- In those patients who are stable on alpha-blocker therapy, PDE5 inhibitors should be initiated at the lowest recommended starting dose (see **DOSAGE and ADMINISTRATION**).
- In those patients already taking an optimized dose of PDE5 inhibitor, alpha-blocker therapy should be initiated at the lowest dose. Stepwise increase 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.

Hepatic Insufficiency: In volunteers with moderate impairment (Child-Pugh B), the C_{max} and AUC following a 10 mg vardenafil dose were increased 130% and 160%, respectively, compared to healthy control subjects. Consequently, a starting dose of 5 mg is recommended for patients with moderate hepatic impairment and the maximum dose should not exceed 10 mg (see **CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations,** and **DOSAGE AND ADMINISTRATION**). Vardenafil has not been evaluated in patients with severe hepatic impairment (Child-Pugh C).

Congenital or Acquired QT Prolongation: In a study of the effect of LEVITRA on QT interval in 59 healthy males (see **CLINICAL PHARMACOLOGY, Electrophysiology**), therapeutic (10 mg) and supratherapeutic (80 mg) doses of LEVITRA and the active control moxifloxacin (400 mg) produced similar increases in QT_c interval. A postmarketing study evaluating the effect of combining LEVITRA with another drug of comparable QT effect showed an additive QT effect when compared with either drug alone (see **CLINICAL PHARMACOLOGY, Electrophysiology**). These observations should be considered in clinical decisions when prescribing LEVITRA to patients with known history of QT prolongation or patients who are taking medications known to prolong the QT interval. Patients taking Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic medications or those with congenital QT prolongation, should avoid using LEVITRA.

Renal Insufficiency: In patients with moderate (CL_{cr} = 30-50 ml/min) to severe (CL_{cr} <30 ml/min) renal impairment, the AUC of vardenafil was 20 – 30% higher compared to that observed in a control group with normal renal function (CL_{cr} >80 ml/min) (see **CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations**). Vardenafil pharmacokinetics have not been evaluated in patients requiring renal dialysis.

General: In humans, vardenafil 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. Vardenafil has not been administered to patients with bleeding disorders or significant active peptic ulceration. Therefore LEVITRA should be administered to these patients after careful benefit-risk assessment.

Treatment for erectile dysfunction should generally 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).

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

Information for Patients

Physicians should discuss with patients the contraindication of LEVITRA with regular and/or intermittent use of organic nitrates. Patients should be counseled that concomitant use of LEVITRA with nitrates could cause blood pressure to suddenly drop to an unsafe level, resulting in dizziness, syncope, or even heart attack or stroke.

Physicians should inform their patients that in some patients concomitant use of PDE5 inhibitors, including LEVITRA, with alpha-blockers can lower blood pressure significantly leading to symptomatic hypotension (e.g., fainting). Patients prescribed LEVITRA who are taking alpha-blockers should be started on the lowest recommended starting dose of LEVITRA (see **Drug Interactions** and **DOSAGE AND ADMINISTRATION**). 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 LEVITRA are prescribed by another healthcare provider.

Physicians should discuss with patients the appropriate use of LEVITRA and its anticipated benefits. It should be explained that sexual stimulation is required for an erection to occur after taking LEVITRA. LEVITRA should be taken approximately 60 minutes before sexual activity. Patients should be counseled regarding the dosing of LEVITRA. Patients should be advised to contact their healthcare provider for dose modification if they are not satisfied with the quality of their sexual performance with LEVITRA or in the case of an unwanted effect. Patients should be advised to contact the prescribing physician if new medications that may interact with LEVITRA are prescribed by another healthcare provider.

Physicians should advise patients to stop use of all PDE5 inhibitors, including LEVITRA, 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 post-marketing 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, including whether such individuals could be adversely affected by use of vasodilators such as PDE5 inhibitors (see **POST-MARKETING EXPERIENCE, Ophthalmologic**).

Physicians should discuss with patients the potential cardiac risk of sexual activity for patients with preexisting cardiovascular risk factors.

The use of LEVITRA 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.

Physicians should 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 LEVITRA 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

Effect of other drugs on LEVITRA

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 **WARNINGS** and **DOSAGE AND ADMINISTRATION**).

In vivo studies: Cytochrome P450 Inhibitors

Cimetidine (400 mg b.i.d.) had no effect on vardenafil bioavailability (AUC) and maximum concentration (C_{max}) of vardenafil when co-administered with 20 mg LEVITRA in healthy volunteers. Erythromycin (500 mg t.i.d.) produced a 4-fold increase in vardenafil AUC and a 3-fold increase in C_{max} when co-administered with LEVITRA 5 mg in healthy volunteers (see **DOSAGE AND**

ADMINISTRATION). It is recommended not to exceed a single 5 mg dose of LEVITRA in a 24-hour period when used in combination with erythromycin.

Ketoconazole (200 mg once daily) produced a 10-fold increase in vardenafil AUC and a 4-fold increase in C_{max} when co-administered with LEVITRA (5 mg) in healthy volunteers. A 5-mg LEVITRA dose should not be exceeded when used in combination with 200 mg once daily ketoconazole. Since higher doses of ketoconazole (400 mg daily) may result in higher increases in C_{max} and AUC, a single 2.5 mg dose of LEVITRA should not be exceeded in a 24-hour period when used in combination with ketoconazole 400 mg daily (see **WARNINGS** and **DOSAGE AND ADMINISTRATION**).

HIV Protease Inhibitors:

Indinavir (800 mg t.i.d.) co-administered with LEVITRA 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. It is recommended not to exceed a single 2.5 mg LEVITRA dose in a 24-hour period when used in combination with indinavir (see **WARNINGS** and **DOSAGE AND ADMINISTRATION**).

Ritonavir (600 mg b.i.d.) co-administered with LEVITRA 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 highly potent CYP3A4 inhibitor, which also inhibits CYP2C9. Ritonavir significantly prolonged the half-life of vardenafil to 26 hours. Consequently, it is recommended not to exceed a single 2.5 mg LEVITRA dose in a 72-hour period when used in combination with ritonavir (see **WARNINGS** and **DOSAGE AND ADMINISTRATION**).

Other CYP3A4 inhibitors: Although specific interactions have not been studied, other CYP3A4 inhibitors, including grapefruit juice would likely increase vardenafil exposure.

Other Drug Interactions: No pharmacokinetic interactions were observed between vardenafil and the following drugs: glyburide, warfarin, digoxin, Maalox, and ranitidine. In the warfarin study, vardenafil had no effect on the prothrombin time or other pharmacodynamic parameters.

Effects of LEVITRA on other drugs

In vitro studies:

Vardenafil and its metabolites had no effect on CYP1A2, 2A6, and 2E1 (Ki >100 μM). 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 μM toward CYP3A4, which is about 20 times higher than the M1 C_{max} values after an 80 mg LEVITRA dose.

In vivo studies:

Nitrates: 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 were potentiated by a 20 mg dose of LEVITRA in healthy middle-aged subjects. These effects were not observed when LEVITRA 20 mg was taken 24 hours before the NTG. Potentiation of the hypotensive effects of nitrates for patients with ischemic heart disease has not been evaluated, and concomitant use of LEVITRA and nitrates is contraindicated (see **CLINICAL PHARMACOLOGY, Pharmacodynamics, Effects on Blood Pressure and Heart Rate when LEVITRA is Combined with Nitrates; CONTRAINDICATIONS**).

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

Alpha-blockers:

Blood pressure effects in patients on stable alpha-blocker treatment:

Two clinical pharmacology studies were conducted in patients with benign prostatic hyperplasia (BPH) on stable-dose alpha-blocker treatment for at least four weeks.

Study 1: This study was designed to evaluate the effect of 5 mg vardenafil 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 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; two and one patient (vardenafil and placebo, respectively) had a decrease in standing SBP of >30 mmHg. 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% C.I.) 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, -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 3. 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 4.

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 tamsulosin 0.4 mg in normotensive BPH patients (Study 1)

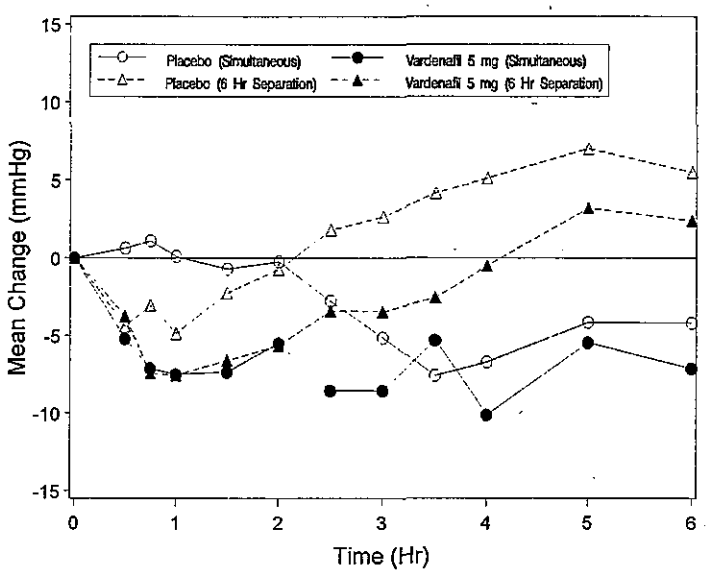
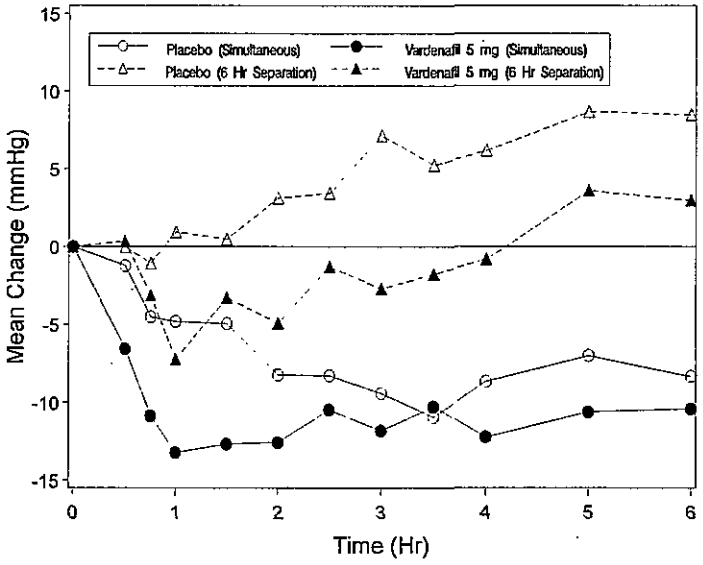


Figure 4: Mean change from baseline in standing systolic blood pressure (mmHg) over 6 hour interval following simultaneous or 6 hr separation administration of vardenafil 5 mg or placebo with stable dose terazosin (5 or 10 mg) in normotensive BPH patients (Study 1)



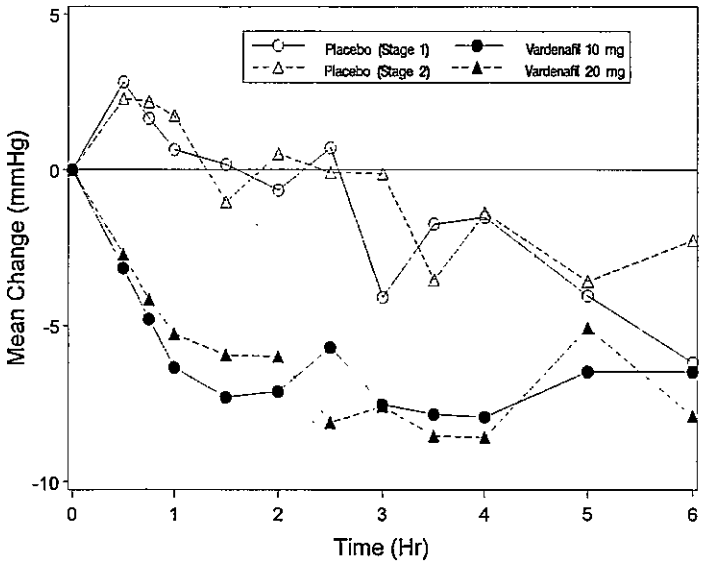
Study 2: This study was designed to evaluate the effect of 10 mg vardenafil (stage 1) and 20 mg vardenafil (stage 2) compared to placebo, when administered to a single cohort of BPH patients (n=23) on stable therapy with tamsulosin 0.4 mg or 0.8 mg daily for at least four weeks. The design was a randomized, 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% C.I.) maximal change from baseline in systolic blood pressure (mmHg) following vardenafil 10 and 20 mg in BPH patients on stable alpha-blocker therapy with tamsulosin 0.4 or 0.8 mg daily (Study 2)

	Vardenafil 10 mg Placebo-subtracted	Vardenafil 20 mg 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 tamsulosin 0.4 mg following simultaneous administration of vardenafil 20 mg or placebo, or following administration of vardenafil 20 mg or placebo separated by 6 hours are shown in Figure 5.

Figure 5: Mean change from baseline in standing systolic blood pressure (mmHg) over 6 hour interval following simultaneous administration of vardenafil 10 mg (Stage 1), vardenafil 20 mg (Stage 2), or placebo with stable dose tamsulosin 0.4 mg in normotensive BPH patients (Study 2)



Concomitant treatment with vardenafil and alpha-blockers should be initiated only if the patient is stable on his alpha-blocker therapy. In those patients who are stable on alpha-blocker therapy, LEVITRA should be initiated at the lowest recommended starting dose (see **DOSAGE and ADMINISTRATION**).

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 simultaneous 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 4. Mean (95% C.I.) maximal change in baseline in systolic blood pressure (mmHg) following vardenafil 10 and 20 mg 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, vardenafil 20 mg or placebo with terazosin (10 mg) in healthy volunteers

TERAZOSIN

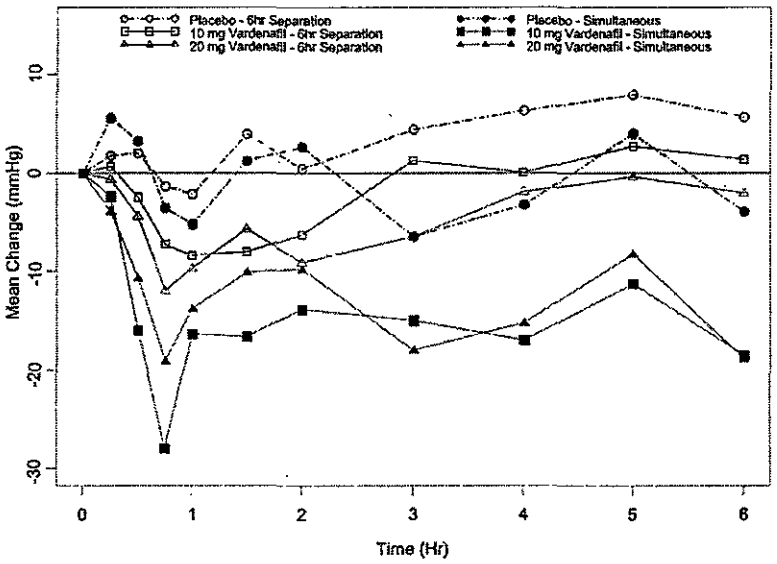
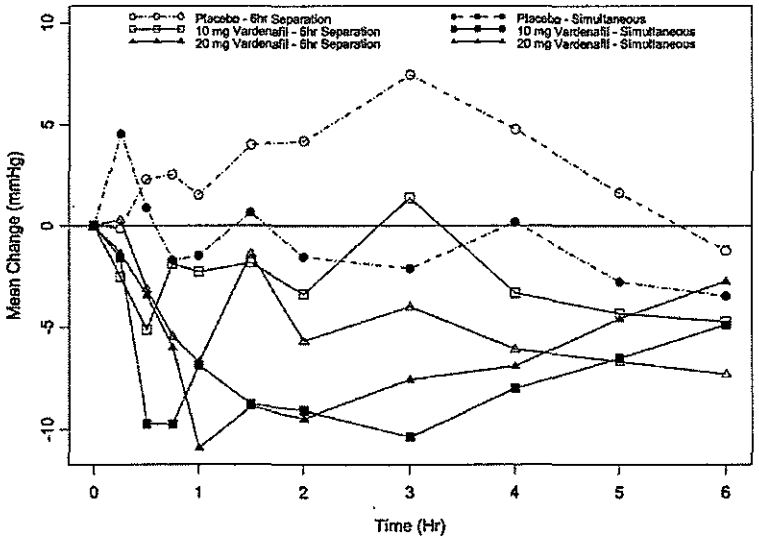


Figure 7: Mean change from baseline in standing systolic blood pressure (mmHg) over 6 hour interval following simultaneous or 6 hr separation administration of vardenafil 10 mg, vardenafil 20 mg or placebo with tamsulosin (0.4 mg) in healthy volunteers

TAMSULOSIN



Ritonavir and indinavir: Upon concomitant administration of 5 mg of LEVITRA with 600 mg BID ritonavir, the C_{max} and AUC of ritonavir were reduced by approximately 20%. Upon administration of 10 mg of LEVITRA with 800 mg TID indinavir, the C_{max} and AUC of indinavir were reduced by 40% and 30%, respectively.

Alcohol: Alcohol (0.5 g/kg body weight: approximately 40 mL of absolute alcohol in a 70 kg person) and vardenafil plasma levels were not altered when dosed simultaneously. LEVITRA (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).
Aspirin: LEVITRA (10 mg and 20 mg) did not potentiate the increase in bleeding time caused by aspirin (two 81 mg tablets).
Other interactions: LEVITRA had no effect on the pharmacodynamics of glyburide (glucose and insulin concentrations) and warfarin (prothrombin time or other pharmacodynamic parameters).

Carcinogenesis, Mutagenesis, Impairment of Fertility

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. 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. 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 male, 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.
There was no effect on sperm motility or morphology after single 20 mg oral doses of vardenafil in healthy volunteers.

Pregnancy, Nursing Mothers and Pediatric Use

LEVITRA is not indicated for use in women, newborns, or children. 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. It is not known if vardenafil is excreted in human breast milk.

Pregnancy Category B: 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 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.

Geriatric Use

Elderly males age 65 years and older have higher vardenafil plasma concentrations than younger males (18 – 45 years), mean C_{max} and AUC were 34% and 52% higher, respectively (see **CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations,** and **DOSAGE AND ADMINISTRATION**). Phase 3 clinical trials included more than 834 elderly patients, and no differences in safety or effectiveness of LEVITRA 5, 10, or 20 mg were noted when these elderly patients were compared to younger patients. However, due to increased vardenafil concentrations in the elderly, a starting dose of 5 mg LEVITRA should be considered in patients ≥65 years of age.

ADVERSE REACTIONS

LEVITRA was administered to over 4430 men (mean age 56, range 18-89 years; 81% White, 6% Black, 2% Asian, 2% Hispanic and 9% Other) during controlled and uncontrolled clinical trials worldwide. Over 2200 patients were treated for 6 months or longer, and 880 patients were treated for at least 1 year.

In placebo-controlled clinical trials, the discontinuation rate due to adverse events was 3.4% for LEVITRA compared to 1.1% for placebo.

When LEVITRA was taken as recommended in placebo-controlled clinical trials, the following adverse events were reported (see Table 5).

Table 5: Adverse Events Reported By ≥2% of Patients Treated with LEVITRA and More Frequent on Drug than Placebo in Fixed and Flexible[γ] Dose Randomized, Controlled Trials of 5 mg, 10 mg, or 20 mg Vardenafil

Adverse Event	Percentage of Patients Reporting Event	
	Placebo N = 1199	LEVITRA N = 2203
Headache	4%	15%
Flushing	1%	11%
Rhinitis	3%	9%
Dyspepsia	1%	4%
Accidental Injury*	2%	3%
Sinusitis	1%	3%
Flu Syndrome	2%	3%
Dizziness	1%	2%
Increased Creatine Kinase	1%	2%
Nausea	1%	2%

* All the events listed in the above table were deemed to be adverse drug reactions with the exception of accidental injury.

[γ] Flexible dose studies started all patients at LEVITRA 10 mg and allowed decrease in dose to 5 mg or increase in dose to 20 mg based on side effects and efficacy.

Back pain was reported in 2.0% of patients treated with LEVITRA and 1.7% of patients on placebo.

Placebo-controlled trials suggested a dose effect in the incidence of some adverse events (headache, flushing, dyspepsia, nausea, rhinitis) over the 5 mg, 10 mg, and 20 mg doses of LEVITRA. The following section identifies additional, less frequent events (<2%) reported during the clinical development of LEVITRA. Excluded from this list are those events 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: anaphylactic reaction (including laryngeal edema), asthenia, face edema, pain

AUDITORY: tinnitus

CARDIOVASCULAR: angina pectoris, chest pain, hypertension, hypotension, myocardial ischemia, myocardial infarction, palpitation, postural hypotension, syncope, tachycardia

DIGESTIVE: abdominal pain, abnormal liver function tests, diarrhea, dry mouth, dysphagia, esophagitis, gastritis, gastroesophageal reflux, GGTP increased, vomiting

MUSCULOSKELETAL: arthralgia, back pain, myalgia, neck pain

NERVOUS: hypertonia, hypesthesia, insomnia, paresthesia, somnolence, vertigo

RESPIRATORY: dyspnea, epistaxis, pharyngitis

SKIN AND APPENDAGES: photosensitivity reaction, pruritus, rash, sweating

OPHTHALMOLOGIC: abnormal vision, blurred vision, chromatopsia, changes in color vision, conjunctivitis (increased redness of the eye), dim vision, eye pain, glaucoma, photophobia, watery eyes

UROGENITAL: abnormal ejaculation, priapism (including prolonged or painful erections)

POST-MARKETING EXPERIENCE

Ophthalmologic

Non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported rarely post-marketing in temporal association with the use of phosphodiesterase type 5 (PDE5) inhibitors, including LEVITRA. 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 **PRECAUTIONS, Information for Patients**).

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 post-marketing experience. It is not possible to determine whether these events are related directly to the use of LEVITRA.

OVERDOSAGE

The maximum dose of LEVITRA for which human data are available is a single 120 mg dose administered to eight healthy male volunteers. The majority of these subjects experienced reversible back pain/myalgia and/or "abnormal vision."

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.

DOSAGE AND ADMINISTRATION

For most patients, the recommended starting dose of LEVITRA is 10 mg, taken orally approximately 60 minutes before sexual activity. The dose may be increased to a maximum recommended dose of 20 mg or decreased to 5 mg based on efficacy and side effects. The maximum recommended dosing frequency is once per day. LEVITRA can be taken with or without food. Sexual stimulation is required for a response to treatment.

Geriatrics: A starting dose of 5 mg LEVITRA should be considered in patients ≥65 years of age (see **CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations** and **PRECAUTIONS**).

Hepatic Impairment: For patients with mild hepatic impairment (Child-Pugh A), no dose adjustment of LEVITRA is required. Vardenafil clearance is reduced in patients with moderate hepatic impairment (Child-Pugh B), and a starting dose of 5 mg LEVITRA is recommended. The maximum dose in patients with moderate hepatic impairment should not exceed 10 mg. LEVITRA has not been evaluated in patients with severe hepatic impairment (Child-Pugh C) (see **CLINICAL PHARMACOLOGY, Metabolism and Excretion, WARNINGS** and **PRECAUTIONS**).

Renal Impairment: For patients with mild (CL_{cr} = 50-80 ml/min), moderate (CL_{cr} = 30-50 ml/min), or severe (CL_{cr} <30 ml/min) renal impairment, no dose adjustment is required. LEVITRA has not been evaluated in patients on renal dialysis (see **CLINICAL PHARMACOLOGY, Metabolism and Excretion** and **PRECAUTIONS**).

Concomitant Medications: The dosage of LEVITRA may require adjustment in patients receiving potent CYP3A4 inhibitors such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, atazanavir, and clarithromycin as well as in other patients receiving moderate CYP3A4 inhibitors such as erythromycin (see **WARNINGS, PRECAUTIONS, Drug Interactions**). For ritonavir, a single dose of 2.5 mg LEVITRA should not be exceeded in a 72-hour period. For indinavir, saquinavir, atazanavir, ketoconazole 400 mg daily, itraconazole 400 mg daily, and clarithromycin, a single dose of 2.5 mg LEVITRA should not be exceeded in a 24-hour period. For ketoconazole 200 mg daily, itraconazole 200 mg daily, and erythromycin, a single dose of 5 mg LEVITRA should not be exceeded in a 24-hour period. For alpha-blockers, caution is advised when PDE5 inhibitors, including LEVITRA, are used concomitantly with alpha-blockers because of the potential for an additive effect on blood pressure. In some patients, concomitant use of these two drug classes can lower blood pressure significantly (see **PRECAUTIONS, Alpha-blockers** and **Drug Interactions**) leading to symptomatic hypotension (e.g., fainting). Concomitant treatment should be initiated only if the patient is stable on his alpha blocker therapy. In those patients who are stable on alpha-blocker therapy, LEVITRA should be initiated at a dose of 5 mg (2.5 mg when used concomitantly with certain CYP3A4 inhibitors - see **Drug Interactions**).

HOW SUPPLIED

LEVITRA (vardenafil HCl) is formulated as orange, film-coated round tablets with debossed "BAYER" cross on one side and "2.5", "5", "10", and "20" on the other side equivalent to 2.5 mg, 5 mg, 10 mg, and 20 mg of vardenafil, respectively.

Package	Strength	NDC Code
Bottles of 30	2.5 mg	0085-1923-01
	5 mg	0085-1945-01
	10 mg	0085-1901-01
	20 mg	0085-1934-01

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

Manufactured by:

Bayer HealthCare

Bayer Pharmaceuticals Corporation
400 Morgan Lane
West Haven, CT 06516
Made in Germany

Marketed by:

GlaxoSmithKline

GlaxoSmithKline
Research Triangle Park
NC 27709

Distributed and Marketed by:

Schering-Plough

Schering Corporation
Kenilworth, NJ 07033

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Rx Only

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