ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Levitra 5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg of vardenafil (as hydrochloride trihydrate).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Orange round tablets marked with the BAYER-cross on one side and "5" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of erectile dysfunction in adult men. Erectile dysfunction is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance.

In order for Levitra to be effective, sexual stimulation is required.

Levitra is not indicated for use by women.

4.2 Posology and method of administration

Use in adult men

The recommended dose is 10 mg taken as needed approximately 25 to 60 minutes before sexual activity. Based on efficacy and tolerability the dose may be increased to 20 mg or decreased to 5 mg. The maximum recommended dose is 20 mg. The maximum recommended dosing frequency is once per day. Levitra can be taken with or without food. The onset of activity may be delayed if taken with a high fat meal (see section 5.2).

Use in elderly men

Since vardenafil clearance is reduced in elderly patients (see section 5.2) a first dose of 5 mg should be used. Based on efficacy and tolerability the dose may be increased to 10 mg and 20 mg.

Use in children and adolescents

Levitra is not indicated for individuals below 18 years of age. There is no relevant indication for use of Levitra in children.

Use in patients with hepatic impairment

A starting dose of 5 mg should be considered in patients with mild and moderate hepatic impairment (Child-Pugh A-B). Based on tolerability and efficacy, the dose may subsequently be increased. The maximum dose recommended in patients with moderate hepatic impairment (Child-Pugh B) is 10 mg (see sections 4.3 and 5.2).

Use in patients with renal impairment

No dosage adjustment is required in patients with mild to moderate renal impairment.

In patients with severe renal impairment (creatinine clearance < 30 ml/min), a starting dose of 5 mg should be considered. Based on tolerability and efficacy the dose may be increased to 10 mg and 20 mg.

Use in patients using other medicinal products

When used in combination with the CYP 3A4 inhibitors such as erythromycin or clarithromycin, the dose of vardenafil should not exceed 5 mg (see section 4.5).

For oral use

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

The coadministration of vardenafil with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated (see sections 4.5 and 5.1).

Levitra is contraindicated in patients who have loss of vision in one eye because of non-arteritic anterior ischemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous PDE5 inhibitor exposure (see section 4.4).

Agents for the treatment of erectile dysfunction should generally not be used in men for whom sexual activity is inadvisable (e.g. patients with severe cardiovascular disorders such as unstable angina or severe cardiac failure [New York Heart Association III or IV]).

The safety of vardenafil has not been studied in the following sub-groups of patients and its use is therefore contraindicated until further information is available:

- severe hepatic impairment (Child-Pugh C),
- end stage renal disease requiring dialysis,
- hypotension (blood pressure <90/50 mmHg),
- recent history of stroke or myocardial infarction (within the last 6 months),
- unstable angina and known hereditary retinal degenerative disorders such as retinitis pigmentosa.

Concomitant use of vardenafil with the potent CYP3A4 inhibitors ketoconazole and itraconazole (oral form) is contraindicated in men older than 75 years.

Concomitant use of vardenafil with HIV protease inhibitors such as ritonavir and indinavir is contraindicated, as they are very potent inhibitors of CYP3A4 (see section 4.5).

4.4 Special warnings and precautions for use

A medical history and physical examination should be undertaken to diagnose erectile dysfunction and determine potential underlying causes, before pharmacological treatment is considered.

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 (see section 4.3). Vardenafil has vasodilator properties, resulting in mild and transient decreases in blood pressure (see section 5.1). Patients with left ventricular outflow obstruction, e.g., aortic stenosis and idiopathic hypertrophic subaortic stenosis, can be sensitive to the action of vasodilators including Type 5 phosphodiesterase inhibitors.

Agents for the treatment of erectile dysfunction should 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 have not been studied. Therefore the use of such combinations is not recommended.

The concomitant use of alpha-blockers and vardenafil may lead to symptomatic hypotension in some patients because both are vasodilators. Concomitant treatment with vardenafil should only be initiated if the patient has been stabilised on his alpha-blocker therapy. In those patients who are stable on alpha-blocker therapy, vardenafil should be initiated at the lowest recommended starting dose of 5 mg. Vardenafil may be administered at any time with tamsulosin. With other alpha blockers a time separation of dosing should be considered when vardenafil is prescribed concomitantly (see section 4.5). In those patients already taking an optimized 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 vardenafil.

Concomitant use of vardenafil with potent CYP 3A4 inhibitors such as itraconazole and ketoconazole (oral form) should be avoided as very high plasma concentrations of vardenafil are reached if the medicinal products are combined (see sections 4.5 and 4.3).

Vardenafil dose adjustment might be necessary if moderate CYP 3A4 inhibitors such as erythromycin and clarithromycin, are given concomitantly (see sections 4.5 and 4.2).

Concomitant intake of grapefruit juice is expected to increase the plasma concentrations of vardenafil. The combination should be avoided (see section 4.5).

Single oral doses of 10 mg and 80 mg of vardenafil have been shown to prolong the QTc interval by a mean of 8 msec and 10 msec, respectively. And single doses of 10 mg vardenafil co-administered concomitantly with 400 mg gatifloxacin, a drug with comparable QT effect, showed an additive QTc effect of 4 msec when compared to either drug alone. The clinical impact of these QT changes is unknown (see section 5.1).
The clinical relevance of this finding is unknown and cannot be generalised to all patients under all circumstances, as it will depend on the individual risk factors and susceptibilities that may be present at any time in any given patient. Medicinal products that may prolong QTc interval, including vardenafil, are best avoided in patients with relevant risk factors, for example, hypokalaemia; congenital QT prolongation; concomitant administration of antiarrhythmic medicinal products in Class 1[a] (e.g. quinidine, procainamide), or Class III (e.g. amiodarone, sotalol).

Visual defects and cases of non-arteritic ischemic optic neuropathy (NAION) have been reported in connection with the intake of Levitra and other PDE5 inhibitors. The patient should be advised that in the case of sudden visual defect, he should stop taking Levitra and consult immediately a physician (see section 4.3).

In vitro studies with human platelets indicate that vardenafil has no antiaggregatory effect on its own, but at high (super-therapeutic) concentrations vardenafil potentiates the antiaggregatory effect of the nitric oxide donor sodium nitroprusside. In humans, vardenafil had no effect on bleeding time alone or in combination with acetylsalicyclic acid (see section 4.5). There is no safety information available on the administration of vardenafil to patients with bleeding disorders or active peptic ulceration. Therefore vardenafil should be administered to these patients only after careful benefit-risk assessment.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on vardenafil

In vitro studies:

Vardenafil is metabolised predominantly by hepatic enzymes via cytochrome P450 (CYP) isoform 3A4, with some contribution from CYP3A5 and CYP2C isoforms. Therefore, inhibitors of these isoenzymes may reduce vardenafil clearance.

In vivo studies:

Co-administration of the HIV protease inhibitor indinavir (800 mg three times a day), a potent CYP3A4 inhibitor, with vardenafil (10 mg) resulted in a 16-fold increase in vardenafil AUC and a 7-fold increase in vardenafil C_{max}. At 24 hours, the plasma levels of vardenafil had fallen to approximately 4% of the maximum vardenafil plasma level (C_{max}).

Co-administration of vardenafil with ritonavir (600 mg twice daily) resulted in a 13-fold increase in vardenafil C_{max} and a 49-fold increase in vardenafil AUC_{0-24} when co-administered with vardenafil 5 mg. The interaction is a consequence of blocking hepatic metabolism of Levitra by ritonavir, a highly potent CYP3A4 inhibitor, which also inhibits CYP2C9. Ritonavir significantly prolonged the half-life of Levitra to 25.7 hours (see section 4.3).

Co-administration of ketoconazole (200 mg), a potent CYP3A4 inhibitor, with vardenafil (5 mg) resulted in a 10-fold increase in vardenafil AUC and a 4-fold increase in vardenafil C_{max} (see section 4.4).

Although specific interaction studies have not been conducted, the concomitant use of other potent CYP3A4 inhibitors (such as itraconazole) can be expected to produce vardenafil plasma levels comparable to those produced by ketoconazole. Concomitant use of vardenafil with potent CYP 3A4 inhibitors such as itraconazole and ketoconazole (oral use) should be avoided (see sections 4.3 and 4.4). In men older than 75 years the concomitant use of vardenafil with itraconazole or ketoconazole is contraindicated (see section 4.3)

Co-administration of erythromycin (500 mg three times a day), a CYP3A4 inhibitor, with vardenafil (5 mg) resulted in a 4-fold increase in vardenafil AUC and a 3-fold increase in C_{max}. Although a specific interaction study has not been conducted, the co-administration of clarithromycin can be expected to result in similar effects on vardenafil AUC and C_{max}. When used in combination with a moderate CYP 3A4 inhibitor such as erythromycin or clarithromycin, vardenafil dose adjustment might be necessary (see sections 4.2 and 4.4). Cimetidine (400 mg twice daily), a non-specific cytochrome P450 inhibitor, had no effect on vardenafil AUC and C_{max} when co-administered with vardenafil (20 mg) to healthy volunteers.

Grapefruit juice being a weak inhibitor of CYP3A4 gut wall metabolism, may give rise to modest increases in plasma levels of vardenafil (see section 4.4).

The pharmacokinetics of vardenafil (20 mg) was not affected by co-administration with the H2-antagonist ranitidine (150 mg twice daily), digoxin, warfarin, glibenclamide, alcohol (mean maximum blood alcohol level of 73 mg/dl) or single doses of antacid (magnesium hydroxide/aluminium hydroxide).

Although specific interaction studies were not conducted for all medicinal products, population pharmacokinetic analysis showed no effect on vardenafil pharmacokinetics of the following concomitant medicinal products: acetylsalicylic acid, ACE-inhibitors, beta-blockers, weak CYP 3A4 inhibitors, diuretics and medicinal products for the treatment of diabetes (sulfonylureas and metformin).

Effects of vardenafil on other medicinal products

There are no data on the interaction of vardenafil and non-specific phosphodiesterase inhibitors such as theophylline or dipyridamole.

In vivo studies:
No potentiation of the blood pressure lowering effect of sublingual nitroglycerin (0.4 mg) was observed when vardenafil (10 mg) was given at varying time intervals (1 h to 24 h) prior to the dose of nitroglycerin in a study in 18 healthy male subjects. Vardenafil 20 mg potentiated the blood pressure lowering effect of sublingual nitroglycerin (0.4mg) taken 1 and 4 hours after vardenafil administration to healthy middle aged subjects. No effect on blood pressure was observed when nitroglycerin was taken 24 hours after administration of a single dose of vardenafil 20 mg. However, there is no information on the possible potentiation of the hypotensive effects of nitrates by vardenafil in patients, and concomitant use is therefore contraindicated (see section 4.3).
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.

Since alpha-blocker monotherapy can cause marked lowering of blood pressure, especially postural hypotension and syncope, interaction studies were conducted with vardenafil. In two interaction studies with healthy normotensive volunteers after forced titration of the alpha-blockers tamsulosin or terazosin to high doses, hypotension (in some cases symptomatic) was reported in a significant number of subjects after co-administration of vardenafil. Among subjects treated with terazosin, hypotension was observed more frequently when vardenafil and terazosin were given simultaneously than when the dosing was separated by a time interval of 6 hours.

Based on the results of interaction studies conducted with vardenafil in patients with benign prostatic hyperplasia (BPH) on stable tamsulosin or terazosin therapy:

- When vardenafil was given at doses of 5, 10 or 20 mg on a background of stable therapy with tamsulosin, there was no symptomatic reduction in blood pressure, although 3/21 tamsulosin treated subjects exhibited transient standing systolic blood pressures of less than 85 mmHg.
- When vardenafil 5 mg was given simultaneously with terazosin 5 or 10 mg, one of 21 patients experienced symptomatic postural hypotension. Hypotension was not observed when vardenafil 5 mg and terazosin administration was separated by 6 hours.

Therefore, 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, vardenafil should be initiated at the lowest recommended starting dose of 5mg. Levitra may be administered at any time with tamsulosin. With other alpha blockers a time separation of dosing should be considered when vardenafil is prescribed concomitantly (see section 4.4).

No significant interactions were shown when warfarin (25 mg), which is metabolised by CYP2C9, or digoxin (0.375 mg) was co-administered with vardenafil (20 mg). The relative bioavailability of glibenclamide (3.5 mg) was not affected when co-administered with vardenafil (20 mg). In a specific study, where vardenafil (20 mg) was co-administered with slow release nifedipine (30 mg or 60 mg) in hypertensive patients, there was an additional reduction on supine systolic blood pressure of 6 mmHg and supine diastolic blood pressure of 5 mmHg accompanied with an increase in heart rate of 4 bpm.

When vardenafil (20 mg) and alcohol (mean maximum blood alcohol level of 73 mg/dl) were taken together, vardenafil did not potentiate the effects of alcohol on blood pressure and heart rate and the pharmacokinetics of vardenafil were not altered.

Vardenafil (10 mg) did not potentiate the increase in bleeding time caused by acetylsalicylic acid (2 x 81 mg).

4.6 Pregnancy and lactation

Levitra is not indicated for use by women. There are no studies of vardenafil in pregnant women.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

As dizziness and abnormal vision have been reported in clinical trials with vardenafil, patients should be aware of how they react to Levitra, before driving or operating machinery.

4.8 Undesirable effects

Over 9,500 patients have received Levitra in clinical trials. The adverse reactions were generally transient and mild to moderate in nature. The most commonly reported adverse drug reactions occurring in ≥ 10% of patients are headache and flushing.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The following adverse reactions have been reported:

System Organ Class	**Very Common (≥1/10)**	**Common (≥1/100 and <1/10)**	**Uncommon (≥1/1,000 and <1/100)***	**Rare (≥1/10,000 and <1/1,000)***	**Not Known (can not be estimated from the available data)**
Immune System Disorders				Hypersensitivity	
Psychiatric Disorders				Anxiety	
Nervous System Disorders	Headache	Dizziness	Somnolence	Syncope Seizure Transient global amnesia	
Eye Disorders incl. Related Investigations			Lacrimation increased Visual Disturbance (incl. Visual brightness) Chromatopsia Conjunctivitis Blurred Vision	Intraocular pressure increased	Non-arteritic-anterior ischemic optic neuropathy Visual defects
Ear and labyrinth Disorders					Sudden deafness**
Cardiac Disorders incl. related Investigations			Tachycardia Palpitations	Angina Pectoris Myocardial ischemia	Myocardial Infarction
Vascular Disorders incl. related Investigations	Flushing		Hypertension Hypotension Orthostatic Hypotension		
Respiratory, Thoracic and Mediastinal Disorders		Nasal Congestion	Dyspnoea Epistaxis	Laryngeal oedema	

System Organ Class	Very Common (≥1/10)	Common (≥1/100 and <1/10)	Uncommon (≥1/1,000 and <1/100)*	Rare (≥1/10,000 and <1/1,000)*	Not Known (can not be estimated from the available data)
Gastrointestinal Disorders incl. related Investigations		Dyspepsia Nausea	Abnormal liver function tests GGTP increased		
Skin and Subcutaneous Tissue Disorders			Photosensitivity reaction Face oedema Rash		
Musculoskeletal and Connective Tissue Disorders incl. Related Investigations			Blood creatine phosphokinase increased Myalgia Back Pain	Muscle Rigidity	
Reproductive System and Breast Disorders				Priapism Erections increased (prolonged or painful erections)	

*For adverse reactions reported in <1% of patients, only those which warrant special attention, because of their possible association with serious disease states or of otherwise clinical relevance are listed.
**Sudden deafness or loss of hearing has been reported in a small number of postmarketing and clinical trial cases with the use of all PDE5 inhibitors, including vardenafil.

Post marketing reports of another medicinal product of this class: Vascular Disorders: Serious cardiovascular events, including cerebrovascular haemorrhage, sudden cardiac death, transient ischaemic attack, unstable angina and ventricular arrhythmia have been reported post marketing in temporal association with another medicinal product in this class.

4.9 Overdose

In single dose volunteer studies, doses up to and including 80 mg per day were tolerated without exhibiting serious adverse reactions.

When vardenafil was administered in higher doses and more frequently than the recommended dosing regimen (40 mg twice daily) cases of severe back pain have been reported. This was not associated with any muscle or neurological toxicity.

In cases of overdose, standard supportive measures should be adopted 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Medicinal product used in erectile dysfunction, ATC code: G04BE09

Vardenafil is an oral therapy for the improvement of erectile function in men with erectile dysfunction. In the natural setting, i.e. with sexual stimulation it restores impaired erectile function by increasing blood flow to the penis.

Penile erection is a haemodynamic process. During sexual stimulation, nitric oxide is released. It activates the enzyme guanylate cyclase, resulting in an increased level of cyclic guanosine monophosphate (cGMP) in the corpus cavernosum. This in turn results in smooth muscle relaxation, allowing increased inflow of blood into the penis. The level of cGMP is regulated by the rate of synthesis via guanylate cyclase and by the rate of degradation via cGMP hydrolysing phosphodiesterases (PDEs).

Vardenafil is a potent and selective inhibitor of the cGMP specific phosphodiesterase type 5 (PDE5), the most prominent PDE in the human corpus cavernosum. Vardenafil potently enhances the effect of endogenous nitric oxide in the corpus cavernosum by inhibiting PDE5. When nitric oxide is released in response to sexual stimulation, inhibition of PDE5 by vardenafil results in increased corpus cavernosum levels of cGMP. Sexual stimulation is therefore required for vardenafil to produce its beneficial therapeutic effects.

In vitro studies have shown that 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 >1000-fold relative to PDE2, PDE3, PDE4, PDE7, PDE8, PDE9 and PDE10).

In a penile plesthysmography (RigiScan) study, vardenafil 20 mg produced erections considered sufficient for penetration (60% rigidity by RigiScan) in some men as early as 15 minutes after dosing. The overall response of these subjects to vardenafil became statistically significant, compared to placebo, 25 minutes after dosing.

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 under 20 mg and – 4.3 mmHg under 40 mg of vardenafil, when compared to placebo. These effects are consistent with the vasodilatory effects of PDE5-inhibitors and are probably due to increased cGMP levels in vascular smooth muscle cells. Single and multiple oral doses of vardenafil up to 40 mg produced no clinically relevant changes in the ECGs of normal male volunteers.
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 Tmax 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/RR1/3) 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 postdose. At Tmax, 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 vardenafil or 50 mg sildenafil were co-administered concomitantly with 400 mg gatifloxacin, a drug with comparable QT effect. Both vardenafil and sildenafil showed an increase of Fredericia QTc effect of 4 msec (vardenafil) and 5 msec (sildenafil) when compared to either drug alone. The actual clinical impact of these QT changes is unknown.

Further information on clinical trials

In clinical trials vardenafil was administered to over 3750 men with erectile dysfunction (ED) aged 18 - 89 years, many of whom had multiple co-morbid conditions. Over 1630 patients have been treated with Levitra for six months or longer. Of these, over 730 have been treated for one year or longer.

The following patient groups were represented: elderly (22%), patients with hypertension (35%), diabetes mellitus (29%), ischaemic heart disease and other cardiovascular diseases (7%), chronic pulmonary disease (5%), hyperlipidaemia (22%), depression (5%), radical prostatectomy (9%). The following groups were not well represented in clinical trials: elderly (>75 years, 2.4%), and patients with certain cardiovascular conditions (see section 4.3). No clinical trials in CNS diseases (except spinal cord injury), patients with severe renal or hepatic impairment, pelvic surgery (except nerve-sparing prostatectomy) or trauma or radiotherapy and hypoactive sexual desire or penile anatomic deformities have been performed.

Across the pivotal trials, treatment with vardenafil resulted in an improvement of erectile function compared to placebo. In the small number of patients who attempted intercourse up to four to five hours after dosing the success rate for penetration and maintenance of erection was consistently greater than placebo.

In fixed dose studies in a broad population of men with erectile dysfunction, 68% (5 mg), 76% (10 mg) and 80% (20 mg) of patients experienced successful penetrations (SEP 2) compared to 49% on placebo over a three month study period. The ability to maintain the erection (SEP 3) in this broad ED population was given as 53% (5 mg), 63% (10 mg) and 65% (20 mg) compared to 29% on placebo.

In pooled data from the major efficacy trials, the proportion of patients experiencing successful penetration on vardenafil were as follows: psychogenic erectile dysfunction (77-87%), mixed erectile dysfunction (69-83%), organic erectile dysfunction (64-75%), elderly (52-75%), ischaemic heart disease (70-73%), hyperlipidemia (62-73%), chronic pulmonary disease (74-78%), depression (59-69%), and patients concomitantly treated with antihypertensives (62-73%).

In a clinical trial in patients with diabetes mellitus, vardenafil significantly improved the erectile function domain score, the ability to obtain and maintain an erection long enough for successful intercourse and penile rigidity compared to placebo at vardenafil doses of 10 mg and 20 mg. The response rates for the ability to obtain and maintain an erection was 61% and 49% on 10 mg and 64% and 54% on 20 mg vardenafil compared to 36% and 23% on placebo for patients who completed three months treatment.

In a clinical trial in post-prostatectomy patients, vardenafil significantly improved the erectile function domain score, the ability to obtain and maintain an erection long enough for successful intercourse and penile rigidity compared to placebo at vardenafil doses of 10 mg and 20 mg. The response rates for the ability to obtain and maintain an erection was 47% and 37% on 10 mg and 48% and 34% on 20 mg vardenafil compared to 22% and 10% on placebo for patients who completed three months treatment. In a flexible-dose clinical trial in patients with Spinal Cord Injury, vardenafil significantly improved the erectile function domain score, the ability to obtain and maintain an erection long enough for successful intercourse and penile rigidity compared to placebo. The number of patients who returned to a normal IIEF domain score ($\geq$26) were 53% on vardenafil compared to 9% on placebo. The response rates for the ability to obtain and maintain an erection were 76% and 59% on vardenafil compared to 41% and 22% on placebo for patients who completed three months treatment which were clinically and statistically significant ($p<0.001$).

The safety and efficacy of vardenafil was maintained in long term studies.

5.2 Pharmacokinetic properties

Absorption

Vardenafil is rapidly absorbed with maximum observed plasma concentrations reached in some men as early as 15 minutes after oral administration. However, 90% of the time, maximum plasma concentrations are reached within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state. The mean absolute oral bioavailability is 15 %. After oral dosing of vardenafil AUC and C_{max} increase almost dose proportionally over the recommended dose range (5 – 20 mg).

When vardenafil is taken with a high fat meal (containing 57% fat), the rate of absorption is reduced, with an increase in the median t_{max} of 1 hour and a mean reduction in C_{max} of 20%. Vardenafil AUC is not affected. After a meal containing 30% fat, the rate and extent of absorption of vardenafil (t_{max}, C_{max} and AUC) are unchanged compared to administration under fasting conditions.

Distribution

The mean steady state volume of distribution for vardenafil is 208 l, indicating distribution into the tissues. Vardenafil and its major circulating metabolite (M1) are highly bound to plasma proteins (approximately 95% for vardenafil or M1). For vardenafil as well as M1, protein binding is independent of total drug concentrations.

Based on measurements of vardenafil in semen of healthy subjects 90 minutes after dosing, not more than 0.00012% of the administered dose may appear in the semen of patients.

Metabolism

Vardenafil is metabolised predominantly by hepatic metabolism via cytochrome P450 (CYP) isoform 3A4 with some contribution from CYP3A5 and CYP2C isoforms.

In humans the one major circulating metabolite (M1) results from desethylation of vardenafil and is subject to further metabolism with a plasma elimination half life of approximately 4 hours. Parts of M1 are in the form of the glucuronide in systemic circulation. Metabolite M1 shows a phosphodiesterase selectivity profile similar to vardenafil and an *in vitro* potency for phosphodiesterase type 5 of approximately 28% compared to vardenafil, resulting in an efficacy contribution of about 7%.

Elimination

The total body clearance of vardenafil is 56 l/h with a resultant terminal half life of approximately 4-5 hours. After oral administration, vardenafil is excreted as metabolites predominantly in the faeces (approximately 91-95% of the administered dose) and to a lesser extent in the urine (approximately 2-6% of the administered dose).

Pharmacokinetics in special patient groups

Elderly
Hepatic clearance of vardenafil in healthy elderly volunteers (65 years and over) was reduced as compared to healthy younger volunteers (18 - 45 years). On average elderly males had a 52% higher AUC, and a 34% higher C_{max} than younger males (see section 4.2).

Renal insufficiency
In volunteers with mild to moderate renal impairment (creatinine clearance 30 – 80 ml/min), the pharmacokinetics of vardenafil were similar to that of a normal renal function control group. In volunteers with severe renal impairment (creatinine clearance < 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 was observed between creatinine clearance and vardenafil exposure (AUC and C_{max}) (see section 4.2). Vardenafil pharmacokinetics has not been studied in patients requiring dialysis (see section 4.3).

Hepatic insufficiency
In patients with mild to moderate hepatic impairment (Child-Pugh A and B), the clearance of vardenafil was reduced in proportion to the degree of hepatic impairment. In patients with mild hepatic impairment (Child-Pugh A), the mean AUC and C_{max} increased 17% and 22% respectively, compared to healthy control subjects. In patients with moderate impairment (Child-Pugh B), the mean AUC and C_{max} increased 160% and 133% respectively, compared to healthy control subjects (see section 4.2). The pharmacokinetics of vardenafil in patients with severely impaired hepatic function (Child-Pugh C) has not been studied (see section 4.3).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
crospovidone
magnesium stearate
microcrystalline cellulose
silica, colloidal anhydrous

Film coat:
macrogol 400
hypromellose
titanium dioxide (E171)
ferric oxide yellow (E172)
ferric oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PP/Aluminium foil blisters in cartons of 2, 4, 8 and 12 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Bayer AG,
D-51368 Leverkusen,
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/248/001-004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 6 March 2003

Date of last renewal : 6 March 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Levitra 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg of vardenafil (as hydrochloride trihydrate).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Orange round tablets marked with the BAYER-cross on one side and "10" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of erectile dysfunction in adult men. Erectile dysfunction is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance.

In order for Levitra to be effective, sexual stimulation is required.

Levitra is not indicated for use by women.

4.2 Posology and method of administration

Use in adult men

The recommended dose is 10 mg taken as needed approximately 25 to 60 minutes before sexual activity. Based on efficacy and tolerability the dose may be increased to 20 mg or decreased to 5 mg. The maximum recommended dose is 20 mg. The maximum recommended dosing frequency is once per day. Levitra can be taken with or without food. The onset of activity may be delayed if taken with a high fat meal (see section 5.2).

Use in elderly men

Since vardenafil clearance is reduced in elderly patients (see section 5.2) a first dose of 5 mg should be used. Based on efficacy and tolerability the dose may be increased to 10 mg and 20 mg.

Use in children and adolescents

Levitra is not indicated for individuals below 18 years of age. There is no relevant indication for use of Levitra in children.

Use in patients with hepatic impairment

A starting dose of 5 mg should be considered in patients with mild and moderate hepatic impairment (Child-Pugh A-B). Based on tolerability and efficacy, the dose may subsequently be increased. The maximum dose recommended in patients with moderate hepatic impairment (Child-Pugh B) is 10 mg. (see sections 4.3 and 5.2).

Use in patients with renal impairment

No dosage adjustment is required in patients with mild to moderate renal impairment.

In patients with severe renal impairment (creatinine clearance < 30 ml/min), a starting dose of 5 mg should be considered. Based on tolerability and efficacy the dose may be increased to 10 mg and 20 mg.

Use in patients using other medicinal products

When used in combination with the CYP 3A4 inhibitors such as erythromycin or clarithromycin, the dose of vardenafil should not exceed 5 mg (see section 4.5).

For oral use.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

The coadministration of vardenafil with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated (see sections 4.5 and 5.1).

Levitra is contraindicated in patients who have loss of vision in one eye because of non-arteritic anterior ischemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous PDE5 inhibitor exposure (see section 4.4).

Agents for the treatment of erectile dysfunction should generally not be used in men for whom sexual activity is inadvisable (e.g. patients with severe cardiovascular disorders such as unstable angina or severe cardiac failure [New York Heart Association III or IV]).

The safety of vardenafil has not been studied in the following sub-groups of patients and its use is therefore contraindicated until further information is available:

- severe hepatic impairment (Child-Pugh C),
- end stage renal disease requiring dialysis,
- hypotension (blood pressure <90/50 mmHg),
- recent history of stroke or myocardial infarction (within the last 6 months),
- unstable angina and known hereditary retinal degenerative disorders such as retinitis pigmentosa.

Concomitant use of vardenafil with the potent CYP3A4 inhibitors ketoconazole and itraconazole (oral form) is contraindicated in men older than 75 years.

Concomitant use of vardenafil with HIV protease inhibitors such as ritonavir and indinavir is contraindicated, as they are very potent inhibitors of CYP3A4 (see section 4.5).

4.4 Special warnings and precautions for use

A medical history and physical examination should be undertaken to diagnose erectile dysfunction and determine potential underlying causes, before pharmacological treatment is considered.

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 (see section 4.3). Vardenafil has vasodilator properties, resulting in mild and transient decreases in blood pressure (see section 5.1). Patients with left ventricular outflow obstruction, e.g., aortic stenosis and idiopathic hypertrophic subaortic stenosis, can be sensitive to the action of vasodilators including Type 5 phosphodiesterase inhibitors.

Agents for the treatment of erectile dysfunction should 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 have not been studied. Therefore the use of such combinations is not recommended.

The concomitant use of alpha-blockers and vardenafil may lead to symptomatic hypotension in some patients because both are vasodilators. Concomitant treatment with vardenafil should only be initiated if the patient has been stabilised on his alpha-blocker therapy. In those patients who are stable on alpha-blocker therapy, vardenafil should be initiated at the lowest recommended starting dose of 5 mg. Vardenafil may be administered at any time with tamsulosin. With other alpha blockers a time separation of dosing should be considered when vardenafil is prescribed concomitantly (see section 4.5). In those patients already taking an optimized 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 vardenafil.

Concomitant use of vardenafil with potent CYP 3A4 inhibitors such as itraconazole and ketoconazole (oral form) should be avoided as very high plasma concentrations of vardenafil are reached if the medicinal products are combined (see sections 4.5 and 4.3).

Vardenafil dose adjustment might be necessary if moderate CYP 3A4 inhibitors such as erythromycin and clarithromycin, are given concomitantly (see sections 4.5 and 4.2).

Concomitant intake of grapefruit juice is expected to increase the plasma concentrations of vardenafil. The combination should be avoided (see section 4.5).

Single oral doses of 10 mg and 80 mg of vardenafil have been shown to prolong the QTc interval by a mean of 8 msec and 10 msec, respectively. And single doses of 10 mg vardenafil co-administered concomitantly with 400 mg gatifloxacin, a drug with comparable QT effect, showed an additive QTc effect of 4 msec when compared to either drug alone. The clinical impact of these QT changes is unknown (see section 5.1).
The clinical relevance of this finding is unknown and cannot be generalised to all patients under all circumstances, as it will depend on the individual risk factors and susceptibilities that may be present at any time in any given patient. Medicinal products that may prolong QTc interval, including vardenafil, are best avoided in patients with relevant risk factors, for example, hypokalaemia; congenital QT prolongation; concomitant administration of antiarrhythmic medicinal products in Class 1[a] (e.g. quinidine, procainamide), or Class III (e.g. amiodarone, sotalol).

Visual defects and cases of non-arteritic ischemic optic neuropathy (NAION) have been reported in connection with the intake of Levitra and other PDE5 inhibitors. The patient should be advised that in the case of sudden visual defect, he should stop taking Levitra and consult immediately a physician (see section 4.3).

In vitro studies with human platelets indicate that vardenafil has no antiaggregatory effect on its own, but at high (super-therapeutic) concentrations vardenafil potentiates the antiaggregatory effect of the nitric oxide donor sodium nitroprusside. In humans, vardenafil had no effect on bleeding time alone or in combination with acetylsalicyclic acid (see section 4.5). There is no safety information available on the administration of vardenafil to patients with bleeding disorders or active peptic ulceration. Therefore vardenafil should be administered to these patients only after careful benefit-risk assessment.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on vardenafil

In vitro studies:

Vardenafil is metabolised predominantly by hepatic enzymes via cytochrome P450 (CYP) isoform 3A4, with some contribution from CYP3A5 and CYP2C isoforms. Therefore, inhibitors of these isoenzymes may reduce vardenafil clearance.

In vivo studies:

Co-administration of the HIV protease inhibitor indinavir (800 mg three times a day), a potent CYP3A4 inhibitor, with vardenafil (10 mg) resulted in a 16-fold increase in vardenafil AUC and a 7-fold increase in vardenafil C_{max}. At 24 hours, the plasma levels of vardenafil had fallen to approximately 4% of the maximum vardenafil plasma level (C_{max}).

Co-administration of vardenafil with ritonavir (600 mg twice daily) resulted in a 13-fold increase in vardenafil C_{max} and a 49-fold increase in vardenafil AUC_{0-24} when co-administered with vardenafil 5 mg. The interaction is a consequence of blocking hepatic metabolism of Levitra by ritonavir, a highly potent CYP3A4 inhibitor, which also inhibits CYP2C9. Ritonavir significantly prolonged the half-life of Levitra to 25.7 hours (see section 4.3).

Co-administration of ketoconazole (200 mg), a potent CYP3A4 inhibitor, with vardenafil (5 mg) resulted in a 10-fold increase in vardenafil AUC and a 4-fold increase in vardenafil C_{max} (see section 4.4).

Although specific interaction studies have not been conducted, the concomitant use of other potent CYP3A4 inhibitors (such as itraconazole) can be expected to produce vardenafil plasma levels comparable to those produced by ketoconazole. Concomitant use of vardenafil with potent CYP 3A4 inhibitors such as itraconazole and ketoconazole (oral use) should be avoided (see sections 4.3 and 4.4). In men older than 75 years the concomitant use of vardenafil with itraconazole or ketoconazole is contraindicated (see section 4.3).

Co-administration of erythromycin (500 mg three times a day), a CYP3A4 inhibitor, with vardenafil (5 mg) resulted in a 4-fold increase in vardenafil AUC and a 3-fold increase in C_{max}. Although a specific interaction study has not been conducted, the co-administration of clarithromycin can be expected to result in similar effects on vardenafil AUC and C_{max}. When used in combination with a moderate CYP 3A4 inhibitor such as erythromycin or clarithromycin, vardenafil dose adjustment might be necessary (see sections 4.2 and 4.4). Cimetidine (400 mg twice daily), a non-specific cytochrome P450 inhibitor, had no effect on vardenafil AUC and C_{max} when co-administered with vardenafil (20 mg) to healthy volunteers.

Grapefruit juice being a weak inhibitor of CYP3A4 gut wall metabolism, may give rise to modest increases in plasma levels of vardenafil (see section 4.4).

The pharmacokinetics of vardenafil (20 mg) was not affected by co-administration with the H2-antagonist ranitidine (150 mg twice daily), digoxin, warfarin, glibenclamide, alcohol (mean maximum blood alcohol level of 73 mg/dl) or single doses of antacid (magnesium hydroxide/aluminium hydroxide).

Although specific interaction studies were not conducted for all medicinal products, population pharmacokinetic analysis showed no effect on vardenafil pharmacokinetics of the following concomitant medicinal products: acetylsalicylic acid, ACE-inhibitors, beta-blockers, weak CYP 3A4 inhibitors, diuretics and medicinal products for the treatment of diabetes (sulfonylureas and metformin).

Effects of vardenafil on other medicinal products

There are no data on the interaction of vardenafil and non-specific phosphodiesterase inhibitors such as theophylline or dipyridamole.

In vivo studies:
No potentiation of the blood pressure lowering effect of sublingual nitroglycerin (0.4 mg) was observed when vardenafil (10 mg) was given at varying time intervals (1 h to 24 h) prior to the dose of nitroglycerin in a study in 18 healthy male subjects. Vardenafil 20 mg potentiated the blood pressure lowering effect of sublingual nitroglycerin (0.4mg) taken 1 and 4 hours after vardenafil administration to healthy middle aged subjects. No effect on blood pressure was observed when nitroglycerin was taken 24 hours after administration of a single dose of vardenafil 20 mg. However, there is no information on the possible potentiation of the hypotensive effects of nitrates by vardenafil in patients, and concomitant use is therefore contraindicated (see section 4.3).
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.

Since alpha-blocker monotherapy can cause marked lowering of blood pressure, especially postural hypotension and syncope, interaction studies were conducted with vardenafil. In two interaction studies with healthy normotensive volunteers after forced titration of the alpha-blockers tamsulosin or terazosin to high doses, hypotension (in some cases symptomatic) was reported in a significant number of subjects after co-administration of vardenafil. Among subjects treated with terazosin, hypotension was observed more frequently when vardenafil and terazosin were given simultaneously than when the dosing was separated by a time interval of 6 hours.

Based on the results of interaction studies conducted with vardenafil in patients with benign prostatic hyperplasia (BPH) on stable tamsulosin or terazosin therapy:

- When vardenafil was given at doses of 5, 10 or 20 mg on a background of stable therapy with tamsulosin, there was no symptomatic reduction in blood pressure, although 3/21 tamsulosin treated subjects exhibited transient standing systolic blood pressures of less than 85 mmHg.
- When vardenafil 5 mg was given simultaneously with terazosin 5 or 10 mg, one of 21 patients experienced symptomatic postural hypotension. Hypotension was not observed when vardenafil 5 mg and terazosin administration was separated by 6 hours.

Therefore, 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, vardenafil should be initiated at the lowest recommended starting dose of 5mg. Levitra may be administered at any time with tamsulosin. With other alpha blockers a time separation of dosing should be considered when vardenafil is prescribed concomitantly (see section 4.4).

No significant interactions were shown when warfarin (25 mg), which is metabolised by CYP2C9, or digoxin (0.375 mg) was co-administered with vardenafil (20 mg). The relative bioavailability of glibenclamide (3.5 mg) was not affected when co-administered with vardenafil (20 mg). In a specific study, where vardenafil (20 mg) was co-administered with slow release nifedipine (30 mg or 60 mg) in hypertensive patients, there was an additional reduction on supine systolic blood pressure of 6 mmHg and supine diastolic blood pressure of 5 mmHg accompanied with an increase in heart rate of 4 bpm.

When vardenafil (20 mg) and alcohol (mean maximum blood alcohol level of 73 mg/dl) were taken together, vardenafil did not potentiate the effects of alcohol on blood pressure and heart rate and the pharmacokinetics of vardenafil were not altered.

Vardenafil (10 mg) did not potentiate the increase in bleeding time caused by acetylsalicylic acid (2 x 81 mg).

4.6 Pregnancy and lactation

Levitra is not indicated for use by women. There are no studies of vardenafil in pregnant women.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

As dizziness and abnormal vision have been reported in clinical trials with vardenafil, patients should be aware of how they react to Levitra, before driving or operating machinery.

4.8 Undesirable effects

Over 9,500 patients have received Levitra in clinical trials. The adverse reactions were generally transient and mild to moderate in nature. The most commonly reported adverse drug reactions occurring in ≥ 10% of patients are headache and flushing.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The following adverse reactions have been reported:

System Organ Class	**Very Common (≥1/10)**	**Common (≥1/100 and <1/ 10)**	**Uncommon (≥1/1,000 and <1/100)***	**Rare (≥1/10,000 and <1/1,000)***	**Not Known (can not be estimated from available data)**
Immune System Disorders				Hypersensitivity	
Psychiatric Disorders				Anxiety	
Nervous System Disorders	Headache	Dizziness	Somnolence	Syncope Seizure Transient global amnesia	
Eye Disorders incl. Related Investigations			Lacrimation increased Visual Disturbance (incl. Visual brightness) Chromatopsia Conjunctivitis Blurred vision	Intraocular pressure increased	Non-arteritic-anterior ischemic optic neuropathy Visual defects
Ear and labyrinth Disorders					Sudden deafness**
Cardiac Disorders incl. related Investigations			Tachycardia Palpitations	Angina Pectoris Myocardial ischemia	Myocardial Infarction
Vascular Disorders incl. related Investigations	Flushing		Hypertension Hypotension Orthostatic Hypotension		
Respiratory, Thoracic and Mediastinal Disorders		Nasal Congestion	Dyspnoea Epistaxis	Laryngeal oedema	
Gastrointestinal Disorders incl. related Investigations		Dyspepsia Nausea	Abnormal liver function tests GGTP increased		

System Organ Class	Very Common (≥1/10)	Common (≥1/100 and <1/ 10)	Uncommon (≥1/1,000 and <1/100)*	Rare (≥1/10,000 and <1/1,000)*	Not Known (can not be estimated from available data)
Skin and Subcutaneous Tissue Disorders			Photosensitivity reaction Face oedema Rash		
Musculoskeletal and Connective Tissue Disorders incl. Related Investigations			Blood creatine phosphokinase increased Myalgia Back Pain	Muscle Rigidity	
Reproductive System and Breast Disorders				Priapism Erections increased (prolonged or painful erections)	

*For adverse reactions reported in <1% of patients, only those which warrant special attention, because of their possible association with serious disease states or of otherwise clinical relevance are listed.
**Sudden deafness or loss of hearing has been reported in a small number of postmarketing and clinical trial cases with the use of all PDE5 inhibitors, including vardenafil.

Post marketing reports of another medicinal product of this class: Vascular Disorders: Serious cardiovascular events, including cerebrovascular haemorrhage, sudden cardiac death, transient ischaemic attack, unstable angina and ventricular arrhythmia have been reported post marketing in temporal association with another medicinal product in this class.

4.9 Overdose

In single dose volunteer studies, doses up to and including 80 mg per day were tolerated without exhibiting serious adverse reactions.

When vardenafil was administered in higher doses and more frequently than the recommended dosing regimen (40 mg twice daily) cases of severe back pain have been reported. This was not associated with any muscle or neurological toxicity.

In cases of overdose, standard supportive measures should be adopted 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Medicinal product used in erectile dysfunction, ATC code: G04BE09

Vardenafil is an oral therapy for the improvement of erectile function in men with erectile dysfunction. In the natural setting, i.e. with sexual stimulation it restores impaired erectile function by increasing blood flow to the penis.

Penile erection is a haemodynamic process. During sexual stimulation, nitric oxide is released. It activates the enzyme guanylate cyclase, resulting in an increased level of cyclic guanosine monophosphate (cGMP) in the corpus cavernosum. This in turn results in smooth muscle relaxation,

allowing increased inflow of blood into the penis. The level of cGMP is regulated by the rate of synthesis via guanylate cyclase and by the rate of degradation via cGMP hydrolysing phosphodiesterases (PDEs).

Vardenafil is a potent and selective inhibitor of the cGMP specific phosphodiesterase type 5 (PDE5), the most prominent PDE in the human corpus cavernosum. Vardenafil potently enhances the effect of endogenous nitric oxide in the corpus cavernosum by inhibiting PDE5. When nitric oxide is released in response to sexual stimulation, inhibition of PDE5 by vardenafil results in increased corpus cavernosum levels of cGMP. Sexual stimulation is therefore required for vardenafil to produce its beneficial therapeutic effects.

In vitro studies have shown that 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 >1000-fold relative to PDE2, PDE3, PDE4, PDE7, PDE8, PDE9 and PDE10).

In a penile plesthysmography (RigiScan) study, vardenafil 20 mg produced erections considered sufficient for penetration (60% rigidity by RigiScan) in some men as early as 15 minutes after dosing. The overall response of these subjects to vardenafil became statistically significant, compared to placebo, 25 minutes after dosing.

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 under 20 mg and – 4.3 mmHg under 40 mg of vardeanfil, when compared to placebo. These effects are consistent with the vasodilatory effects of PDE5-inhibitors and are probably due to increased cGMP levels in vascular smooth muscle cells. Single and multiple oral doses of vardenafil up to 40 mg produced no clinically relevant changes in the ECGs of normal male volunteers.
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 Tmax 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/RR1/3) 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 postdose. At Tmax, 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 vardenafil or 50 mg sildenafil were co-administered concomitantly with 400 mg gatifloxacin, a drug with comparable QT effect. Both vardenafil and sildenafil showed an increase of Fredericia QTc effect of 4 msec (vardenafil) and 5 msec (sildenafil) when compared to either drug alone. The actual clinical impact of these QT changes is unknown.

Further information on clinical trials

In clinical trials vardenafil was administered to over 3750 men with erectile dysfunction (ED) aged 18 - 89 years, many of whom had multiple co-morbid conditions. Over 1630 patients have been treated with Levitra for six months or longer. Of these, over 730 have been treated for one year or longer. The following patient groups were represented: elderly (22%), patients with hypertension (35%), diabetes mellitus (29%), ischaemic heart disease and other cardiovascular diseases (7%), chronic pulmonary disease (5%), hyperlipidaemia (22%), depression (5%), radical prostatectomy (9%). The following groups were not well represented in clinical trials: elderly (>75 years, 2.4%), and patients with certain cardiovascular conditions (see section 4.3). No clinical trials in CNS diseases (except spinal cord injury), patients with severe renal or hepatic impairment, pelvic surgery (except nerve-sparing

prostatectomy) or trauma or radiotherapy and hypoactive sexual desire or penile anatomic deformities have been performed.

Across the pivotal trials, treatment with vardenafil resulted in an improvement of erectile function compared to placebo. In the small number of patients who attempted intercourse up to four to five hours after dosing the success rate for penetration and maintenance of erection was consistently greater than placebo.

In fixed dose studies in a broad population of men with erectile dysfunction, 68% (5 mg), 76% (10 mg) and 80% (20 mg) of patients experienced successful penetrations (SEP 2) compared to 49% on placebo over a three month study period. The ability to maintain the erection (SEP 3) in this broad ED population was given as 53% (5 mg), 63% (10 mg) and 65% (20 mg) compared to 29% on placebo.

In pooled data from the major efficacy trials, the proportion of patients experiencing successful penetration on vardenafil were as follows: psychogenic erectile dysfunction (77-87%), mixed erectile dysfunction (69-83%), organic erectile dysfunction (64-75%), elderly (52-75%), ischaemic heart disease (70-73%), hyperlipidemia (62-73%), chronic pulmonary disease (74-78%), depression (59-69%), and patients concomitantly treated with antihypertensives (62-73%).

In a clinical trial in patients with diabetes mellitus, vardenafil significantly improved the erectile function domain score, the ability to obtain and maintain an erection long enough for successful intercourse and penile rigidity compared to placebo at vardenafil doses of 10 mg and 20 mg. The response rates for the ability to obtain and maintain an erection was 61% and 49% on 10 mg and 64% and 54% on 20 mg vardenafil compared to 36% and 23% on placebo for patients who completed three months treatment.

In a clinical trial in post-prostatectomy patients, vardenafil significantly improved the erectile function domain score, the ability to obtain and maintain an erection long enough for successful intercourse and penile rigidity compared to placebo at vardenafil doses of 10 mg and 20 mg. The response rates for the ability to obtain and maintain an erection was 47% and 37% on 10 mg and 48% and 34% on 20 mg vardenafil compared to 22% and 10% on placebo for patients who completed three months treatment. In a flexible-dose clinical trial in patients with Spinal Cord Injury, vardenafil significantly improved the erectile function domain score, the ability to obtain and maintain an erection long enough for successful intercourse and penile rigidity compared to placebo. The number of patients who returned to a normal IIEF domain score ($\geq$26) were 53% on vardenafil compared to 9% on placebo. The response rates for the ability to obtain and maintain an erection were 76% and 59% on vardenafil compared to 41% and 22% on placebo for patients who completed three months treatment which were clinically and statistically significant ($p<0.001$).

The safety and efficacy of vardenafil was maintained in long term studies.

5.2 Pharmacokinetic properties

Absorption

Vardenafil is rapidly absorbed with maximum observed plasma concentrations reached in some men as early as 15 minutes after oral administration. However, 90% of the time, maximum plasma concentrations are reached within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state. The mean absolute oral bioavailability is 15 %. After oral dosing of vardenafil AUC and C_{max} increase almost dose proportionally over the recommended dose range (5 – 20 mg).

When vardenafil is taken with a high fat meal (containing 57% fat), the rate of absorption is reduced, with an increase in the median t_{max} of 1 hour and a mean reduction in C_{max} of 20%. Vardenafil AUC is not affected. After a meal containing 30% fat, the rate and extent of absorption of vardenafil (t_{max}, C_{max} and AUC) are unchanged compared to administration under fasting conditions.

Distribution

The mean steady state volume of distribution for vardenafil is 208 l, indicating distribution into the tissues. Vardenafil and its major circulating metabolite (M1) are highly bound to plasma proteins (approximately 95% for vardenafil or M1). For vardenafil as well as M1, protein binding is independent of total drug concentrations.

Based on measurements of vardenafil in semen of healthy subjects 90 minutes after dosing, not more than 0.00012% of the administered dose may appear in the semen of patients.

Metabolism

Vardenafil is metabolised predominantly by hepatic metabolism via cytochrome P450 (CYP) isoform 3A4 with some contribution from CYP3A5 and CYP2C isoforms.

In humans the one major circulating metabolite (M1) results from desethylation of vardenafil and is subject to further metabolism with a plasma elimination half life of approximately 4 hours. Parts of M1 are in the form of the glucuronide in systemic circulation. Metabolite M1 shows a phosphodiesterase selectivity profile similar to vardenafil and an *in vitro* potency for phosphodiesterase type 5 of approximately 28% compared to vardenafil, resulting in an efficacy contribution of about 7%.

Elimination

The total body clearance of vardenafil is 56 l/h with a resultant terminal half life of approximately 4-5 hours. After oral administration, vardenafil is excreted as metabolites predominantly in the faeces (approximately 91-95% of the administered dose) and to a lesser extent in the urine (approximately 2-6% of the administered dose).

Pharmacokinetics in special patient groups

Elderly
Hepatic clearance of vardenafil in healthy elderly volunteers (65 years and over) was reduced as compared to healthy younger volunteers (18 - 45 years). On average elderly males had a 52% higher AUC, and a 34% higher C_{max} than younger males (see section 4.2).

Renal insufficiency
In volunteers with mild to moderate renal impairment (creatinine clearance 30 – 80 ml/min), the pharmacokinetics of vardenafil were similar to that of a normal renal function control group. In volunteers with severe renal impairment (creatinine clearance < 30 ml/min) the mean AUC was increased by 21% and the mean Cmax decreased by 23%, compared to volunteers with no renal impairment. No statistically significant correlation was observed between creatinine clearance and vardenafil exposure (AUC and C_{max}) (see section 4.2). Vardenafil pharmacokinetics has not been studied in patients requiring dialysis (see section 4.3).

Hepatic insufficiency
In patients with mild to moderate hepatic impairment (Child-Pugh A and B), the clearance of vardenafil was reduced in proportion to the degree of hepatic impairment. In patients with mild hepatic impairment (Child-Pugh A), the mean AUC and C_{max} increased 17% and 22% respectively, compared to healthy control subjects. In patients with moderate impairment (Child-Pugh B), the mean AUC and C_{max} increased 160% and 133% respectively, compared to healthy control subjects (see section 4.2). The pharmacokinetics of vardenafil in patients with severely impaired hepatic function (Child-Pugh C) has not been studied (see section 4.3).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
crospovidone
magnesium stearate
microcrystalline cellulose
silica, colloidal anhydrous

Film coat:
macrogol 400
hypromellose
titanium dioxide (E171)
ferric oxide yellow (E172)
ferric oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PP/Aluminium foil blisters in cartons of 2, 4, 8 and 12 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Bayer AG,
D-51368 Leverkusen,
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/248/005-008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 6 March 2003

Date of last renewal : 6 March 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Levitra 20 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg of vardenafil (as hydrochloride trihydrate).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Orange round tablets marked with the BAYER-cross on one side and “20” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of erectile dysfunction in adult men. Erectile dysfunction is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance.

In order for Levitra to be effective, sexual stimulation is required.

Levitra is not indicated for use by women.

4.2 Posology and method of administration

Use in adult men

The recommended dose is 10 mg taken as needed approximately 25 to 60 minutes before sexual activity. Based on efficacy and tolerability the dose may be increased to 20 mg or decreased to 5 mg. The maximum recommended dose is 20 mg. The maximum recommended dosing frequency is once per day. Levitra can be taken with or without food. The onset of activity may be delayed if taken with a high fat meal (see section 5.2).

Use in elderly men

Since vardenafil clearance is reduced in elderly patients (see section 5.2) a first dose of 5 mg should be used. Based on efficacy and tolerability the dose may be increased to 10 mg and 20 mg.

Use in children and adolescents

Levitra is not indicated for individuals below 18 years of age. There is no relevant indication for use of Levitra in children.

Use in patients with hepatic impairment

A starting dose of 5 mg should be considered in patients with mild and moderate hepatic impairment (Child-Pugh A-B). Based on tolerability and efficacy, the dose may subsequently be increased. The maximum dose recommended in patients with moderate hepatic impairment (Child-Pugh B) is 10 mg (see sections 4.3 and 5.2).

Use in patients with renal impairment

No dosage adjustment is required in patients with mild to moderate renal impairment.

In patients with severe renal impairment (creatinine clearance < 30 ml/min), a starting dose of 5 mg should be considered. Based on tolerability and efficacy the dose may be increased to 10 mg and 20 mg.

Use in patients using other medicinal products

When used in combination with the CYP 3A4 inhibitors such as erythromycin or clarithromycin, the dose of vardenafil should not exceed 5 mg (see section 4.5).

For oral use

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

The coadministration of vardenafil with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated (see sections 4.5 and 5.1).

Levitra is contraindicated in patients who have loss of vision in one eye because of non-arteritic anterior ischemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous PDE5 inhibitor exposure (see section 4.4).

Agents for the treatment of erectile dysfunction should generally not be used in men for whom sexual activity is inadvisable (e.g. patients with severe cardiovascular disorders such as unstable angina or severe cardiac failure [New York Heart Association III or IV]).

The safety of vardenafil has not been studied in the following sub-groups of patients and its use is therefore contraindicated until further information is available:

- severe hepatic impairment (Child-Pugh C),
- end stage renal disease requiring dialysis,
- hypotension (blood pressure <90/50 mmHg),
- recent history of stroke or myocardial infarction (within the last 6 months),
- unstable angina and known hereditary retinal degenerative disorders such as retinitis pigmentosa.

Concomitant use of vardenafil with the potent CYP3A4 inhibitors ketoconazole and itraconazole (oral form) is contraindicated in men older than 75 years.

Concomitant use of vardenafil with HIV protease inhibitors such as ritonavir and indinavir is contraindicated, as they are very potent inhibitors of CYP3A4 (see section 4.5).

4.4 Special warnings and precautions for use

A medical history and physical examination should be undertaken to diagnose erectile dysfunction and determine potential underlying causes, before pharmacological treatment is considered.

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 (see section 4.3). Vardenafil has vasodilator properties, resulting in mild and transient decreases in blood pressure (see section 5.1). Patients with left ventricular outflow obstruction, e.g., aortic stenosis and idiopathic hypertrophic subaortic stenosis, can be sensitive to the action of vasodilators including Type 5 phosphodiesterase inhibitors.

Agents for the treatment of erectile dysfunction should 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 have not been studied. Therefore the use of such combinations is not recommended.

The concomitant use of alpha-blockers and vardenafil may lead to symptomatic hypotension in some patients because both are vasodilators. Concomitant treatment with vardenafil should only be initiated if the patient has been stabilised on his alpha-blocker therapy. In those patients who are stable on alpha-blocker therapy, vardenafil should be initiated at the lowest recommended starting dose of 5 mg. Vardenafil may be administered at any time with tamsulosin. With other alpha blockers a time separation of dosing should be considered when vardenafil is prescribed concomitantly (see section 4.5). In those patients already taking an optimized 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 vardenafil.

Concomitant use of vardenafil with potent CYP 3A4 inhibitors such as itraconazole and ketoconazole (oral form) should be avoided as very high plasma concentrations of vardenafil are reached if the medicinal products are combined (see sections 4.5 and 4.3).

Vardenafil dose adjustment might be necessary if moderate CYP 3A4 inhibitors such as erythromycin and clarithromycin, are given concomitantly (see sections 4.5 and 4.2).

Concomitant intake of grapefruit juice is expected to increase the plasma concentrations of vardenafil. The combination should be avoided (see section 4.5).

Single oral doses of 10 mg and 80 mg of vardenafil have been shown to prolong the QTc interval by a mean of 8 msec and 10 msec, respectively. And single doses of 10 mg vardenafil co-administered concomitantly with 400 mg gatifloxacin, a drug with comparable QT effect, showed an additive QTc effect of 4 msec when compared to either drug alone. The clinical impact of these QT changes is unknown (see section 5.1).
The clinical relevance of this finding is unknown and cannot be generalised to all patients under all circumstances, as it will depend on the individual risk factors and susceptibilities that may be present at any time in any given patient. Medicinal products that may prolong QTc interval, including vardenafil, are best avoided in patients with relevant risk factors, for example, hypokalaemia; congenital QT prolongation; concomitant administration of antiarrhythmic medicinal products in Class 1[a] (e.g. quinidine, procainamide), or Class III (e.g. amiodarone, sotalol).

Visual defects and cases of non-arteritic ischemic optic neuropathy (NAION) have been reported in connection with the intake of Levitra and other PDE5 inhibitors. The patient should be advised that in the case of sudden visual defect, he should stop taking Levitra and consult immediately a physician (see section 4.3).

In vitro studies with human platelets indicate that vardenafil has no antiaggregatory effect on its own, but at high (super-therapeutic) concentrations vardenafil potentiates the antiaggregatory effect of the nitric oxide donor sodium nitroprusside. In humans, vardenafil had no effect on bleeding time alone or in combination with acetylsalicyclic acid (see section 4.5). There is no safety information available on the administration of vardenafil to patients with bleeding disorders or active peptic ulceration. Therefore vardenafil should be administered to these patients only after careful benefit-risk assessment.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on vardenafil

In vitro studies:

Vardenafil is metabolised predominantly by hepatic enzymes via cytochrome P450 (CYP) isoform 3A4, with some contribution from CYP3A5 and CYP2C isoforms. Therefore, inhibitors of these isoenzymes may reduce vardenafil clearance.

In vivo studies:

Co-administration of the HIV protease inhibitor indinavir (800 mg three times a day), a potent CYP3A4 inhibitor, with vardenafil (10 mg) resulted in a 16-fold increase in vardenafil AUC and a 7-fold increase in vardenafil C_{max}. At 24 hours, the plasma levels of vardenafil had fallen to approximately 4% of the maximum vardenafil plasma level (C_{max}).

Co-administration of vardenafil with ritonavir (600 mg twice daily) resulted in a 13-fold increase in vardenafil C_{max} and a 49-fold increase in vardenafil AUC_{0-24} when co-administered with vardenafil 5 mg. The interaction is a consequence of blocking hepatic metabolism of Levitra by ritonavir, a highly potent CYP3A4 inhibitor, which also inhibits CYP2C9. Ritonavir significantly prolonged the half-life of Levitra to 25.7 hours (see section 4.3).

Co-administration of ketoconazole (200 mg), a potent CYP3A4 inhibitor, with vardenafil (5 mg) resulted in a 10-fold increase in vardenafil AUC and a 4-fold increase in vardenafil C_{max} (see section 4.4).

Although specific interaction studies have not been conducted, the concomitant use of other potent CYP3A4 inhibitors (such as itraconazole) can be expected to produce vardenafil plasma levels comparable to those produced by ketoconazole. Concomitant use of vardenafil with potent CYP 3A4 inhibitors such as itraconazole and ketoconazole (oral use) should be avoided (see sections 4.3 and 4.4). In men older than 75 years the concomitant use of vardenafil with itraconazole or ketoconazole is contraindicated (see section 4.3).

Co-administration of erythromycin (500 mg three times a day), a CYP3A4 inhibitor, with vardenafil (5 mg) resulted in a 4-fold increase in vardenafil AUC and a 3-fold increase in C_{max}. Although a specific interaction study has not been conducted, the co-administration of clarithromycin can be expected to result in similar effects on vardenafil AUC and C_{max}. When used in combination with a moderate CYP 3A4 inhibitor such as erythromycin or clarithromycin, vardenafil dose adjustment might be necessary (see sections 4.2 and 4.4). Cimetidine (400 mg twice daily), a non-specific cytochrome P450 inhibitor, had no effect on vardenafil AUC and C_{max} when co-administered with vardenafil (20 mg) to healthy volunteers.

Grapefruit juice being a weak inhibitor of CYP3A4 gut wall metabolism, may give rise to modest increases in plasma levels of vardenafil (see section 4.4).

The pharmacokinetics of vardenafil (20 mg) was not affected by co-administration with the H2-antagonist ranitidine (150 mg twice daily), digoxin, warfarin, glibenclamide, alcohol (mean maximum blood alcohol level of 73 mg/dl) or single doses of antacid (magnesium hydroxide/aluminium hydroxide).

Although specific interaction studies were not conducted for all medicinal products, population pharmacokinetic analysis showed no effect on vardenafil pharmacokinetics of the following concomitant medicinal products: acetylsalicylic acid, ACE-inhibitors, beta-blockers, weak CYP 3A4 inhibitors, diuretics and medicinal products for the treatment of diabetes (sulfonylureas and metformin).

Effects of vardenafil on other medicinal products

There are no data on the interaction of vardenafil and non-specific phosphodiesterase inhibitors such as theophylline or dipyridamole.

In vivo studies:
No potentiation of the blood pressure lowering effect of sublingual nitroglycerin (0.4 mg) was observed when vardenafil (10 mg) was given at varying time intervals (1 h to 24 h) prior to the dose of nitroglycerin in a study in 18 healthy male subjects. Vardenafil 20 mg potentiated the blood pressure lowering effect of sublingual nitroglycerin (0.4mg) taken 1 and 4 hours after vardenafil administration to healthy middle aged subjects. No effect on blood pressure was observed when nitroglycerin was taken 24 hours after administration of a single dose of vardenafil 20 mg. However, there is no information on the possible potentiation of the hypotensive effects of nitrates by vardenafil in patients, and concomitant use is therefore contraindicated (see section 4.3).

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.

Since alpha-blocker monotherapy can cause marked lowering of blood pressure, especially postural hypotension and syncope, interaction studies were conducted with vardenafil. In two interaction studies with healthy normotensive volunteers after forced titration of the alpha-blockers tamsulosin or terazosin to high doses, hypotension (in some cases symptomatic) was reported in a significant number of subjects after co-administration of vardenafil. Among subjects treated with terazosin, hypotension was observed more frequently when vardenafil and terazosin were given simultaneously than when the dosing was separated by a time interval of 6 hours.

Based on the results of interaction studies conducted with vardenafil in patients with benign prostatic hyperplasia (BPH) on stable tamsulosin or terazosin therapy:

- When vardenafil was given at doses of 5, 10 or 20 mg on a background of stable therapy with tamsulosin, there was no symptomatic reduction in blood pressure, although 3/21 tamsulosin treated subjects exhibited transient standing systolic blood pressures of less than 85 mmHg.
- When vardenafil 5 mg was given simultaneously with terazosin 5 or 10 mg, one of 21 patients experienced symptomatic postural hypotension. Hypotension was not observed when vardenafil 5 mg and terazosin administration was separated by 6 hours.

Therefore, 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, vardenafil should be initiated at the lowest recommended starting dose of 5mg. Levitra may be administered at any time with tamsulosin. With other alpha blockers a time separation of dosing should be considered when vardenafil is prescribed concomitantly (see section 4.4).

No significant interactions were shown when warfarin (25 mg), which is metabolised by CYP2C9, or digoxin (0.375 mg) was co-administered with vardenafil (20 mg). The relative bioavailability of glibenclamide (3.5 mg) was not affected when co-administered with vardenafil (20 mg). In a specific study, where vardenafil (20 mg) was co-administered with slow release nifedipine (30 mg or 60 mg) in hypertensive patients, there was an additional reduction on supine systolic blood pressure of 6 mmHg and supine diastolic blood pressure of 5 mmHg accompanied with an increase in heart rate of 4 bpm.

When vardenafil (20 mg) and alcohol (mean maximum blood alcohol level of 73 mg/dl) were taken together, vardenafil did not potentiate the effects of alcohol on blood pressure and heart rate and the pharmacokinetics of vardenafil were not altered.

Vardenafil (10 mg) did not potentiate the increase in bleeding time caused by acetylsalicylic acid (2 x 81 mg).

4.6 Pregnancy and lactation

Levitra is not indicated for use by women. There are no studies of vardenafil in pregnant women.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

As dizziness and abnormal vision have been reported in clinical trials with vardenafil, patients should be aware of how they react to Levitra, before driving or operating machinery.

4.8 Undesirable effects

Over 9,500 patients have received Levitra in clinical trials. The adverse reactions were generally transient and mild to moderate in nature. The most commonly reported adverse drug reactions occurring in ≥ 10% of patients are headache and flushing.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The following adverse reactions have been reported:

System Organ Class	**Very Common (≥1/10)**	**Common (≥1/100 and <1/ 10)**	**Uncommon (≥1/1,000 and <1/100)***	**Rare (≥1/10,000 and <1/1,000)***	**Not Known (can not be estimated from available data)**
Immune System Disorders				Hypersensitivity	
Psychiatric Disorders				Anxiety	
Nervous System Disorders	Headache	Dizziness	Somnolence	Syncope Seizure Transient global amnesia	
Eye Disorders incl. Related Investigations			Lacrimation increased Visual Disturbance (incl. Visual brightness) Chromatopsia Conjunctivitis Blurred vision	Intraocular pressure increased	Non-arteritic-anterior ischemic optic neuropathy Visual defects
Ear and labyrinth Disorders					Sudden deafness**
Cardiac Disorders incl. related Investigations			Tachycardia Palpitations	Angina Pectoris Myocardial ischemia	Myocardial Infarction
Vascular Disorders incl. related Investigations	Flushing		Hypertension Hypotension Orthostatic Hypotension		
Respiratory, Thoracic and Mediastinal Disorders		Nasal Congestion	Dyspnoea Epistaxis	Laryngeal oedema	
Gastrointestinal Disorders incl. related Investigations		Dyspepsia Nausea	Abnormal liver function tests GGTP increased		

System Organ Class	Very Common (≥1/10)	Common (≥1/100 and <1/ 10)	Uncommon (≥1/1,000 and <1/100)*	Rare (≥1/10,000 and <1/1,000)*	Not Known (can not be estimated from available data)
Skin and Subcutaneous Tissue Disorders			Photosensitivity reaction Face oedema Rash		
Musculoskeletal and Connective Tissue Disorders incl. Related Investigations			Blood creatine phosphokinase increased Myalgia Back Pain	Muscle Rigidity	
Reproductive System and Breast Disorders				Priapism Erections increased (prolonged or painful erections)	

*For adverse reactions reported in <1% of patients, only those which warrant special attention, because of their possible association with serious disease states or of otherwise clinical relevance are listed.
**Sudden deafness or loss of hearing has been reported in a small number of postmarketing and clinical trial cases with the use of all PDE5 inhibitors, including vardenafil.

Post marketing reports of another medicinal product of this class: Vascular Disorders: Serious cardiovascular events, including cerebrovascular haemorrhage, sudden cardiac death, transient ischaemic attack, unstable angina and ventricular arrhythmia have been reported post marketing in temporal association with another medicinal product in this class.

4.9 Overdose

In single dose volunteer studies, doses up to and including 80 mg per day were tolerated without exhibiting serious adverse reactions.

When vardenafil was administered in higher doses and more frequently than the recommended dosing regimen (40 mg twice daily) cases of severe back pain have been reported. This was not associated with any muscle or neurological toxicity.

In cases of overdose, standard supportive measures should be adopted 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Medicinal product used in erectile dysfunction, ATC code: G04BE09

Vardenafil is an oral therapy for the improvement of erectile function in men with erectile dysfunction. In the natural setting, i.e. with sexual stimulation it restores impaired erectile function by increasing blood flow to the penis.

Penile erection is a haemodynamic process. During sexual stimulation, nitric oxide is released. It activates the enzyme guanylate cyclase, resulting in an increased level of cyclic guanosine monophosphate (cGMP) in the corpus cavernosum. This in turn results in smooth muscle relaxation,

allowing increased inflow of blood into the penis. The level of cGMP is regulated by the rate of synthesis via guanylate cyclase and by the rate of degradation via cGMP hydrolysing phosphodiesterases (PDEs).

Vardenafil is a potent and selective inhibitor of the cGMP specific phosphodiesterase type 5 (PDE5), the most prominent PDE in the human corpus cavernosum. Vardenafil potently enhances the effect of endogenous nitric oxide in the corpus cavernosum by inhibiting PDE5. When nitric oxide is released in response to sexual stimulation, inhibition of PDE5 by vardenafil results in increased corpus cavernosum levels of cGMP. Sexual stimulation is therefore required for vardenafil to produce its beneficial therapeutic effects.

In vitro studies have shown that 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 >1000-fold relative to PDE2, PDE3, PDE4, PDE7, PDE8, PDE9 and PDE10).

In a penile plesthysmography (RigiScan) study, vardenafil 20 mg produced erections considered sufficient for penetration (60% rigidity by RigiScan) in some men as early as 15 minutes after dosing. The overall response of these subjects to vardenafil became statistically significant, compared to placebo, 25 minutes after dosing.

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 under 20 mg and – 4.3 mmHg under 40 mg of vardeanfil, when compared to placebo. These effects are consistent with the vasodilatory effects of PDE5-inhibitors and are probably due to increased cGMP levels in vascular smooth muscle cells. Single and multiple oral doses of vardenafil up to 40 mg produced no clinically relevant changes in the ECGs of normal male volunteers.
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 Tmax 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/RR1/3) 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 postdose. At Tmax, 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 vardenafil or 50 mg sildenafil were co-administered concomitantly with 400 mg gatifloxacin, a drug with comparable QT effect. Both vardenafil and sildenafil showed an increase of Fredericia QTc effect of 4 msec (vardenafil) and 5 msec (sildenafil) when compared to either drug alone. The actual clinical impact of these QT changes is unknown.

Further information on clinical trials

In clinical trials vardenafil was administered to over 3750 men with erectile dysfunction (ED) aged 18 - 89 years, many of whom had multiple co-morbid conditions. Over 1630 patients have been treated with Levitra for six months or longer. Of these, over 730 have been treated for one year or longer. The following patient groups were represented: elderly (22%), patients with hypertension (35%), diabetes mellitus (29%), ischaemic heart disease and other cardiovascular diseases (7%), chronic pulmonary disease (5%), hyperlipidaemia (22%), depression (5%), radical prostatectomy (9%). The following groups were not well represented in clinical trials: elderly (>75 years, 2.4%), and patients with certain cardiovascular conditions (see section 4.3). No clinical trials in CNS diseases (except spinal cord injury), patients with severe renal or hepatic impairment, pelvic surgery (except nerve-sparing

prostatectomy) or trauma or radiotherapy and hypoactive sexual desire or penile anatomic deformities have been performed.

Across the pivotal trials, treatment with vardenafil resulted in an improvement of erectile function compared to placebo. In the small number of patients who attempted intercourse up to four to five hours after dosing the success rate for penetration and maintenance of erection was consistently greater than placebo.

In fixed dose studies in a broad population of men with erectile dysfunction, 68% (5 mg), 76% (10 mg) and 80% (20 mg) of patients experienced successful penetrations (SEP 2) compared to 49% on placebo over a three month study period. The ability to maintain the erection (SEP 3) in this broad ED population was given as 53% (5 mg), 63% (10 mg) and 65% (20 mg) compared to 29% on placebo.

In pooled data from the major efficacy trials, the proportion of patients experiencing successful penetration on vardenafil were as follows: psychogenic erectile dysfunction (77-87%), mixed erectile dysfunction (69-83%), organic erectile dysfunction (64-75%), elderly (52-75%), ischaemic heart disease (70-73%), hyperlipidemia (62-73%), chronic pulmonary disease (74-78%), depression (59-69%), and patients concomitantly treated with antihypertensives (62-73%).

In a clinical trial in patients with diabetes mellitus, vardenafil significantly improved the erectile function domain score, the ability to obtain and maintain an erection long enough for successful intercourse and penile rigidity compared to placebo at vardenafil doses of 10 mg and 20 mg. The response rates for the ability to obtain and maintain an erection was 61% and 49% on 10 mg and 64% and 54% on 20 mg vardenafil compared to 36% and 23% on placebo for patients who completed three months treatment.

In a clinical trial in post-prostatectomy patients, vardenafil significantly improved the erectile function domain score, the ability to obtain and maintain an erection long enough for successful intercourse and penile rigidity compared to placebo at vardenafil doses of 10 mg and 20 mg. The response rates for the ability to obtain and maintain an erection was 47% and 37% on 10 mg and 48% and 34% on 20 mg vardenafil compared to 22% and 10% on placebo for patients who completed three months treatment. In a flexible-dose clinical trial in patients with Spinal Cord Injury, vardenafil significantly improved the erectile function domain score, the ability to obtain and maintain an erection long enough for successful intercourse and penile rigidity compared to placebo. The number of patients who returned to a normal IIEF domain score ($\geq$26) were 53% on vardenafil compared to 9% on placebo. The response rates for the ability to obtain and maintain an erection were 76% and 59% on vardenafil compared to 41% and 22% on placebo for patients who completed three months treatment which were clinically and statistically significant ($p<0.001$).

The safety and efficacy of vardenafil was maintained in long term studies.

5.2 Pharmacokinetic properties

Absorption

Vardenafil is rapidly absorbed with maximum observed plasma concentrations reached in some men as early as 15 minutes after oral administration. However, 90% of the time, maximum plasma concentrations are reached within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state. The mean absolute oral bioavailability is 15 %. After oral dosing of vardenafil AUC and C_{max} increase almost dose proportionally over the recommended dose range (5 – 20 mg).

When vardenafil is taken with a high fat meal (containing 57% fat), the rate of absorption is reduced, with an increase in the median t_{max} of 1 hour and a mean reduction in C_{max} of 20%. Vardenafil AUC is not affected. After a meal containing 30% fat, the rate and extent of absorption of vardenafil (t_{max}, C_{max} and AUC) are unchanged compared to administration under fasting conditions.

Distribution

The mean steady state volume of distribution for vardenafil is 208 l, indicating distribution into the tissues. Vardenafil and its major circulating metabolite (M1) are highly bound to plasma proteins (approximately 95% for vardenafil or M1). For vardenafil as well as M1, protein binding is independent of total drug concentrations.

Based on measurements of vardenafil in semen of healthy subjects 90 minutes after dosing, not more than 0.00012% of the administered dose may appear in the semen of patients.

Metabolism

Vardenafil is metabolised predominantly by hepatic metabolism via cytochrome P450 (CYP) isoform 3A4 with some contribution from CYP3A5 and CYP2C isoforms.

In humans the one major circulating metabolite (M1) results from desethylation of vardenafil and is subject to further metabolism with a plasma elimination half life of approximately 4 hours. Parts of M1 are in the form of the glucuronide in systemic circulation. Metabolite M1 shows a phosphodiesterase selectivity profile similar to vardenafil and an *in vitro* potency for phosphodiesterase type 5 of approximately 28% compared to vardenafil, resulting in an efficacy contribution of about 7%.

Elimination

The total body clearance of vardenafil is 56 l/h with a resultant terminal half life of approximately 4-5 hours. After oral administration, vardenafil is excreted as metabolites predominantly in the faeces (approximately 91-95% of the administered dose) and to a lesser extent in the urine (approximately 2-6% of the administered dose).

Pharmacokinetics in special patient groups

Elderly
Hepatic clearance of vardenafil in healthy elderly volunteers (65 years and over) was reduced as compared to healthy younger volunteers (18 - 45 years). On average elderly males had a 52% higher AUC, and a 34% higher C_{max} than younger males (see section 4.2).

Renal insufficiency
In volunteers with mild to moderate renal impairment (creatinine clearance 30 – 80 ml/min), the pharmacokinetics of vardenafil were similar to that of a normal renal function control group. In volunteers with severe renal impairment (creatinine clearance < 30 ml/min) the mean AUC was increased by 21% and the mean Cmax decreased by 23%, compared to volunteers with no renal impairment. No statistically significant correlation was observed between creatinine clearance and vardenafil exposure (AUC and C_{max}) (see section 4.2). Vardenafil pharmacokinetics has not been studied in patients requiring dialysis (see section 4.3).

Hepatic insufficiency
In patients with mild to moderate hepatic impairment (Child-Pugh A and B), the clearance of vardenafil was reduced in proportion to the degree of hepatic impairment. In patients with mild hepatic impairment (Child-Pugh A), the mean AUC and C_{max} increased 17% and 22% respectively, compared to healthy control subjects. In patients with moderate impairment (Child-Pugh B), the mean AUC and C_{max} increased 160% and 133% respectively, compared to healthy control subjects (see section 4.2). The pharmacokinetics of vardenafil in patients with severely impaired hepatic function (Child-Pugh C) has not been studied (see section 4.3).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
crospovidone
magnesium stearate
microcrystalline cellulose
silica, colloidal anhydrous

Film coat:
macrogol 400
hypromellose
titanium dioxide (E171)
ferric oxide yellow (E172)
ferric oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PP/Aluminium foil blisters in cartons of 2, 4, 8 and 12 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Bayer AG,
D-51368 Leverkusen,
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/248/009-012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 6 March 2003

Date of last renewal : 6 March 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu.

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Bayer HealthCare AG
D-51368 Leverkusen
Germany

B CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription.

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCTS**

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON TEXT

1. NAME OF THE MEDICINAL PRODUCT

Levitra 5 mg film-coated tablets
vardenafil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg vardenafil (as hydrochloride trihydrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

2 film-coated tablets
4 film-coated tablets
8 film-coated tablets
12 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG,
D-51368 Leverkusen,
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/248/001 2 Tablets
EU/1/03/248/002 4 Tablets
EU/1/03/248/003 8 Tablets
EU/1/03/248/004 12 Tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Levitra 5 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

Levitra 5 mg film-coated tablets
vardenafil

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bayer AG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON TEXT

1. NAME OF THE MEDICINAL PRODUCT

Levitra 10 mg film-coated tablets
vardenafil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg vardenafil (as hydrochloride trihydrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

2 film-coated tablets
4 film-coated tablets
8 film-coated tablets
12 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG,
D-51368 Leverkusen,
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/248/005 2 Tablets
EU/1/03/248/006 4 Tablets
EU/1/03/248/007 8 Tablets
EU/1/03/248/008 12 Tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Levitra 10 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

Levitra 10 mg film-coated tablets
vardenafil

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bayer AG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON TEXT

1. NAME OF THE MEDICINAL PRODUCT

Levitra 20 mg film-coated tablets
vardenafil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 20 mg vardenafil (as hydrochloride trihydrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

2 film-coated tablets
4 film-coated tablets
8 film-coated tablets
12 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG,
D-51368 Leverkusen,
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/248/009 2 Tablets
EU/1/03/248/010 4 Tablets
EU/1/03/248/011 8 Tablets
EU/1/03/248/012 12 Tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Levitra 20 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

Levitra 20 mg film-coated tablets
vardenafil

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bayer AG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Levitra 5 mg film-coated tablets
Vardenafil

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT LEVITRA IS AND WHAT IT IS USED FOR

Levitra belongs to a group of medicines which are used to treat difficulties in getting or keeping an erection (erectile dysfunction).

About erection difficulties

At least one in ten men has trouble getting or keeping an erection at some time. There may be physical or psychological causes, or a mixture of both. Whatever the cause is, due to muscle and blood vessel changes not enough blood stays in the penis to make it hard and keep it hard.

How Levitra works

Levitra will only work when you are sexually stimulated. It reduces the action of the natural chemical in your body which makes erections go away. LEVITRA allows an erection to last long enough for you to satisfactorily complete sexual activity.

2. BEFORE YOU TAKE LEVITRA

Do not take Levitra
- If you are allergic (hypersensitive) to vardenafil or any of the other ingredients of Levitra. See the ingredients in section 6. Signs of an allergic reaction include a rash, itching, swollen face or lips and shortness of breath.
- If you are taking medicines containing nitrates, such as glycerol trinitrate for angina, or nitric oxide donors**,** such as amyl nitrite. Taking these medicines with Levitra could seriously affect your blood pressure.
- If you are taking ritonavir or indinavir, medicines for HIV.
- If you are over 75 years of age and are taking ketoconazole or itraconazole, anti-fungal medicines
- If you have a severe heart or liver problem
- If you are having kidney dialysis
- If you have recently had a stroke or heart attack
- If you have or have had low blood pressure
- If your family has a history of degenerative eye diseases (such as *retinitis pigmentosa*)

- If you have ever had a condition involving loss of vision due to damage to the optic nerve from insufficient blood supply known as non-arteritic ischemic optic neuropathy (NAION)

Take special care with Levitra
- If you have heart trouble. It may be risky for you to have sex
- If you suffer from irregular heart beat (cardiac arrythmia) or inherited heart diseases affecting your electrocardiogram
- If you have a physical condition affecting the shape of the penis. This includes conditions called *angulation, Peyronie's disease* and *cavernosal fibrosis*
- If you have an illness that can cause erections which won't go away *(priapism*). These include *sickle cell disease, multiple myeloma* and *leukaemia*
- If you have stomach ulcers (also called *gastric* or *peptic* ulcers)
- If you have a bleeding disorder (such as *haemophilia*)
- If you are using any other treatments for erection difficulties
- If you experience sudden decrease or loss of vision, stop taking Levitra and contact your doctor immediately.

Levitra is for men of 18 years and over
It is not intended for use by women, children or men under 18.

Using other medicines
Please tell your doctor or pharmacist if you are using or have recently used any other medicines, including medicines obtained without a prescription.
Levitra will usually be fine with most medicines. But some may cause problems, especially these:
- Nitrates, medicines for angina, or nitric oxide donors**,** such as amyl nitrite. Taking these medicines with Levitra could seriously affect your blood pressure. *Talk to a doctor without taking Levitra*
- Medicine for the treatment of arrythmias, such as quinidine, procainamide, amiodarone or sotalol
- Ritonavir or indinavir, medicines for HIV. *Talk to a doctor without taking Levitra*
- Ketoconazole or itraconazole, anti-fungal medicines
- Erythromycin, or clarithromycin, macrolide antibiotics
- Alpha-blockers, a type of medicine used to treat high blood pressure and enlargement of the prostate (as benign prostatic hyperplasia)
-

Taking Levitra with food and drink
- You can take Levitra with or without food – but preferably not after a heavy or high-fat meal as this may delay the effect.
- Don't drink grapefruit juice when you use Levitra. It can interfere with the usual effect of the medicine.
- Alcoholic drink can make erection difficulties worse.

Pregnancy and breast-feeding
Levitra is not for use by women.

Driving and using machines
Levitra might make some people feel dizzy or affect their vision. If you feel dizzy, or if your vision is affected after taking Levitra don't drive or operate any tools or machines.

3. HOW TO TAKE LEVITRA

Always take Levitra exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The usual dose is 10 mg.

Take a Levitra tablet about 25 to 60 minutes before sexual activity. With sexual stimulation you may achieve an erection anywhere from 25 minutes up to four to five hours after taking Levitra.
- Swallow one tablet with a glass of water

Don’t use Levitra more than once a day.

Tell the doctor if you think Levitra is too strong or too weak. He or she may suggest a different dose, depending on how well it works for you.

If you take more Levitra than you should
Men who take too much Levitra may experience more side effects or may get severe back pain. If you take more Levitra than you should, tell your doctor.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Levitra can cause side effects, although not everybody gets them. Most of the effects are mild or moderate. The chance of having a side effect is described by the following categories:

Very common *(affects more than 1 user in 10)*
- Headache
- Flushing

Common *(affects 1 to 10 users in 100)*
- Indigestion
- Feeling sick *(nausea)*
- Dizziness
- Blocked or runny nose

Uncommon *(affects 1 to 10 users in 1,000)*
- Sensitivity of the skin to sunlight
- High or low blood pressure
- Back or muscle pain
- Effects on vision
- Bloodshot or watery eyes
- Rash
- Sleepiness
- Effect in results of blood tests to check liver function
- Increase in blood of a muscle enzyme (creatine phosphokinase)
- Breathlessness
- Fast heart beat or pounding heart
- Nose bleeds
- Facial swelling

Rare *(affects 1 to 10 users in 10,000)*
- Fainting
- Muscle stiffness
- Increase pressure in the eye (glaucoma)
- Prolonged or painful erections
- Allergic reaction
- Effects on the heart (such as angina)
- Anxiety
- Swelling inside the throat
- Temporary loss of memory (such as transient global amnesia)
- Seizure

Partial, sudden, temporary or permanent decrease or loss of vision in one or both eyes has been experienced by patients.
Sudden decrease or loss of hearing has been reported.

If any of the side effects gets serious or if you notice any side effects not listed in this leaflet, please tell your doctor.

5. HOW TO STORE LEVITRA

Keep out of the reach and sight of children.

Do not use Levitra after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Levitra contains
- The active substance is vardenafil. Each tablet contains 5 mg of vardenafil (as hydrochloride trihydrate).
- The other ingredients of the tablets are:
  Tablet core: crospovidone, magnesium stearate, microcrystalline cellulose, colloidal anhydrous silica.
  Film coat: macrogol 400, hypromellose, titanium dioxide (E171), ferric oxide yellow (E172), ferric oxide red (E172).

What Levitra looks like and contents of the pack
Levitra 5 mg film-coated tablets are orange with the BAYER cross on one side and the strength (5) on the other side. The tablets are provided in blister packs containing 2, 4, 8 or 12 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: Bayer AG, D-51368 Leverkusen, Germany.

Manufacturer: Bayer HealthCare AG, D-51368 Leverkusen, Germany.

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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Portugal
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Slovenija
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Slovenská republika
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Sverige
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This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Levitra 10 mg film-coated tablets
Vardenafil

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- Erythromycin or clarithromycin, macrolide antibiotics
- Alpha-blockers, a type of medicine used to treat high blood pressure and enlargement of the prostate (as benign prostatic hyperplasia)

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Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: Bayer AG, D-51368 Leverkusen, Germany.

Manufacturer: Bayer HealthCare AG, D-51368 Leverkusen, Germany.

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Slovenská republika
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This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Levitra 20 mg film-coated tablets
Vardenafil

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2. BEFORE YOU TAKE LEVITRA

Do not take Levitra
- If you are allergic (hypersensitive) to vardenafil or any of the other ingredients of Levitra. See the ingredients in section 6. Signs of an allergic reaction include a rash, itching, swollen face or lips and shortness of breath.
- If you are taking medicines containing nitrates, such as glycerol trinitrate for angina, or nitric oxide donors**,** such as amyl nitrite. Taking these medicines with Levitra could seriously affect your blood pressure.
- If you are taking ritonavir or indinavir, medicines for HIV.
- If you are over 75 years of age and are taking ketaconazole or itraconazole, anti-fungal medicines
- If you have a severe heart or liver problem
- If you are having kidney dialysis
- If you have recently had a stroke or heart attack
- If you have or have had low blood pressure
- If your family has a history of degenerative eye diseases (such as *retinitis pigmentosa*)

- If you have ever had a condition involving loss of vision due to damage to the optic nerve from insufficient blood supply known as non-arteritic ischemic optic neuropathy (NAION)

Take special care with Levitra
- If you have heart trouble. It may be risky for you to have sex
- If you suffer from irregular heart beat (cardiac arrythmia) or inherited heart diseases affecting your electrocardiogram
- If you have a physical condition affecting the shape of the penis. This includes conditions called *angulation, Peyronie's disease* and *cavernosal fibrosis*
- If you have an illness that can cause erections which won't go away *(priapism*). These include *sickle cell disease, multiple myeloma* and *leukaemia*
- If you have stomach ulcers (also called *gastric* or *peptic* ulcers)
- If you have a bleeding disorder (such as *haemophilia*)
- If you are using any other treatments for erection difficulties
- If you experience sudden decrease or loss of vision, stop taking Levitra and contact your doctor immediately.

Levitra is for men of 18 years and over
It is not intended for use by women, children or men under 18.

Using other medicines
Please tell your doctor or pharmacist if you are using or have recently used any other medicines, including medicines obtained without a prescription
Levitra will usually be fine with most medicines. But some may cause problems, especially these:
- Nitrates, medicines for angina, or nitric oxide donors**,** such as amyl nitrite. Taking these medicines with Levitra could seriously affect your blood pressure. *Talk to a doctor without taking Levitra*
- Medicine for the treatment of arrythmias, such as quinidine, procainamide, amiodarone or sotalol
- Ritonavir or indinavir, medicines for HIV. *Talk to a doctor without taking Levitra*
- Ketoconazole or itraconazole, anti-fungal medicines
- Erythromycin or clarithromycin, macrolide antibiotics
- Alpha-blockers, a type of medicine used to treat high blood pressure and enlargement of the prostate (as benign prostatic hyperplasia)

Taking Levitra with food and drink

- You can take Levitra with or without food – but preferably not after a heavy or high-fat meal as this may delay the effect.
- Don't drink grapefruit juice when you use Levitra. It can interfere with the usual effect of the medicine.
- Alcoholic drink can make erection difficulties worse.

Pregnancy and breast-feeding

Levitra is not for use by women.

Driving and using machines

Levitra might make some people feel dizzy or affect their vision. If you feel dizzy, or if your vision is affected after taking Levitra don't drive or operate any tools or machines.

3. HOW TO TAKE LEVITRA

Always take Levitra exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The usual dose is 10 mg.

Take a Levitra tablet about 25 to 60 minutes before sexual activity. With sexual stimulation you may achieve an erection anywhere from 25 minutes up to four to five hours after taking Levitra.

- Swallow one tablet with a glass of water

Don't use Levitra more than once a day.

Tell the doctor if you think Levitra is too strong or too weak. He or she may suggest a different dose, depending on how well it works for you.

If you take more Levitra than you should
Men who take too much Levitra may experience more side effects or may get severe back pain. If you take more Levitra than you should, tell your doctor.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Levitra can cause side effects, although not everybody gets them. Most of the effects are mild or moderate. The chance of having a side effect is described by the following categories:

Very common *(affects more than 1 user in 10)*

- Headache
- Flushing

Common *(affects 1 to 10 users in 100)*

- Indigestion
- Feeling sick *(nausea)*
- Dizziness
- Blocked or runny nose

Uncommon *(affects 1 to 10 users in 1,000)*

- Sensitivity of the skin to sunlight
- High or low blood pressure
- Back or muscle pain
- Effects on vision
- Bloodshot or watery eyes
- Rash
- Sleepiness
- Effect in results of blood tests to check liver function
- Increase in blood of a muscle enzyme (creatine phosphokinase)
- Breathlessness
- Fast heart beat or pounding heart
- Nose bleeds
- Facial swelling

Rare *(affects 1 to 10 users in 10,000)*

- Fainting
- Muscle stiffness
- Increase pressure in the eye (glaucoma)
- Prolonged or painful erections
- Allergic reaction
- Effects on the heart (such as angina)
- Anxiety
- Swelling inside the throat
- Temporary loss of memory (such as transient global amnesia)
- Seizure

Partial, sudden, temporary or permanent decrease or loss of vision in one or both eyes has been experienced by patients.
Sudden decrease or loss of hearing has been reported.

If any of the side effects gets serious or if you notice any side effects not listed in this leaflet, please tell your doctor.

5. HOW TO STORE LEVITRA

Keep out of the reach and sight of children.

Do not use Levitra after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Levitra contains

- The active substance is vardenafil. Each tablet contains 20 mg of vardenafil (as hydrochloride trihydrate).
- The other ingredients of the tablets are:
  Tablet core: crospovidone, magnesium stearate, microcrystalline cellulose, colloidal anhydrous silica.
  Film coat: macrogol 400, hypromellose, titanium dioxide (E171), ferric oxide yellow (E172), ferric oxide red (E172).

What Levitra looks like and contents of the pack
Levitra 20 mg film-coated tablets are orange with the BAYER cross on one side and the strength (20) on the other side. The tablets are provided in blister packs containing 2, 4, 8 or 12 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: Bayer AG, D-51368 Leverkusen, Germany.

Manufacturer: Bayer HealthCare AG, D-51368 Leverkusen, Germany.

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu.