

**SCHEDULING STATUS:**

S4

**PROPRIETARY NAMES AND DOSAGE FORMS:**

**LEVITRA 5**  
**LEVITRA 10**  
**LEVITRA 20**  
**LEVITRA ODT 10**

Tablets

**COMPOSITION:**

LEVITRA 5:	Each tablet contains vardenafil monohydrochloride trihydrate equivalent to 5 mg vardenafil.
LEVITRA 10:	Each tablet contains vardenafil monohydrochloride trihydrate equivalent to 10 mg vardenafil.
LEVITRA 20:	Each tablet contains vardenafil monohydrochloride trihydrate equivalent to 20 mg vardenafil.
LEVITRA ODT 10:	Each orodispersible tablet contains vardenafil monohydrochloride trihydrate equivalent to 10 mg vardenafil.

LEVITRA film-coated tablets contain the following inactive ingredients: crospovidone, magnesium stearate; microcrystalline cellulose, colloidal silicon dioxide (anhydrous), macrogol 400, hypromellose, titanium dioxide, ferric oxide yellow, ferric oxide red.

LEVITRA orodispersible tablet contains the following inactive ingredients: aspartame, flavour peppermint, magnesium stearate, crospovidone, mannitol, silica colloidal hydrated, sorbitol.

**PHARMACOLOGICAL CLASSIFICATION:**

A 7.1.5 Vasodilators – peripheral

**PHARMACOLOGICAL ACTION:****Pharmacodynamic properties:**

Vardenafil is a selective inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase type 5 (PDE5), the most abundant phosphodiesterase (PDE) isoenzyme in the human penile corpus cavernosum. PDE5 is responsible for the degradation of cGMP in the corpus cavernosum.

By inhibiting PDE5, the enzyme responsible for cGMP degradation in the corpus cavernosum, vardenafil enhances the effect of endogenous nitric oxide (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.

Because sexual stimulation is required to initiate the local release of nitric oxide, the inhibition of PDE5 has little effect in the absence of sexual stimulation. LEVITRA thus potentiates the natural response to sexual stimulation.

**Pharmacokinetic properties:***Absorption:*

- LEVITRA film-coated tablets:

LEVITRA is well absorbed after oral administration. In 90 % of the time,  $C_{max}$  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 LEVITRA, AUC and  $C_{max}$  increase almost dose-proportionally over the dose range 5 to 20 mg.

When LEVITRA is taken with a high fat meal, the rate of absorption is reduced with an increase in the median  $T_{max}$  of 60 minutes and a mean reduction in  $C_{max}$  of 20 %. The AUC of vardenafil was not affected. After a normal meal (containing 30 % fat), vardenafil's pharmacokinetic parameters ( $C_{max}$ ,  $T_{max}$ , and AUC) were not affected.

Based on these results LEVITRA can be taken with or without food.

- LEVITRA orodispersible tablets:

The median time to reach  $C_{max}$  in patients receiving LEVITRA 10 mg orodispersible tablets in the fasted state varied between 45 to 90 minutes. After administration of 10 mg LEVITRA orodispersible tablets to patients, mean vardenafil AUC was increased by 21 to 29 % while mean  $C_{max}$  was 8 to 19 % lower in comparison to 10 mg LEVITRA film coated tablets. A high fat meal had no effect on vardenafil AUC and  $T_{max}$  while it resulted in a mean reduction in vardenafil  $C_{max}$  by 35 %. Based on these results LEVITRA 10 mg orodispersible tablets can be taken before or after food. If LEVITRA orodispersible tablet is taken with water, the AUC is reduced by 29 % and median  $T_{max}$  is shortened by 60 minutes while  $C_{max}$  is not affected. LEVITRA orodispersible tablets should be taken without water.

Bioequivalence studies have shown that LEVITRA 10 mg orodispersible tablets is not bioequivalent to LEVITRA 10 mg film-coated tablets; therefore, the orodispersible formulation should not be used as an equivalent to LEVITRA 10 mg film-coated tablets.

*Distribution:*

The mean steady-state volume of distribution ( $V_{ss}$ ) for vardenafil is 208 l, indicating distribution into the tissues.

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

Based upon measurements of vardenafil in semen of healthy subjects 90 minutes after dosing, not more than 0,00012 % of the administered dose was present in the semen of patients.

*Metabolism:*

- LEVITRA film-coated tablets:

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

Mean elimination half-life ( $t_{1/2}$ ) is about 4 to 5 hours.

The major circulating metabolite (M1) results from desethylation at the piperazine moiety of vardenafil, and is subject to further metabolism. The plasma elimination half-life of the metabolite M1 is approximately 4 hours, comparable to the parent drug.

Parts of M1 are in the form of its glucuronide-conjugate (glucuronic acid) in systemic circulation.

The plasma concentration of non-glucuronidated M1 is about 26 % that of the parent compound. The metabolite M1 shows a phosphodiesterase selectivity profile similar to that of vardenafil and an *in vitro* inhibitory potency for PDE5 of approximately 28 %.

- LEVITRA orodispersible tablets:

The mean terminal half-life of vardenafil in patients receiving LEVITRA 10 mg orodispersible tablets varied between about 4 to 6 hours. The elimination half-life of the metabolite M1 is between 3 to 5 hours, similar to parent drug.

### *Elimination:*

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

### **Pharmacokinetics in special patient groups:**

#### *Geriatric patients (above 65 years):*

On average, geriatric males had a 52 % higher AUC than younger males which is within the variability observed in clinical trials.

Vardenafil AUC and  $C_{max}$  in geriatric patients taking LEVITRA ODT 10 were increased by 31 to 39 % and 16 to 21 %, respectively, in comparison to patients aged 45 years and below. Vardenafil was not found to accumulate in the plasma in patients aged 45 years and below or in 65 years or over following once-daily dosing of 10 mg orodispersible tablets over ten days.

#### *Patients with renal insufficiency:*

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

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

#### *Patients with hepatic insufficiency:*

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's AUC and  $C_{max}$  were increased 1,2-fold, compared to healthy control subjects. No dose adjustment is required in patients with mild hepatic impairment.

In patients with moderate hepatic impairment (Child-Pugh B), vardenafil's AUC was increased 2,6-fold and  $C_{max}$  was increased 2,3-fold, compared to healthy control subjects. Therefore, in patients with moderate hepatic impairment, a 5 mg starting dose should be considered, which may subsequently be increased to a maximum of 10 mg.

The pharmacokinetics of vardenafil has not been studied in patients with severe hepatic impairment (Child-Pugh C).

### **Preclinical safety data:**

LEVITRA's preclinical data revealed no genotoxicity, carcinogenicity, and toxicity to reproduction.

### **INDICATION:**

Treatment of erectile dysfunction.

### **CONTRA-INDICATIONS:**

Contra-indicated in patients with a known hypersensitivity to any of the components of the tablet.

LEVITRA is contra-indicated in patients who are concomitantly treated with nitrates or nitric oxide donors. Doctors should discuss with patients the contra-indications of LEVITRA.

- Women, newborns and children.
- End-stage renal disease requiring dialysis.
- Anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease).
- Conditions which may predispose to priapism (such as sickle cell anaemia, multiple myeloma or leukaemia).
- Hypotension (resting systolic blood pressure of < 90 mmHg).
- Uncontrolled hypertension (> 170/110 mmHg).
- Recent history of stroke, life-threatening arrhythmia or myocardial infarction (within last 6 months).
- Uncontrolled cardiac failure.
- Unstable angina.
- Known hereditary degenerative retinal disorders such as retinitis pigmentosa.
- Bleeding disorders.
- Active peptic ulceration.
- Severe impairment of liver function.
- Concomitant use of LEVITRA with the HIV protease inhibitors indinavir and ritonavir.

In addition to the above, the following applies to LEVITRA ODT 10:

- Moderate hepatic impairment (see "Special precautions").
- People with phenylketonuria.
- Patients with rare hereditary fructose intolerance.

#### **WARNINGS:**

**Prior to initiating any treatment for erectile dysfunction, doctors/physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity. LEVITRA should not be used in men for whom sexual activity is not recommended because of their underlying cardiovascular status.**

In a study of the effect of LEVITRA on QT interval in healthy males, LEVITRA produced increases in QTc interval.

A post-marketing study evaluating the effect of combining LEVITRA with another medicine of comparable QT effect showed an additive QT effect when compared with either medicine alone. These observations should be considered 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.

Transient vision loss and cases of non-arteritic ischaemic optic neuropathy have been reported in connection with the intake of LEVITRA. The patient should be advised that in the case of sudden vision loss, he should stop taking LEVITRA and consult immediately a physician (see "Side effects").

Consistent with vasodilatory effects of alpha-blockers and LEVITRA, 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"). In those patients who are stable on alpha-blocker therapy, LEVITRA should be initiated at the lowest recommended starting dose of 5 mg LEVITRA film-coated tablets. Patients treated with alpha-blockers should not use LEVITRA ODT 10 as a starting dose. LEVITRA may be administered at any time with tamsulosin. In those patients already taking an optimised dose of LEVITRA, 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 LEVITRA.

#### **INTERACTIONS:**

##### **CYP inhibitors:**

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

Cimetidine (400 mg b.i.d.), a non-specific cytochrome P450 inhibitor, had no effect on vardenafil AUC and  $C_{max}$  when co-administered with LEVITRA (20 mg) to healthy volunteers.

Erythromycin (500 mg t.i.d.), a CYP3A4 inhibitor, caused a 4-fold increase in vardenafil AUC and a 3-fold increase in  $C_{max}$  when co-administered with LEVITRA (5 mg) to healthy volunteers.

Ketoconazole (200 mg), which is a potent CYP3A4 inhibitor, caused a 10-fold increase in vardenafil (the active ingredient in LEVITRA) AUC and a 4-fold increase in  $C_{max}$  when co-administered with LEVITRA (5 mg) to healthy volunteers.

Co-administration of LEVITRA (10 mg) with the HIV protease inhibitor indinavir (800 mg t.i.d.) resulted in a 16-fold increase in vardenafil (the active ingredient in LEVITRA) AUC and a 7-fold increase in vardenafil  $C_{max}$ . At 24 hours after co-administration, the plasma levels of vardenafil were approximately 4 % of the maximum vardenafil plasma level ( $C_{max}$ ).

Ritonavir (600 mg b.i.d) resulted in a 13-fold increase in vardenafil  $C_{max}$  and a 49-fold increase in vardenafil AUC<sub>0-24</sub> 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. Concomitant use of potent CYP3A4 inhibitors such as ketoconazole, itraconazole, indinavir or ritonavir can be expected to produce markedly increased vardenafil plasma levels.

A maximum dose of 5 mg should not be exceeded if used in combination with erythromycin or clarithromycin (see "Warnings").

A maximum dose of 5 mg vardenafil should not be exceeded if used in combination with ketoconazole and itraconazole.

LEVITRA must not be taken with dosages of ketoconazole and itraconazole higher than 200 mg (see "Warnings").

Concomitant use with the HIV protease inhibitors indinavir or ritonavir, which are highly potent inhibitors of CYP3A4, is contra-indicated (see "Contra-indications" and "Warnings").

#### **Nitrates, nitric oxide donors:**

The blood pressure lowering effect of sublingual nitroglycerin (0,4 mg) taken 1 and 4 hours after LEVITRA administration were potentiated by LEVITRA in healthy middle aged subjects. Concomitant use of LEVITRA with nitrates is contra-indicated.

#### **Others:**

LEVITRA (20 mg), when co-administered with glibenclamide (glyburide, 3,5 mg), did not affect the relative bioavailability of glibenclamide (no effect on AUC and  $C_{max}$  of glibenclamide). There was no evidence that vardenafil (the active ingredient in LEVITRA) 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 LEVITRA (20 mg). Vardenafil pharmacokinetics was not affected by co-administration of Warfarin.

No relevant pharmacokinetic interaction was shown when LEVITRA (20 mg), was co-administered with nifedipine (30 or 60 mg). The combined treatment of LEVITRA and nifedipine did not lead to pharmacodynamic interaction (as compared to placebo, LEVITRA produced mean additional blood pressure reductions of 5,9 mmHg and 5,2 mmHg for supine systolic and diastolic blood pressure, respectively).

#### **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 two interaction studies with healthy normotensive volunteers after forced titration of the alpha-blockers tamsulosin or terazosin to high doses over 14 days or fewer, hypotension (in some cases symptomatic) was reported in a significant number of subjects after co-administration of LEVITRA.

**Concomitant treatment should be initiated only if the patient is stable on his alpha-blocker therapy. In those patients who are stable on alpha-blocker therapy, LEVITRA should be initiated at the lowest recommended starting dose of 5 mg LEVITRA. Patients treated with alpha-blockers should not use LEVITRA ODT 10 as starting dose. LEVITRA may be administered at any time with tamsulosin. With other alpha-blockers a time separation of dosing should be considered when LEVITRA is prescribed concomitantly (see “Warnings”).**

Lack of pharmacokinetic interaction was shown when digoxin (0,375 mg) in steady-state was co-administered with LEVITRA (20 mg) over 14 days every other day. There was no evidence that vardenafil (the active ingredient in LEVITRA) pharmacokinetics were altered by co-administration of digoxin.

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

Bioavailability of LEVITRA (20 mg) was not affected by co-administration of the H<sub>2</sub>-antagonists ranitidine (150 mg b.i.d.) and cimetidine (400 mg b.i.d.).

LEVITRA (10 mg and 20 mg) did not influence the bleeding time when taken alone or in combination with low dose acetylsalicylic acid (2 x 81 mg tablets).

LEVITRA (20 mg) did not potentiate the hypotensive effects of alcohol (0,5 g/kg body weight). 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 CYP3A4-inhibitors, diuretics and medications for the treatment of diabetes (sulfonylureas and metformin) on the pharmacokinetics of vardenafil.

## **DOSAGE AND DIRECTIONS FOR USE:**

LEVITRA film-coated tablets are for oral use and can be taken with or without food.

LEVITRA ODT 10 is an orodispersible tablet that is placed on the tongue and dissolves in the mouth in the presence of saliva. It should be taken by itself without food or liquid in the mouth. It should be taken immediately upon release from the blister. LEVITRA ODT 10 can be taken with or without food.

### **Recommended adult dose:**

The recommended starting dose is 10 mg LEVITRA taken as needed (approximately one hour) before sexual activity.

However, the medicine may be taken anywhere from 25 minutes to at least up to 4 to 5 hours before sexual activity.

The maximum recommended dose frequency is once per day. LEVITRA can be taken with or without food.

Sexual stimulation is required for a natural response to treatment.

### **Dose range:**

The recommended daily dose of LEVITRA is 5 to 20 mg.

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 once daily.

### *Special populations:*

- Geriatrics (above 65 years):

Dosage adjustments are not required in elderly patients.

- Children:

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). Vardenafil (the active ingredient in LEVITRA) clearance is reduced in patients with moderate hepatic impairment (Child-Pugh B), supporting a starting dose of 5 mg LEVITRA film-coated tablets, which may subsequently be increased to 10 mg LEVITRA film-coated tablets. Patients with moderate hepatic impairment (Child-Pugh B) should not use LEVITRA ODT 10.

The pharmacokinetics of vardenafil has not been studied in patients with severe hepatic impairment (Child-Pugh C) (see "Pharmacokinetic properties").

- Patients with renal impairment:

No dose adjustment is needed in patients with mild ( $CL_{cr} > 50$  to 80 ml/min), moderate ( $CL_{cr} > 30$  to 50 ml/min), or severe ( $CL_{cr} < 30$  ml/min) renal impairment.

The pharmacokinetics of vardenafil (the active ingredient in LEVITRA) has not been studied in patients requiring dialysis.

## **SIDE EFFECTS AND SPECIAL PRECAUTIONS:**

### **Side 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 reaction reported by  $\geq 1$  % of the patients treated with LEVITRA film-coated tablets or LEVITRA 10 mg orodispersible tablets and more frequent on drug than placebo in placebo controlled trials on 5 mg , 10 mg and 20 mg vardenafil.

<b>System organ class</b>	<b>Adverse drug reaction: Medical entity (ME)</b>	<b>Vardenafil (n = 9155)</b>	<b>Placebo (n = 5500)</b>
Nervous system disorders	Headache	11,1 %	2,7 %
	Dizziness	1,4 %	0,8 %
Vascular disorders	Vasodilation	9,6 %	1,1 %
Respiratory, thoracic and mediastinal disorders	Nasal congestion	4,2 %	0,7 %
	Sinus congestion	1,1 %	0,6 %
Gastrointestinal disorders	Dyspepsia	2,5 %	0,4 %
	Diarrhoea	1,1 %	1,0 %
	Gastrointestinal and abdominal pains	1,3 %	0,4 %
	Nausea	1,1 %	0,8 %
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 %

*All clinical trials (ADRs):*

The following adverse drug reactions were reported in patients given LEVITRA film-coated tablets or LEVITRA orodispersible tablets in all clinical trials.

Table: Adverse drug reaction reported in patients in all clinical trials world-wide which are either reported as drug-related in  $\geq 0,1$  % of the patients or rare and considered serious in their nature.

System organ class	Very Common $\geq 10$ %	Common $\geq 1$ % to $< 10$ %	Uncommon $\geq 0,1$ % to $< 1$ %	Rare $\geq 0,01$ % to $< 0,1$ %
Infection and infestations				Conjunctivitis
Immune system disorders			Allergic oedema and angioedema	Allergic reaction
Psychiatric disorders			Sleep disorder	
Nervous system disorders	Headache	Dizziness	Paraesthesia and dysesthesia Somnolence	Syncope Amnesia Seizure
Eye disorders including related investigations			Visual disturbance Ocular hyperaemia Visual color distortions Eye pain and eye discomfort Photophobia	Increase in intraocular pressure
Ear and labyrinth disorders			Tinnitus Vertigo	
Cardiac disorders including related investigations			Palpitation Tachycardia	Angina pectoris Myocardial infarction Ventricular tachyarrhythmias
Vascular disorders including related investigations		Vasodilatation		Hypotension
Respiratory, thoracic and mediastinal disorders		Nasal congestion	Dyspnoea Sinus congestion	
Gastrointestinal disorders including related investigations		Dyspepsia	Nausea Gastrointestinal and abdominal pain Dry mouth Diarrhoea Gastrooesophageal reflux disease Gastritis Vomiting	
Hepatobiliary system disorder			Increase in transaminases	
Skin and subcutaneous tissue disorders			Erythema Rash	
Musculoskeletal and connective tissue disorders including 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

*Post-marketing:*

**Myocardial infarction (MI)** has been reported in temporal association with the use of LEVITRA 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 (NAION)**, a cause of decreased vision including permanent loss of vision, has been reported rarely post-marketing in temporal association with the use of phosphodiesterase type 5 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"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors.

**Visual disturbances including vision loss** (temporary or permanent) have been reported rarely post-marketing in temporal association with the use of phosphodiesterase type 5 inhibitors, including LEVITRA. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, such as LEVITRA, 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.

#### **Special precautions:**

##### *General:*

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

**The safety of LEVITRA ODT 10 has not been studied in patients with moderate hepatic impairment, therefore use of LEVITRA ODT 10 in these patients is not recommended (see "Contra-indications").**

Concomitant use of the potent cytochrome P450 (CYP) 3A4 inhibitors; e.g. ketoconazole, itraconazole, indinavir and ritonavir can be expected to produce markedly increased plasma levels of vardenafil, the active ingredient in LEVITRA (see "Interactions").

A maximum dose of 5 mg LEVITRA film-coated tablets should not be exceeded when used in combination with erythromycin or clarithromycin.

A maximum dose of 5 mg LEVITRA film-coated tablets should not be exceeded if used in combination with ketoconazole and itraconazole. LEVITRA must not be taken with dosages of ketoconazole and itraconazole higher than 200 mg (see "Interactions").

Concomitant use with indinavir or ritonavir, which are highly potent inhibitors of CYP3A4, is contra-indicated (see "Contra-indications" and "Interactions").

LEVITRA has not been administered to patients with bleeding disorders or active peptic ulceration. Therefore LEVITRA should not be given to these patients (see "Contra-indications").

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

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

**Aspartame:** LEVITRA ODT 10 contains aspartame, a source of phenylalanine which may be harmful to people with phenylketonuria (see "Contra-indications").

**Sorbitol:** LEVITRA ODT 10 contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take LEVITRA ODT 10 (see "Contra-indications").

#### **Effects on ability to drive and use machines:**

As dizziness and abnormal vision or eye disorder were reported in clinical trials with LEVITRA, patients should exercise caution when driving, operating hazardous machinery or performing hazardous tasks.

## **KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:**

In single dose volunteer studies, LEVITRA was tested in doses up to and including 80 mg per day. When 40 mg was administered twice daily, cases of severe back pain were observed. In cases of overdose, standard supportive measures should be taken as required. Renal dialysis is not expected to accelerate clearance as vardenafil (the active ingredient in LEVITRA) is highly bound to plasma proteins and not significantly eliminated in the urine.

## **IDENTIFICATION:**

LEVITRA 5: Orange (light-orange to grey-orange) film-coated round tablet. One side is embossed "BAYER" and the other "5".  
LEVITRA 10: Orange (light-orange to grey-orange) film-coated round tablet. One side is embossed "BAYER" and the other "10".  
LEVITRA 20: Orange (light-orange to grey-orange) film-coated round tablet. One side is embossed "BAYER" and the other "20".  
LEVITRA ODT 10: White uncoated tablet, round, biconvex without tablet markings.

## **PRESENTATIONS:**

LEVITRA tablets: Polypropylene (clear/opaque)/alu or alu/alu blister packs of 2 or 4 or 12 tablets.  
LEVITRA ODT 10: Alu/alu blister packs of 1 or 2 or 4 orodispersible tablets.

## **STORAGE INSTRUCTIONS:**

LEVITRA tablets: Store at or below 25 °C in a dry place. Store in the manufacturer's original container.  
KEEP OUT OF REACH OF CHILDREN.

LEVITRA ODT 10: Store at or below 30 °C in a dry place. Store in the manufacturer's original container.  
KEEP OUT OF REACH OF CHILDREN..

## **REGISTRATION NUMBERS:**

LEVITRA 5: 36/7.1.5/0515  
LEVITRA 10: 36/7.1.5/0516  
LEVITRA 20: 36/7.1.5/0517  
LEVITRA ODT 10: 44/7.1.5/1049

## **NAME AND BUSINESS ADDRESS OF THE HOLDER OF CERTIFICATE OF REGISTRATION:**

Bayer (Pty) Ltd  
Reg. No.: 1968/011192/07  
27 Wrench Road  
ISANDO  
1609

## **DATE OF PUBLICATION OF THIS PACKAGE INSERT:**

26 October 2012