LEVITRA®

NAME OF THE MEDICINAL PRODUCT

Levitra 5 mg / 10 mg / 20 mg film-coated tablets
Levitra 10 mg orodispersible tablets (ODT)

QUALITATIVE AND QUANTITATIVE COMPOSITION

LEVITRA ® 5 mg film-coated tablet: each film-coated tablet contains 5 mg of Vardenafil (5.926 mg of Vardenafil monohydrochloride trihydrate)

LEVITRA ® 10 mg film-coated tablet: each film-coated tablet contains 10 mg of Vardenafil (11.852 mg of Vardenafil monohydrochloride trihydrate)

LEVITRA ® 20 mg film-coated tablet: each film-coated tablet contains 20 mg of Vardenafil (23.705 mg of Vardenafil monohydrochloride trihydrate)

LEVITRA ® 10 mg orodispersible tablet: each orodispersible tablet contains 10 mg of Vardenafil (11.852 mg of Vardenafil monohydrochloride trihydrate)

For full list of excipients, see **List of Excipients**.

PHARMACEUTICAL FORM

Levitra film-coated tablet: orange round, marked with BAYER-cross on one side and “5”, “10” or “20” on the other side.

Levitra 10 mg orodispersible tablet: white round biconvex without tablet marking.

CLINICAL PARTICULARS

Indications

Treatment of erectile dysfunction (inability to achieve or maintain penile erection sufficient for satisfactory sexual performance).
In order for vardenafil to be effective, sexual stimulation is required.

Dosage and method of administration

Method of administration

Levitra film-coated tablets:
Oral use
Levitra film-coated tablets can be taken with or without food.

Levitra orodispersible tablets:
Levitra 10 mg orodispersible tablet is not bioequivalent to Levitra 10mg film-coated tablet (see *Pharmacokinetic Properties*).

Oral use
Levitra 10 mg orodispersible tablet should be placed on the tongue, where it will rapidly disintegrate, and then swallowed.Levitra orodispersible tablets must be taken without liquid and immediately upon release from the blister.
Levitra 10mg orodispersible tablets can be taken under fed or fasted conditions..

Dosage regimen

Levitra film-coated tablets:
The recommended starting dose is one Levitra 10mg film-coated tablet taken as needed approximately 25 –60 minutes before sexual activity. Based on efficacy and tolerability, the dose may be increased to one Levitra 20mg film-coated tablet or decreased to one 5 mg Levitra film-coated tablet.
The maximum daily recommended dose for is one Levitra 20 mg film-coated tablet.
The maximum recommended dose frequency is once per day.

Levitra orodispersible tablets:
Levitra 10mg orodispersible tablets are taken as needed approximately 60 minutes before sexual activity.
The maximum daily recommended dose is one Levitra 10mg orodispersible tablet.
The maximum recommended dose frequency is once per day.

In clinical trials Levitra was shown to be efficacious when taken up to 4-5 hours before sexual activity.
Sexual stimulation is required for a natural response to treatment (see *Pharmacodynamics Properties*).

Additional information on special populations

Geriatric patients (above 65 years):
Hepatic clearance of healthy elderly volunteers was reduced. The AUC and Cmax in the elderly are higher by 52% and 34% as compared to young male volunteers (18-45 years). Therefore, a starting dose of 5mg should be considered in patients ≥ 65 years.

Pediatric patients
Levitra is not indicated for use in children.

Patients with hepatic impairment:
No dose adjustment is needed in patients with mild hepatic impairment Child-Pugh A. Levitra 10mg orodispersible tablets are not indicated as a starting dose in patients with mild hepatic impairment Child-Pugh A.
As vardenafil clearance is reduced in patients with moderate hepatic impairment Child-Pugh B, a starting dose of one Levitra 5 mg film-coated tablet is recommended, which may subsequently be increased to a maximum dose of one Levitra 10mg film-coated tablet, based on tolerability and efficacy. Patients with moderate or severe hepatic impairment Child Pugh B or Child Pugh C should not use Levitra 10 mg orodispersible tablets.

Patients with renal impairment:
No dose adjustment is needed in patients with mild CrCl > 50-80 mL/min and moderate CrCl > 30-50 mL/min renal impairment.
In patients with severe renal impairment CrCl < 30 mL/min, a starting dose of 5 mg should be considered. The pharmacokinetics of vardenafil has not been studied in patients requiring dialysis (see *Pharmacokinetic Properties*).

Use in women:
Levitra is not indicated for use in women.

Patients with concomitant use of alpha-blockers:
Consistent with vasodilatory effects of alpha-blockers and vardenafil, the concomitant use of Levitra with alpha-blockers may lead to symptomatic hypotension in some patients. Concomitant treatment should only be initiated if the patient is stable on his alpha-blocker therapy (see *Interactions with other medicinal products and other forms of interaction*). In those patients who are stable on alpha-blocker therapy, treatment should be initiated at the lowest recommended starting dose using Levitra film-coated tablets. Patients treated with alpha-blockers should not use Levitra 10 mg orodispersible tablets as a starting dose. Levitra may be administered at any time with alfuzosin or tamsulosin. With other alpha-blockers an appropriate time interval between dosing should be considered when Levitra is prescribed concomitantly (see *Interactions with other medicinal products and other forms of interaction*). 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 a phosphodiesterase(PDE5) inhibitor including vardenafil.

Patients with concomitant use of CYP3A4 inhibitors:
The dosage of Levitra film-coated tablets may require adjustment in patients receiving certain moderate or potent cytochrome P450 (CYP) 3A4 inhibitors e.g. ketoconazole, itraconazole, erythromycin and clarithromycin (see *Special warnings and precautions for use* and *Interactions with other medicinal products and other forms of interaction*).

A maximum dose of one Levitra 5mg film-coated tablet should not be exceeded when used in combination with the CYP3A4 inhibitors erythromycin or clarithromycin (see

Special warnings and precautions for use and Interactions with other medicinal products and other forms of interaction).

A maximum dose of one Levitra 5mg film-coated tablet should not be exceeded when used in combination with CYP3A4 inhibitors ketoconazole or itraconazole at a dose of 200 mg or below per day. Levitra should not be taken with dosages of ketoconazole or itraconazole higher than 200 mg daily.

Concomitant use with medicinal products containing cobicistat, HIV protease inhibitors such as indinavir and ritonavir, and combinations of these is contraindicated, as they are very potent inhibitors of CYP3A4 (see *Contraindications, Special warnings and precautions for use* and *Interactions with other medicinal products and other forms of interaction*).

The Levitra 10 mg ODT is contraindicated in patients receiving moderate or potent CYP3A4 inhibitors.

Contraindications
Contraindicated in patients with hypersensitivity to the active substance or to any of the excipients.

Consistent with the effects of PDE inhibition on the nitric oxide / cGMP – pathway, PDE5 inhibitors may potentiate the hypotensive effects of nitrates. Levitra is contraindicated in patients who are concomitantly treated with nitrates or nitric oxide donors (see *Interactions with other medicinal products and other forms of interaction*).

The safety of Levitra 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), endstage renal disease requiring dialysis, hypotension (resting systolic blood pressure of <90 mmHg), recent history of stroke or myocardial infarction (within last 6 months), unstable angina, and known hereditary degenerative retinal disorders such as retinitis pigmentosa.

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

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

Concomitant use of Levitra with medicinal products containing cobicistat, HIV Protease inhibitors such as indinavir or ritonavir, and combinations of these is contraindicated, as they are potent inhibitors of CYP 3A4 (see *Dosage and method of administration, Special warnings and precautions for use and Interactions with other medicinal products and other forms of interaction*).

Concomitant use of Levitra with Riociguat, a stimulator of soluble guanylate cyclase (sGC) is contraindicated. *(See section "Riociguat")*

Levitra 10mg orodispersible tablets are contraindicated in patients receiving moderate or

very potent CYP 3A4 inhibitors such as cobicistat, ketoconazole, itraconazole, ritonavir, indinavir, erythromycin and clarithromycin.

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 phosphodiesterase 5 (PDE5) inhibitor exposure (see Special Warnings and Precautions of Use).

Special warnings and precautions for use

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

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

In a study of the effect of Levitra on QT interval in 59 healthy male volunteers, therapeutic and supratherapeutic doses of Levitra,10 and 80 mg, respectively, produced increases in QTc interval (see *Pharmacodynamics Properties*). A post-marketing study evaluating the effect of combining vardenafil with another drug of comparable QT effect showed an additive QT effect when compared with either drug alone (see *Pharmacodynamics Properties*). These observations should be considered in clinical decisions when prescribing Levitra to patients with known history of QT prolongation or patients who are taking medications known to prolong the QT interval. Patients taking Class IA e.g. quinidine, procainamide or Class III e.g. amiodarone, sotalol antiarrhythmic medications or those with congenital QT prolongation, should avoid using Levitra.

Agents for the treatment of erectile dysfunction should generally be used with caution in patients with anatomical deformation of the penis such as angulation, cavernosal fibrosis or Peyronie's disease or in patients who have conditions which may predispose them to priapism such as sickle cell anaemia, multiple myeloma or leukaemia.

The safety and efficacy or combinations of Levitra orodispersible tablets with Levitra film-coated tablets or other treatments for erectile dysfunction have not been studied. Therefore the use of such combinations is not recommended. Tolerability of the maximum dose of Levitra 20mg film-coated tablets may be lower in elderly patients (> 65 years old) (see *Dosage and Method of Administration*).

Two cases of priapism were reported in Phase I clinical study with 40mg vardenafil (twice the maximum recommended dose). In the event of an erection that persists longer than 4 hours, the patients should be instructed to seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency could result.

The safety of Levitra 10 mg orodispersible tablets has not been studied in patients with moderate or severe hepatic impairment, Child Pugh B or Child Pugh C, therefore use of the Levitra 10 mg orodispersible tablets in these patients is not recommended.

Transient vision loss and cases of non-arteritic anterior ischemic optic neuropathy (NAION) have been reported in connection with the intake of PDE5 inhibitors, including Levitra.
An observational case-crossover study evaluated the risk of NAION when PDE5 inhibitor use, as a class, occurred immediately before NAION onset (within 5 half-lives), compared to PDE5 inhibitor use in a prior time period. The results suggest an approximate 2-fold increase in the risk of NAION, with a risk estimate of 2.15 (95% CI 1.06, 4.34). A similar study reported a consistent result, with a risk estimate of 2.27 (95%CI 0.99, 5.20).
Neither the rare postmarketing reports, nor the association of PDE5 inhibitor use and NAION in the observational studies, substantiate a causal relationship between PDE5 inhibitor use and NAION (see section 'Description of selected adverse reactions').
The patient should be advised that in the case of sudden vision loss, he should stop taking Levitra and immediately consult a physician (see *Undesirable effects*).

Vardenafil has not been studied in patients with spinal cord injury or other CNS disease, hypoactive sexual desire and in patients who have undergone pelvic surgery (except nerve-sparing prostatectomy), pelvic trauma or radiotherapy. Therefore, the use of vardenafil in these patients is not recommended.

Vardenafil should be used with caution in patients with uncontrolled hypertension, patients who have suffered life-threatening arrhythmias within the last 6 months and patients with history of cardiac failure or coronary artery disease causing unstable angina.

The concomitant use of Levitra ODT with alpha-blockers may lead to symptomatic hypotension in some patients (see *Undesirable effects*). Patients treated with alpha-blockers should not use Levitra 10 mg orodispersible tablets to initiate therapy. Concomitant treatment should only be initiated if the patient is stable on his alpha-blocker therapy (see *Interactions with other medicinal products and other forms of interaction*). In those patients who are stable on alpha-blocker therapy, treatment should be initiated at the lowest recommended starting dose using the Levitra film-coated tablet. Levitra may be administered at any time with tamsulosin or alfuzosin. With other alpha-blockers an appropriate time interval between dosing should be considered when Vardenafil is prescribed concomitantly (see *Interactions with other medicinal products and other forms of interaction*). In those patients already taking an optimized dose of Levitra, alpha-blocker therapy should be initiated at the lowest recommended dose. Stepwise increase in alpha-blocker dose may be associated with further lowering of blood pressure in patients taking a PDE5 inhibitor including vardenafil.

Concomitant use of the moderate or potent CYP 3A4 inhibitors cobicistat, ketoconazole, itraconazole, erythromycin, clarithromycin, indinavir, or ritonavir can be expected to produce markedly increased vardenafil plasma levels.

A maximum dose of one Levitra 5mg film-coated tablet should not be exceeded if used

in combination with erythromycin or clarithromycin.

A maximum dose of Levitra 5mg film-coated tablet should not be exceeded if used in combination with dosages of ketoconazole or itraconazole ≤ 200 mg. Levitra film-coated tablets must not be taken with dosages of ketoconazole or itraconazole > 200 mg (see *Dosage and method of administration and Interactions with other medicinal products and other forms of interaction*).

Concomitant use with medicinal products containing cobicistat, HIV Protease inhibitors such as indinavir or ritonavir, and combinations of these is contraindicated, as they are potent inhibitors of CYP3A4 (see '*Dosage and method of administration', Contraindications* and '*Interactions with other medicinal products and other forms of interaction'*).

Concomitant treatment should only be initiated if the patient is stable on his alpha-blocker therapy (see *Interaction with other medicinal products and other forms of interaction*). In those patients who are stable on alpha-blocker therapy, treatment should be initiated at the lowest recommended starting dose using the Levitra film-coated tablets.

Levitra may be administered at any time with alfuzosin or tamsulosin. With terazosin and other alpha-blockers an appropriate time interval between dosing should be considered when Levitra FCTs are prescribed concomitantly (see *Interaction with other medicinal products and other forms of interaction*).

In those patients already taking an optimized dose of Levitra FCT, alpha-blocker therapy should be initiated at the lowest starting dose. Stepwise increase in alpha-blocker dose may be associated with further lowering of blood pressure in patients taking a PDE5 inhibitor, including Levitra FCT.

Grapefruit juice being a weak inhibitor of CYP3A4 gut wall metabolism, may give rise to modest increases in plasma levels of vardenafil. The effects of the concomitant use of vardenafil and grapefruit juice have not been studied, and should be avoided.

Vardenafil has not been administered to patients with bleeding disorders or significant active peptic ulceration. Therefore vardenafil should be given to these patients only after careful benefit-risk assessment.

In humans, Levitra has no effect on bleeding time alone or with acetylsalicylic acid. *In vitro* studies with human platelets indicate that vardenafil alone did not inhibit platelet aggregation induced by a variety of platelet agonists. With supertherapeutic concentrations of vardenafil a small concentration dependent enhancement of the antiaggregatory effect of sodium nitroprusside, a nitric oxide donor, was observed.

The combination of heparin and vardenafil had no effect on bleeding time in rats, but this interaction has not been studied in humans.

Levitra 10 mg orodispersible tablets contain 1.8mg aspartame, a source of phenylalanine which may be harmful for people with phenylketonuria.
Levitra 10 mg orodispersible tablets contain 7.96mg sorbitol. Patients with rare hereditary problems of fructose intolerance should not take Levitra 10 mg orodispersible

tablets.

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

Interactions with other medicinal products and other forms of interaction

CYP inhibitors:
Vardenafil is metabolized predominantly by hepatic enzymes via CYP 3A4, with some contribution from CYP3A5 and CYP2C isoforms. Therefore, inhibitors of these enzymes may reduce Vardenafil clearance.

Cimetidine 400 mg b.i.d., a non-specific cytochrome P450 inhibitor, had no effect on Vardenafil AUC and Cmax when co-administered with Levitra 20mg film-coated tablets to healthy volunteers.

Erythromycin 500 mg t.i.d., a CYP3A4 inhibitor, caused a 4-fold 300% increase in Vardenafil AUC and a 3-fold 200 % increase in Cmax when co-administered with Levitra 5mg film-coated tablets to healthy volunteers.

Ketoconazole 200 mg, which is a potent CYP3A4 inhibitor, caused a 10-fold 900 % increase in Vardenafil AUC and a 4-fold 300 % increase in Cmax when co-administered with Levitra 5mg film-coated tablets to healthy volunteers.

Indinavir, 800 mg t.i.d., a HIV protease inhibitor, caused a 16-fold, 1500%, increase in vardenafil AUC and a 7-fold, 600%, increase in Cmax when co-administered with Levitra 10 mg film-coated tablets. Twenty-four hours after co-administration, the plasma levels of vardenafil were approximately 4% of the maximum vardenafil plasma level, Cmax.

Ritonavir, 600 mg b.i.d., a HIV protease inhibitor and a very potent CYP3A4 inhibitor, which also inhibits CYP2C9, caused a 49-fold increase in vardenafil AUC0-24 and in a 13-fold increase in Cmax when co-administered with Levitra 5 mg film-coated tablets. Ritonavir significantly prolonged the half-life of vardenafil to 25.7 hours.

Concomitant use of the moderate or potent CYP 3A4 inhibitors cobicistat, ketoconazole, itraconazole, erythromycin, clarithromycin, indinavir, or ritonavir can be expected to produce markedly increased vardenafil plasma levels. A maximum dose of one Levitra 5mg film-coated tablet should not be exceeded if used in combination with dosages of ketoconazole or itraconazole≤ 200 mg. Levitra film-coated tablets must not be taken with dosages of ketoconazole or itraconazole >200 mg (see *Dosage and method of administration* and *Interactions with other medicinal products and other forms of interaction*). A maximum dose of one Levitra 5 mg film-coated tablet should not be exceeded if used in combination with erythromycin or clarithromycin.

Concomitant use with medicinal products containing cobicistat, HIV protease inhibitors such as indinavir or ritonavir, and combinations of these is contraindicated, as they are

potent inhibitors of CYP3A4 (see *Dosage and method of administration, Contraindications and Special warnings and precautions for use*).

The use of Levitra orodispersible tablets in combination with cobicistat, erythromycin, ketoconazole, itraconazole, clarithromycin, indinavir or ritonavir is contraindicated.

Nitrates, Nitric Oxide Donors

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.

No potentiation of the blood pressure lowering effect of sublingual nitroglycerin (0.4 mg) was observed when Levitra 10 mg film-coated tablet was given at varying time intervals (24 h to down to 1 h) prior to the nitroglycerin dose in a study in 18 healthy male subjects.

The blood pressure lowering effect of sublingual nitrates (0.4 mg) taken 1 and 4 hours after vardenafil administration were potentiated by a 20 mg dose of Levitra film-coated tablets in healthy middle-aged subjects. These effects were not observed when vardenafil 20 mg was taken 24 hours before the nitroglycerin.

However, there is no information on the potential hypotensive effects of vardenafil when given in combination with nitrates in patients, and concomitant use is therefore contraindicated (see *Contraindications*).

Alpha-blockers
Since alpha-blocker monotherapy can cause marked lowering of blood pressure, especially postural hypotension and syncope, interaction studies were conducted with Levitra film-coated tablets in normotensive volunteers after short-term alpha-blockade and in patients with benign prostatic hyperplasia (BPH) on stable alpha-blocker therapy.

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

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

Among subjects treated with terazosin, hypotension standing systolic blood pressure <85 mm Hg was observed more frequently when vardenafil and terazosin were given to achieve Cmax simultaneously than when the doses were administered to separate Cmax by 6 hours. Because these studies were conducted using healthy volunteers after forced titration of the alpha-blocker to high doses, these studies may have limited clinical relevance.

Three interaction studies were conducted with Levitra film-coated tablets in patients with benign prostatic hyperplasia (BPH) on stable alpha-blocker therapy consisting of alfuzosin , tamsulosin or terazosin .Levitra film-coated tablet 5mg or 10 mg were administered four hours after alfuzosin dosing. The four-hour dosing interval was chosen to elicit the maximum potential interaction. No clinically relevant mean maximal additional reduction in blood pressure was observed over the 10-hour interval following dosing with vardenafil 4 hours after alfuzosin. Two patients one dose with Levitra 5 mg film-coated tablets and the other with Levitra 10 mg film-coated tablets , experienced decreases from baseline in standing systolic blood pressure >30 mm Hg. No instances of standing systolic blood pressure <85 mm Hg were observed during this study. Four patients, one dosed with placebo, two dosed with Levitra 5 mg film-coated tablets and one dosed with Levitra 10 mg film-coated tablets, reported dizziness. Based on these results no time interval between dosing with alfuzosin and Levitra is required.
In a subsequent study in patients with BPH, when Levitra film-coated tablets 10 mg and 20 mg were dosed simultaneously with 0.4 or 0.8 mg of tamsulosin no cases of standing systolic blood pressure <85 mm Hg were observed. Based on these results no time interval between dosing with tamsulosin and Levitra is required. When Levitra film-coated tablet 5 mg were dosed simultaneously with 5 or 10 mg of terazosin, 1 out of 21 patients experienced symptomatic postural hypotension. Hypotension was not observed when vardenafil was dosed 6 hours after terazosin administration. This should be considered when deciding about a time separation of dosing between Levitra and terazosin.

No cases of syncope in this study or in the earlier alfuzosin or terazosin studies.

Concomitant treatment should be initiated only if the patient is stable on his alpha-blocker therapy. In those patients who are stable on alpha-blocker therapy, Levitra should be initiated at the lowest recommended starting dose. Patients treated with alpha-blockers should not use Levitra 10 mg orodispersible tablets to initiate therapy. Levitra may be administered at any time with tamsulosin or alfuzosin. With terazosin and other alpha-blockers an appropriate time interval between dosing should be considered when Levitra is prescribed concomitantly (see *Special Warnings and Precautions for Use*).

In those patients already taking an optimized dose of Levitra film-coated tablets, alpha-blocker therapy should be initiated at the lowest dose. Stepwise increase in alpha-blocker dose may be associated with further lowering of blood pressure in patients taking a PDE5 inhibitor including vardenafil.

Riociguat

Animal models showed an additive systemic blood pressure lowering effect when sildenafil or vardenafil was combined with riociguat. Increasing the dose of sildenafil or vardenafil resulted in a greater than proportional decrease in systemic blood pressure in some cases.

In an explanatory study, single doses of riociguat administered to patients with pulmonary arterial hypertension (PAH) treated with sildenafil showed additive hemodynamic effects. A higher rate of discontinuation, predominantly due to

hypotension, was observed in PAH patients treated with a combination of sildenafil and riociguat compared to those treated with sildenafil alone.

Concomitant use of Levitra with Riociguat, a stimulator of sGC, is contraindicated *(See Contraindications*)

Others

Lack of pharmacokinetic interaction was shown when Levitra 20 mg film-coated tablets were co-administered to patients receiving 0.375 mg of digoxin, at steady state every other day for 14 days. There was no evidence that Vardenafil pharmacokinetics were altered by co-administration of Digoxin.

In vitro data suggest that effects of vardenafil on P-gp substrates more sensitive than digoxin cannot be excluded. Published literature shows that dabigatran is an example for a highly sensitive P-gp substrate.

Single doses of Maalox (antacid; magnesium hydroxide/aluminium hydroxide) did not affect the AUC or the Cmax of Vardenafil.

The bioavailability of Levitra 20mg film-coated tablets was not affected by co-administration of 150 mg b.i.d. of the H2-antagonist Ranitidine.

Levitra 10 mg and 20mg film-coated tablets did not influence the bleeding time when taken alone or in
combination with low dose Acetylsalicylic Acid (2x 81 mg tablets)

Levitra 20 mg film-coated tablets did not potentiate the hypotensive effects of Alcohol 0.5 g /kg bodyweight. The pharmacokinetics of Vardenafil was not altered.

Population pharmacokinetic investigations of phase III data revealed no significant effect of Acetylsalicylic Acid, ACE-inhibitors, beta-blockers, weak CYP 3A4-inhibitors, diuretics and medications for the treatment of diabetes sulfonylureas and metformin on the pharmacokinetics of Vardenafil.

Levitra film-coated tablets 20 mg, when co-administered with glibenclamide (Glyburide, 3.5 mg), did not affect the relative bioavailability of glibenclamide (no effect on AUC and Cmax of glibenclamide). There was no evidence that vardenafil pharmacokinetics were altered by co-administration of glibenclamide.

No pharmacokinetic and pharmacodynamic (prothrombin time and clotting factor II, VII and X) interaction was shown when warfarin (25 mg) was co-administered with 20 mg Levitra film-coated tablets. Vardenafil pharmacokinetics was not affected by co-administration of Warfarin.

No relevant pharmacokinetic interaction was shown when 20 mg Levitra film-coated tablets were co-administered with nifedipine (30 or 60 mg). The combined treatment of Levitra film-coated tablets and nifedipine did not lead to pharmacodynamic interaction

(as compared to placebo, Levitra film-coated tablets produced mean additional blood pressure reductions of 5.9 mm Hg and 5.2 mm Hg for supine systolic and diastolic blood pressure, respectively).

Food and dietary products: when Vardenafil is taken with a high fat meal (containing 57% fat), the rate of absorption is reduced with an increase in the median time of maximal plasma concentration of 60 minutes and a mean reduction in peak plasma concentration of 20 % . Vardenafil bioavailability was not affected. After a normal meal (containing 30 % fat) Vardenafil pharmacokinetic parameter were not affected at all. Based on these results Vardenafil can be taken with or without food.

Pregnancy and lactation Not applicable.

Undesirable effects

Placebo controlled clinical trials (ADRs):
When Levitra film-coated tablets or Levitra orodispersible tablets were taken as recommended, the following adverse drug reactions were reported in placebo controlled clinical trials:

Table: Adverse Drug Reactions reported by ≥ 1% of patients treated with Levitra film-coated tablets or Levitra 10mg orodispersible tablets and more frequent on drug than placebo in all
placebo controlled trials of 5 mg, 10 mg, and 20 mg vardenafil.

System Organ Class	Adverse drug reaction Medical Entity (ME)	Vardenafil (n = 9155)	Placebo (n = 5500)
Nervous System Disorders	HEADACHE	11.1%	2.7%
	DIZZINESS	1.4%	0.8%
Vascular Disorders	VASODILATATION	9.6%	1.1%
Respiratory, Thoracic and Mediastinal Disorders	NASAL CONGESTION	4.2%	0.7%
	SINUS CONGESTION	1.1%	0.6%
Gastrointestinal Disorders	DIARRHOEA	1.1%	1.0%
	DYSPEPSIA	2.5%	0.4%
	GASTROINTESTINAL AND ABDOMINAL PAINS	1.3%	0.4%
	NAUSEA	1.1%	0.5%
Musculoskeletal and Connective Tissue Disorders	BACK PAIN	1.3%	1.0%
	INCREASED MUSCLE TONE AND CRAMPING	1.1%	0.6%
	INCREASE IN CREATINE PHOSPHOKINASE (CPK)	1.2%	0.8%

Tabulated list of adverse reactions:

The frequencies of ADRs reported with Levitra are summarized in the table below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000).

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

System Organ Class	Very Common ≥ 10%	Common ≥ 1% to < 10%	Uncommon ≥ 0.1% to < 1%	Rare ≥ 0.01% to < 0.1%
Infection and Infestations				CONJUNCTIVITIS
Immune System Disorders			ALLERGIC EDEMA AND ANGIOEDEMA	HYPERSENSITIVITY
Psychiatric Disorders			SLEEP DISORDER	ANXIETY
Nervous System Disorders	HEADACHE	DIZZINESS*	PARAESTHESIA AND DYSESTHESIA SOMNOLENCE	SYNCOPE AMNESIA SEIZURE
Eye Disorders incl. related Investigations			VISUAL DISTURBANCE OCULAR HYPERAEMIA VISUAL COLOR DISTORTIONS EYE PAIN AND EYE DISCOMFORT PHOTOPHOBIA	INCREASE IN INTRAOCULAR PRESSURE LACRIMATION INCREASED
Ear and Labyrinth Disorders			TINNITUS VERTIGO	
Cardiac Disorders incl. related Investigations			PALPITATIONS TACHYCARDIA	ANGINA PECTORIS MYOCARDIAL INFARCTION VENTRICULAR TACHY-ARRHYTHMIAS
Vascular Disorders incl.		VASO-		HYPOTENSION

System Organ Class	Very Common ≥ 10%	Common ≥ 1% to < 10%	Uncommon ≥ 0.1% to < 1%	Rare ≥ 0.01% to < 0.1%
related Investigations		DILATION		HYPERTENSION
Respiratory, Thoracic and Mediastinal Disorders		NASAL CONGESTION	DYSPNOEA SINUS CONGESTION	EPISTAXIS
Gastrointestinal Disorders incl. related Investigations		DYSPEPSIA	NAUSEA GASTRO-INTESTINAL AND ABDOMINAL PAIN DRY MOUTH DIARRHOEA GASTRO-OESOPHAGEAL REFLUX DISEASE GASTRITIS VOMITING	
Hepatobiliary System Disorder			INCREASE IN TRANSAMINASES	INCREASE IN GAMMA-GLUTAMYL-TRANSFERASE
Skin and Subcutaneous Tissue Disorders			ERYTHEMA RASH	PHOTOSENSITIVITY REACTION

System Organ Class	Very Common ≥ 10%	Common ≥ 1% to < 10%	Uncommon ≥ 0.1% to < 1%	Rare ≥ 0.01% to < 0.1%
Musculoskeletal and Connective Tissue Disorders incl. related Investigations			**BACK PAIN** **INCREASE IN CREATINE PHOSPHOKINASE** **INCREASED MUSCLE TONE AND CRAMPING** **MYALGIA**	
Reproductive System and Breast Disorders			**INCREASE IN ERECTION**	**PRIAPISM**
General Disorders and Administration Site Conditions			**FEELING UNWELL**	**CHEST PAIN**

Description of selected adverse reactions

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

Non-arteritic anterior ischemic optic neuropathy, a cause of decreased vision including permanent loss of vision, has been reported rarely post-marketing in temporal association with the use of PDE5 inhibitors, including Levitra. Most, but not all, of these patients had underlying anatomic or vascular risk factors for development of NAION, including: low cup to disc ratio "crowded disc", > 50 years of age, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors.
Two observational case-crossover studies evaluated the risk of NAION after PDE5 inhibitor use, as a class. The results suggest an approximate 2-fold increase in the risk of NAION. However, a causal relationship between PDE5 inhibitor use and NAION has not been substantiated (see section 'Special warnings and precautions for use').

Visual disturbances including vision loss temporary or permanent have been reported rarely post-marketing in temporal association with the use of PDE5 inhibitors, including

Levitra. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient's underlying vascular risk factors or to other factors.

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

Overdose

In single dose volunteer studies, Vardenafil was tested in doses up to and including 120 mg per day. Single doses up to 80 mg vardenafil and multiple doses up to 40 mg vardenafil administered once daily over 4 weeks were tolerated without producing serious adverse side effects.

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

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

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

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

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

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

Vardenafil thus potentiates the natural response to sexual stimulation.

Trials on purified enzyme preparations have shown that vardenafil is a potent and highly selective inhibitor of PDE5, with an IC50 for human PDE5 of 0.7 nM.

The inhibitory effect of vardenafil is more potent on PDE5 than on other known phosphodiesterases , > 15-fold relative to PDE6, > 130-fold relative to PDE1, > 300-fold relative to PDE11, and > 1,000-fold relative to PDE2, 3, 4, 7, 8, 9, and 10. *In vitro*, vardenafil causes an elevation of cGMP in the isolated human corpus cavernosum resulting in muscle relaxation.

In the conscious rabbit, vardenafil causes a penile erection which is dependent upon endogenous nitric oxide synthesis and is potentiated by nitric oxide donors.

Mechanism of action:
In a placebo controlled study, using Rigiscan for measurements of rigidity, 20 mg of vardenafil produced erections sufficient for penetration ≥ 60% rigidity by Rigiscan in some men as early as 15 minutes. The overall response of these subjects to vardenafil became statistically significant compared to placebo at 25 minutes post dosing.

Pharmacokinetic Properties

Absorption:
Levitra film-coated tablets
Vardenafil is rapidly absorbed after oral administration. Cmax is reached as early as 15 minutes, in 90%of the time Cmax is reached within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state.
Due to a considerable first-pass effect, the mean absolute oral bioavailability is about 15 %.
After oral dosing of Vardenafil AUC and Cmax 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 Tmax of 60 minutes and a mean reduction in Cmax of 20 %. Vardenafil AUC was not affected. After a normal meal (containing 30 % fat) Vardenafil pharmacokinetic parameter (Cmax, Tmax , and AUC) were not affected at all.
Based on these results Vardenafil can be taken with or without food.

Levitra orodispersible tablets
Vardenafil is rapidly absorbed after administration of Levitra 10mg orodispersible tablets without water. The median time to reach Cmax varied between 45 to 90 minutes and was similar or slightly delayed by 8 to 45 mincompared to the film-coated tablets. Mean vardenafil AUC was increased by 21 to 29% middle aged and elderly ED patients or 44% young healthy subjects with 10mg orodispersible tablets compared to film-coated tablets as a result of local oral absorption of a small amount of drug in the oral cavity. There was no consistent difference in mean Cmax between orodispersible tablets and film-coated tablets.
In subjects taking Levitra 10mg orodispersible tablets with a high fat meal no effect on vardenafil AUC and tmax was observed, while vardenafil Cmax was reduced by 35% in the fed condition. Based on these results Levitra 10mg orodispersible tablets can be taken with or without food.

If Levitra 10mg orodispersible tablets are taken with water, the AUC is reduced by 29%, C max remains unchanged and median tmax is shortened by 60minutes compared to intake without water. Levitra 10mg orodispersible tablets must be taken without liquid.

Bioequivalence studies have shown that Levitra 10 mg orodispersible tablets are not bioequivalent to Levitra 10 mg film-coated tablets; therefore, the orodispersible formulation should not be used as an equivalent to tablets other vardenafil formulations.

Distribution:
The mean steady state volume of distribution (Vss) for Vardenafil is 208 L, indicating distribution into the tissues.
Vardenafil and its major circulating metabolite (M1) are highly bound to plasma proteinsabout 95 % for parent drug or M1. This protein binding is reversible and independent of total drug concentrations.
Based upon measurements of Vardenafil in semen of healthy subjects 90 minutes after dosing, not
more than 0.00012% of the administered dose may appear in the semen of patients.

Metabolism/ Biotransformation:

Vardenafil is metabolized predominantly by hepatic enzymes via CYP3A4, with some contribution from CYP3A5 and CYP2C9 isoforms.

The elimination half- life
of metabolite M1, the major circulating metabolite in humans is between 3 to 5 hours, similar to parent drug. M1 results from desethylation at the piperazine moiety of Vardenafil, and is subject to further metabolism.

M1 in the form of its glucuronic acid conjugate is found in systemic circulation. The plasma concentration of non-glucuronidated M1 is about 26% that of the parent compound. M1 shows a phosphodiesterase selectivity profile similar to that of Vardenafil and an in vitro PDE5 inhibitory of approximately 28% compared to Vardenafil, resulting in an efficacy contribution of about 7%.

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

Pharmacokinetics in special populations

Geriatric patients :

Vardenafil hepatic clearance in healthy elderly volunteers ≥ 65 years was reduced as compared to volunteers of younger age ≤ 45 years. On average, geriatric males taking vardenafil had a 52 % higher AUC than younger males which is within the variability observed in clinical trials.

Vardenafil AUC and Cmax in elderly patients ≥ 65 years taking Levitra 10 mg orodispersible tablets were increased by 31 to 39% and 16 to 21% respectively, in comparison to patients aged ≤45 years. Vardenafil was not found to accumulate in the plasma in patients aged ≤ 45 years or ≥65 years following once-daily dosing of the Levitra 10 mg orodispersible tablet over ten days.

No overall differences in safety or effectiveness were observed between elderly and younger subjects in placebo controlled clinical trials.

Patients with renal impairment:
In patients with mild CrCl > 50 - 80 mL/min to moderate CrCl > 30 - 50 mL/min renal impairment,
vardenafil pharmacokinetics were similar to that of a normal renal function control group. In volunteers with severe renal impairment CrCl < 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 between creatinine clearance and Vardenafil plasma exposureAUC and Cmax was observed.

The pharmacokinetics of vardenafil has not been studied in patients requiring dialysis.

Patients with hepatic impairment:
In patients with mild to moderate hepatic impairment Child-Pugh A and B, vardenafil clearance was reduced in proportion to the degree of hepatic impairment.
In patients with mild hepatic impairment Child-Pugh A, Vardenafil AUC and Cmax were increased 1.2-fold AUC by 17%, and Cmax by 22%, compared to healthy control subjects.
In patients with moderate hepatic impairment Child-Pugh B, Vardenafil AUC was increased by
160% and Cmax was increased by 130%, compared to healthy control subjects. The pharmacokinetics of Vardenafil has not been studied in patients with severe hepatic impairment Child- Pugh C.

Preclinical safety data
Preclinical data revealed no special hazard for humans based on conventional studies of safety
pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity, and toxicity to reproduction.

PHARMACEUTICAL PARTICULARS

List of excipients

Levitra film-coated tablets:
Tablet core: crospovidone, magnesium stearate, microcrystalline cellulose, colloidal silicon dioxide (silica colloidal anhydrous).

Film coat: polyethylene glycol (macrogol 400), hypromellose (hydoxypropylmethylcellulose), titanium dioxide (E171), ferric oxide yellow (E172), ferric oxide red (E172).

Levitra orodispersible tablets:
Aspartame, flavour peppermint, magnesium stearate, and Pharmaburst® B2 (crospovidone, mannitol, silica colloidal hydrated, and sorbitol). -

Instructions for use/handling

Store below 30°C

Storage condition
Refer to outer carton.

Presentation
Levitra film-coated tablets: 4 tablets
Levitra 10mg orodispersible tablets: 1x1s, 1x2s and 1x4s. Not all presentation may be available in the market.

Levitra 10 mg orodispersible tablets:
Store in the original package

Manufactured by:
Bayer AG
Kaiser-Wilhelm-Allee
51368 Leverkusen
Germany

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