5% of all reports). When medical treatment was necessary, acetaminophen or non-steroidal anti-inflammatory drugs were generally effective; however, in a small percentage of subjects who required treatment, a mild narcotic (e.g., codeine) was used. In the 1-year open label extension study, back pain and myalgia were reported in 5.5% and 1.3% of patients, respectively. Diagnostic testing, including measures for inflammation, muscle injury, or renal damage revealed no evidence of medically significant underlying pathology. In studies of tadalafil for once daily use, adverse reactions of back pain and myalgia were generally mild or moderate with a discontinuation rate of <1% across all indications.

Across all studies with any tadalafil dose, changes in color vision were reported in <0.1% of patients.

The following section identifies additional events (<2%) reported in controlled clinical trials of tadalafil (a component of ENTADFI) including trials for an unapproved use of ENTADFI. A causal relationship of these events to tadalafil is uncertain. Excluded from this list are those events that were minor, those with no plausible relation to drug use, and reports too imprecise to be meaningful:

- Body as a Whole — asthenia, face edema, fatigue, pain, peripheral edema
- Cardiovascular — angina pectoris, chest pain, hypotension, myocardial infarction, postural hypotension, palpitations, syncope, tachycardia
- Digestive — abnormal liver function tests, dry mouth, dysphagia, esophagitis, gastritis, GGTP increased, loose stools, nausea, upper abdominal pain, vomiting, gastroesophageal reflux disease, hemorrhoidal hemorrhage, rectal hemorrhage
- Musculoskeletal — arthralgia, neck pain
- Nervous — dizziness, hypesthesia, insomnia, paresthesia, somnolence, vertigo
- Renal and Urinary — renal impairment
- Respiratory — dyspnea, epistaxis, pharyngitis
- Skin and Appendages — pruritus, rash, sweating
- Ophthalmologic — blurred vision, changes in color vision, conjunctivitis (including conjunctival hyperemia), eye pain, lacrimation increase, swelling of eyelids
- Otologic — sudden decrease or loss of hearing, tinnitus
- Urogenital — erection increased, spontaneous penile erection

## 6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of finasteride monotherapy and tadalafil. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

### 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

## 7 DRUG INTERACTIONS

### 7.1 Effects of Other Drugs on ENTADFI

*CYP3A4* (e.g., *Ketoconazole*) — Concomitant use of strong inhibitors (e.g., ketoconazole) of CYP3A4 is not recommended as they may increase tadalafil exposure.

### 7.2 Effects of ENTADFI on Other Drugs

Nitrates — Administration of ENTADFI to patients who are using any form of organic nitrate, is contraindicated. In clinical pharmacology studies, tadalafil was shown to potentiate the hypotensive effect of nitrates. In a patient who has taken ENTADFI, where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should elapse 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 [*see Contraindications (4), and Clinical Pharmacology (12.2)*].

Guanylate Cyclase Stimulators — Administration of ENTADFI to patients taking a guanylate cyclase (GC) stimulator is contraindicated. ENTADFI may potentiate the hypotensive effects of GC stimulators [*see Contraindications (4)*].

Alpha-Blockers — 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 [see *Warnings and Precautions (5.3)*, and *Clinical Pharmacology (12.2)*].

Antihypertensives — PDE5 inhibitors, including tadalafil, are mild systemic vasodilators. Clinical pharmacology studies were conducted to assess the effect of tadalafil on the potentiation of the blood-pressure-lowering effects of selected antihypertensive medications (amlodipine, angiotensin II receptor blockers, bendrofluazide, enalapril, and metoprolol). Small reductions in blood pressure occurred following coadministration of tadalafil with these agents compared with placebo [see *Warnings and Precautions (5.3)* and *Clinical Pharmacology (12.2)*].

### **7.3 Alcohol**

Both alcohol and tadalafil, a PDE5 inhibitor, act as mild vasodilators. When mild vasodilators are taken in combination, blood-pressure-lowering effects of each individual compound may be increased. 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. Tadalafil did not affect alcohol plasma concentrations and alcohol did not affect tadalafil plasma concentrations [see *Warnings and Precautions (5.12)* and *Clinical Pharmacology (12.2)*].

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### Risk Summary

ENTADFI 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 ENTADFI, 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 5 $\alpha$ -reductase inhibitor that prevents conversion of testosterone to 5 $\alpha$ -dihydrotestosterone (DHT), a hormone necessary for normal development of male genitalia. Abnormal male genital development is an expected consequence when conversion of testosterone to 5 $\alpha$ -dihydrotestosterone (DHT) is inhibited by 5 $\alpha$ -reductase inhibitors. These outcomes are similar to those reported in male infants with genetic 5 $\alpha$ -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 ENTADFI capsules because of possible exposure of a male fetus [*see Warnings and Precautions (5.7)*].

## 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**

ENTADFI 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 ENTADFI, 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.

#### **8.4 Pediatric Use**

The safety and effectiveness of ENTADFI have not been established in patients less than 18 years of age.

#### **8.5 Geriatric Use**

ENTADFI is a combination of finasteride and tadalafil.

##### Finasteride:

Of the total number of finasteride-treated patients in clinical studies for BPH, 1480 and 105 patients were 65 and over and 75 and over, respectively. No overall differences in safety or effectiveness of finasteride have been observed between patients 65 years of age and older and younger adult patients [see *Clinical Pharmacology 12.3*].

##### Tadalafil:

Of the total number of tadalafil-treated patients in clinical studies which included an indication for which ENTADFI is not approved, approximately 40 percent were over 65 years of age, while approximately 10 percent were 75 years of age and over. No overall differences in safety or effectiveness of tadalafil have been observed between patients over 65 years of age and younger adult patients. However, in placebo-controlled studies with tadalafil for use as needed for a use for which ENTADFI is not approved, diarrhea was reported more frequently in patients 65 years of age and older who were treated with tadalafil (2.5% of patients). A greater sensitivity in some older individuals should be considered [see *Clinical Pharmacology (12.3)*].

#### **8.6 Hepatic Impairment**

The effect of hepatic impairment on finasteride pharmacokinetics has not been studied. However, finasteride is extensively metabolized in the liver. Exercise caution 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. [see *Clinical Pharmacology (12.3)*].

#### **8.7 Renal Impairment**

Due to increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to influence clearance by dialysis, ENTADFI use is not recommended in patients with creatinine clearance less than 50 mL/min or on hemodialysis [see *Clinical Pharmacology (12.3)*].

## **10 OVERDOSAGE**

In cases of overdose, standard supportive measures should be adopted as required. Hemodialysis contributes negligibly to tadalafil elimination.

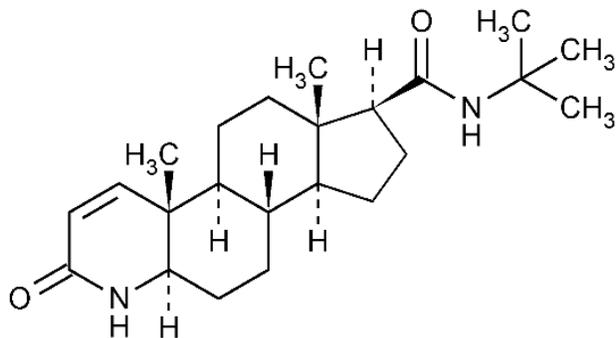
## 11 DESCRIPTION

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

### Finasteride:

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

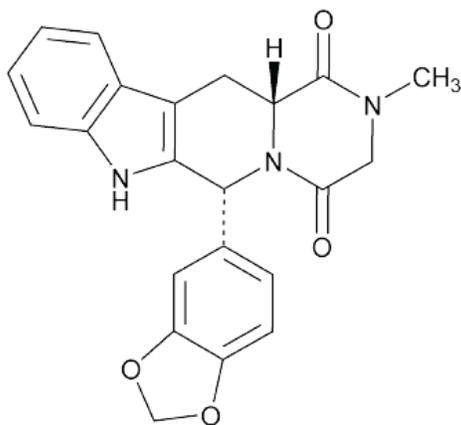
The chemical designation of finasteride is 4-azaandrost-1-ene-17-carboxamide, N-(1,1-dimethylethyl)-3-oxo-, (5 $\alpha$ ,17 $\beta$ )-. The empirical formula of finasteride is C<sub>23</sub>H<sub>36</sub>N<sub>2</sub>O<sub>2</sub> and its molecular weight is 372.55. Its structural formula is:



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

### Tadalafil:

Tadalafil is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). Tadalafil has the empirical formula C<sub>22</sub>H<sub>19</sub>N<sub>3</sub>O<sub>4</sub> representing a molecular weight of 389.41. The structural formula is:



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

ENTADFI is available as size 3, white opaque capsules for oral administration. Each ENTADFI capsule contains finasteride 5 mg and tadalafil 5 mg and the following inactive ingredients: colloidal silicon dioxide, lactose monohydrate, magnesium stearate, silicified microcrystalline cellulose, sodium lauryl sulfate, and sodium starch glycolate. The capsule shell is composed of carrageenan, hypromellose, potassium chloride, titanium dioxide, and is printed with an edible black printing ink.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

ENTADFI is a combination of finasteride and tadalafil.

#### Finasteride:

The development and enlargement of the prostate gland is dependent on the potent androgen, 5 $\alpha$ -dihydrotestosterone (DHT). Type II 5 $\alpha$ -reductase metabolizes testosterone to DHT in the prostate gland, liver and skin. DHT induces androgenic effects by binding to androgen receptors in the cell nuclei of these organs.

Finasteride is a competitive and specific inhibitor of Type II 5 $\alpha$ -reductase with which it slowly forms a stable enzyme complex. Turnover from this complex is extremely slow ( $t_{1/2}$  ~ 30 days). This has been demonstrated both *in vivo* and *in vitro*. Finasteride has no affinity for the androgen receptor. In man, the 5 $\alpha$ -reduced steroid metabolites in blood and urine are decreased after administration of finasteride.

#### Tadalafil:

The mechanism for reducing BPH symptoms has not been established. Studies *in vitro* have demonstrated that tadalafil is a selective inhibitor of phosphodiesterase 5 (PDE5). PDE5 is found in the smooth muscle of the corpus cavernosum, prostate, and bladder as well as in vascular and visceral smooth muscle, skeletal muscle, urethra, platelets, kidney, lung, cerebellum, heart, liver, testis, seminal vesicle, and pancreas.

*In vitro* studies have shown that the effect of tadalafil is more potent on PDE5 than on other phosphodiesterases. These studies have shown that tadalafil is >10,000-fold more potent for PDE5 than for PDE1, PDE2, PDE4, and PDE7 enzymes, which are found in the heart, brain, blood vessels, liver, leukocytes, skeletal muscle, and other organs. Tadalafil is >10,000-fold more potent for PDE5 than for PDE3, an enzyme found in the heart and blood vessels. Additionally, tadalafil is 700-fold more potent for PDE5 than for PDE6, which is found in the retina and is responsible for phototransduction. Tadalafil is >9,000-fold more potent for PDE5 than for PDE8, PDE9, and PDE10. Tadalafil is 14-fold more potent for PDE5 than for PDE11A1 and 40-fold more potent for PDE5 than for PDE11A4, two of the four known forms of PDE11. PDE11 is an enzyme found in human prostate, testes, skeletal muscle and in other tissues (e.g., adrenal cortex). *In vitro*, tadalafil inhibits human recombinant PDE11A1 and, to a lesser degree, PDE11A4 activities at concentrations within the therapeutic range. The physiological role and clinical consequence of PDE11 inhibition in humans have not been defined.

## 12.2 Pharmacodynamics

### Finasteride:

In man, a single 5-mg oral dose of finasteride produces a rapid reduction in serum DHT concentration, with the maximum effect observed 8 hours after the first dose. The suppression of DHT is maintained throughout the 24-hour dosing interval and with continued treatment. Daily dosing of finasteride at 5 mg/day for up to 4 years has been shown to reduce the serum DHT concentration by approximately 70%. The median circulating level of testosterone increased by approximately 10-20% but remained within the physiologic range. In a separate study in healthy men treated with finasteride 1 mg per day (n=82) or placebo (n=69), mean circulating levels of testosterone and estradiol were increased by approximately 15% as compared to baseline, but these remained within the physiologic range.

In patients receiving finasteride 5 mg/day, increases of about 10% were observed in luteinizing hormone (LH) and follicle-stimulating hormone (FSH), but levels remained within the normal range. In healthy volunteers, treatment with finasteride did not alter the response of LH and FSH to gonadotropin-releasing hormone indicating that the hypothalamic-pituitary-testicular axis was not affected.

In patients with BPH, finasteride has no effect on circulating levels of cortisol, prolactin, thyroid-stimulating hormone, or thyroxine. No clinically meaningful effect was observed on the plasma lipid profile (i.e., total cholesterol, low density lipoproteins, high density lipoproteins and triglycerides) or bone mineral density.

Adult males with genetically inherited Type II 5 $\alpha$ -reductase deficiency also have decreased levels of DHT. Except for the associated urogenital defects present at birth, no other clinical abnormalities related to Type II 5 $\alpha$ -reductase deficiency have been observed in these individuals. These individuals have a small prostate gland throughout life and do not develop BPH.

In patients with BPH treated with finasteride (1-100 mg/day) for 7-10 days prior to prostatectomy, an approximate 80% lower DHT content was measured in prostatic tissue removed at surgery, compared to placebo; testosterone tissue concentration was increased up to 10 times over pretreatment levels, relative to placebo. Intraprostatic content of PSA was also decreased.

In healthy male volunteers treated with finasteride 5 mg/day for 14 days, discontinuation of therapy resulted in a return of DHT levels to pretreatment levels in approximately 2 weeks. In patients treated for three months, prostate volume, which declined by approximately 20%, returned to close to baseline value after approximately three months of discontinuation of therapy.

### Tadalafil:

#### *Effects on Blood Pressure*

Tadalafil 20 mg administered to healthy male subjects produced no significant difference compared to placebo in supine systolic and diastolic blood pressure (difference in the mean maximal decrease of 1.6/0.8 mm Hg, respectively) and in standing systolic and diastolic blood pressure (difference in the mean maximal decrease of 0.2/4.6 mm Hg, respectively). In addition, there was no significant effect on heart rate.

### *Effects on Blood Pressure When Administered with Nitrates*

In clinical pharmacology studies, tadalafil (5 to 20 mg) was shown to potentiate the hypotensive effect of nitrates. Therefore, the use of ENTADFI in patients taking any form of nitrates is contraindicated [*see Contraindications (4)*].

A study was conducted to assess the degree of interaction between nitroglycerin and tadalafil, should nitroglycerin be required in an emergency situation after tadalafil was taken. This was a double-blind, placebo-controlled, crossover study in 150 male subjects at least 40 years of age (including subjects with diabetes mellitus and/or controlled hypertension) and receiving daily doses of tadalafil 20 mg or matching placebo for 7 days. Subjects were administered a single dose of 0.4 mg sublingual nitroglycerin (NTG) at pre-specified timepoints, following their last dose of tadalafil (2, 4, 8, 24, 48, 72, and 96 hours after tadalafil). The objective of the study was to determine when, after tadalafil dosing, no apparent blood pressure interaction was observed. In this study, a significant interaction between tadalafil and NTG was observed at each timepoint up to and including 24 hours. At 48 hours, by most hemodynamic measures, the interaction between tadalafil and NTG was not observed, although a few more tadalafil subjects compared to placebo experienced greater blood-pressure lowering at this timepoint. After 48 hours, the interaction was not detectable (see Figure 1).











**Table 9: Alfuzosin (10 mg/day) Study: Mean Maximal Decrease (95% CI) in Systolic Blood Pressure**

Placebo-subtracted mean maximal decrease in systolic blood pressure (mm Hg)	Tadalafil 20 mg
Supine	2.2 (-0.9,-5.2)
Standing	4.4 (-0.2, 8.9)

Blood pressure was measured manually at 1, 2, 3, 4, 6, 8, 10, 20, and 24 hours after tadalafil or placebo dosing. There was 1 outlier (subject with a standing systolic blood pressure <85 mm Hg) following administration of tadalafil 20 mg. There were no subjects with a decrease from baseline in standing systolic blood pressure of >30 mm Hg at one or more time points. No severe adverse events potentially related to blood pressure effects were reported. No syncope was reported.

*Effects on Blood Pressure When Administered with Antihypertensives*

*Amlodipine* — A study was conducted to assess the interaction of amlodipine (5 mg daily) and tadalafil 10 mg. There was no effect of tadalafil on amlodipine blood levels and no effect of amlodipine on tadalafil blood levels. The mean reduction in supine systolic/diastolic blood pressure due to tadalafil 10 mg in subjects taking amlodipine was 3/2 mm Hg, compared to placebo. In a similar study using tadalafil 20 mg, there were no clinically significant differences between tadalafil and placebo in subjects taking amlodipine.

*Angiotensin II receptor blockers (with and without other antihypertensives)* — A study was conducted to assess the interaction of angiotensin II receptor blockers and tadalafil 20 mg. Subjects in the study were taking any marketed angiotensin II receptor blocker, either alone, as a component of a combination product, or as part of a multiple antihypertensive regimen. Following dosing, ambulatory measurements of blood pressure revealed differences between tadalafil and placebo of 8/4 mm Hg in systolic/diastolic blood pressure.

*Bendrofluazide* — A study was conducted to assess the interaction of bendrofluazide (2.5 mg daily) and tadalafil 10 mg. Following dosing, the mean reduction in supine systolic/diastolic blood pressure due to tadalafil 10 mg in subjects taking bendrofluazide was 6/4 mm Hg, compared to placebo.

*Enalapril* — A study was conducted to assess the interaction of enalapril (10 to 20 mg daily) and tadalafil 10 mg. Following dosing, the mean reduction in supine systolic/diastolic blood pressure due to tadalafil 10 mg in subjects taking enalapril was 4/1 mm Hg, compared to placebo.

*Metoprolol* — A study was conducted to assess the interaction of sustained-release metoprolol (25 to 200 mg daily) and tadalafil 10 mg. Following dosing, the mean reduction in supine systolic/diastolic blood pressure due to tadalafil 10 mg in subjects taking metoprolol was 5/3 mm Hg, compared to placebo.

*Effects on Blood Pressure When Administered with Alcohol*

Alcohol and PDE5 inhibitors, including tadalafil, are mild systemic vasodilators. The interaction of tadalafil with alcohol was evaluated in 3 clinical pharmacology studies. In 2 of these, alcohol was administered at a dose of 0.7 g/kg, which is equivalent to approximately 6 ounces of 80-proof vodka in an 80-kg male, and tadalafil was administered at a dose of 10 mg in one study and

20 mg in another. In both these studies, all patients imbibed the entire alcohol dose within 10 minutes of starting. In one of these two studies, blood alcohol levels of 0.08% were confirmed. In these two studies, more patients had clinically significant decreases in blood pressure on the combination of tadalafil and alcohol as compared to alcohol alone. Some subjects reported postural dizziness, and orthostatic hypotension was observed in some subjects. When tadalafil 20 mg was administered with a lower dose of alcohol (0.6 g/kg, which is equivalent to approximately 4 ounces of 80-proof vodka, administered in less than 10 minutes), orthostatic hypotension was not observed, dizziness occurred with similar frequency to alcohol alone, and the hypotensive effects of alcohol were not potentiated.

Tadalafil did not affect alcohol plasma concentrations and alcohol did not affect tadalafil plasma concentrations.

#### *Effects on Exercise Stress Testing*

The effects of tadalafil on cardiac function, hemodynamics, and exercise tolerance were investigated in a single clinical pharmacology study. In this blinded crossover trial, 23 subjects with stable coronary artery disease and evidence of exercise-induced cardiac ischemia were enrolled. The primary endpoint was time to cardiac ischemia. The mean difference in total exercise time was 3 seconds (tadalafil 10 mg minus placebo), which represented no clinically meaningful difference. Further statistical analysis demonstrated that tadalafil was non-inferior to placebo with respect to time to ischemia. Of note, in this study, in some subjects who received tadalafil followed by sublingual nitroglycerin in the post-exercise period, clinically significant reductions in blood pressure were observed, consistent with the augmentation by tadalafil of the blood-pressure-lowering effects of nitrates.

#### *Effects on Vision*

Single oral doses of phosphodiesterase inhibitors have demonstrated transient dose-related impairment of color discrimination (blue/green), using the Farnsworth-Munsell 100-hue test, with peak effects near the time of peak plasma levels. This finding is consistent with the inhibition of PDE6, which is involved in phototransduction in the retina. In a study to assess the effects of a single dose of tadalafil 40 mg on vision (N=59), no effects were observed on visual acuity, intraocular pressure, or pupillometry. Across all clinical studies with tadalafil, reports of changes in color vision were rare (<0.1% of patients).

#### *Effects on Sperm Characteristics*

Three studies were conducted in men to assess the potential effect on sperm characteristics of tadalafil 10 mg (one 6 month study) and 20 mg (one 6 month and one 9 month study) administered daily. There were no adverse effects on sperm morphology or sperm motility in any of the three studies. In the study of 10 mg tadalafil for 6 months and the study of 20 mg tadalafil for 9 months, results showed a decrease in mean sperm concentrations relative to placebo, although these differences were not clinically meaningful. This effect was not seen in the study of 20 mg tadalafil taken for 6 months. In addition there was no adverse effect on mean concentrations of reproductive hormones, testosterone, luteinizing hormone or follicle stimulating hormone with either 10 or 20 mg of tadalafil compared to placebo.

#### *Effects on Cardiac Electrophysiology*

The effect of a single 100-mg dose of tadalafil on the QT interval was evaluated at the time of peak tadalafil concentration in a randomized, double-blinded, placebo, and active (intravenous ibutilide) -controlled crossover study in 90 healthy males aged 18 to 53 years. The mean change in QTc (Fridericia QT correction) for tadalafil, relative to placebo, was 3.5 milliseconds (two-sided 90% CI=1.9, 5.1). The mean change in QTc (Individual QT correction) for tadalafil, relative to placebo, was 2.8 milliseconds (two-sided 90% CI=1.2, 4.4). A 100-mg dose of tadalafil (20 times the highest recommended dose) was chosen because this dose yields exposures covering those observed upon coadministration of tadalafil with strong CYP3A4 inhibitors or those observed in renal impairment. In this study, the mean increase in heart rate associated with a 100-mg dose of tadalafil compared to placebo was 3.1 beats per minute.

### 12.3 Pharmacokinetics

The pharmacokinetic parameter of finasteride and tadalafil after single dose administration of ENTADFI under fasted conditions are summarized in Table 10.

**Table 10: Pharmacokinetic Parameters of Finasteride and Tadalafil After Single Dose Administration of ENTADFI**

	Finasteride		Tadalafil	
	Mean	CV (%)	Mean	CV (%)
$C_{max}$ (ng/mL)	43.224	(24.1)	106.751	(23.6)
$T_{max}$ (hours) <sup>a</sup>	2.00	(1.00-4.07)	3.00	(1.00-4.05)
$AUC_t$ (ng*h/mL)	335.811	(28.0)	2507.502	(31.9)
$AUC_{\infty}$ (ng*h/mL)	339.832	(28.5)	2682.645	(35.3)
$t_{1/2}$ (hours)	6.63	(24.5)	22.33	(24.9)

Abbreviations: CV = coefficient of variation

a. Median and range are presented

#### **Absorption**

##### *Finasteride*

In a study of 15 healthy young subjects, the mean bioavailability of finasteride 5 mg tablets was 63% (range 34-108%).

##### *Tadalafil*

Absolute bioavailability of tadalafil following oral dosing has not been determined.

##### *Effect of Food*

The  $C_{max}$  of finasteride and tadalafil were decreased by 29% and 23%, respectively, after administration of ENTADFI following consumption of a high-fat, high-calorie meal (i.e., 1011 calorie meal in which 53% of calories are derived from fat) compared with the fasted state. The administration of ENTADFI with high-fat, high-calorie meal did not affect the extent of absorption ( $AUC_t$  and  $AUC_{\infty}$ ) for finasteride and tadalafil.

#### **Distribution**

##### *Finasteride*

Mean steady-state volume of distribution was 76 liters (range, 44-96 liters). Approximately 90% of circulating finasteride is bound to plasma proteins.

Finasteride has been shown to cross the blood brain barrier but does not appear to distribute preferentially to the CSF.

In two studies of healthy subjects (n=69) receiving finasteride 5 mg/day for 6-24 weeks, finasteride concentrations in semen ranged from undetectable (<0.1 ng/mL) to 10.54 ng/mL. In an earlier study using a less sensitive assay, finasteride concentrations in the semen of 16 subjects receiving finasteride 5 mg/day ranged from undetectable (<1.0 ng/mL) to 21 ng/mL. Thus, based on a 5-mL ejaculate volume, the amount of finasteride in semen was estimated to be 50- to 100-fold less than the dose of finasteride (5 µg) that had no effect on circulating DHT levels in men [*see also Use in Specific Populations (8.3)*].

### *Tadalafil*

The mean apparent volume of distribution following oral administration is approximately 63 L, indicating that tadalafil is distributed into tissues. At therapeutic concentrations, 94% of tadalafil in plasma is bound to proteins.

Less than 0.0005% of the administered dose appeared in the semen of healthy subjects.

### ***Elimination***

#### *Metabolism*

##### *Finasteride*

Finasteride is extensively metabolized in the liver, primarily via CYP3A4. Two metabolites, the t-butyl side chain monohydroxylated and monocarboxylic acid metabolites, have been identified that possess no more than 20% of the 5 $\alpha$ -reductase inhibitory activity of finasteride.

##### *Tadalafil*

Tadalafil is predominantly metabolized by CYP3A4 to a catechol metabolite. The catechol metabolite undergoes extensive methylation and glucuronidation to form the methylcatechol and methylcatechol glucuronide conjugate, respectively. The major circulating metabolite is the methylcatechol glucuronide. Methylcatechol concentrations are less than 10% of glucuronide concentrations. In vitro data suggests that metabolites are not expected to be pharmacologically active at observed metabolite concentrations.

#### *Excretion*

##### *Finasteride*

Following an oral dose of <sup>14</sup>C-finasteride in man (n=6), a mean of 39% (range, 32-46%) of the dose was excreted in the urine in the form of metabolites; 57% (range, 51-64%) was excreted in the feces.

##### *Tadalafil*

Tadalafil is excreted predominantly as metabolites, mainly in the feces (approximately 61% of the dose) and to a lesser extent in the urine (approximately 36% of the dose).

### ***Specific Populations***

#### *Geriatric Patients*

No dosage adjustment of ENTADFI is necessary in the elderly. In patients with BPH following single and multiple doses of 20 mg tadalafil, no statistically significant differences in exposure (AUC and  $C_{max}$ ) were observed between elderly (70 to 85 years) and younger ( $\leq 60$  years of age) subjects. Healthy male elderly subjects (65 years or over) had a lower renal clearance of tadalafil, resulting in 25% higher exposure (AUC) with no effect on  $C_{max}$  relative to that observed in healthy subjects 19 to 45 years of age. No dose adjustment is warranted based on age alone. However, greater sensitivity to medications in some older individuals should be considered [see *Use in Specific Populations (8.5)*].

Although the elimination rate of finasteride is decreased in the elderly, these findings are of no clinical significance [see *Use in Specific Populations (8.5)*].

**Table 11: Mean (SD) Noncompartmental Pharmacokinetic Parameters After Multiple Finasteride Doses of 5 mg/day in Older Men**

	Mean ( $\pm$ SD)	
	45-60 years old (n=12)	$\geq 70$ years old (n=12)
AUC (ng*hr/mL)	389 (98)	463 (186)
$C_{max}$ (ng/mL)	46.2 (8.7)	48.4 (14.7)
$T_{max}$ (hours)	1.8 (0.7)	1.8 (0.6)
$t_{1/2}$ (hours) <sup>a</sup>	6.0 (1.5)	8.2 (2.5)

<sup>a</sup> First-dose values; all other parameters are last-dose values

### ***Race***

The effect of race on the pharmacokinetics of finasteride or tadalafil has not been studied.

### ***Patients with Diabetes Mellitus***

In male patients with diabetes mellitus after a 10 mg tadalafil dose, exposure (AUC) was reduced approximately 19% and  $C_{max}$  was 5% lower than that observed in healthy subjects. The dose of tadalafil in ENTADFI is 5 mg per day. No dose adjustment is warranted with ENTADFI in patients with diabetes mellitus.

### ***Patients with Renal Impairment***

#### ***Finasteride***

In patients with chronic renal impairment, with creatinine clearances ranging from 9.0 to 55 mL/min, AUC, maximum plasma concentration, half-life, and protein binding of finasteride after a single dose of <sup>14</sup>C-finasteride were similar to values obtained in healthy volunteers. Plasma concentrations of metabolites were significantly higher in patients with renal impairment (based on a 60% increase in total radioactivity AUC). The increased plasma concentrations of finasteride metabolites were not clinically meaningful.

#### ***Tadalafil***

In clinical pharmacology studies using single-dose tadalafil (5 to 10 mg), tadalafil exposure (AUC) doubled in subjects with creatinine clearance 30 to 80 mL/min. In subjects with end-stage renal disease on hemodialysis, there was a 2-fold increase in  $C_{max}$  and 2.7- to 4.8-fold increase in AUC following single-dose administration of 10 or 20 mg tadalafil. Exposure to total methylcatechol (unconjugated plus glucuronide) was 2- to 4-fold higher in subjects with renal impairment, compared to those with normal renal function. Hemodialysis (performed between

24- and 30-hour post-dose) contributed negligibly to tadalafil or metabolite elimination. In a clinical pharmacology study (N=28) at a dose of 10 mg, back pain was reported as a limiting adverse event in male patients with creatinine clearance 30 to 50 mL/min. At a dose of 5 mg, the incidence and severity of back pain was not significantly different than in the general population. In patients on hemodialysis taking 10- or 20-mg tadalafil, there were no reported cases of back pain [see *Use in Specific Populations* (8.7)].

### ***Patients with Hepatic Impairment***

#### *Finasteride*

The effect of hepatic impairment on finasteride pharmacokinetics has not been studied.

#### *Tadalafil*

In clinical pharmacology studies, tadalafil exposure (AUC) in patients with mild or moderate hepatic impairment (Child-Pugh Class A or B) was comparable to exposure in healthy subjects when a dose of 10 mg was administered. Insufficient data are available for patients with severe hepatic impairment (Child-Pugh Class C) [see *Use in Specific Populations* (8.6)].

### ***Drug Interaction Studies***

#### *Clinical Studies*

#### *Finasteride*

No drug interactions of clinical importance have been identified for finasteride. Finasteride does not appear to affect the cytochrome P450-linked drug metabolizing enzyme system. Compounds that have been tested in man have included antipyrine, digoxin, propranolol, theophylline, and warfarin and no clinically meaningful interactions were found.

Although specific interaction studies were not performed, finasteride was concomitantly used in clinical studies with acetaminophen, acetylsalicylic acid,  $\alpha$ -blockers, angiotensin-converting enzyme (ACE) inhibitors, analgesics, anti-convulsant, beta-adrenergic blocking agents, diuretics, calcium channel blockers, cardiac nitrates, HMG-CoA reductase inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), benzodiazepines, H<sub>2</sub> antagonists and quinolone anti-infectives without evidence of clinically significant adverse interactions.

#### *Tadalafil*

Antacids — Simultaneous administration of an antacid (magnesium hydroxide/aluminum hydroxide) and tadalafil reduced the apparent rate of absorption of tadalafil without altering exposure (AUC) to tadalafil.

H<sub>2</sub> Antagonists (e.g., Nizatidine) — An increase in gastric pH resulting from administration of nizatidine had no significant effect on pharmacokinetics.

CYP3A4 inhibitors — Ketoconazole (400 mg daily), a selective and strong inhibitor of CYP3A4, increased tadalafil 20 mg single-dose exposure (AUC) by 312% and C<sub>max</sub> by 22%, relative to the values for tadalafil 20 mg alone. Ketoconazole (200 mg daily) increased tadalafil 10-mg single-dose exposure (AUC) by 107% and C<sub>max</sub> by 15%, relative to the values for tadalafil 10 mg alone.

HIV Protease inhibitors — Ritonavir (500 mg or 600 mg twice daily at steady state), an inhibitor of CYP3A4, CYP2C9, CYP2C19, and CYP2D6, increased tadalafil 20-mg single-dose exposure (AUC) by 32% with a 30% reduction in  $C_{max}$ , relative to the values for tadalafil 20 mg alone. Ritonavir (200 mg twice daily), increased tadalafil 20-mg single-dose exposure (AUC) by 124% with no change in  $C_{max}$ , relative to the values for tadalafil 20 mg alone.

CYP3A4 inducers — Rifampin (600 mg daily), a CYP3A4 inducer, reduced tadalafil 10-mg single-dose exposure (AUC) by 88% and  $C_{max}$  by 46%, relative to the values for tadalafil 10 mg alone.

Aspirin — Tadalafil did not potentiate the increase in bleeding time caused by aspirin.

CYP1A2 substrates — Tadalafil had no significant effect on the pharmacokinetics of theophylline (CYP1A2 substrate). When tadalafil was administered to subjects taking theophylline, a small augmentation (3 beats per minute) of the increase in heart rate associated with theophylline was observed.

CYP2C9 substrates — Tadalafil had no significant effect on exposure (AUC) to S-warfarin or R-warfarin (CYP2C9 substrate), nor did tadalafil affect changes in prothrombin time induced by warfarin.

CYP3A4 substrates — Tadalafil had no significant effect on exposure (AUC) to midazolam or lovastatin (CYP3A4 substrates).

P-glycoprotein (P-gp) substrates — Coadministration of tadalafil (40 mg once per day) for 10 days did not have a significant effect on the steady-state pharmacokinetics of digoxin (P-gp substrate) administered 0.25 mg/day in healthy subjects.

#### *In Vitro Studies*

Tadalafil does not inhibit or induce CYP1A2, CYP3A4, CYP2C9, CYP2C19, CYP2D6, and CYP2E1.

## **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  $AUC_{(0-24 \text{ hr})}$  for animals and mean  $AUC_{(0-24 \text{ hr})}$  for man ( $0.4 \mu\text{g}\cdot\text{hr}/\text{mL}$ ). 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  $\geq 10$  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.

## 14 CLINICAL STUDIES

The efficacy of ENTADFI is based on an adequate and well-controlled study of tadalafil co-administered with finasteride. Below is the description of this study.

Tadalafil for once daily use initiated together with finasteride was shown to be effective in treating the signs and symptoms of BPH in men with an enlarged prostate (>30 cc) for up to 26 weeks. 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 (see Table 12). 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, as shown in Table 12 and in Figure 4. The incremental benefit of ENTADFI beyond 26 weeks is unknown.

**Table 12: 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) <sup>a</sup>	n	(N=345) <sup>a</sup>		p-value <sup>b</sup>
Total Symptom Score (IPSS)						
Baseline <sup>c</sup>	349	17.4	344	17.1		
Change from Baseline to Week 4 <sup>b</sup>	340	-2.3	330	-4.0	-1.7	<0.001

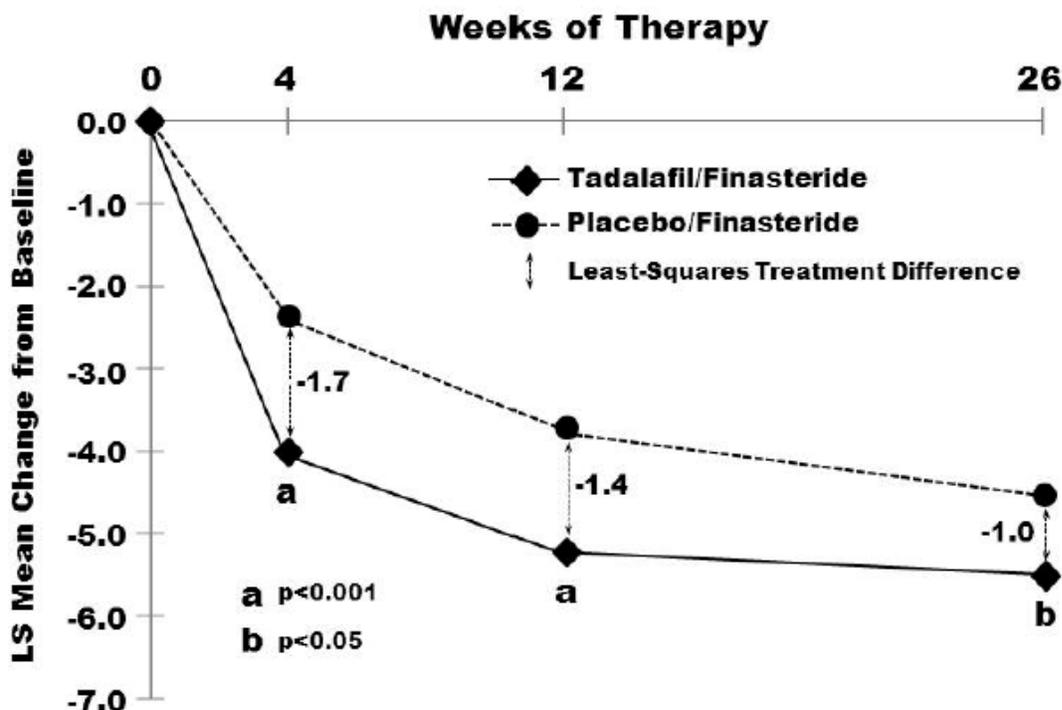
Change from Baseline to Week 12 <sup>b</sup>	318	-3.8	317	-5.2	-1.4	0.001
Change from Baseline to Week 26 <sup>b</sup>	295	-4.5	308	-5.5	-1.0	0.022

<sup>a</sup> Overall ITT population.

<sup>b</sup> Mixed model for repeated measurements.

<sup>c</sup> Unadjusted mean.

**Figure 4: Mean Total IPSS Changes By Visit in BPH Patients Taking Tadalafil Together with Finasteride**



## 16 HOW SUPPLIED/STORAGE AND HANDLING

ENTADFI is a combination of finasteride and tadalafil.

### *How Supplied*

ENTADFI capsules contain finasteride 5 mg and tadalafil 5 mg. The size 3 capsules have an opaque white cap and body with a black two-line bar printed on the cap and body.

ENTADFI is supplied as follows: HDPE bottles with a low moisture polyester coil and sealed with a heat-sealed foil HDPE cap as 30-count per bottle (NDC 69681-125-30) or 90-count per bottle (NDC 69681-125-90).

### *Storage and Handling*

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

## 17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Patient Information).

### Cardiovascular Risk

Inform patients that concomitant use of ENTADFI with nitrates could cause blood pressure to suddenly drop to an unsafe level, resulting in dizziness, syncope, or even heart attack or stroke. Advise patients not to take ENTADFI with nitrates unless directly instructed to do so by a health care provider [*see Warnings and Precautions (5.1 and 5.3)*].

### Concomitant Use with Guanylate Cyclase (GC) Stimulators

Advise patients not to take GC stimulators when taking ENTADFI because concomitant use may cause blood pressure to drop to an unsafe level [*see Contraindications (4)*].

### Concomitant Use with Alpha-blockers or Other Antihypertensives

Advise patients of the potential for ENTADFI to augment the blood-pressure-lowering effect of alpha-blockers and antihypertensive medications [*see Warnings and Precautions (5.3)*].

### Increased Risk of High-Grade Prostate Cancer

Inform patients that there was an increase in high-grade prostate cancer in men treated with 5 $\alpha$ -reductase inhibitors indicated for BPH treatment, including finasteride, compared to those treated with placebo in studies looking at the use of these drugs to prevent prostate cancer [*see Warnings and Precautions (5.5)*].

### Risks to Male Fetus from Topical Exposure of ENTADFI to Pregnant Females

Inform patients that pregnant females should not handle crushed or open ENTADFI capsules because of the possibility of absorption of finasteride and the subsequent potential risk to the male fetus of a pregnant individual. Advise pregnant females who come in contact with crushed or open ENTADFI capsules to immediately wash the area with soap and water [*see Warnings and Precautions (5.7)*].

### Prolonged Erection and Priapism

Inform patients that ENTADFI may cause prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration). Advise patients that priapism, if not treated promptly, can result in irreversible damage to the erectile tissue. Advise patients who have an erection lasting greater than 4 hours, whether painful or not, to seek emergency medical attention [*see Warnings and Precautions (5.9)*].

### Ocular Adverse Reactions

Advise patients to stop use of all PDE5 inhibitors, including ENTADFI, and seek medical attention in the event of a sudden loss of vision in one or both eyes. Inform patients that such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision, including possible permanent loss of vision, that has been reported rarely postmarketing in temporal association with the use of all PDE5 inhibitors [*see Warnings and Precautions (5.10)*].

### Sudden Hearing Loss

Advise patients to stop taking PDE5 inhibitors, including ENTADFI, and seek prompt medical attention in the event of sudden decrease or loss of hearing. Inform patients that these events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors, such as ENTADFI [*Warning and Precautions (5.5)*].

Concomitant Use with Alcohol

Advise 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 [*see Warnings and Precautions (5.12)*].

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

**ENTADFI is for use by men only**

Read this important information before you start taking ENTADFI and each time you get a refill. There may be new information. You may also find it helpful to share this information with your partner. This information does not take the place of talking with your healthcare provider. You and your healthcare provider should talk about ENTADFI when you start taking it and at regular checkups. If you do not understand the information, or have questions, talk with your healthcare provider or pharmacist.

## **What Is The Most Important Information I Should Know About ENTADFI?**

**ENTADFI can cause your blood pressure to drop suddenly to an unsafe level if it is taken with certain other medicines.** You could get dizzy, faint, or have a heart attack or stroke. Never take ENTADFI with any nitrate or guanylate cyclase stimulator medicines.

Do not take ENTADFI if you **take any medicines called “nitrates.”** Nitrates are commonly used to treat angina. Angina is a symptom of heart disease and can cause pain in your chest, jaw, or down your arm.

- Medicines called nitrates include nitroglycerin that is found in tablets, sprays, ointments, pastes, or patches. Nitrates can also be found in other medicines such as isosorbide dinitrate or isosorbide mononitrate. Some recreational drugs called “poppers” also contain nitrates, such as amyl nitrite and butyl nitrite.

Do not take ENTADFI if you take medicines called guanylate cyclase stimulators which include:

- Riociguat (Adempas®) a medicine that treats pulmonary arterial hypertension and chronic-thromboembolic pulmonary hypertension.

Ask your healthcare provider or pharmacist if you are not sure if any of your medicines are nitrates or guanylate cyclase stimulators, such as riociguat.

Do not take ENTADFI if you are a woman who is pregnant or may potentially be pregnant.

- ENTADFI may harm your unborn baby. Do not touch or handle crushed or open ENTADFI capsules (See **“Who Should Not Take ENTADFI?”** and **“A warning about ENTADFI and pregnancy”**).

Tell all of your healthcare providers that you take ENTADFI. If you need emergency medical care for a heart problem, it will be important for your healthcare provider to know when you last took ENTADFI.

**After taking a single capsule, the tadalafil active ingredient of ENTADFI remains in your body for more than 2 days.** The active ingredient can remain longer if you have problems with

your kidneys or liver, or you are taking certain other medications (see **“Can Other Medicines Affect ENTADFI?”**).

Stop sexual activity and get medical help right away if you get symptoms such as chest pain, dizziness, or nausea during sex. Sexual activity can put an extra strain on your heart, especially if your heart is already weak from a heart attack or heart disease.

See also **“What Are The Possible Side Effects Of ENTADFI?”**

**You should see your doctor regularly while taking ENTADFI.** Follow your doctor's advice about when to have these checkups.

**Checking for prostate cancer.** Your doctor has prescribed ENTADFI for BPH and not for treatment of prostate cancer — but a man can have BPH and prostate cancer at the same time. Your doctor may continue checking for prostate cancer while you take ENTADFI.

**About Prostate-Specific Antigen (PSA).** Your doctor may have done a blood test called PSA for the screening of prostate cancer. Because ENTADFI decreases PSA levels, you should tell your doctor(s) that you are taking ENTADFI. Changes in PSA levels will need to be evaluated by your doctor(s). Any increase in follow-up PSA levels from their lowest point may signal the presence of prostate cancer and should be evaluated, even if the test results are still within the normal range. You should also tell your doctor if you have not been taking ENTADFI as prescribed because this may affect the PSA test results. For more information, talk to your doctor.

## **What Is ENTADFI?**

ENTADFI is a prescription medicine taken by mouth for the treatment of men with symptoms of benign prostatic hyperplasia (BPH).

BPH is a condition that happens in men, where the prostate gland enlarges which can cause urinary symptoms.

## **Who Should NOT Take ENTADFI?**

**ENTADFI is for use by MEN only.**

**Do not take ENTADFI if you:**

- are a woman who is pregnant or may potentially be pregnant. ENTADFI may harm your unborn baby. Do not touch or handle crushed or open ENTADFI capsules (see **“A warning about ENTADFI and pregnancy”**).
- **take any medicines called “nitrates”.**
- use recreational drugs called “poppers” like amyl nitrite and butyl nitrite. (See **“What Is The Most Important Information I Should Know About ENTADFI?”**)
- take any medicines called guanylate cyclase stimulators, such as riociguat.

- **are allergic to ENTADFI or ADCIRCA®, or any of its ingredients.** See the end of this leaflet for a complete list of ingredients in ENTADFI. Symptoms of an allergic reaction may include:
  - **rash**
  - **hives**
  - swelling of the lips, tongue, or throat
  - difficulty breathing or swallowing

Call your healthcare provider or get help right away if you have any of the symptoms of an allergic reaction listed above.

### **A Warning About ENTADFI and pregnancy:**

Women who are or may potentially be pregnant must not use ENTADFI. They should also not handle crushed or open capsules of ENTADFI.

If a woman who is pregnant with a male baby absorbs finasteride, one of the active ingredients in ENTADFI, after oral use or through the skin, it may cause the male baby to be born with abnormalities of the sex organs. If a woman who is pregnant comes into contact with the active ingredient in ENTADFI, a doctor should be consulted.

### **What Should I Tell My Healthcare Provider Before Taking ENTADFI?**

ENTADFI is not right for everyone. **Only your healthcare provider and you can decide if ENTADFI is right for you.** Before taking ENTADFI, tell your healthcare provider about all your medical problems, including if you:

- **have heart problems** such as angina, heart failure, irregular heartbeats, or have had a heart attack.
- **have pulmonary hypertension**
- **have low blood pressure or** have high blood pressure that is not controlled
- **have had a stroke**
- **have liver problems**
- **have kidney problems or require dialysis**
- **have retinitis pigmentosa**, a rare genetic (runs in families) eye disease
- **have ever had severe vision loss, including a condition called NAION**
- **have stomach ulcers**
- **have a bleeding problem**
- **have a deformed penis shape** or Peyronie's disease

- **have had an erection that lasted more than 4 hours**
- **have blood cell problems** such as sickle cell anemia, multiple myeloma, or leukemia

## Can Other Medicines Affect ENTADFI?

Tell your healthcare provider about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements. ENTADFI and other medicines may affect each other. Always check with your healthcare provider before starting or stopping any medicines. Especially tell your healthcare provider if you take any of the following\*:

- medicines called nitrates (see **“What Is The Most Important Information I Should Know About ENTADFI?”**)
- medicines called guanylate cyclase stimulators, such as riociguat (Adempas®), used to treat pulmonary hypertension
- medicines called alpha blockers. These include Hytrin® (terazosin HCl), Flomax® (tamsulosin HCl), Cardura® (doxazosin mesylate), Minipress® (prazosin HCl), Uroxatral® (alfuzosin HCl), Jalyn® (dutasteride and tamsulosin HCl) or Rapaflo® (silodosin). Alpha-blockers are sometimes prescribed for prostate problems or high blood pressure. If ENTADFI is taken with certain alpha blockers, your blood pressure could suddenly drop. You could get dizzy or faint.
- medicines to treat high blood pressure (hypertension)
- medicines called HIV protease inhibitors, such as ritonavir (Norvir®, Kaletra®)
- some types of oral antifungals such as ketoconazole (Nizoral®), itraconazole (Sporanox®)
- some types of antibiotics such as clarithromycin (Biaxin®), telithromycin (Ketek®), erythromycin (several brand names exist. Please consult your healthcare provider to determine if you are taking this medicine).
- medicines or treatments for ED.
- Tadalafil is also marketed as ADCIRCA for the treatment of pulmonary arterial hypertension. Do not take both ENTADFI and ADCIRCA. Do not take sildenafil citrate (Revatio®) with ENTADFI.

## How Should I Take ENTADFI?

- Take ENTADFI exactly as your healthcare provider prescribes it.
- **ENTADFI should be taken without food.**
- If you take too much ENTADFI, call your healthcare provider or emergency room right away.
- **Do not take ENTADFI more than one time each day.**
- Take one ENTADFI capsule every day at about the same time of day.

- If you miss a dose, you may take it when you remember but do not take more than one dose per day.
- Do not share ENTADFI with anyone else; it was prescribed only for you.

## What Should I Avoid While Taking ENTADFI?

- Do not use erectile dysfunction (ED) medicines or ED treatments while taking ENTADFI (unless you discuss with your healthcare provider).
- Do not drink too much alcohol when taking ENTADFI (for example, 5 glasses of wine or 5 shots of whiskey). Drinking too much alcohol can increase your chances of getting a headache or getting dizzy, increasing your heart rate, or lowering your blood pressure.

## What Are The Possible Side Effects Of ENTADFI?

See “What Is The Most Important Information I Should Know About ENTADFI?”

**The most common side effects with tadalafil, an active ingredient in ENTADFI, are:** headache, indigestion, back pain, muscle aches, flushing, and stuffy or runny nose. These side effects usually go away after a few hours. Men who get back pain and muscle aches usually get it 12 to 24 hours after taking ENTADFI. Back pain and muscle aches usually go away within 2 days.

**The most common side effects with finasteride monotherapy are:** trouble getting or keeping an erection (impotence), decrease in sex drive, decreased volume of ejaculate, ejaculation disorders, and enlarged or painful breast. You should promptly report to your doctor any changes in your breasts such as lumps, pain or nipple discharge.

Call your healthcare provider if you get any side effect that bothers you or one that does not go away.

**Uncommon side effects with tadalafil, an active ingredient in ENTADFI include:**

An erection that won't go away (priapism). If you get an erection that lasts more than 4 hours, get medical help right away. Priapism must be treated as soon as possible or lasting damage can happen to your penis, including the inability to have erections.

Color vision changes, such as seeing a blue tinge (shade) to objects or having difficulty telling the difference between the colors blue and green.

In rare instances, men taking PDE5 inhibitors (oral erectile dysfunction medicines, including tadalafil) reported a sudden decrease or loss of vision in one or both eyes. It is uncertain whether PDE5 inhibitors directly cause the vision loss. If you experience sudden decrease or loss of vision, stop taking PDE5 inhibitors, including ENTADFI, and call a healthcare provider right away.

Sudden loss or decrease in hearing, sometimes with ringing in the ears and dizziness, has been rarely reported in people taking PDE5 inhibitors, including tadalafil. It is not possible to determine whether these events are related directly to the PDE5 inhibitors, to other diseases or

medications, to other factors, or to a combination of factors. If you experience these symptoms, stop taking ENTADFI and contact a healthcare provider right away.

The following have been reported in general use with finasteride 5 mg, an active ingredient in ENTADFI, and finasteride at lower doses:

- allergic reactions, including rash, itching, hives, and swelling of the lips, tongue, throat, and face
- rarely, some men may have testicular pain
- blood in semen
- trouble getting or keeping an erection that continued after stopping the medication
- problems with ejaculation that continued after stopping the medication
- male infertility and/or poor quality of semen. Improvement in the quality of semen has been reported after stopping the medication.
- depression
- decrease in sex drive that continued after stopping the medication
- in rare cases, male breast cancer has been reported.

These are not all the possible side effects of ENTADFI. For more information, ask your healthcare provider or pharmacist.

## **How Should I Store ENTADFI?**

Store ENTADFI at room temperature between 59° and 86°F (15° and 30°C).

**Keep ENTADFI and all medicines out of the reach of children.**

**Women should not handle crushed or open ENTADFI capsules when they are pregnant or may potentially be pregnant** because of the possibility of absorption of finasteride and the subsequent potential risk to a male fetus.

## **General Information About ENTADFI:**

Medicines are sometimes prescribed for conditions other than those described in patient information leaflets. Do not use ENTADFI for a condition for which it was not prescribed. Do not give ENTADFI to other people, even if they have the same symptoms that you have. It may harm them.

This is a summary of the most important information about ENTADFI. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about ENTADFI that is written for health providers. For more information you can also visit [www.verupharma.com](http://www.verupharma.com), or call 1-8##-###-####.

## **What Are The Ingredients In ENTADFI?**

Active Ingredients: finasteride and tadalafil

Inactive Ingredients: carrageenan, hypromellose, lactose monohydrate, potassium chloride, sodium starch glycolate, sodium lauryl sulfate, silicified microcrystalline cellulose, colloidal silicon dioxide, titanium dioxide, and magnesium stearate.

## What is BPH?

BPH is an enlargement of the prostate gland. The prostate is located below the bladder. As the prostate enlarges, it may slowly restrict the flow of urine. This can lead to symptoms such as:

- a weak or interrupted urinary stream
- a feeling that you cannot empty your bladder completely
- a feeling of delay or hesitation when you start to urinate
- a need to urinate often, especially at night
- a feeling that you must urinate right away.

In some men, BPH can lead to serious problems, including urinary tract infections, a sudden inability to pass urine (acute urinary retention), as well as the need for surgery.

## What ENTADFI does:

ENTADFI contains finasteride and tadalafil. Finasteride lowers levels of a hormone called DHT (dihydrotestosterone), which is a cause of prostate growth. Lowering DHT leads to shrinkage of the enlarged prostate gland in most men. This can lead to gradual improvement in urine flow and symptoms over the next several months. ENTADFI will help reduce the risk of developing a sudden inability to pass urine (urinary retention) and the need for surgery related to an enlarged prostate. Tadalafil may reduce BPH symptoms by inhibiting the action of an enzyme called PDE5 (phosphodiesterase 5), which relaxes the smooth muscle found in the part of the prostate that surrounds the urethra resulting in the release of the restriction to the flow of urine through the urethra. However, since each case of BPH is different, you should know that:

- Even though the prostate shrinks, you may NOT notice an improvement in urine flow or symptoms.
- You may need to take ENTADFI for up to 26 weeks to see whether it improves your symptoms.
- Therapy with ENTADFI may reduce your risk for a sudden inability to pass urine and empty your bladder and the need for surgery for an enlarged prostate.

This Patient Information has been approved by the U.S. Food and Drug Administration

Rx only

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