HIGHLIGHTS OF PRESCRIBING INFORMATION

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

STAXYN (vardenafil hydrochloride) orally disintegrating tablets
Initial U.S. Approval: 2003

----------RECENT MAJOR CHANGES----------

Dosage and Administration, Concomitant Medications (2.4)	9/2015
Contraindications, Guanylate Cyclase (GC) Stimulators (4.2)	9/2015

----------INDICATIONS AND USAGE----------

- STAXYN is a phosphodiesterase 5 (PDE5) inhibitor indicated for the treatment of erectile dysfunction. (1)

----------DOSAGE AND ADMINISTRATION----------

- STAXYN is not interchangeable with vardenafil 10 mg film-coated tablets (LEVITRA). STAXYN provides higher systemic exposure compared to vardenafil 10 mg film-coated tablets (LEVITRA). (2.1)
- STAXYN is taken as needed, orally, approximately 60 minutes before sexual activity. (2.1)
- The maximum recommended dosing frequency is one tablet per day. (2.1)
- STAXYN should be placed on the tongue where it will disintegrate. It should be taken without liquid. (2.1)
- STAXYN may be taken with or without food. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

- STAXYN 10 mg: White, round, orally disintegrating tablets (not scored) (3)

----------CONTRAINDICATIONS----------

- Administration with nitrates and nitric oxide donors (2.4, 4.1)
- Administration with guanylate cyclase (GC) stimulators, such as riociguat (2.4, 4.2)

----------WARNINGS AND PRECAUTIONS----------

- Cardiovascular Effects: Patients should not use STAXYN if sex is inadvisable due to cardiovascular status. (5.1)
- Potent and Moderate CYP3A4 Inhibitors: Do not use STAXYN in patients taking potent or moderate CYP3A4 inhibitors. (5.2, 7.2)
- Risk of Priapism: In the event that an erection lasts more than 4 hours, the patient should seek immediate medical assistance. (5.3)
- Effects on the Eye: Patients should stop use of STAXYN, and seek medical attention in the event of sudden loss of vision in one or both eyes, which could be a sign of non arteritic anterior ischemic optic neuropathy (NAION). STAXYN should be used with caution, and only when the anticipated benefits outweigh the risks, in patients with a history of NAION. Patients with a "crowded" optic disc may also be at an increased risk of NAION. (5.4, 6.2)
- Sudden Hearing Loss: Patients should stop STAXYN and seek medical attention in the event of sudden decrease or loss in hearing. (5.5, 6.2)
- Alpha-Blockers: Caution is advised when PDE5 inhibitors are co-administered with alpha-blockers. In some patients, concomitant use of these two drug classes can lower blood pressure significantly leading to symptomatic hypotension (for example, fainting). In patients taking alpha-blockers, do not initiate vardenafil therapy with STAXYN. (2.4, 5.6)
- QT Prolongation: Patients with congenital QT syndrome or taking class IA or III antiarrhythmics should avoid using STAXYN. (5.7, 12.2)
- Phenylketonurics: Each STAXYN tablet contains 1.01 mg phenylalanine per tablet, which could be harmful for patients with phenylketonuria. (5.12)

----------ADVERSE REACTIONS----------

Adverse reactions reported by ≥ 2% of patients treated with STAXYN: Headache, flushing, nasal congestion, dyspepsia, dizziness, back pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bayer HealthCare Pharmaceuticals at 1-888-84-BAYER (1-888-842-2937) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*

----------DRUG INTERACTIONS----------

- STAXYN can potentiate the hypotensive effects of nitrates, alpha-blockers, and antihypertensives. (7.1)
- Do not use STAXYN with moderate or potent CYP3A4 inhibitors as co-administration will result in significant increases in plasma vardenafil concentrations. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- Do not use STAXYN in patients with moderate or severe hepatic impairment. (8.6)
- Do not use STAXYN in patients on renal dialysis. (8.7)

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

Revised: 9/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 General
2.2 Use with Food
2.3 Use in Special Populations
2.4 Concomitant Medications
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
4.1 Nitrates
4.2 Guanylate Cyclase (GC) Stimulators
5 WARNINGS AND PRECAUTIONS
5.1 Cardiovascular Effects
5.2 Potential for Drug Interactions with Potent or Moderate CYP3A4 Inhibitors
5.3 Risk of Priapism
5.4 Effects on the Eye
5.5 Sudden Hearing Loss
5.6 Alpha-Blockers
5.7 Congenital or Acquired QT Prolongation
5.8 Hepatic Impairment
5.9 Renal Impairment
5.10 Combination with Other Erectile Dysfunction Therapies
5.11 Effects on Bleeding
5.12 Phenylketonurics
5.13 Fructose Intolerance
5.14 Sexually Transmitted Disease
6 ADVERSE REACTIONS
6.1 Clinical Studies Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Potential for Pharmacodynamic Interactions with STAXYN
7.2 Effect of Other Drugs on Vardenafil
7.3 Effects of Vardenafil on Other Drugs
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Hepatic Impairment
8.7 Renal Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 Other Vardenafil Clinical Trials Using Film-Coated Tablets
16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
16.2 Recommended Storage
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

STAXYN® is indicated for the treatment of erectile dysfunction.

2 DOSAGE AND ADMINISTRATION

2.1 General

STAXYN is available in 10 mg orally disintegrating tablets. STAXYN is not interchangeable with vardenafil 10 mg film-coated tablets (LEVITRA). STAXYN provides higher systemic exposure compared to vardenafil 10 mg film-coated tablets (LEVITRA). *[See Clinical Pharmacology (12.3).]*

STAXYN should be taken orally, as needed, approximately 60 minutes before sexual activity. The maximum dosing frequency is one STAXYN tablet per day. Sexual stimulation is required for a response to treatment.

STAXYN should be placed on the tongue where it will disintegrate. The tablet should be taken without liquid. It should be taken immediately upon removal from the blister.

Those patients who require a lower or higher dose of vardenafil need to be prescribed vardenafil film-coated tablets *[see Patient Counseling Information (17.11)]*.

2.2 Use with Food

STAXYN can be taken with or without food.

2.3 Use in Special Populations

Hepatic Impairment: Do not use STAXYN in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment *[see Warnings and Precautions (5.8) and Clinical Pharmacology (12.3)]*.

Renal Impairment: Do not use STAXYN in patients on renal dialysis *[see Warnings and Precautions (5.9) and Clinical Pharmacology (12.3)]*.

2.4 Concomitant Medications

Nitrates: Concomitant use with nitrates in any form is contraindicated *[see Contraindications (4.1)]*.

Guanylate Cyclase (GC) Stimulators, such as riociguat: Concomitant use is contraindicated *[see Contraindications (4.2)]*.

CYP3A4 Inhibitors: Do not use STAXYN with potent or moderate CYP3A4 inhibitors such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, atazanavir, clarithromycin and erythromycin *[see Warnings and Precautions (5.2) and Drug Interactions (7.2)]*.

Alpha-Blockers: In those patients who are stable on alpha-blocker therapy, PDE5 inhibitors should be initiated at the lowest recommended starting dose. Stepwise increase in alpha-blocker dose may be associated with further lowering of blood pressure in patients taking a phosphodiesterase (PDE5) inhibitor including vardenafil. In patients taking alpha-blockers, do not initiate vardenafil therapy with STAXYN. Lower doses of vardenafil film-coated tablets should be used as initial therapy in these patients *[see Dosage and Administration (2.4)]*. Patients taking alpha-blockers who have previously used vardenafil film-coated tablets may change to STAXYN at the advice of their healthcare provider. *[See Warnings and Precautions (5.6)* and *Drug Interactions (7.1).]*

A time interval between dosing should be considered when STAXYN is prescribed concomitantly with alpha-blocker therapy *[see Clinical Pharmacology (12.2)]*.

3 DOSAGE FORMS AND STRENGTHS

STAXYN is available in 10 mg white, round, orally disintegrating tablets (not scored), no debossing.

4 CONTRAINDICATIONS

4.1 Nitrates

Administration of STAXYN with nitrates (either regularly and/or intermittently) and nitric oxide donors is contraindicated *[see Clinical Pharmacology (12.2)]*. Consistent with the effects of PDE5 inhibition on the nitric oxide/cyclic guanosine monophosphate pathway, PDE5 inhibitors, including STAXYN, may potentiate the hypotensive effects of nitrates. A suitable time interval following STAXYN dosing for the safe administration of nitrates or nitric oxide donors has not been determined.

4.2 Guanylate Cyclase (GC) Stimulators

Do not use STAXYN in patients who are using a GC stimulator, such as riociguat. PDE5 inhibitors, including STAXYN may potentiate the hypotensive effects of GC stimulators.

5 WARNINGS AND PRECAUTIONS

The evaluation of erectile dysfunction should include a medical assessment, a determination of potential underlying causes and the identification of appropriate treatment.

Before prescribing STAXYN, it is important to note the following:

5.1 Cardiovascular Effects

General

Physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity. Therefore, treatment for erectile dysfunction, including STAXYN, should not be used in men for whom sexual activity is not recommended because of their underlying cardiovascular status.

There are no controlled clinical data on the safety or efficacy of vardenafil in the following patients; and therefore its use is not recommended until further information is available: unstable angina; hypotension (resting systolic blood pressure of <90 mmHg); uncontrolled hypertension (>170/110 mmHg); recent history of stroke, life-threatening arrhythmia, or myocardial infarction (within the last 6 months); severe cardiac failure.

Left Ventricular Outflow Obstruction

Patients with left ventricular outflow obstruction (for example, aortic stenosis and idiopathic hypertrophic subaortic stenosis) can be sensitive to the action of vasodilators including PDE5 inhibitors.

Blood Pressure Effects

Vardenafil has systemic vasodilatory properties that resulted in transient decreases in supine blood pressure in healthy volunteers (mean maximum decrease of 7 mmHg systolic and 8 mmHg diastolic) *[see Clinical Pharmacology (12.2)]*. While this normally would be expected to be of little consequence in most patients, prior to prescribing STAXYN, physicians should carefully consider whether their patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects.

5.2 Potential for Drug Interactions with Potent or Moderate CYP3A4 Inhibitors

Concomitant administration with potent CYP3A4 inhibitors (such as ritonavir, indinavir, ketoconazole) or moderate CYP3A4 inhibitors (such as erythromycin) increases plasma concentrations of vardenafil. Do not use STAXYN in patients taking potent or moderate CYP3A4 inhibitors. *[See Dosage and Administration (2.4), Drug Interactions (7.2) and Patient Counseling Information (17.11).]*

5.3 Risk of Priapism

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, including vardenafil. In the event that an erection persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency may result.

STAXYN should be used with caution by patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis, or Peyronie's disease) or by patients who have conditions that may predispose them to priapism (such as sickle cell anemia, multiple myeloma, or leukemia).

5.4 Effects on the Eye

Physicians should advise patients to stop use of all phosphodiesterase type 5 (PDE5) inhibitors, including STAXYN, and seek medical attention in the event of 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 2.5–11.8 cases per 100,000 in males aged ≥50. An observational study evaluated whether recent use of PDE5 inhibitors, as a class, was associated with acute onset of NAION. The results suggest an approximate 2 fold increase in the risk of NAION within 5 half-lives of PDE5 inhibitor use. From this information, it is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors *[see Adverse Reactions (6.2)]*.

Physicians should consider whether their 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, PDE5 inhibitors, including Staxyn, should be used 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 STAXYN, for this uncommon condition.

STAXYN has not been evaluated in patients with known hereditary degenerative retinal disorders, including retinitis pigmentosa, therefore its use is not recommended until further information is available in those patients.

5.5 Sudden Hearing Loss

Physicians should advise patients to stop taking all PDE5 inhibitors, including STAXYN, 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 vardenafil. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors *[see Adverse Reactions (6.2)]*.

5.6 Alpha-Blockers

In patients taking alpha-blockers, do not initiate vardenafil therapy with STAXYN. Patients treated with alpha-blockers who have previously used vardenafil film-coated tablets may be changed to STAXYN at the advice of their healthcare provider. Caution is advised when PDE5 inhibitors are co-administered with alpha-blockers. PDE5 inhibitors, including STAXYN, 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 (7.1) and Clinical Pharmacology (12.2)]* leading to symptomatic hypotension (for example, fainting). Consideration should be given to the following:

- Patients should be stable on alpha-blocker therapy prior to initiating a PDE5 inhibitor. Patients who demonstrate hemodynamic instability on alpha-blocker therapy alone are at increased risk of symptomatic hypotension with concomitant use of PDE5 inhibitors.
- In those patients who are stable on alpha-blocker therapy, PDE5 inhibitors should be initiated at the lowest recommended starting dose. In patients taking alpha-blockers, do not initiate vardenafil therapy with STAXYN. Lower doses of vardenafil film-coated tablets should be used as initial therapy in these patients *[see Dosage and Administration (2.4)]*.
- In those patients already taking an optimized dose of PDE5 inhibitor, alpha-blocker therapy should be initiated at the lowest dose. Stepwise increases in alpha-blocker dose may be associated with further lowering of blood pressure in patients taking a PDE5 inhibitor.
- Safety of combined use of PDE5 inhibitors and alpha-blockers may be affected by other variables, including intravascular volume depletion and other anti-hypertensive drugs.

5.7 Congenital or Acquired QT Prolongation

In a study of the effect of vardenafil on QT interval in 59 healthy males *[see Clinical Pharmacology (12.2)]*, therapeutic (10 mg film-coated tablets) and supratherapeutic (80 mg) doses of vardenafil and the active control moxifloxacin (400 mg) produced similar increases in QTc interval. A postmarketing study evaluating the effect of combining vardenafil with another drug of comparable QT effect showed an additive QT effect when compared with either drug alone *[see Clinical Pharmacology (12.2)]*. These observations should be considered in clinical decisions when prescribing vardenafil to patients with known history of QT prolongation or patients who are taking medications known to prolong the QT interval.

Patients taking Class 1A (for example, quinidine, procainamide) or Class III (for example, amiodarone, sotalol) antiarrhythmic medications or those with congenital QT prolongation, should avoid using STAXYN.

5.8 Hepatic Impairment

Do not use STAXYN in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment *[see Dosage and Administration (2.3) Clinical Pharmacology (12.3)] and Use in Specific Populations (8.6)]*.

5.9 Renal Impairment

Do not use STAXYN in patients on renal dialysis, as vardenafil has not been evaluated in this population *[see Dosage and Administration (2.3) and Use in Specific Populations (8.7)]*.

5.10 Combination with Other Erectile Dysfunction Therapies

The safety and efficacy of STAXYN used in combination with other treatments for erectile dysfunction have not been studied. Therefore, the use of such combinations is not recommended.

5.11 Effects on Bleeding

In humans, vardenafil film-coated tablet alone in doses up to 20 mg does not prolong the bleeding time. There is no clinical evidence of any additive prolongation of the bleeding time when vardenafil is administered with aspirin. STAXYN has not been administered to patients with bleeding disorders or significant active peptic ulceration. Therefore STAXYN should be administered to these patients after careful benefit-risk assessment.

5.12 Phenylketonurics

STAXYN contains aspartame, a source of phenylalanine which may be harmful for people with phenylketonuria.

Phenylketonurics: Each STAXYN tablet contains 1.01 mg phenylalanine per tablet.

5.13 Fructose Intolerance

STAXYN contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take STAXYN.

5.14 Sexually Transmitted Disease

The use of STAXYN offers no protection against sexually transmitted diseases. Counseling of patients about protective measures necessary to guard against sexually transmitted diseases, including the Human Immunodeficiency Virus (HIV), should be considered.

6 ADVERSE REACTIONS

The following serious adverse reactions with the use of STAXYN (vardenafil) are discussed elsewhere in the labeling:

- Cardiovascular effects *[see Contraindications (4.1) and Warnings and Precautions (5.1)]*
- Priapism *[see Warnings and Precautions (5.3)]*
- QT Prolongation *[see Warnings and Precautions (5.7)]*
- Effects on eye *[see Warnings and Precautions (5.4)]*
- Sudden hearing loss *[see Warnings and Precautions (5.5)]*

6.1 Clinical Studies 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.

STAXYN: Safety of STAXYN was evaluated in two identical multi-national, randomized, double-blind, placebo-controlled trials. In both pivotal studies, enrollment was stratified so that approximately 50% of patients were ≥65 years old. Approximately 8% (n=29) were ≥75 years old. An integrated analysis of both studies included a total of 355 subjects that received STAXYN compared to 340 subjects that received placebo (mean age was 61.7, range 21.0 to 88.0; 68% White, 5% Black, 6% Asian, 11% Hispanic and 11% Other). The discontinuation rates due to adverse reactions were 1.4% for STAXYN compared to 0.6% for placebo. Table 1 below details the most frequently reported adverse reactions.

Table 1: Adverse drug reactions reported by ≥2% of the patients treated with STAXYN and more frequent on drug than placebo in controlled trials

Adverse Drug Reaction	STAXYN (n=355)	Placebo (n=340)
Headache	14.4%	1.8%
Flushing	7.6%	0.6%
Nasal Congestion	3.1%	0.3%
Dyspepsia	2.8%	0%
Dizziness	2.3%	0%
Back Pain	2%	0.3%

Adverse drug reactions reported in the STAXYN placebo controlled trials were comparable to the adverse drug reactions reported in earlier vardenafil film-coated tablets placebo controlled trials.

All Vardenafil Studies: Vardenafil film-coated tablets and STAXYN has been administered to over 17,000 men (mean age 54.5, range 18–89 years; 70% White, 5% Black, 13% Asian, 4% Hispanic and 8% Other) during controlled and uncontrolled clinical trials worldwide. The number of patients treated for 6 months or longer was 3357, and 1350 patients were treated for at least 1 year.

In the placebo-controlled clinical trials for vardenafil film-coated tablets and STAXYN, the discontinuation rate due to adverse events was 1.9% for vardenafil compared to 0.8% for placebo.

Placebo-controlled trials suggested a dose effect in the incidence of some adverse reactions (for example, dizziness, headache, flushing, dyspepsia, nausea, nasal congestion) over the 5 mg, 10 mg, and 20 mg doses of vardenafil film-coated tablets.

The following section identifies additional, less frequent adverse reactions (<2%) reported during the clinical development of vardenafil film-coated tablets and STAXYN. Excluded from this list are those adverse reactions that are infrequent and minor, those events that may be commonly observed in the absence of drug therapy, and those events that are not reasonably associated with the drug:

Body as a whole: allergic edema and angioedema, feeling unwell, allergic reactions, chest pain

Auditory: tinnitus, vertigo

Cardiovascular: palpitation, tachycardia, angina pectoris, myocardial infarction, ventricular tachyarrhythmias, hypotension

Digestive: nausea, gastrointestinal and abdominal pain, dry mouth, diarrhea, gastroesophageal reflux disease, gastritis, vomiting, increase in transaminases

Musculoskeletal: increase in creatine phosphokinase (CPK), increased muscle tone and cramping, myalgia

Nervous: paresthesia and dysesthesia, somnolence, sleep disorder, syncope, amnesia, seizure

Respiratory: dyspnea, sinus congestion

Skin and appendages: erythema, rash

Ophthalmologic: visual disturbance, ocular hyperemia, visual color distortions, eye pain and eye discomfort, photophobia, increase in intraocular pressure, conjunctivitis

Urogenital: increase in erection, priapism

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of vardenafil in the film-coated tablet formulation. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency or establish a causal relationship to drug exposure.

Ophthalmologic: Non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported rarely postmarketing in temporal association with the use of PDE5 inhibitors, including vardenafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for development of NAION, including but not necessarily limited to: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors *[see Warnings and Precautions (5.4) and Patient Counseling Information (17.8)]*.

Visual disturbances including vision loss (temporary or permanent), such as visual field defect, retinal vein occlusion, and reduced visual acuity, have also been reported rarely in postmarketing experience. It is not possible to determine whether these events are related directly to the use of vardenafil.

Neurologic: Seizure, seizure recurrence and transient global amnesia have been reported postmarketing in temporal association with vardenafil.

Otologic: Cases of sudden decrease or loss of hearing have been reported postmarketing in temporal association with the use of PDE5 inhibitors, including vardenafil. In some cases, medical conditions and other factors were reported that may have also played a role in the otologic adverse events. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related directly to the use of vardenafil, to the patient's underlying risk factors for hearing loss, a combination of these factors, or to other factors *[see Patient Counseling Information (17.9)]*.

7 DRUG INTERACTIONS

The drug interaction studies described below were conducted using vardenafil film-coated tablets.

7.1 Potential for Pharmacodynamic Interactions with STAXYN

Nitrates: Concomitant use of STAXYN and nitrates is contraindicated. The blood pressure lowering effects of sublingual nitrates (0.4 mg) taken 1 and 4 hours after vardenafil and increases in heart rate when taken at 1, 4 and 8 hours after vardenafil were potentiated by a 20 mg dose of vardenafil in healthy middle-aged subjects. These effects were not observed when vardenafil 20 mg was taken 24 hours before the nitroglycerin (NTG). Potentiation of the hypotensive effects of nitrates for patients with ischemic heart disease has not been evaluated, and concomitant use of STAXYN and nitrates is contraindicated *[see Contraindications (4.1) and Clinical Pharmacology (12.2)]*.

Alpha-Blockers: Patients taking alpha-blockers should not initiate vardenafil therapy with STAXYN. Patients treated with alpha-blockers who have previously used vardenafil film-coated tablets may be switched to STAXYN at the advice of their healthcare provider. Caution is advised when PDE5 inhibitors are co-administered with alpha-blockers. PDE5 inhibitors, including STAXYN 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. Clinical pharmacology studies have been conducted with co-administration of vardenafil with alfuzosin, terazosin or tamsulosin. *[See Dosage and Administration (2.4), Warnings and Precautions (5.6), and Clinical Pharmacology (12.2).]*

Antihypertensives: STAXYN may add to the blood pressure lowering effect of antihypertensive agents. In a clinical pharmacology study of patients with erectile dysfunction, single doses of 20 mg vardenafil caused a mean maximum decrease in supine blood pressure of 7 mmHg systolic and 8 mmHg diastolic (compared to placebo), accompanied by a

mean maximum increase of heart rate of 4 beats per minute. The maximum decrease in blood pressure occurred between 1 and 4 hours after dosing. Following multiple dosing for 31 days, similar blood pressure responses were observed on Day 31 as on Day 1.

Alcohol: Vardenafil 20 mg did not potentiate the hypotensive effects of alcohol during the 4-hour observation period in healthy volunteers when administered with alcohol (0.5 g/kg body weight: approximately 40 mL of absolute alcohol in a 70 kg person). Alcohol and vardenafil plasma levels were not altered when dosed simultaneously.

7.2 Effect of Other Drugs on Vardenafil

In vitro studies

Studies in human liver microsomes showed that vardenafil is metabolized primarily by cytochrome P450 (CYP) isoforms 3A4/5, and to a lesser degree by CYP2C9. Therefore, inhibitors of these enzymes are expected to reduce vardenafil clearance *[see Dosage and Administration (2.4) and Warnings and Precautions (5.2)]*.

In vivo studies

Do not use STAXYN with moderate and potent CYP3A4 inhibitors such as erythromycin, grapefruit juice, clarithromycin, ketoconazole, itraconazole, indinavir, saquinavir, atazanavir, ritonavir as the systemic concentration of vardenafil is increased in their presence *[see Warnings and Precautions (5) and Dosage and Administration (2.4)]*.

<u>Potent CYP3A4 inhibitors</u>

Ketoconazole (200 mg once daily) produced a 10-fold increase in vardenafil area under the curve (AUC) and a 4-fold increase in maximum concentration (C_{max}) when co-administered with vardenafil 5 mg in healthy volunteers. *[See Dosage and Administration (2.4) and Warnings and Precautions (5).]*

Indinavir (800 mg t.i.d.) co-administered with vardenafil 10 mg resulted in a 16-fold increase in vardenafil AUC, a 7-fold increase in vardenafil C_{max} and a 2-fold increase in vardenafil half-life. *[See Dosage and Administration (2.4) and Warnings and Precautions (5).]*

Ritonavir (600 mg b.i.d.) co-administered with vardenafil 5 mg resulted in a 49-fold increase in vardenafil AUC and a 13-fold increase in vardenafil C_{max}. The interaction is a consequence of blocking hepatic metabolism of vardenafil by ritonavir, a HIV protease inhibitor and a highly potent CYP3A4 inhibitor, which also inhibits CYP2C9. *[See Dosage and Administration (2.4) and Warnings and Precautions (5.2).]*

<u>Moderate CYP3A4 inhibitors</u>

Erythromycin (500 mg t.i.d.) produced a 4-fold increase in vardenafil AUC and a 3-fold increase in vardenafil C_{max} when co-administered with vardenafil 5 mg in healthy volunteers *[see Dosage and Administration (2) and Warnings and Precautions (5)]*.

Other Drug Interactions

No pharmacokinetic interactions were observed between vardenafil and the following drugs: glyburide, warfarin, digoxin, an antacid based on magnesium-aluminum hydroxide, and ranitidine. In the warfarin study, vardenafil had no effect on the prothrombin time or other pharmacodynamic parameters.

Cimetidine (400 mg b.i.d.) had no effect on AUC and C_{max} of vardenafil when co-administered with 20 mg vardenafil in healthy volunteers.

7.3 Effects of Vardenafil on Other Drugs

In vitro studies

Vardenafil and its metabolites had no effect on CYP1A2, 2A6, and 2E1 (Ki >100 micromolar). Weak inhibitory effects toward other isoforms (CYP2C8, 2C9, 2C19, 2D6, 3A4) were found, but Ki values were in excess of plasma concentrations achieved following dosing. The most potent inhibitory activity was observed for vardenafil metabolite M1, which had a Ki of 1.4 micromolar toward CYP3A4, which is about 20 times higher than the M1 C_{max} values after an 80 mg vardenafil dose.

In vivo studies

Nifedipine: Vardenafil 20 mg, when co-administered with slow-release nifedipine 30 mg or 60 mg once daily, did not affect the relative AUC or C_{max} of nifedipine, a drug that is metabolized via CYP3A4. Nifedipine did not alter the plasma levels of vardenafil when taken in combination. In these patients whose hypertension was controlled with nifedipine, vardenafil 20 mg produced mean additional supine systolic/diastolic blood pressure reductions of 6/5 mmHg compared to placebo.

Ritonavir and Indinavir: Upon concomitant administration of 5 mg vardenafil with 600 mg b.i.d. ritonavir, the C_{max} and AUC of ritonavir were reduced by approximately 20%. Upon administration of 10 mg of vardenafil (film-coated tablets) with 800 mg t.i.d. indinavir, the C_{max} and AUC of indinavir were reduced by 40% and 30%, respectively.

Aspirin: Vardenafil 10 mg and 20 mg did not potentiate the increase in bleeding time caused by aspirin (two 81 mg tablets).

Other Interactions: Vardenafil had no effect on the pharmacodynamics of glyburide (glucose and insulin concentrations) and warfarin (prothrombin time or other pharmacodynamic parameters).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B: STAXYN is not indicated for use in women. There are no studies of STAXYN use in pregnant women.

No evidence of specific potential for teratogenicity, embryotoxicity or fetotoxicity was observed in rats and rabbits that received vardenafil at up to 18 mg/kg/day during organogenesis. This dose is approximately 100 fold (rat) and 29 fold (rabbit) greater than the AUC values for unbound vardenafil and its major metabolite in humans given the maximum recommended human dose (MRHD) of 20 mg.

In the rat pre-and postnatal development study, the NOAEL (no observed adverse effect level) for maternal toxicity was 8 mg/kg/day. Retarded physical development of pups in the absence of maternal effects was observed following maternal exposure to 1 and 8 mg/kg possibly due to vasodilatation and/or secretion of the drug into milk. The number of living pups born to rats exposed pre- and postnatally was reduced at 60 mg/kg/day. Based on the results of the pre- and postnatal study, the developmental NOAEL is less than 1 mg/kg/day. Based on plasma exposures in the rat developmental toxicity study, 1 mg/kg/day in the pregnant rat is estimated to produce total AUC values for unbound vardenafil and its major metabolite comparable to the human AUC at the MRHD of 20 mg. There are no adequate and well-controlled trials of vardenafil in pregnant women.

8.3 Nursing Mothers

STAXYN is not indicated for use in women. It is not known if vardenafil is excreted in human breast milk.

Vardenafil was secreted into the milk of lactating rats at concentrations approximately 10-fold greater than found in the plasma. Following a single oral dose of 3 mg/kg, 3.3% of the administered dose was excreted into the milk within 24 hours.

8.4 Pediatric Use

STAXYN is not indicated for use in pediatric patients. Safety and efficacy in children has not been established.

8.5 Geriatric Use

Vardenafil AUC and C_{max} in elderly males 65 years or older taking STAXYN were increased by 39% and 21%, respectively, in comparison to patients aged 45 years and below. No overall differences in safety or effectiveness were observed between patients ≥65 years old and those < 65 years old in placebo-controlled clinical trials *[see Clinical Pharmacology (12.3)]*.

8.6 Hepatic Impairment

Do not use STAXYN in patients with moderate or severe hepatic impairment.

In volunteers with mild hepatic impairment (Child-Pugh A), the C_{max} and AUC following a 10 mg vardenafil (film-coated tablets) dose were increased by 22% and 17%, respectively, compared to healthy control subjects. STAXYN can be used

in patients with mild hepatic impairment. In volunteers with moderate hepatic impairment (Child-Pugh B), the C_{max} and AUC following a 10 mg vardenafil (film-coated tablets) dose were increased by 130% and 160%, respectively, compared to healthy control subjects. Vardenafil has not been evaluated in patients with severe (Child-Pugh C) hepatic impairment. Do not use STAXYN in patients with moderate to severe hepatic impairment. *[See Warnings and Precautions (5.8) and Dosage and Administration (2).]*

8.7 Renal Impairment

Do not use STAXYN in patients on renal dialysis.

In volunteers with mild renal impairment (CLcr = 50–80 mL/min), the pharmacokinetics of vardenafil 20 mg film-coated tablets were similar to those observed in a control group with normal renal function. In the moderate (CLcr = 30–50 mL/min) or severe (CLcr <30 mL/min) renal impairment groups, the AUC of vardenafil was 20–30% higher compared to that observed in a control group with normal renal function (CLcr >80 mL/min). STAXYN can be used in patients with mild, moderate or severe renal impairment. Do not use STAXYN in patients on renal dialysis as vardenafil has not been evaluated in such patients *[see Dosage and Administration (2.3) and Warnings and Precautions (5.9)]*.

10 OVERDOSAGE

The maximum dose of vardenafil for which human data are available is a single 120 mg dose of the film–coated tablets administered to healthy male volunteers. The majority of these subjects experienced reversible back pain/myalgia and/or "abnormal vision." Single doses up to 80 mg vardenafil and multiple doses up to 40 mg vardenafil administered once daily over 4 weeks were tolerated without producing serious adverse side effects.

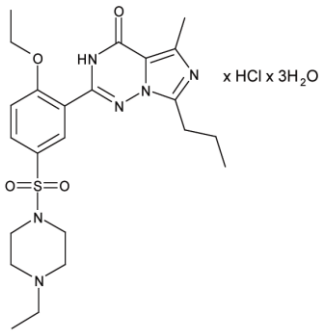
When 40 mg of vardenafil was administered twice daily, cases of severe back pain were observed. No muscle or neurological toxicity was identified.

In cases of overdose, standard supportive measures should be taken as required. Renal dialysis is not expected to accelerate clearance because vardenafil is highly bound to plasma proteins and is not significantly eliminated in the urine.

11 DESCRIPTION

STAXYN (vardenafil hydrochloride) is an oral therapy for the treatment of erectile dysfunction. This monohydrochloride salt of vardenafil is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific PDE5.

Vardenafil HCl is designated chemically as piperazine, 1-[[3-(1,4-dihydro-5-methyl-4-oxo-7-propylimidazo[5,1-f][1,2,4]triazin-2-yl)-4-ethoxyphenyl]sulfonyl]-4-ethyl-, monohydrochloride and has the following structural formula:



Vardenafil HCl is a nearly colorless, solid substance with a molecular weight of 579.1 g/mol and a solubility of 0.11 mg/mL in water.

STAXYN is formulated as white round orally disintegrating tablets with no debossing. Each tablet contains 11.85 mg vardenafil hydrochloride, which corresponds to 10 mg vardenafil, and the following inactive ingredients: aspartame, peppermint flavor, magnesium stearate, and Pharmaburst™ B2 (crospovidone, mannitol, silica colloidal hydrated, and sorbitol).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Penile erection is a hemodynamic process initiated by the relaxation of smooth muscle in the corpus cavernosum and its associated arterioles. During sexual stimulation, nitric oxide is released from nerve endings and endothelial cells in the corpus cavernosum. Nitric oxide activates the enzyme guanylate cyclase resulting in increased synthesis of cyclic guanosine monophosphate (cGMP) in the smooth muscle cells of the corpus cavernosum. The cGMP in turn triggers smooth muscle relaxation, allowing increased blood flow into the penis, resulting in erection. The tissue concentration of cGMP is regulated by both the rates of synthesis and degradation via phosphodiesterases (PDEs). The most abundant PDE in the human corpus cavernosum is the cGMP-specific PDE5; therefore, the inhibition of PDE5 enhances erectile function by increasing the amount of cGMP. Because sexual stimulation is required to initiate the local release of nitric oxide, the inhibition of PDE5 has no effect in the absence of sexual stimulation.

In vitro studies have shown that vardenafil is a selective inhibitor of PDE5. The inhibitory effect of vardenafil is more selective on PDE5 than for other known phosphodiesterases (>15-fold relative to PDE6, >130-fold relative to PDE1, >300-fold relative to PDE11, and >1,000-fold relative to PDE2, 3, 4, 7, 8, 9, and 10).

12.2 Pharmacodynamics

The pharmacodynamic studies described below were conducted using vardenafil film-coated tablets.

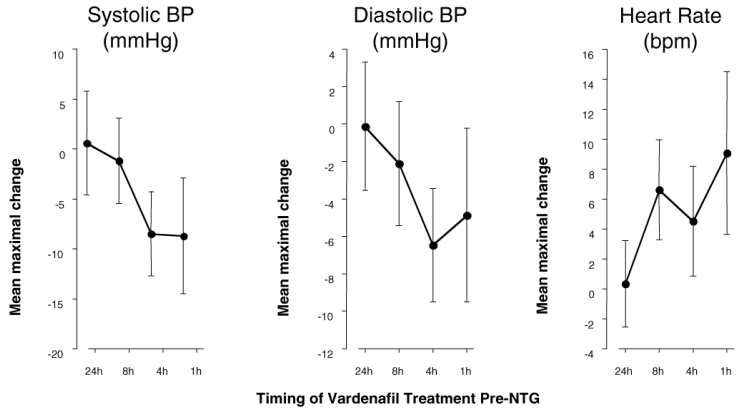
Effects on Blood Pressure

In a clinical pharmacology study of patients with erectile dysfunction, single doses of vardenafil 20 mg film-coated tablets caused a mean maximum decrease in supine blood pressure of 7 mmHg systolic and 8 mmHg diastolic (compared to placebo), accompanied by a mean maximum increase of heart rate of 4 beats per minute. The maximum decrease in blood pressure occurred between 1 and 4 hours after dosing. Following multiple dosing for 31 days, similar blood pressure responses were observed on Day 31 as on Day 1. Vardenafil may add to the blood pressure lowering effects of antihypertensive agents *[see Drug Interactions (7)]*.

Effects on Blood Pressure and Heart Rate when Vardenafil is Combined with Nitrates

A study was conducted in which the blood pressure and heart rate response to 0.4 mg nitroglycerin (NTG) sublingually was evaluated in 18 healthy subjects following pretreatment with vardenafil 20 mg film-coated tablets at various times before NTG administration. Vardenafil 20 mg caused an additional time-related reduction in blood pressure and increase in heart rate in association with NTG administration. The blood pressure effects were observed when vardenafil 20 mg was dosed 1 or 4 hours before NTG and the heart rate effects were observed when 20 mg was dosed 1, 4, or 8 hours before NTG. Additional blood pressure and heart rate changes were not detected when vardenafil 20 mg film-coated tablet was dosed 24 hours before NTG *(see Figure 1).*

Figure 1: Placebo-subtracted point estimates (with 90% CI) of mean maximal blood pressure and heart rate effects of pre-dosing with vardenafil 20 mg at 24, 8, 4, and 1 hour before 0.4 mg NTG sublingually



Because the disease state of patients requiring nitrate therapy is anticipated to increase the likelihood of hypotension, the use of vardenafil by patients on nitrate therapy or on nitric oxide donors is contraindicated *[see Contraindications (4.1)]*.

Blood Pressure Effects in Patients on Stable Alpha-Blocker Treatment

Three clinical pharmacology studies were conducted in patients with benign prostatic hyperplasia (BPH) on stable-dose alpha-blocker treatment , consisting of alfuzosin, tamsulosin or terazosin.

Study 1: This study was designed to evaluate the effect of 5 mg vardenafil film-coated tablets compared to placebo when administered to BPH patients on chronic alpha-blocker therapy in two separate cohorts: tamsulosin 0.4 mg daily (cohort 1, n=21) and terazosin 5 or 10 mg daily (cohort 2, n=21). The design was a randomized, double blind, cross-over study with four treatments: vardenafil 5 mg or placebo administered simultaneously with the alpha-blocker and vardenafil 5 mg or placebo administered 6 hours after the alpha-blocker. Blood pressure and pulse were evaluated over the 6-hour interval after vardenafil dosing. For blood pressure (BP) results, *see Table 2*. One patient, after simultaneous treatment with 5 mg vardenafil and 10 mg terazosin, exhibited symptomatic hypotension with standing blood pressure of 80/60 mmHg occurring one hour after administration and subsequent mild dizziness and moderate lightheadedness lasting for 6 hours. For vardenafil and placebo, five and two patients, respectively, experienced a decrease in standing systolic blood pressure (SBP) of >30 mmHg following simultaneous administration of terazosin. Hypotension was not observed when vardenafil 5 mg and terazosin were administered 6 hours apart. Following simultaneous administration of vardenafil 5 mg and tamsulosin, two patients had a standing SBP of <85 mmHg. A decrease in standing SBP of >30 mmHg was observed in two patients on tamsulosin receiving simultaneous vardenafil and in one patient receiving simultaneous placebo treatment. When tamsulosin and vardenafil 5 mg were separated by 6 hours, two patients had a standing SBP <85 mmHg and one patient had a decrease in SBP of >30 mmHg. There were no severe adverse events related to hypotension reported during the study. There were no cases of syncope.

Table 2: Mean (95% CI) maximal change from baseline in systolic blood pressure (mmHg) following vardenafil 5 mg in BPH patients on stable alpha-blocker therapy (study 1)

Alpha-Blocker		Simultaneous dosing of Vardenafil 5 mg and Alpha-Blocker, Placebo-Subtracted	Dosing of Vardenafil 5 mg and Alpha-Blocker Separated by 6 Hours, Placebo-Subtracted
Terazosin 5 or 10 mg daily	Standing SBP	-3 (-6.7, 0.1)	-4 (-7.4, -0.5)
	Supine SBP	-4 (-6.7, -0.5)	-4 (-7.1, -0.7)
Tamsulosin 0.4 mg daily	Standing SBP	-6 (-9.9, -2.1)	-4 (-8.3, -0.5)
	Supine SBP	-4 (-7, -0.8)	-5 (-7.9, -1.7)

Blood pressure effects (standing SBP) in normotensive men on stable dose tamsulosin 0.4 mg following simultaneous administration of vardenafil 5 mg or placebo, or following administration of vardenafil 5 mg or placebo separated by 6 hours are shown in *Figure 2*. Blood pressure effects (standing SBP) in normotensive men on stable dose terazosin (5 or 10 mg) following simultaneous administration of vardenafil 5 mg or placebo, or following administration of vardenafil 5 mg or placebo separated by 6 hours, are shown in *Figure 3*.

Figure 2: Mean change from baseline in standing systolic blood pressure (mmHg) over 6 hour interval following simultaneous or 6 hr separation administration of vardenafil 5 mg or placebo with stable dose tamsulosin 0.4 mg in normotensive BPH patients (study 1)

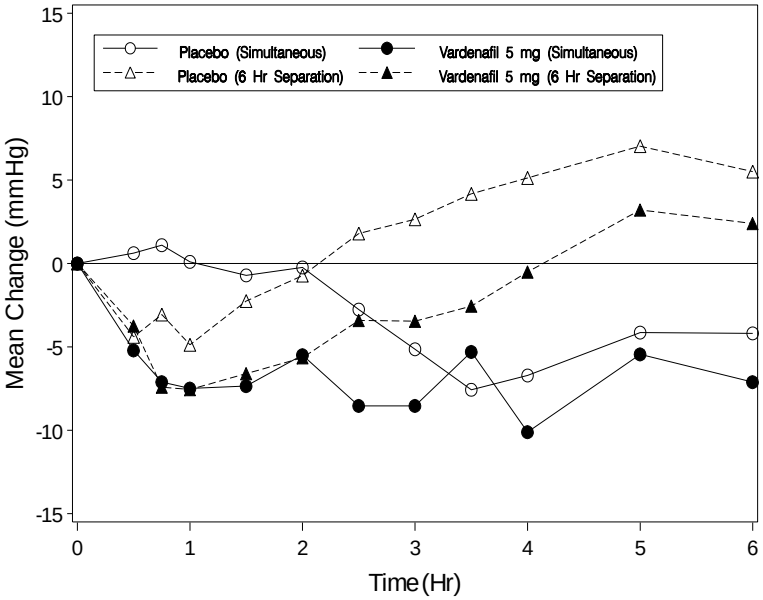
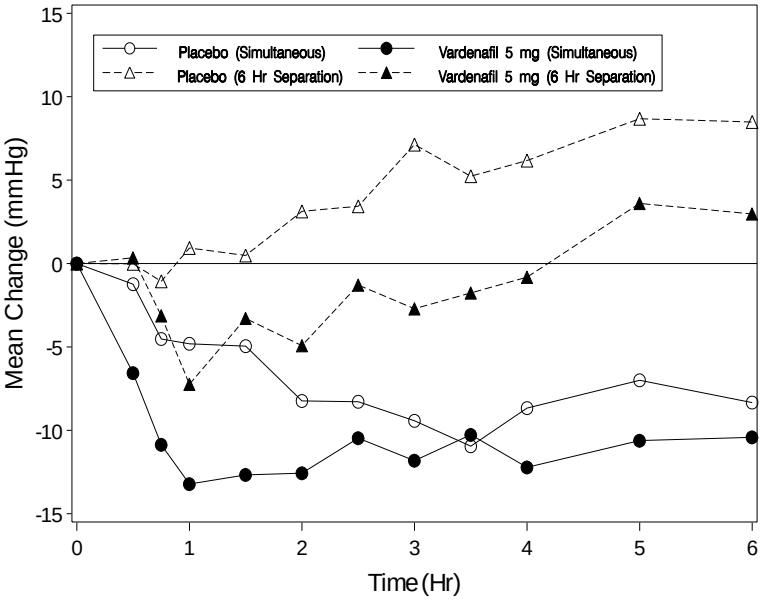


Figure 3: Mean change from baseline in standing systolic blood pressure (mmHg) over 6 hour interval following simultaneous or 6 hr separation administration of vardenafil 5 mg or placebo with stable dose terazosin (5 or 10 mg) in normotensive BPH patients (study 1)



Study 2: This study was designed to evaluate the effect of 10 mg vardenafil (film-coated tablets) (stage 1) and 20 mg vardenafil (film-coated tablets) (stage 2) compared to placebo, when administered to a single cohort of BPH patients (n=23) on stable therapy with tamsulosin 0.4 mg or 0.8 mg daily for at least four weeks. The design was a randomized, double blind, two-period, cross-over study. Vardenafil or placebo was given simultaneously with tamsulosin. Blood pressure and pulse were evaluated over the 6-hour interval after vardenafil dosing. For BP results *see Table 3*. One patient experienced a decrease from baseline in standing SBP of >30 mmHg following vardenafil 10 mg. There were no other instances of outlier blood pressure values (standing SBP <85 mmHg or decrease from baseline in standing SBP of >30 mmHg). Three patients reported dizziness following vardenafil 20 mg. There were no cases of syncope.

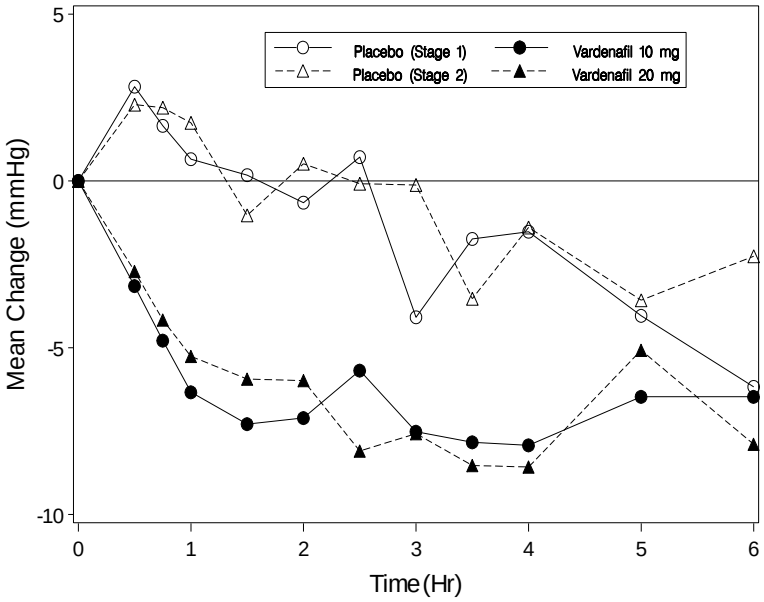
Table 3: Mean (95% CI) maximal change from baseline in systolic blood pressure (mmHg) following vardenafil 10 and 20 mg (film-coated tablets) in BPH patients on stable alpha-blocker therapy with tamsulosin 0.4 or 0.8 mg daily (study 2)

	Vardenafil 10 mg	Vardenafil 20 mg

	Placebo-subtracted	Placebo-subtracted
Standing SBP	-4 (-6.8, -0.3)	-4 (-6.8, -1.4)
Supine SBP	-5 (-8.2, -0.8)	-4 (-6.3, -1.8)

Blood pressure effects (standing SBP) in normotensive men on stable dose of tamsulosin 0.4 mg following simultaneous administration of vardenafil 10 mg, vardenafil 20 mg or placebo are shown in *Figure 4*.

Figure 4: Mean change from baseline in standing systolic blood pressure (mmHg) over 6 hour interval following simultaneous administration of vardenafil 10 mg film-coated tablet (stage 1), vardenafil 20 mg film-coated tablet (Stage 2), or placebo with stable dose tamsulosin 0.4 mg in normotensive BPH patients (study 2)



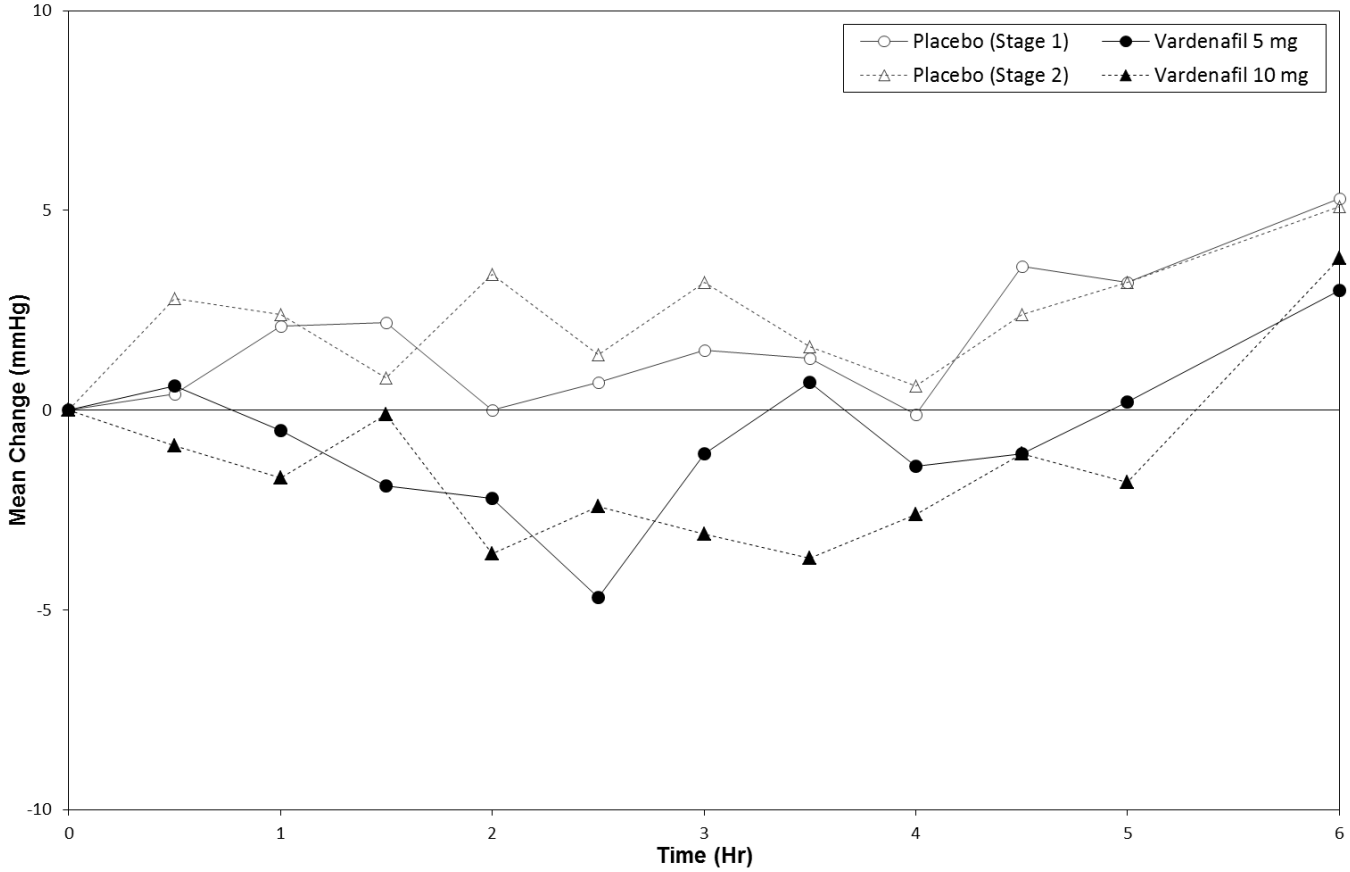
Study 3: This study was designed to evaluate the effect of single doses of 5 mg vardenafil (stage 1) and 10 mg vardenafil (stage 2) compared to placebo, when administered to a single cohort of BPH patients (n=24) on stable therapy with alfuzosin 10 mg daily for at least four weeks. The design was a randomized, double blind, 3-period cross-over study. Vardenafil or placebo was administered 4 hours after the administration of alfuzosin. Blood pressure and pulse were evaluated over a 10-hour interval after dosing of vardenafil or placebo. For BP results see Table 4.

Table 4: Mean (95% C.I.) maximal change from baseline in systolic blood pressure (mmHg) following vardenafil 5 and 10 mg in BPH patients on stable alpha-blocker therapy with alfuzosin 10 mg daily (Study 3)

	Vardenafil 5 mg Placebo-subtracted	**Vardenafil 10 mg Placebo-subtracted**
Standing SBP	-2 (-5.8, 1.2)	-5 (-8.8, -1.6)
Supine SBP	-1 (-4.1, 2.1)	-6 (-9.4, -2.8)

One patient experienced decreases from baseline in standing systolic blood pressure >30 mm Hg after administration of vardenafil 5 mg film-coated tablets and vardenafil 10 mg film-coated tablets. No instances of standing systolic blood pressure <85 mm Hg were observed during this study. Four patients, one dosed with placebo, two dosed with vardenafil 5 mg film-coated tablets and one dosed with vardenafil 10 mg film-coated tablets, reported dizziness. Blood pressure effects (standing SBP) in normotensive men on a stable dose of alfuzosin 10 mg following administration of vardenafil 5 mg, vardenafil 10 mg, or placebo separated by 4 hours, are shown in Figure 5.

Figure 5: Mean change from baseline in standing systolic blood pressure (mmHg) over 6 hour interval following 4 hr separation administration of vardenafil 5 mg (stage 1), vardenafil 10 mg (stage 2) or placebo with stable dose alfuzosin 10 mg in BPH patients (Study 3)



Blood Pressure Effects in Normotensive Men After Forced Titration with Alpha-Blockers

Two randomized, double blind, placebo-controlled clinical pharmacology studies with healthy normotensive volunteers (age range, 45–74 years) were performed after forced titration of the alpha-blocker terazosin to 10 mg daily over 14 days (n=29), and after initiation of tamsulosin 0.4 mg daily for five days (n=24). There were no severe adverse events related to hypotension in either study. Symptoms of hypotension were a cause for withdrawal in 2 subjects receiving terazosin and in 4 subjects receiving tamsulosin. Instances of outlier blood pressure values (defined as standing SBP <85 mmHg and/or a decrease from baseline of standing SBP >30 mmHg) were observed in 9/24 subjects receiving tamsulosin and 19/29 receiving terazosin. The incidence of subjects with standing SBP <85 mmHg given vardenafil and terazosin to achieve simultaneously the amount of time at the maximum concentration in serum (T_{max}) led to early termination of that arm of the study. In most (7/8) of these subjects, instances of standing SBP <85 mmHg were not associated with symptoms. Among subjects treated with terazosin, outlier values were observed more frequently when vardenafil and terazosin were given to achieve simultaneous T_{max} than when dosing was administered to separate T_{max} by 6 hours. There were 3 cases of dizziness observed with concomitant administration of terazosin and vardenafil. Seven subjects experienced dizziness mainly occurring with simultaneous T_{max} administration of tamsulosin. There were no cases of syncope.

Table 5: Mean (95% CI) maximal change in baseline in systolic blood pressure (mmHg) following vardenafil 10 and 20 mg (film-coated tablets) in healthy volunteers on daily alpha-blocker therapy

		Dosing of Vardenafil and Alpha-Blocker Separated by 6 Hours		Simultaneous dosing of Vardenafil and Alpha-Blocker	
Alpha-Blocker		Vardenafil 10 mg Placebo-Subtracted	Vardenafil 20 mg Placebo-Subtracted	Vardenafil 10 mg Placebo-Subtracted	Vardenafil 20 mg Placebo-Subtracted
Terazosin 10 mg daily	Standing SBP	-7 (-10, -3)	-11 (-14, -7)	-23 (-31, 16)*	-14 (-33, 11)*
	Supine SBP	-5 (-8, -2)	-7 (-11, -4)	-7 (-25, 19)*	-7 (-31, 22)*
Tamsulosin 0.4 mg daily	Standing SBP	-4 (-8, -1)	-8 (-11, -4)	-8 (-14, -2)	-8 (-14, -1)
	Supine SBP	-4 (-8, 0)	-7 (-11, -3)	-5 (-9, -2)	-3 (-7, 0)

* Due to the sample size, confidence intervals may not be an accurate measure for these data. These values represent the range for the difference.

Figure 6: Mean change from baseline in standing systolic blood pressure (mmHg) over 6 hour interval following simultaneous or 6 hr separation administration of vardenafil 10 mg and 20 mg (film-coated tablets) or placebo with terazosin (10 mg) in healthy volunteers

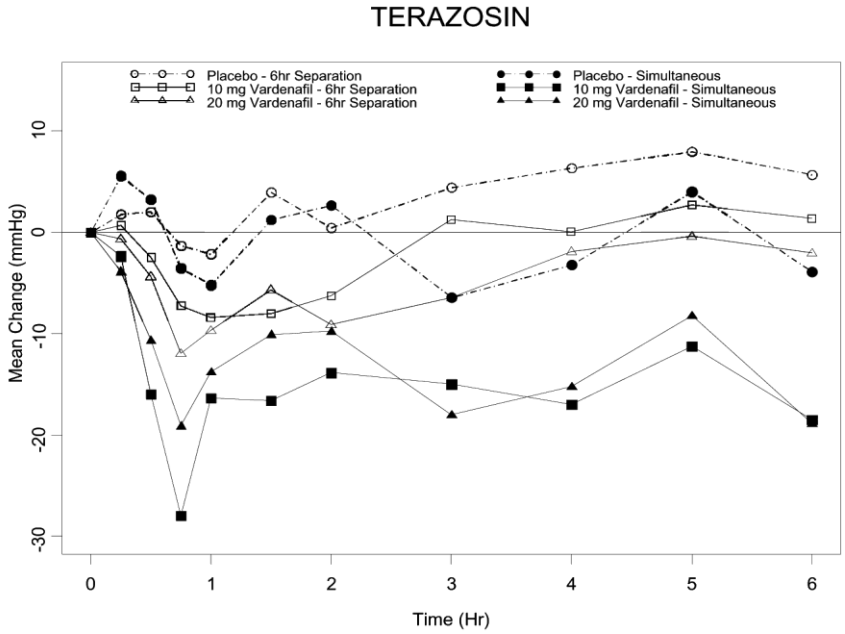
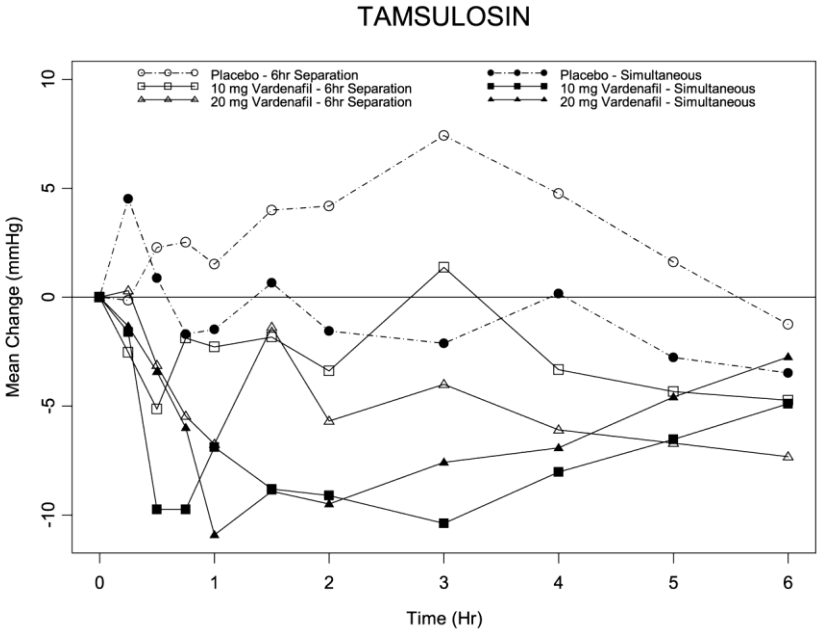


Figure 7: Mean change from baseline in standing systolic blood pressure (mmHg) over 6 hour interval following simultaneous or 6 hr separation administration of vardenafil 10 mg and 20 mg (film-coated tablets) or placebo with tamsulosin (0.4 mg) in healthy volunteers



Effects on Cardiac Electrophysiology

The effect of 10 mg and 80 mg vardenafil, administered as film-coated tablets, on QT interval was evaluated in a single-dose, double-blind, randomized, placebo- and active-controlled (moxifloxacin 400 mg) crossover study in 59 healthy males (81% White, 12% Black, 7% Hispanic) aged 45–60 years. The QT interval was measured at one hour post dose because this time point approximates the average time of peak vardenafil concentration. The 80 mg dose of vardenafil (four times the highest recommended dose of the film-coated tablets) was chosen because this dose yields plasma concentrations covering those observed upon co-administration of a low-dose of vardenafil (5 mg) and 600 mg b.i.d. of ritonavir. Of the CYP3A4 inhibitors that have been studied, ritonavir causes the most significant drug-drug interaction with vardenafil. Table 6 summarizes the effect on mean uncorrected QT and mean corrected QT interval (QTc) with different methods of correction (Fridericia and a linear individual correction method) at one hour post-dose. No single correction method is known to be more valid than the other. In this study, the mean increase in heart rate associated with a 10 mg dose of vardenafil, administered as a film-coated tablet, compared to placebo was 5 beats/minute and with an 80 mg dose of vardenafil the mean increase was 6 beats/minute.

Table 6: Mean QT and QTc changes in msec (90% CI) from baseline relative to placebo at 1 hour post-dose with different methodologies to correct for the effect of heart rate

Drug/Dose	QT Uncorrected (msec)	Fridericia QT Correction (msec)	Individual QT Correction (msec)
Vardenafil 10 mg	-2 (-4, 0)	8 (6, 9)	4 (3, 6)
Vardenafil 80 mg	-2 (-4, 0)	10 (8, 11)	6 (4, 7)
Moxifloxacin* 400 mg	3 (1, 5)	8 (6, 9)	7 (5, 8)

* Active control (drug known to prolong QT)

Therapeutic and supratherapeutic doses of vardenafil and the active control moxifloxacin produced similar increases in QTc interval. This study, however, was not designed to make direct statistical comparisons between the drugs or the dose levels. The clinical impact of these QTc changes is unknown *[see Warnings and Precautions (5)]*.

In a separate postmarketing study of 44 healthy volunteers, single doses of 10 mg vardenafil (film-coated tablet) resulted in a placebo-subtracted mean change from baseline of QTcF (Fridericia correction) of 5 msec (90% CI: 2,8). Single doses of gatifloxacin 400 mg resulted in a placebo-subtracted mean change from baseline QTcF of 4 msec (90% CI: 1,7). When vardenafil 10mg (film-coated tablets) and gatifloxacin 400 mg were co-administered, the mean QTcF change from baseline was additive when compared to either drug alone and produced a mean QTcF change of 9 msec from baseline (90% CI: 6,11). The clinical impact of these QT changes is unknown *[see Warnings and Precautions (5.7)]*.

Effects on Exercise Treadmill Test in Patients with Coronary Artery Disease (CAD)

In two independent trials that assessed 10 mg (n=41) and 20 mg (n=39) vardenafil (film-coated tablets), respectively, vardenafil did not alter the total treadmill exercise time compared to placebo. The patient population included men aged 40–80 years with stable exercise-induced angina documented by at least one of the following: 1) prior history of myocardial infarction (MI), coronary artery bypass graft (CABG), percutaneous transluminal coronary angioplasty (PTCA), or stenting (not within 6 months); 2) positive coronary angiogram showing at least 60% narrowing of the diameter of at least one major coronary artery; or 3) a positive stress echocardiogram or stress nuclear perfusion study.

Results of these studies showed that vardenafil did not alter the total treadmill exercise time compared to placebo (vardenafil 10 mg vs. placebo: 433±109 and 426±105 seconds, respectively; 20 mg vardenafil vs. placebo: 414±114 and 411±124 seconds, respectively). The total time to angina was not altered by vardenafil when compared to placebo (10 mg vardenafil vs. placebo: 291±123 and 292±110 seconds; 20 mg vardenafil vs. placebo: 354±137 and 347±143 seconds, respectively). The total time to 1 mm or greater ST-segment depression was similar to placebo in both the 10 mg and the 20 mg vardenafil groups (10 mg vardenafil vs. placebo: 380±108 and 334±108 seconds; 20 mg vardenafil vs. placebo: 364±101 and 366±105 seconds, respectively).

Effects on Eye

Single oral doses of phosphodiesterase inhibitors have demonstrated transient dose-related impairment of color discrimination (blue/green) using the Farnsworth-Munsell 100-hue (FM-100) test and reductions in electroretinogram (ERG) b-wave amplitudes, with peak effects near the time of peak plasma levels. These findings are consistent with the inhibition of PDE6 in rods and cones, which is involved in phototransduction in the retina. The findings were most evident one hour after administration, diminishing but still present 6 hours after administration. In a single dose study in 25 normal males, vardenafil (film-coated tablets) 40 mg, twice the maximum daily recommended dose, did not alter visual acuity, intraocular pressure, fundoscopic and slit lamp findings.

In another double-blind, placebo-controlled clinical trial, at least 15 doses of 20 mg vardenafil were administered over 8 weeks versus placebo to 52 males. Thirty-two (32) males (62% of the patients) completed the trial. Retinal function was measured by ERG and FM-100 test 2, 6 and 24 hours after dosing. The trial was designed to detect changes in retinal function that might occur in more than 10% of patients. Vardenafil did not produce clinically significant ERG or FM-100 effects in healthy men compared to placebo. Two patients on vardenafil in the trial reported episodes of transient cyanopsia (objects appear blue).

Effects on Sperm Motility Morphology

There was no effect on sperm motility or morphology after single 20 mg oral doses of vardenafil film-coated tablets in healthy volunteers.

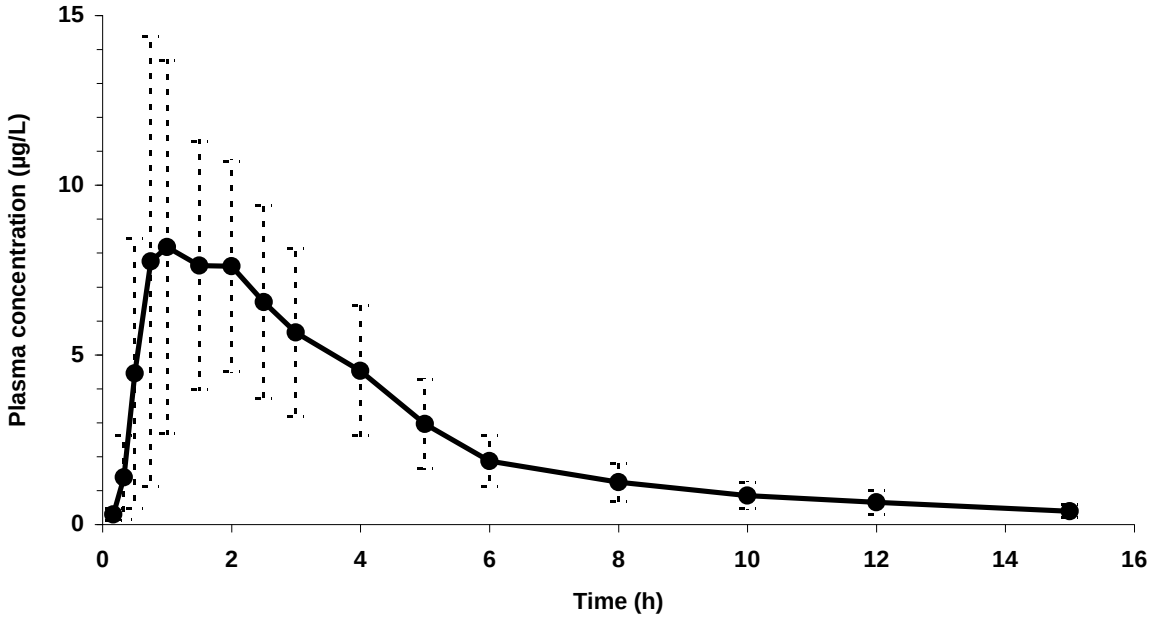
12.3 Pharmacokinetics

The pharmacokinetics of vardenafil and its M1 metabolite from STAXYN have been evaluated in healthy male volunteers (18–50 years) and in young (18–45 years) and elderly (≥ 65 years) erectile dysfunction patients. Studies have shown that STAXYN provides higher systemic exposure of vardenafil compared to vardenafil 10 mg film-coated tablets.

Absorption

Mean vardenafil plasma concentrations measured after the administration of a single oral dose STAXYN to patients with erectile dysfunction (18- 45 years) are depicted in *Figure 8*.

Figure 8: Vardenafil Plasma Concentration (Mean ± SD) Profile for STAXYN in men age 18–45 years with erectile dysfunction



The median time to reach C_{max} (T_{max}) in patients receiving STAXYN in the fasted state was 1.5 h [range: 0.75 – 2.5 h]. After administration of STAXYN to elderly (≥ 65 years) and young (18–45 years) patients with erectile dysfunction, mean vardenafil AUC was increased by 21 to 29%, respectively while mean C_{max} was lower by 19% and 8%, respectively, in comparison to 10 mg vardenafil (film-coated tablets). In a study of healthy male volunteers (18–50 years), the mean C_{max} and AUC of vardenafil from STAXYN were higher by 15% and 44%, respectively compared to 10 mg vardenafil film-coated tablets.

Vardenafil was not found to accumulate in plasma when STAXYN was dosed daily over ten days.

Effect of food: A high fat meal had no effect on vardenafil AUC and T_{max} from STAXYN in healthy volunteers and reduced C_{max} by 35%. Clinical trials for STAXYN were conducted without regard to meals. STAXYN can be taken with or without food.

Effect of water: When STAXYN was swallowed with water, the AUC of vardenafil was reduced by 29% and median T_{max} was shortened by 60 minutes while C_{max} was not affected. In clinical trials, dosing was done without water. STAXYN should be taken without liquid.

Distribution

The mean steady-state volume of distribution (Vss) for vardenafil is 208 L, indicating extensive tissue distribution. Vardenafil and its major circulating metabolite, M1, are highly bound to plasma proteins (about 95% for parent drug and M1). This protein binding is reversible and independent of total drug concentrations.

Following a single oral dose of 20 mg vardenafil film-coated tablet in healthy volunteers, a mean of 0.00018% of the administered dose was obtained in semen 1.5 hours after dosing.

Metabolism

Vardenafil is metabolized predominantly by the hepatic enzyme CYP3A4, with contribution from the CYP3A5 and CYP2C isoforms. The major circulating metabolite, M1, results from desethylation at the piperazine moiety of vardenafil. M1 is subject to further metabolism. The plasma concentration of M1 is approximately 26% that of the parent compound. This metabolite shows a phosphodiesterase selectivity profile similar to that of vardenafil and an *in vitro* inhibitory potency for PDE5 28% of that of vardenafil. Therefore, M1 accounts for approximately 7% of total pharmacologic activity.

Excretion

The mean terminal half-life of vardenafil in patients receiving STAXYN tablets varied between about 4–6 hours. The elimination half-life of the metabolite M1 is between 3 to 5 hours. After oral administration, vardenafil is excreted as metabolites predominantly in the feces (approximately 91–95% of administered oral dose) and to a lesser extent in the urine (approximately 2–6% of administered oral dose). Vardenafil is a high clearance drug with a plasma clearance of 56.4 L/h following intravenous administration.

Pharmacokinetics in Specific Populations

Pediatrics

STAXYN is not indicated for use in pediatric patients. Vardenafil trials were not conducted in the pediatric population.

Geriatrics

Vardenafil AUC and C_{max} in elderly patients (65 years or older) taking STAXYN were increased by 39% and 21%, respectively, in comparison to patients aged 45 years and below *[see Use in Specific Populations (8.5)]*.

Hepatic Impairment

In volunteers with mild hepatic impairment (Child-Pugh A), the C_{max} and AUC following a 10 mg vardenafil (film-coated tablets) dose were increased by 22% and 17%, respectively, compared to healthy control subjects. In volunteers with moderate hepatic impairment (Child-Pugh B), the C_{max} and AUC following a 10 mg vardenafil (film-coated tablets) dose were increased by 130% and 160%, respectively, compared to healthy control subjects. Vardenafil has not been evaluated in patients with severe (Child-Pugh C) hepatic impairment. *[See Dosage and Administration (2.3), Warnings and Precautions (5.8), and Use in Specific Populations (8.6).]*

Renal Impairment

In volunteers with mild renal impairment (CLcr = 50–80 mL/min), the pharmacokinetics of vardenafil were similar to those observed in a control group with normal renal function. In the moderate (CLcr = 30–50 mL/min) or severe (CLcr <30 mL/min) renal impairment groups, the AUC of vardenafil was 20–30% higher compared to that observed in a control group with normal renal function (CLcr >80 mL/min). Vardenafil pharmacokinetics have not been evaluated in patients requiring renal dialysis *[see Dosage and Administration (2.3), Warnings and Precautions (5.9), and Use in Specific Populations (8.7)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Vardenafil was not carcinogenic in rats and mice when administered daily for 24 months. In these studies systemic drug exposures (AUCs) for unbound (free) vardenafil and its major metabolite were approximately 400- and 170-fold for male and female rats, respectively, and 21-and 37-fold for male and female mice, respectively, the exposures observed in human males given the maximum recommended human dose (MRHD) of 20 mg.

Mutagenesis

Vardenafil was not mutagenic as assessed in either the *in vitro* bacterial Ames assay or the forward mutation assay in Chinese hamster V_{79} cells. Vardenafil was not clastogenic as assessed in either the *in vitro* chromosomal aberration test or the *in vivo* mouse micronucleus test.

Impairment of Fertility

Vardenafil did not impair fertility in male and female rats administered doses up to 100 mg/kg/day for 28 days prior to mating in males, and for 14 days prior to mating and through day 7 of gestation in females. In a corresponding 1-month rat toxicity study, this dose produced an AUC value for unbound vardenafil 200 fold greater than AUC in humans at the MRHD of 20 mg.

14 CLINICAL STUDIES

The efficacy and safety of STAXYN were evaluated in two identical multi-national, randomized, double-blind, placebo-controlled trials (studies 1 and 2). STAXYN was dosed without regard to meals on an as-needed basis in men with erectile dysfunction (ED), many of whom had multiple other medical conditions. In both pivotal studies, randomization was stratified so that approximately 50% of patients were ≥65 years old. Primary efficacy assessment was by means of the Erectile Function (EF) Domain score of the validated International Index of Erectile Function (IIEF) Questionnaire and two questions from the Sexual Encounter Profile (SEP) dealing with the ability to achieve vaginal penetration (SEP2), and the ability to maintain an erection long enough for successful intercourse (SEP3). The primary endpoints were assessed at 3 months.

Study 1 evaluated 355 mainly European (Belgium, France, Germany, Spain, South Africa, and Netherlands) patients (mean age 61.9; 67% White, 4% Black, 3% Asian, 26% Unknown). The mean baseline EF domain scores were 13 for both placebo and STAXYN groups. Study 2 evaluated 331 mainly North American (USA, Canada, Mexico, and Australia) patients (mean age 61.7; 69% White, 5% Black, 4% Asian, 22% Hispanic). The mean baseline EF domain scores were 12 for STAXYN and 13 for placebo.

In both studies STAXYN demonstrated clinically meaningful and statistically significant improvements over placebo in all 3 primary efficacy variables (see Table 7).

Table 7: Change from Baseline for the Primary Efficacy Variables in Studies 1 and 2

	Study 1			**Study 2**		
	Placebo	**STAXYN**	**p-value**	**Placebo**	**STAXYN**	**p-value**
EF Domain Score	**(N=172)**	**(N=181)**		**(N=160)**	**(N=167)**	
Endpoint	14	21		14	21	
Change from baseline	1.6	8.7	<.0001	1.5	8.5	<.0001
Insertion of Penis (SEP2)	**(N=169)**	**(N=179)**		**(N=161)**	**(N=168)**	
Endpoint	45%	74%		43%	69%	
Change from baseline	6.9%	35.9%	<.0001	4.8%	30.8%	<.0001
Maintenance of Erection (SEP3)	**(N=164)**	**(N=178)**		**(N=160)**	**(N=168)**	
Endpoint	26%	65%		27%	60%	
Change from baseline	11.6%	51.6%	<.0001	12.4%	45.9%	<.0001

14.1 Other Vardenafil Clinical Trials Using Film-Coated Tablets

Patients with ED and Diabetes Mellitus

Vardenafil demonstrated clinically meaningful and statistically significant improvement in erectile function in a prospective, fixed-dose [10 and 20 mg vardenafil film-coated tablets], double-blind, placebo-controlled trial of patients with diabetes mellitus (n=439; mean age 57 years, range 33–81; 80% White, 9% Black, 8% Hispanic, and 3% Other).

Significant improvements in the EF Domain were shown in this study (EF Domain scores of 17 on 10 mg vardenafil and 19 on 20 mg vardenafil compared to 13 on placebo; p <0.0001).

Vardenafil significantly improved the overall per-patient rate of achieving an erection sufficient for penetration (SEP2) (61% on 10 mg and 64% on 20 mg vardenafil compared to 36% on placebo; p <0.0001).

Vardenafil demonstrated a clinically meaningful and statistically significant increase in the overall per-patient rate of maintenance of erection to successful intercourse (SEP3) (49% on 10 mg, 54% on 20 mg vardenafil compared to 23% on placebo; p <0.0001).

Patients with ED after Radical Prostatectomy

Vardenafil demonstrated clinically meaningful and statistically significant improvement in erectile function in a prospective, fixed-dose 10 and 20 mg vardenafil film-coated tablets, double-blind, placebo-controlled trial in post-prostatectomy patients (n=427, mean age 60, range 44–77 years; 93% White, 5% Black, 2% Other).

Significant improvements in the EF Domain were shown in this study (EF Domain scores of 15 on 10 mg vardenafil and 15 on 20 mg vardenafil compared to 9 on placebo; p <0.0001).

Vardenafil significantly improved the overall per-patient rate of achieving an erection sufficient for penetration (SEP2) (47% on 10 mg and 48% on 20 mg vardenafil compared to 22% on placebo; p <0.0001).

Vardenafil demonstrated a clinically meaningful and statistically significant increase in the overall per-patient rate of maintenance of erection to successful intercourse (SEP3) (37% on 10 mg, 34% on 20 mg vardenafil compared to 10% on placebo; p <0.0001).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

STAXYN (vardenafil HCl) are white, round orally disintegrating tablets with no debossing. STAXYN orally disintegrating tablets are packaged into foil blisterpacks and supplied as a 4 tablet unit.

Package	Strength	NDC Code
1 blister card containing 4 tablets	10 mg	0173-0822-04

In addition to the active ingredient, vardenafil, each tablet contains aspartame, peppermint flavor, magnesium stearate, and Pharmaburst™ B2 (crospovidone, mannitol, silica colloidal hydrated, and sorbitol).

16.2 Recommended Storage

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

STAXYN is dispensed in blisterpacks. The patient should be advised to examine the blisterpack before use and not use if blisters are torn, broken, or missing.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

Use with Other Formulations of Vardenafil

Inform patients that STAXYN is not interchangeable with vardenafil film-coated tablets (LEVITRA) as it provides higher systemic exposure. They should also discuss that the maximum dosage is one STAXYN tablet per 24 hours.

Nitrates

Discuss with patients that STAXYN is contraindicated with regular and/or intermittent use of organic nitrates. Patients should be counseled that concomitant use of vardenafil with nitrates could cause blood pressure to suddenly drop to an unsafe level, resulting in dizziness, syncope, or even heart attack or stroke.

Guanylate Cyclase (GC) Stimulators

Inform patients that Staxyn is contraindicated in patients who use guanylate cyclase stimulators, such as riociguat.

Cardiovascular

Discuss with patients the potential cardiac risk of sexual activity for patients with preexisting cardiovascular risk factors.

Concomitant Use with Drugs which Lower Blood Pressure

Inform patients that in some patients concomitant use of PDE5 inhibitors, including STAXYN, with alpha-blockers can lower blood pressure significantly leading to symptomatic hypotension (for example, fainting). Patients who are taking alpha-blockers should only use STAXYN when previous treatment with vardenafil film-coated tablets has been well tolerated *[see Dosage and Administration (2) and Drug Interactions (7)]*. Patients should be advised of the possible occurrence of symptoms related to postural hypotension and appropriate countermeasures. Patients should be advised to contact the prescribing physician if other anti-hypertensive drugs or new medications that may interact with STAXYN are prescribed by another healthcare provider.

Recommended Administration

Discuss with patients the appropriate use of STAXYN and its anticipated benefits. It should be explained that sexual stimulation is required for an erection to occur after taking STAXYN. STAXYN should be taken approximately 60 minutes before sexual activity. Patients should be counseled regarding the dosing of STAXYN, especially regarding the maximum daily dose. Patients should be advised to contact their healthcare provider if they are not satisfied with the quality of their sexual performance with STAXYN or in the case of an unwanted effect.

Priapism

Inform patients that there have been rare reports of prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) for vardenafil and this class of compounds. In the event that an erection persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency may result.

Drug Interactions

Advise patients to contact the prescribing physician if new medications that may interact with STAXYN are prescribed by another healthcare provider.

Sudden Loss of Vision

Inform patients to stop use of all PDE5 inhibitors, including STAXYN, and seek medical attention in the event of 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 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. It is not possible to determine whether these events were related directly to the use of PDE5 inhibitors or to other factors. Physicians should also discuss with patients the increased risk of NAION in individuals who have already experienced NAION in one eye. Physicians should also discuss with patients the increased risk of NAION among the general population in patients with a “crowded” optic disc, although evidence is insufficient to support screening of prospective users of PDE5 inhibitor, including Staxyn, for this uncommon condition *[see Warnings and Precautions (5.4) and [see Adverse Reactions (6.1)]*.

Sudden Hearing Loss

Advise patients to stop taking PDE5 inhibitors, including STAXYN, 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 STAXYN. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors *[see Adverse Reactions (6)]*.

Sexually Transmitted Disease

Inform Patients that STAXYN offers no protection against sexually transmitted diseases. Counsel patients that protective measures necessary to guard against sexually transmitted diseases, including the Human Immunodeficiency Virus (HIV), should be considered.

Dose Adjustment

STAXYN is available only in a single strength. Patients who require a different dosage should be prescribed vardenafil film-coated tablets (LEVITRA).

FDA-approved patient labeling

STAXYN® (stax-in)

(vardenafil HCl)
orally disintegrating tablets

Read the Patient Information about STAXYN before you start taking it and again 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 leaflet does not take the place of talking with your doctor. You and your doctor should talk about STAXYN when you start taking it and at regular checkups. If you do not understand the information, or have questions, talk with your doctor or pharmacist.

WHAT IMPORTANT INFORMATION SHOULD YOU KNOW ABOUT STAXYN?

STAXYN is not interchangeable with vardenafil film-coated tablets (LEVITRA).

STAXYN can cause your blood pressure to drop suddenly to an unsafe level if it is taken with certain other medicines. With a sudden drop in blood pressure, you could get dizzy, faint, or have a heart attack or stroke.

STAXYN contains phenylalanine which can be harmful to people who have phenylketonuria. Talk to your doctor if you have phenylketonuria.

Do not take STAXYN if you:

- Take any medicines called "nitrates" (often used to control chest pain, also known as angina)
- Use recreational drugs called "poppers" like amyl nitrate and butyl nitrate.
- Take riociguat (Adempas®), a guanulate cyclase stimulator, a medicine that treats pulmonary arterial hypertension and chronic-thromboembolic pulmonary hypertension.

(See *"Who Should Not Take STAXYN?"*)

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

WHAT IS STAXYN?

STAXYN is a prescription medicine taken by mouth for the treatment of erectile dysfunction (ED) in men.

ED is a condition where the penis does not harden and expand when a man is sexually excited, or when he cannot keep an erection. A man who has trouble getting or keeping an erection should see his doctor for help if the condition bothers him. STAXYN may help a man with ED get and keep an erection when he is sexually excited.

STAXYN does not:

- Cure ED.
- Increase a man's sexual desire.
- Protect a man or his partner from sexually transmitted diseases, including HIV. Speak to your doctor about ways to guard against sexually transmitted diseases.
- Serve as a male form of birth control.

STAXYN is only for men with ED. STAXYN is not for women or children. STAXYN must be used only under a doctor's care.

HOW DOES STAXYN WORK?

When a man is sexually stimulated, his body's normal physical response is to increase blood flow to his penis. This results in an erection. STAXYN helps increase blood flow to the penis and may help men with ED get and keep an erection satisfactory for sexual activity. Once a man has completed sexual activity, blood flow to his penis decreases, and his erection goes away.

WHO CAN TAKE STAXYN?

Talk to your doctor to decide if STAXYN is right for you.

STAXYN has been shown to be effective in men over the age of 18 years who have erectile dysfunction, including men with diabetes.

WHO SHOULD NOT TAKE STAXYN?

Do not take STAXYN if you:

- **Take any medicines called "nitrates**" (see "*What important information should you know about STAXYN?*"). 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 nitrate and butyl nitrate. Do not use STAXYN if you are using these drugs. Ask your doctor or pharmacist if you are not sure if any of your medicines are nitrates.
- **Take riociguat, a guanylate cyclase stimulator,** a medicine that treats pulmonary arterial hypertension and chronic-throembolic pulmonary hypertension.
- **Have been told by your healthcare provider to not have sexual activity because of health problems.** Sexual activity can put an extra strain on your heart, especially if your heart is already weak from a heart attack or heart disease.

WHAT SHOULD YOU DISCUSS WITH YOUR DOCTOR BEFORE TAKING STAXYN?

Before taking STAXYN, tell your doctor about all your medical problems, including if you:

- Have heart problems such as angina, heart failure, irregular heartbeats, or have had a heart attack. Ask your doctor if it is safe for you to have sexual activity.
- Have low blood pressure or have high blood pressure that is not controlled.
- Have pulmonary hypertension
- Have had a stroke.
- Have had a seizure.
- Or any family members have a rare heart condition known as prolongation of the QT interval (long QT syndrome).
- Have liver problems.
- Have kidney problems and require dialysis.
- Have retinitis pigmentosa, a rare genetic (runs in families) eye disease.
- Have ever had severe vision loss, or if you have an eye condition called non-arteritic anterior ischemic optic neuropathy (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.
- Have hearing problems.
- Have phenylketonuria.
- Have fructose intolerance.

CAN OTHER MEDICATIONS AFFECT STAXYN?

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

- Medicines called nitrates (see "*What important information should you know about STAXYN?*").
- Medicines that treat abnormal heartbeat. These include quinidine, procainamide, amiodarone and sotalol.
- Ritonavir (Norvir®) or indinavir sulfate (Crixivan®) saquinavir (Fortavase® or Invirase®) or atazanavir (Reyataz®) or other HIV protease inhibitors.
- Ketoconazole or itraconazole (such as Nizoral® or Sporanox®).
- Erythromycin or clarithromycin.
- Other medicines or treatments for ED.

Patients taking these drugs should not use STAXYN.

Patients taking alpha-blockers should not initiate vardenafil therapy with STAXYN. Patients taking alpha-blockers who have previously used vardenafil film-coated tablets may switch to STAXYN at the advice of their healthcare provider.

- Medicines called alpha-blockers. These include Hytrin® (terazosin HCl), Flomax® (tamsulosin HCl), Cardura® (doxazosin mesylate), Minipress® (prazosin HCl) or Uroxatral® (alfuzosin HCl), Rapaflo® (silodosin). Alpha-blockers are sometimes prescribed for prostate problems or high blood pressure. In some patients the use of PDE5 inhibitor drugs, including STAXYN, with alpha-blockers can lower blood pressure significantly leading to fainting.
- Patients should contact the prescribing physician if alpha-blockers or other drugs that lower blood pressure are prescribed by another healthcare provider.

HOW SHOULD YOU TAKE STAXYN?

Take STAXYN exactly as your doctor prescribes. STAXYN comes in 10 mg orally disintegrating tablets. The dose is one STAXYN tablet. **Do not take more than one STAXYN a day.** Doses should be taken at least 24 hours apart.

- If you have prostate problems or high blood pressure, for which you take medicines called alpha-blockers, you should not start treatment for erectile dysfunction with STAXYN. Your doctor may prescribe a lower dose of vardenafil film-coated tablet.

Take 1 STAXYN tablet about 1 hour (60 min) before sexual activity. Some form of sexual stimulation is needed for an erection to happen with STAXYN. STAXYN may be taken with or without meals.

Place on the tongue where it will dissolve rapidly. The tablet should be taken whole and not crushed or split.

The tablet should not be taken with liquid.

It should be taken immediately upon removal from the blister.

Call your doctor or emergency room immediately if you accidentally took more STAXYN than prescribed.

If you receive STAXYN in a blisterpack, examine the blisterpack before use. Do not use if blisters are torn, broken, or missing.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF STAXYN?

The most common side effects with STAXYN are headache, flushing, stuffy or runny nose, indigestion, upset stomach, dizziness, and back pain. These side effects usually go away after a few hours. Call your doctor if you get a side effect that bothers you or one that will not go away.

STAXYN may uncommonly cause:

- **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 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 vardenafil) reported a sudden decrease or loss of vision in one or both eyes. It is not possible to determine whether these events are related directly to these medicines, to other factors such as high blood pressure or diabetes, or to a combination of these. If you experience sudden decrease or loss of vision, stop taking PDE5 inhibitors, including STAXYN, and call a doctor 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 vardenafil. 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 STAXYN and contact a doctor right away.

These are not all the side effects of STAXYN. For more information, ask your doctor or pharmacist.

HOW SHOULD STAXYN BE STORED?

- Store STAXYN at room temperature between 59–86° F (15–30° C).
- Keep STAXYN and all medicines out of the reach of children.

GENERAL INFORMATION ABOUT STAXYN

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

This leaflet summarizes the most important information about STAXYN. If you would like more information, talk with your healthcare provider. You can ask your doctor or pharmacist for information about STAXYN that is written for health professionals.

For more information you can also visit www.STAXYN.com or call 1-888-825-5249.

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WHAT ARE THE INGREDIENTS OF STAXYN?

Active Ingredient: vardenafil hydrochloride

Inactive Ingredients of STAXYN: Aspartame, peppermint flavor, magnesium stearate and Pharmaburst™ B2 (crospovidone, mannitol, silica colloidal hydrated, and sorbitol)

Phenylketonurics: STAXYN contains 1.01 mg phenylalanine per tablet.

Products cited in STAXYN USPI

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