

PRODUCT INFORMATION
LEVITRA® 10 film-coated tablets
(vardenafil, BAYER)

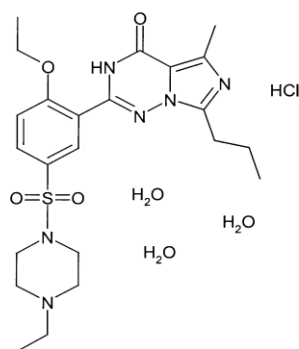
NAME OF THE MEDICINE

Vardenafil, as vardenafil hydrochloride trihydrate is 2-[2-ethoxy-5-(4-ethyl-piperazine-1-sulfonyl)-phenyl]-5-methyl-7-propyl-3*H*-imidazo[5,1-*f*][1,2,4]triazin-4-one hydrochloride trihydrate. It is a nearly colourless solid. Vardenafil hydrochloride trihydrate is soluble in 0.1M HCl, very slightly soluble in water, freely soluble in methanol, soluble in ethanol and slightly soluble in acetone.

The empirical formula of vardenafil hydrochloride trihydrate is C₂₃H₃₂N₆O₄S.HCl.3H₂O and its molecular weight is 579.1 g/mol. Its chemical structure is shown in Figure 1.

(CAS number: 224785-90-4)

Figure 1



DESCRIPTION

Levitra 10 is available as film-coated tablets, containing 11.852 mg of vardenafil hydrochloride trihydrate.

Levitra 10 contains the following excipients: crospovidone, magnesium stearate, microcrystalline cellulose, colloidal anhydrous silica, macrogol 400, hypromellose, titanium dioxide (CI77891), iron oxide yellow (CI77492), iron oxide red (CI77491).

The tablets are orange film-coated round tablets marked with BAYER cross on one side and the dose strength “10” on the other side.

PHARMACOLOGY

Penile erection is a haemodynamic process based on the relaxation of smooth muscle in the corpus cavernosum and its associated arterioles. During sexual stimulation, from nerve ends in the corpus cavernosum, nitric oxide (NO) is released, which activates the enzyme guanylate cyclase, resulting in an increased level of cyclic guanosine monophosphate (cGMP) in the corpus cavernosum. This in turn triggers smooth muscle relaxation, allowing increased inflow of blood into the penis resulting in erection. The actual cGMP level is regulated by the rate of synthesis via the guanylate cyclase on the one hand, and by the rate of degradation via cGMP hydrolyzing phosphodiesterases (PDEs) on the other hand.

The most prominent PDE in the human corpus cavernosum is the cGMP specific phosphodiesterase type 5 (PDE5).

By inhibiting PDE5, the enzyme responsible for cGMP degradation in the corpus cavernosum, vardenafil potently enhances the effect of endogenous NO, locally released in corpus cavernosum upon sexual stimulation. The inhibition of PDE5 by vardenafil leads to increased cGMP levels in the corpus cavernosum, resulting in smooth muscle relaxation and inflow of blood to the corpus cavernosum. Vardenafil thus potentiates the natural response to sexual stimulation.

In vitro assays have shown that vardenafil is a selective inhibitor of PDE5, with an IC₅₀ of 0.7 nM for human platelet PDE5.

The inhibitory effect of vardenafil is more potent on PDE5 than on 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). *In vitro*, vardenafil causes an elevation of cGMP in the isolated human corpus cavernosum resulting in muscle relaxation.

In the conscious rabbit, vardenafil causes a penile erection which is dependent upon endogenous NO synthesis and is potentiated by NO donors.

Effects on Visual Perception

In a specific clinical trial, evaluation of visual function at a vardenafil dose of 40 mg (twice the maximum recommended daily dose) revealed no effects of vardenafil on visual acuity, visual fields, intraocular pressure, ERG latency, fundoscopic and slit lamp findings. A subset of patients was found to have mild and transient impairment of colour discrimination in the blue/green range and in the purple range 1 hour after dosing. These changes had improved by 6 hours and no changes were present at 24 hours. The majority of these patients had no subjective visual symptoms.

In other trials, daily use of vardenafil at doses of 10 mg to 40 mg for 31 days was not associated with changes in visual acuity, intraocular pressure, or findings on fundoscopic or slit lamp examination.

Effects on Blood Pressure

Vardenafil causes mild and transient decreases in blood pressure which, in the majority of the cases, do not translate into clinical effects. The mean maximum decreases in supine systolic blood pressure following 20 mg and 40 mg vardenafil were -6.9 mmHg with 20 mg and -4.3 mmHg with 40 mg of vardenafil, when compared to placebo.

Effects on Cardiac Parameters

A single dose, double blind, crossover, randomised trial in 59 healthy males compared the effects on the QT interval of vardenafil (10 mg and 80 mg), sildenafil (50 mg and 400 mg) and placebo. Moxifloxacin (400 mg) was included as an active internal control. Effects on the QT interval were measured one hour post-dose (average t_{max} for vardenafil). The primary objective of this study was to rule out a greater than 10 msec effect (i.e., to demonstrate lack of effect) of a single 80 mg oral dose of vardenafil on QTc interval compared to placebo, as measured by the change in Fridericia's correction formula (QTcF=QT/RR^{1/3}) from baseline at the 1 hour post-dose time point. The vardenafil results showed an increase in QTc (Fridericia) of 8 msec (90% CI: 6-9) and 10 msec (90% CI: 8-11) at 10 and 80 mg doses compared to placebo and an increase in QTci of 4 msec (90% CI: 3-6) and 6 msec (90% CI: 4-7) at 10 and 80 mg doses compared to placebo, at one hour post-dose. At t_{max}, only the mean change in QTcF for vardenafil 80 mg was out of the study established limit (mean 10 msec, 90% CI: 8-11). When using the individual correction formulae, none of the values were out of the limit.

In a separate postmarketing study of 44 healthy volunteers, single doses of 10 mg Levitra 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 Levitra 10 mg 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) at one hour post-dose. The clinical impact of these QT changes is unknown.

Effects on Exercise Performance in Patients with Coronary Artery Disease

In a two-period, placebo-controlled, cross-over trial, 10 mg vardenafil did not alter the total treadmill exercise time compared to placebo in 39 male patients aged 48-77 years with coronary artery disease and exercise induced ischaemia. The total time to angina was not altered compared to placebo; however, the total time to 1 mm or greater ST-segment depression was prolonged 15% in the vardenafil group compared to the placebo group ($p < 0.001$). All patients who entered the trial completed the exercise treadmill tests without significant drug-related side effects.

Pharmacokinetics

Absorption

Vardenafil is rapidly absorbed after oral administration. C_{max} is reached as early as 15 minutes, in 90% of the time C_{max} is reached within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state.

There is extensive first-pass metabolism of vardenafil, resulting in considerable inter-subject and intra-subject variability in the observed pharmacokinetic parameters. The mean absolute bioavailability is approximately 15% after a 10 mg dose. After oral dosing of vardenafil, AUC and C_{max} increase almost dose proportionally over the recommended dose range (5 mg – 20 mg).

When vardenafil was taken with a high fat meal (~57% fat), the mean C_{max} was reduced by approximately 20%, median t_{max} was delayed by approximately 1 hour, and mean AUC was not affected. After a 'normal meal' (~30% fat) pharmacokinetic parameters were not significantly affected. Based on these results vardenafil can be taken with or without food.

Distribution

The mean steady state volume of distribution (V_{ss}) for vardenafil is about 2.5 L/kg, indicating distribution into the tissues.

Vardenafil and its major circulating metabolite (M1) are highly bound to plasma proteins (about 95% for parent drug or M1). This protein binding is reversible and independent of total drug concentrations.

Based upon measurements of vardenafil in semen of healthy subjects 90 minutes after dosing, not more than 0.0002% of the administered dose may appear in the semen of patients.

Metabolism

Vardenafil is metabolised predominantly by hepatic enzymes via CYP 3A4, with some contribution from CYP 3A5 and CYP 2C9 isoforms. Mean terminal elimination half-life from plasma is approximately 4 – 5 hours.

In humans, the major circulating metabolite (M1) results from desethylation at the piperazine moiety of vardenafil, and is subject to further metabolism. The terminal plasma elimination half-life of the metabolite M1 is approximately 4 hours, comparable to the parent drug. M1 is also present in its glucuronide-conjugated (glucuronic acid) form in systemic circulation. The plasma concentration of non-glucuronidated M1 is about 26% that of the parent compound. The metabolite M1 shows a phosphodiesterase selectivity profile similar to that of vardenafil and an *in vitro* inhibitory potency for PDE5 of approximately 28% compared to vardenafil, resulting in an efficacy contribution of about 7%.

Excretion

The total body clearance of vardenafil is 56 L/hour with a resultant terminal half-life of about 4 – 5 hours.

After oral administration, vardenafil is excreted as metabolites predominantly in the faeces (approximately 91 – 95% of administered oral dose) and to a lesser extent in the urine (approximately 2 – 6% of administered oral dose).

Pharmacokinetics in Special Populations

Elderly

No dosage adjustment is required in elderly patients. Vardenafil half-life in healthy elderly volunteers (65 years or over) was reduced as compared to volunteers of younger age (45 years and below). On average, elderly males had a 52% higher AUC than younger males which is within the variability observed in clinical trials.

Renal Insufficiency

In patients with mild ($CL_{cr} > 50 - 80$ mL/min) to moderate ($CL_{cr} > 30 - 50$ mL/min) renal impairment vardenafil pharmacokinetics were similar to that of a normal renal function control group. In volunteers with severe renal impairment ($CL_{cr} < 30$ mL/min) the mean AUC was increased by 21% and the mean C_{max} decreased by 23%, compared to volunteers with no renal impairment. No statistically significant correlation between creatinine clearance and vardenafil plasma exposure (AUC and C_{max}) was observed. Based on these data, no dose adjustment is needed in patients with impaired renal function.

The pharmacokinetics of vardenafil have not been studied in patients requiring dialysis and Levitra should not be used in this situation.

Hepatic Impairment

In patients with mild to moderate hepatic impairment (Child-Pugh A and B), vardenafil clearance was reduced in proportion to the degree of hepatic impairment.

In patients with mild hepatic impairment (Child-Pugh A), vardenafil AUC and C_{max} were increased 1.2-fold (AUC by 17% and C_{max} by 22%) following a 10 mg vardenafil dose, compared to healthy control subjects. In patients with moderate hepatic impairment (Child-Pugh B), vardenafil AUC was increased 2.6-fold (an increase of 160%) and C_{max} was increased 2.3-fold (an increase of 130%), compared to healthy control subjects.

Therefore, in patients with mild hepatic impairment, Levitra 5 mg should be used as a starting dose, which may subsequently be increased to 10 mg and 20 mg based on tolerability and efficacy. The maximum dose recommended in patients with moderate hepatic impairment (Child-Pugh B) is Levitra 10 mg.

The pharmacokinetics of vardenafil have not been studied in patients with severe hepatic impairment (Child-Pugh C). Levitra should not be used in this population.

CLINICAL TRIALS

In a placebo controlled Rigiscan study, Levitra (vardenafil) 20 mg produced erections sufficient for penetration ($\geq 60\%$ rigidity by Rigiscan) in some men as early as 15 minutes. The overall response of these subjects to vardenafil became statistically significant compared to placebo at 25 minutes post dosing.

Vardenafil demonstrated clinically meaningful and statistically significant improvement of erectile function compared to placebo in all major efficacy trials including special populations.

Across all trials, vardenafil was administered to over 3750 men with erectile dysfunction (ED) aged 18 to 89 years, many of whom had multiple other medical conditions. Over 1630 patients were treated with vardenafil for 6 months or longer.

In all major efficacy trials, including studies in post-prostatectomy patients and patients with diabetes, vardenafil 10 mg and 20 mg produced statistically significant and clinically meaningful improvements, compared to placebo, in the International Index of Erectile Function (IIEF) erectile function domain score, the percentage of patients achieving successful penetration and maintenance of erections, and the percentage of patients who rated their erections as improved (Table 1 and Table 2).

Table 1: IIEF erectile function domain score and global assessment at Week 12 (Intention-to-treat population) ‡

Study Population	IIEF erectile function domain score			Percentage of patients rating erections as improved		
	Placebo	Vardenafil 10 mg	Vardenafil 20 mg	Placebo	Vardenafil 10 mg	Vardenafil 20 mg
General	15.0	20.6	21.4	30%	72%	78%
General	13.2	20.9	21.5	19%	73%	73%
Diabetic	12.6	17.1	19.0	13%	54%	70%
Prostatectomy	9.2	15.3	15.3	9%	58%	60%

‡ Last available observation used in patients with no data at Week 12.

Table 2: Percentage of patients achieving successful penetration and maintenance of erection at Week 12 (Intention-to-treat population) ‡

Study Population	Penetration			Maintenance of erection		
	Placebo	Vardenafil 10 mg	Vardenafil 20 mg	Placebo	Vardenafil 10 mg	Vardenafil 20 mg
General	52%	76%	81%	32%	65%	65%
General	45%	76%	80%	25%	62%	64%
Diabetic	36%	61%	64%	23%	49%	54%
Prostatectomy	22%	47%	48%	10%	37%	34%

‡ Last available observation used in patients with no data at Week 12.

In a randomised, double blind, placebo controlled, fixed dose trial in 749 patients, based on a global assessment question (GAQ), vardenafil improved erections in 56%, 77%, and 81% of the patients on 5 mg, 10 mg, and 20 mg, respectively, at 6 months compared to 23% on placebo.

In pooled data from the major efficacy trials, including special population studies, those patients who had successful penetration on first dose of treatment were 37% on placebo, 68% for 10 mg, and 70% for 20 mg. For those patients who had successful penetration on first dose, on average, patients on vardenafil 10 mg and 20 mg responded successfully in 86% and 90% of all subsequent attempts, respectively, over a 3 month study period. Vardenafil was efficacious in patients regardless of baseline severity, aetiology (organic, psychogenic and mixed), duration of ED, ethnicity and age as determined in subgroup analyses.

In post-prostatectomy patients, vardenafil demonstrated clinically meaningful and statistically significant improvement in erectile function in a 3 month prospective, fixed dose, placebo controlled, double blind trial. Erectile function domain score, the rate of obtaining an erection sufficient for penetration, the rate of maintaining an erection sufficient for successful intercourse, and hardness were significantly improved compared to placebo for the tested doses of 10 mg and 20 mg at all time points. Improved erectile function response rates as based on GAQ were 57% on 10 mg, and 60% on 20 mg compared to 9% on placebo at 3 months. In the subgroup of patients with bilateral nerve-sparing prostatectomy the response rates as based on GAQ in patients at 3 months were 61% for 10 mg, and 66% for 20 mg, compared to 8% for placebo.

In patients with diabetes mellitus, vardenafil demonstrated clinically meaningful and statistically significant improvement in erectile function in a 3 month prospective, fixed dose, placebo controlled, double blind trial. Significant improvements were shown in the erectile function domain score, the rate of obtaining an erection sufficient for penetration, the rate of maintaining an erection sufficient for successful intercourse, and hardness, when 10 mg and 20 mg vardenafil doses were compared to placebo. These improvements were seen at all time points during three months of treatment. In this population, which is typically more resistant to therapy, response rates at 3 months for improvement of erection as based on GAQ were 54% on 10 mg, and 70% on 20 mg vardenafil compared to 13% on placebo. Patients in the active treatment group were continued on blinded active therapy of vardenafil for a total of 6 months. These patients demonstrated response rates of 66% and 74% for 10 mg and 20 mg, respectively.

INDICATIONS

Levitra is indicated for the treatment of erectile dysfunction in adult males (inability to achieve or maintain penile erection sufficient for satisfactory sexual performance).

Levitra is not indicated for use by women.

CONTRAINDICATIONS

- Patients with known hypersensitivity to the active substance or to any of the excipients.
- Co-administration with nitrates, nitric oxide donors, or organic nitrites in any form either regularly or intermittently. Drugs which must not be used concomitantly include, but are not limited to, glyceryl trinitrate (injection, tablets, sprays or patches), isosorbide salts, sodium nitroprusside, amyl nitrite, nicorandil or organic nitrates in any form. Consistent with the effects of PDE inhibition on the nitric oxide/cGMP – pathway, PDE5 inhibitors may potentiate the hypotensive effects of nitrates.
- Concomitant use with very potent inhibitors of CYP 3A4 (e.g., HIV protease inhibitors such as indinavir or ritonavir).

- Concomitant use of Levitra with riociguat, a stimulator of soluble guanylate cyclase (sGC) as it may lead to potentially life-threatening symptomatic hypotension and syncope.
- Patients who have loss of vision in one eye because of non-arteritic anterior ischaemic optic neuropathy (NAION), regardless of whether this episode was in connection with previous exposure to PDE5 inhibitor.
- Known hereditary degenerative retinal disorders such as retinitis pigmentosa.
- Patients in whom sexual intercourse is inadvisable due to cardiovascular risk factors (see PRECAUTIONS). The possibility of undiagnosed cardiovascular disorders in men with erectile dysfunction should be considered before prescribing the medicine.
- Patients with the following cardiac conditions: unstable angina; resting or orthostatic hypotension (systolic blood pressure < 90 mmHg); uncontrolled hypertension; myocardial infarction, stroke, cardiac ischaemia (except stable angina) or life-threatening arrhythmia within the previous 6 months; and uncontrolled arrhythmia.
- Severe hepatic impairment.
- End-stage renal disease requiring dialysis.

PRECAUTIONS

Cardiovascular Disease

Prior to initiating any treatment for erectile dysfunction, physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity. Vardenafil has vasodilator properties which may result in mild and transient decreases in blood pressure. Patients with left ventricular outflow obstruction, e.g., aortic stenosis and idiopathic hypertrophic subaortic stenosis, can be sensitive to the action of vasodilators including PDE5 inhibitors.

In men for whom sexual activity is not recommendable because of their underlying cardiovascular status, agents for the treatment of erectile dysfunction should generally not be used.

In a study of the effect of vardenafil on QT interval in 59 healthy males, therapeutic (10 mg) and supratherapeutic (80 mg) doses of vardenafil produced increases in QTc interval (see PHARMACOLOGY, Effects on Cardiac Parameters). A postmarketing study evaluating the effect of combining vardenafil with gatifloxacin, another drug of comparable QT effect showed an additive QT effect when compared with either drug alone (see PHARMACOLOGY, Effects on Cardiac Parameters). These observations should be considered in clinical decisions when prescribing vardenafil to patients, including those with a known history of QT prolongation or patients who are taking medications known to prolong QT interval. Patients with congenital QT prolongation (long QT syndrome) and those taking Class IA (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications should avoid using vardenafil.

Other Pre-existing Medical Conditions

Agents for the treatment of erectile dysfunction should generally be used with caution in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis

or Peyronie's disease) or in patients who have conditions which may predispose them to priapism (such as sickle cell anaemia, multiple myeloma or leukaemia).

The safety and efficacy of combinations of vardenafil with other treatments for erectile dysfunction (including other PDE5 inhibitors) have not been studied. Therefore the use of such combinations is not recommended.

Vardenafil has not been administered to patients with bleeding disorders or significant active peptic ulceration. Therefore vardenafil should be given to these patients only after careful benefit-risk assessment. In humans, vardenafil has no effect on bleeding time alone or with aspirin. *In vitro* studies with human platelets indicate that vardenafil alone did not inhibit platelet aggregation induced by a variety of platelet agonists. With supertherapeutic concentrations of vardenafil a small concentration-dependent enhancement of the antiaggregatory effect of sodium nitroprusside, a NO donor, was observed. The combination of heparin and vardenafil had no effect on bleeding time in rats, but this interaction has not been studied in humans.

Use with Alpha-blockers

Caution is advised when PDE5 inhibitors are co-administered with alpha-blockers. PDE5 inhibitors, including Levitra tablets 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 INTERACTIONS WITH OTHER MEDICINES) leading to symptomatic hypotension (e.g., 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 haemodynamic 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, vardenafil should be initiated at the lowest recommended starting dose of 5 mg. Patients treated with alpha-blockers who have previously used 5 mg film-coated tablets may be switched to a higher dose.
- In those patients already taking an optimised 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.

Use with CYP 3A4 Inhibitors

Concomitant use of moderate (e.g., erythromycin), potent (e.g., clarithromycin, ketoconazole, itraconazole) or very potent CYP 3A4 inhibitors (e.g., HIV protease inhibitors such as indinavir or ritonavir) can be expected to produce markedly increased vardenafil plasma levels. A maximum vardenafil dose of 5 mg should not be exceeded if used in combination with ketoconazole, itraconazole, erythromycin or clarithromycin. Levitra must not be taken with dosages of ketoconazole and itraconazole higher than 200 mg (see DOSAGE AND ADMINISTRATION). Concomitant use with indinavir or ritonavir is

contraindicated, as these drugs are very potent inhibitors of CYP 3A4 (See CONTRAINDICATIONS and INTERACTIONS WITH OTHER MEDICINES).

NAION

Transient vision loss and cases of non-arteritic ischemic optic neuropathy (NAION) have been reported in connection with the intake of PDE5 inhibitors, including vardenafil. The patient should be advised that in case of sudden vision loss, he should stop taking Levitra and consult a physician immediately (see ADVERSE EFFECTS).

Sudden Decrease or Loss of Hearing

Physicians should advise patients to stop taking PDE5 inhibitors, including vardenafil, 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 EFFECTS).

Ability to Drive and Use Machines

Patients should be aware of how they react to vardenafil before driving or operating machinery. Due to the vasodilatory properties of PDE5 inhibitors, concomitant use with alpha-blockers, may contribute to dizziness.

Effects on Fertility

In a specific clinical trial, single oral doses of 20 mg of vardenafil did not produce any effects on sperm motility or morphology or a variety of parameters indicative for male reproductive function. Based upon measurements of vardenafil in semen of healthy subjects 90 minutes after dosing, not more than 0.0002% of the administered dose appeared in the semen of patients.

Studies in rats showed no effects on fertility, reproductive performance or reproductive organ morphology in males or females given oral doses of vardenafil up to 100 mg/kg/day (systemic exposure > 200 times that expected at the maximum recommended dose of 20 mg, based on AUC).

Use in Pregnancy (Category B3)

Vardenafil is not indicated for use by women.

Studies in rats have shown that vardenafil and/or its metabolites cross the placenta and distribute to the fetus. No evidence of embryofetal toxicity or teratogenicity was observed in pregnant rats or rabbits given oral doses of vardenafil up to 18 mg/kg/day. These doses were associated with systemic exposure to vardenafil 125- (rat) or 7- (rabbit) fold greater than that expected at the maximum recommended dose of 20 mg, based on AUC. Higher doses were associated with maternal toxicity, increased embryonic resorptions and delayed fetal development in both species.

Administration of vardenafil 60 mg/kg/day to pregnant rats during late gestation and throughout lactation resulted in increased postnatal pup mortality and delayed physical development. The no-effect-dose of 8 mg/kg/day was associated with systemic exposure approximately 28-fold that expected in humans at the maximum recommended dose of 20 mg vardenafil.

There are no studies of vardenafil in pregnant women.

Use in Lactation

Vardenafil is not indicated for use by women.

Vardenafil and/or its metabolites are excreted in the milk of lactating rats at concentrations up to 19-fold higher than the corresponding maternal plasma concentrations. Increased pre- and post-natal mortality and delayed physical development was observed in offspring from rats treated with oral vardenafil at 60 mg/kg/day during gestation and lactation.

There are no human data on the excretion of vardenafil into breast milk or on the safety of vardenafil exposure in infants.

Genotoxicity

Vardenafil was not genotoxic in assays for gene mutation (reverse mutations in bacterial cells and forward mutations in Chinese hamster V79 cells *in vitro*) or chromosomal damage (Chinese hamster V79 cells *in vitro* and mouse micronucleus assay *in vivo*).

Carcinogenicity

Vardenafil showed no carcinogenic activity when administered orally to rats at doses up to 75 (males) or 25 (females) mg/kg/day or via the drinking water to mice at doses up to 150 (males) or 193 (females) mg/kg/day. The highest doses in these studies were associated with systemic exposure (AUC) to vardenafil > 300 (rats) or about 25 (mice) times that expected in men taking 20 mg/day vardenafil.

INTERACTIONS WITH OTHER MEDICINES

Vardenafil is metabolised predominantly by hepatic enzymes via cytochrome P450 (CYP) isoform 3A4, with some contribution from CYP 3A5 and CYP 2C isoforms. Therefore, inhibitors of these enzymes may reduce vardenafil clearance.

Demonstrated Interactions

Macrolide Antibiotics

Erythromycin (500 mg three times a day), a CYP 3A4 inhibitor, caused a 4-fold increase in vardenafil AUC and a 3-fold increase in C_{max} when co-administered with vardenafil (5 mg) to healthy volunteers. When used in combination with erythromycin or clarithromycin, a maximum vardenafil dose of 5 mg should not be exceeded.

Potent CYP 3A4 inhibitors

Ketoconazole

Ketoconazole (200 mg), which is a potent CYP 3A4 inhibitor, caused a 10-fold increase in vardenafil AUC and a 4-fold increase in C_{max} when co-administered with Levitra 5 mg to healthy volunteers. When used in combination with ketoconazole, a maximum vardenafil dose of 5 mg should not be exceeded. Levitra must not be taken with dosages of ketoconazole higher than 200 mg (see DOSAGE AND ADMINISTRATION).

Indinavir

Indinavir is a potent CYP 3A4 inhibitor. Co-administration of Levitra 10 mg with the HIV protease inhibitor indinavir (800 mg three times a day) resulted in a 16-fold increase in vardenafil AUC and a 7-fold increase in vardenafil C_{max} . At 24 hours after co-administration, the plasma levels of vardenafil were approximately 4% of the maximum

varденафил плазма ниво (C_{max}). Конкомитант употреба на индинавир и варденафил е контраиндицирано.

Ritonavir

Ritonavir (600 mg twice daily) resulted in a 13-fold increase of vardenafil C_{max} and a 49-fold increase in vardenafil AUC_{0-24} when co-administered with Levitra 5 mg. The interaction is a consequence of blocking hepatic metabolism of vardenafil by ritonavir, a very potent CYP 3A4 inhibitor, which also inhibits CYP 2C9. Ritonavir significantly prolonged the half-life of vardenafil to 25.7 hours. Concomitant use with ritonavir is contraindicated.

Potential Interactions

Other CYP 3A4 Inhibitors

Concomitant use of other moderate or potent CYP 3A4 inhibitors (such as clarithromycin, itraconazole or other HIV protease inhibitors) can also be expected to produce markedly increased vardenafil plasma levels (See Demonstrated Interactions). A maximum dose of Levitra 5 mg should not be exceeded if used in combination with ketoconazole, itraconazole, erythromycin or clarithromycin.

Nitrates, Nitric Oxide Donors

There is limited information on the potential hypotensive effects of vardenafil when given in combination with nitrates. Based on experience with other PDE5 inhibitors, some patients may experience clinically significant hypotension if vardenafil and nitrates are co-administered. Concomitant use is therefore contraindicated (see CONTRAINDICATIONS).

Nitrates should not be administered for at least 24 hours (approximately 5 half-lives) after the last dose of vardenafil. A longer washout period should be observed if the patient has been taking concomitant drugs, such as CYP 3A4 inhibitors, which impair vardenafil metabolism.

Nicorandil is a hybrid of potassium channel opener and nitrate. Due to the nitrate component it has the potential to have serious interaction with vardenafil (see CONTRAINDICATIONS).

Antihypertensive Agents

Limited information is available on concomitant use of vardenafil and antihypertensive agents. Population pharmacokinetic investigations of Phase III data revealed no significant effect of ACE-inhibitors, beta-blockers or diuretics on the pharmacokinetics of vardenafil. However, a potential for additive hypotensive effect exists, and until further information is available, caution should be exercised when prescribing vardenafil in combination with antihypertensive agents.

Alpha-blockers

Since alpha-blocker monotherapy can cause marked lowering of blood pressure, especially postural hypotension and syncope, interaction studies were conducted with vardenafil.

Hypotension, in some cases symptomatic, was reported in a significant number of subjects after co-administration of Levitra film-coated tablets to healthy normotensive volunteers force titrated, over a period of 14 days or less, to high doses of the alpha-blockers tamsulosin or terazosin.

Among subjects treated with terazosin, hypotension, standing systolic blood pressure below 85 mmHg, was observed more frequently when vardenafil and terazosin were given to achieve C_{max} simultaneously than when the doses were administered to separate C_{max} by 6 hours. Because these studies were conducted using healthy volunteers, after force titration of the alpha-blocker to high doses (subjects were not stable on alpha-blocker therapy), these studies may have limited clinical relevance.

Three interaction studies were conducted with Levitra film-coated tablets in patients with benign prostatic hyperplasia (BPH) on stable alpha-blocker therapy consisting of alfuzosin, tamsulosin or terazosin.

When Levitra film-coated tablets were given at doses of 5 mg, 10 mg or 20 mg on a background of stable therapy with tamsulosin, there was no clinically relevant mean maximal additional reduction in blood pressure. When Levitra 5 mg film-coated tablets were dosed simultaneously with 0.4 mg of tamsulosin, 2 of 21 patients experienced a standing systolic blood pressure below 85 mm Hg. When Levitra 5 mg film-coated tablets were dosed 6 hours after tamsulosin administration, 2 of 21 patients experienced a standing systolic blood pressure below 85 mm Hg.

Levitra film-coated tablets 5 mg or 10 mg were administered four hours after alfuzosin dosing. The four-hour dosing interval was chosen to elicit the maximum potential interaction. No clinically relevant mean maximal additional reduction in blood pressure was observed over the 10-hour interval following dosing with Levitra film-coated tablets 4 hours after alfuzosin. One patient experienced decreases from baseline in standing systolic blood pressure greater than 30 mm Hg on two occasions i.e., after administration of Levitra 5 mg film-coated tablet and Levitra 10 mg film-coated tablet. No instances of standing systolic blood pressure below 85 mm Hg were observed during this study. Four patients, one dosed with placebo, two dosed with Levitra 5 mg film-coated tablets and one dosed with Levitra 10 mg film-coated tablets, reported dizziness. Based on these results no time interval between dosing with alfuzosin and Levitra is required.

In a subsequent study in patients with BPH, when Levitra 10 mg and 20 mg film-coated tablets were dosed simultaneously with 0.4 or 0.8 mg of tamsulosin no cases of standing systolic blood pressure below 85 mmHg were observed. Based on these results no time interval between dosing with tamsulosin and Levitra is required.

When Levitra 5 mg film-coated tablets were dosed simultaneously with 5 or 10 mg of terazosin, 1 out of 21 patients experienced symptomatic postural hypotension. Hypotension was not observed when Levitra was dosed 6 hours after terazosin administration. This should be considered when deciding about a time separation of dosing between Levitra and terazosin. There was no case of syncope in this study or in the earlier alfuzosin or terazosin studies.

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.

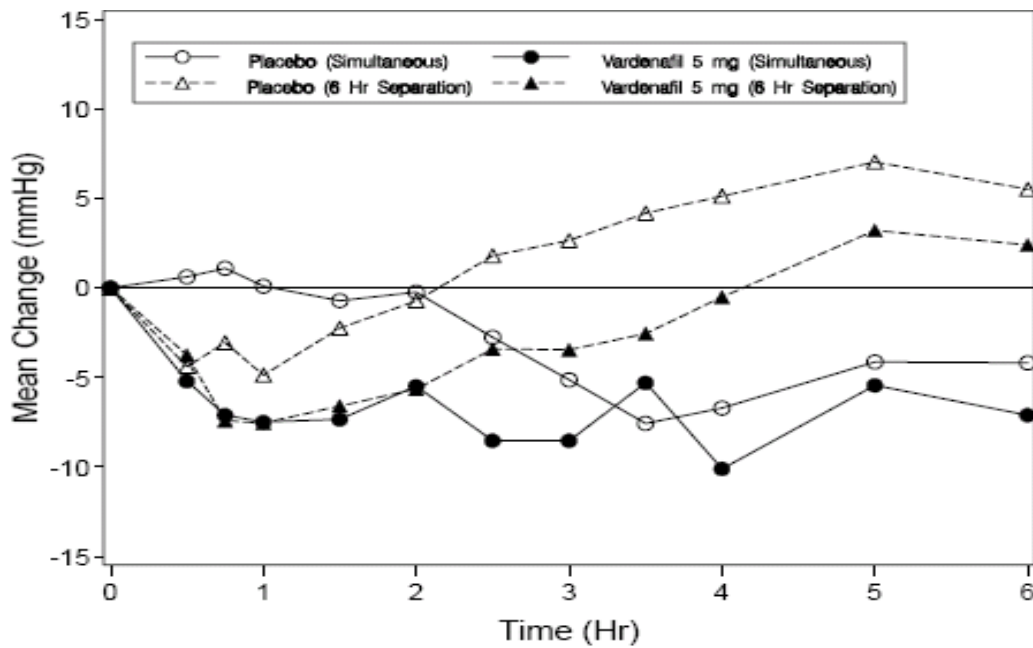
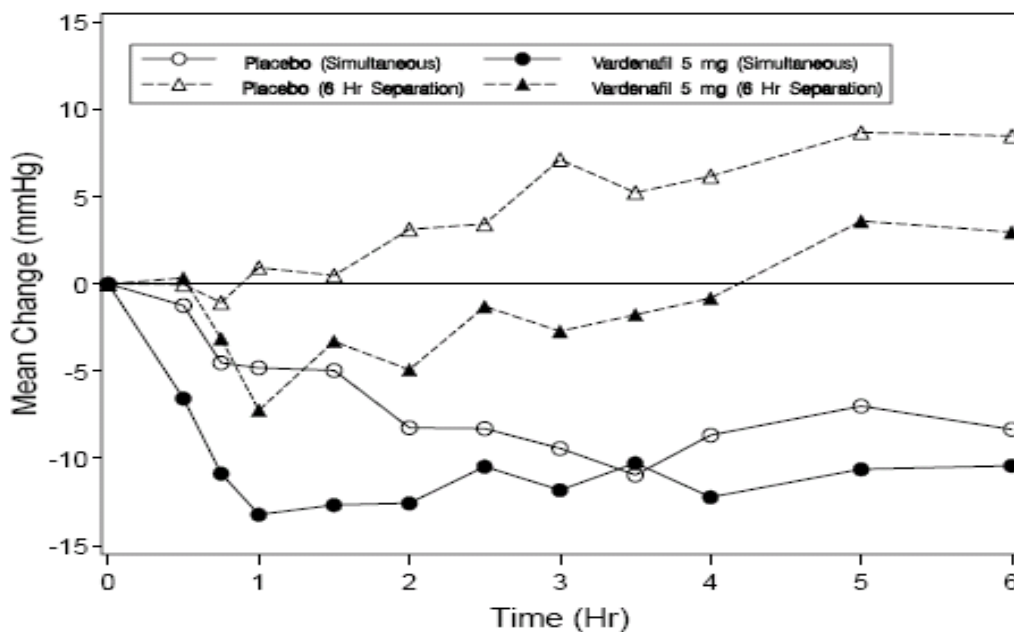


Figure 3: Mean change from baseline in standing systolic blood pressure (mmHg) over 6 hour interval following simultaneous or 6 hr separation administration of vardenafil 5 mg or placebo with stable dose terazosin (5 or 10 mg) in normotensive BPH patients.



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 the lowest recommended starting dose of 5 mg.

Levitra may be administered at any time with alfuzosin or tamsulosin. With terazosin and other alpha-blockers, an appropriate time interval (separation of at least 6 hours) between dosing is recommended when Levitra is prescribed concomitantly (see DOSAGE AND ADMINISTRATION). Safety of combined use of PDE5 inhibitors and alpha-blockers may be affected by other variables, including intravascular volume depletion and other anti-hypertensive medication.

Riociguat

Preclinical studies showed an additive systemic blood pressure lowering effect when PDE5 inhibitors were combined with riociguat. In clinical studies, riociguat has been shown to augment the hypotensive effects of PDE5 inhibitors. There was no evidence of a favourable clinical effect of the combination in the population studied. Concomitant use of PDE5 inhibitors, including Levitra with guanylate cyclase stimulators, such as riociguat, is contraindicated as it may potentially lead to life-threatening episodes of symptomatic hypotension or syncope (See CONTRAINDICATIONS).

Interactions Shown Not to Exist

Glibenclamide

Vardenafil (20 mg), when co-administered with glibenclamide (3.5 mg), did not affect the relative bioavailability of glibenclamide (no effect on AUC and C_{max} of glibenclamide).

Warfarin

No pharmacokinetic or pharmacodynamic (prothrombin time and clotting Factor II, VII and X) interactions were shown when warfarin (25 mg) was co-administered with vardenafil (20 mg). Vardenafil pharmacokinetics were not affected by co-administration of warfarin.

Nifedipine

Co-administration of vardenafil (20 mg) did not alter the bioavailability (AUC and C_{max}) of nifedipine (30 mg or 60 mg). The combined treatment of vardenafil and nifedipine did not lead to pharmacodynamic interaction (as compared to placebo, vardenafil produced mean additional blood pressure reductions of 5.9 mmHg and 5.2 mmHg for supine systolic and diastolic blood pressure, respectively).

Digoxin

Lack of pharmacokinetic interaction was shown when digoxin (0.375 mg daily) in steady-state was co-administered with vardenafil (20 mg) over 14 days every other day.

Antacids

Single doses of Mylanta (magnesium hydroxide/aluminium hydroxide) did not affect the bioavailability (AUC) or the maximum concentration (C_{max}) of vardenafil.

Ranitidine, Cimetidine

Bioavailability of vardenafil (20 mg) was not affected by co-administration of the H₂-antagonists ranitidine (150 mg twice daily) and cimetidine, a non-specific cytochrome P450 inhibitor (400 mg twice daily).

Aspirin

Vardenafil (10 mg) did not influence bleeding time when taken alone or in combination with low dose aspirin (2 x 81 mg tablets).

Ethanol

Vardenafil (20 mg) did not potentiate the hypotensive effects of ethanol (0.5 g/kg bodyweight). The pharmacokinetics of ethanol and vardenafil were not significantly altered by co-administration.

Other Drugs

Population pharmacokinetic investigations of Phase III data revealed no significant effect of aspirin, weak CYP 3A4 inhibitors, and medications for the treatment of diabetes (sulfonylureas and metformin) on the pharmacokinetics of vardenafil.

ADVERSE EFFECTS

Vardenafil was generally very well tolerated. Adverse events were generally transient and mild to moderate in nature.

Placebo Controlled Clinical Trials

When vardenafil was taken as recommended, the following adverse drug reactions were reported more commonly with vardenafil than placebo in placebo controlled clinical trials (as of March 2004) (Table 3):

Table 3: Adverse Drug Reactions reported by $\geq 1\%$ of patients treated with Levitra and more frequent on drug than placebo in all placebo controlled trials of 5 mg, 10 mg, and 20 mg vardenafil.

System Organ Class	Adverse drug reaction	Vardenafil N = 3293	Placebo N = 1861
Nervous System Disorders	Headache	10.4%	2.0%
	Dizziness	1.6%	0.3%
Vascular Disorders	Flushing [incl. Hot Flush, Feeling Hot, Erythema]	11.3%	0.8%
Respiratory, Thoracic and Mediastinal Disorders	Nasal congestion [incl. Oedema Mucosal, Rhinitis, Rhinorrhoea]	4.0%	0.3%
Gastrointestinal Disorders	Dyspepsia	2.5%	<0.1%
	Nausea	1.2%	0.3%

Dizziness was found to be more frequent in patients also taking alpha-blockers.

All Clinical Trials

Levitra has been administered to 17 748 men 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. When Levitra film-coated tablet or Levitra orodispersible tablet was taken as recommended, the following adverse drug reactions were reported in all clinical trials.

Table 4: Adverse drug reactions reported in patients in all clinical trials world-wide which are either reported as drug-related in $\geq 0.1\%$ of the patients or rare and considered serious in their nature.

System Organ Class	Very Common $\geq 10\%$	Common $\geq 1\%$ to $<10\%$	Uncommon $\geq 0.1\%$ to $<1\%$	Rare $\geq 0.01\%$ to $< 0.1\%$
Immune System Disorders			Allergic oedema and angioedema	Allergic reaction

System Organ Class	Very Common ≥ 10%	Common ≥ 1% to <10%	Uncommon ≥ 0.1% to <1%	Rare ≥ 0.01% to < 0.1%
Infections and Infestations				Conjunctivitis
Psychiatric Disorders			Sleep disorder	
Nervous System Disorders	Headache	Dizziness*	Somnolence Paraesthesia and dysesthesia	Syncope Amnesia Seizure
Eye Disorders incl. related Investigations			Visual disturbance Visual colour distortions Ocular hyperaemia Eye pain and eye discomfort Photophobia	Increase in intraocular pressure
Ear and Labyrinth Disorders			Tinnitus Vertigo	
Cardiac Disorders incl. related Investigations			Palpitation Tachycardia	Angina pectoris Myocardial infarction Ventricular tachyarrhythmias
Vascular Disorders incl. related Investigations		Vasodilatation		Hypotension
Respiratory, Thoracic and Mediastinal Disorders		Nasal congestion	Dyspnoea Sinus congestion	
Gastrointestinal Disorders incl. related Investigations		Dyspepsia	Gastrointestinal and abdominal pain Diarrhoea Dry mouth Gastritis Gastrooesophageal reflux disease Vomiting Nausea	
Hepatobiliary System Disorder			Increase in transaminases	
Skin and Subcutaneous Tissue Disorders			Rash Erythema	

System Organ Class	Very Common ≥ 10%	Common ≥ 1% to <10%	Uncommon ≥ 0.1% to <1%	Rare ≥ 0.01% to < 0.1%
Musculoskeletal and Connective Tissue Disorders incl. related Investigations			Back pain Myalgia Increase in creatine kinase Increased muscle tone and cramping	
Reproductive System and Breast Disorders			Increase in erection	Priapism
General Disorders and Administration Site Conditions			Feeling unwell	Chest pain

*In a pooled analysis of placebo-controlled fix-dose studies comparing 5 mg, 10 mg and 20 mg of vardenafil film-coated tablets a higher rate of dizziness was seen in elderly subjects (≥ 65 years) with doses of 10 mg or higher than in younger subjects (4.2% vs. 1.2%). Due to the vasodilatory properties of PDE5 inhibitors, concomitant use with alpha-blockers, may contribute to dizziness.

Post-Marketing Experience

From post-marketing experience with another drug of this class, the following serious adverse events have been reported:

Body system:

Cardiovascular:

Adverse Events:

cerebrovascular haemorrhage, myocardial infarction, pulmonary haemorrhage, subarachnoid and intracerebral haemorrhages, sudden cardiac death, transient ischaemic attack, ventricular arrhythmia

Nervous system:

seizure

Special senses:

decreased vision / temporary vision loss

Urogenital:

haematuria

Ear and labyrinth disorders:

sudden deafness

Myocardial infarction (MI) has been reported in temporal association with the use of vardenafil and sexual activity, but it was not possible to determine whether MI is related directly to vardenafil, or to sexual activity, to the patient's underlying cardiovascular disease, or to a combination of these factors.

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 PDE5 inhibitors, including vardenafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for development of NAION, including: 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.

Visual disturbances including vision loss (temporary or permanent) have been reported rarely post-marketing in temporal association with the use of PDE5 inhibitors, including vardenafil. 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 to other factors.

Sudden decrease or loss of hearing has been reported in a small number of postmarketing and clinical trials cases with the use of all PDE5 inhibitors, including vardenafil. It is not possible to determine whether these reported events are related directly to the use of Levitra, to the underlying risk factors for hearing loss, a combination of these factors or to other factors.

DOSAGE AND ADMINISTRATION

The recommended starting dose of Levitra is 10 mg, taken orally 25 to 60 minutes before sexual activity. Sexual activity can be initiated as soon as 15 minutes and as long as 4 – 5 hours after taking Levitra. Depending on co-morbidities and concomitant medications, it may be necessary to commence on a lower dose of 5 mg film-coated tablet.

The maximum recommended dose frequency is once daily.

Levitra can be taken with or without food.

Sexual stimulation is required for a natural response to treatment.

Dose Range

Based on efficacy and tolerability, the Levitra dose may be increased to 20 mg or decreased to 5 mg. The maximum recommended dose is 20 mg once daily.

Elderly (above 65 years)

Dose adjustment is not warranted based on age alone. It should be considered that co-morbidities increase with age.

Children (from birth to 18 years)

Levitra is not indicated for use in children.

Hepatic Impairment

In patients with mild and moderate hepatic impairment (Child-Pugh A and B), 5 mg should be used as a starting dose, which may subsequently be increased to a higher dose based on tolerability and efficacy. The maximum dose recommended in patients with moderate hepatic impairment (Child-Pugh B) is Levitra 10 mg.

The pharmacokinetics of vardenafil have not been studied in patients with severe hepatic impairment (Child-Pugh C), therefore Levitra should not be used in these patients.

Renal Impairment

No dose adjustment is needed in 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.

The pharmacokinetics of vardenafil have not been studied in patients requiring dialysis, therefore Levitra should not be used in these patients.

Concomitant Alpha-blockers

Consistent with vasodilatory effects of alpha-blockers and vardenafil, the concomitant use of Levitra with alpha-blockers may lead to symptomatic hypotension in some patients. Concomitant treatment should only be initiated if the patient is stable on his alpha-blocker therapy (see PRECAUTIONS and INTERACTIONS WITH OTHER MEDICINES). In those patients who are stable on alpha-blocker therapy, Levitra should be initiated at the lowest recommended starting dose of 5 mg. Patients treated with alpha-blockers who have previously used 5 mg film-coated tablets may be switched to a higher dose.

Levitra may be administered at any time with alfuzosin or tamsulosin. With other alpha-blockers a time separation of dosing should be considered when Levitra is prescribed concomitantly (see PRECAUTIONS and INTERACTIONS WITH OTHER MEDICINES).

In those patients already taking an optimised dose of vardenafil, 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, including vardenafil.

Concomitant Use of Potent CYP 3A4 Inhibitors

The dosage of Levitra may require adjustment in patients receiving certain CYP 3A4 inhibitors.

A maximum dose of 5 mg should not be exceeded when Levitra is used in combination with the potent cytochrome P450 (CYP) 3A4 inhibitors ketoconazole, itraconazole, erythromycin or clarithromycin. Levitra must not be taken with dosages of ketoconazole and itraconazole higher than 200 mg daily. Concomitant use with indinavir and ritonavir is contraindicated, as these medicines are very potent inhibitors of CYP 3A4 (see INTERACTIONS WITH OTHER MEDICINES).

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 eight healthy male volunteers. The majority of these subjects experienced reversible back pain/myalgia and/or "abnormal vision".

The adverse side effects observed were similar both in type and severity to those observed throughout clinical development.

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

Contact Poisons Information Centre 131126 for advice on management.

PRESENTATION & STORAGE CONDITIONS

Levitra 10 is registered in blister packs of 1 (sample pack), 2, 4, 6 and 8 tablets. Not all pack sizes may be marketed.

Levitra 10 contains vardenafil hydrochloride trihydrate equivalent to 10 mg of vardenafil.

Store below 25 °C.

NAME AND ADDRESS OF THE SPONSOR

Bayer Australia Ltd
ABN 22 000 138 714
875 Pacific Highway
PYMBLE NSW 2073

POISON SCHEDULE OF THE MEDICINE

PRESCRIPTION ONLY MEDICINE

DATE OF FIRST INCLUSION IN THE ARTG

8 April 2003

DATE OF MOST RECENT AMENDMENT

3 March 2017

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