PRODUCT INFORMATION
LEVITRA® 10 mg orodispersible tablets (vardenafil)

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

The empirical formula of vardenafil hydrochloride trihydrate is C\textsubscript{23}H\textsubscript{32}N\textsubscript{6}O\textsubscript{4}S.HCl.3H\textsubscript{2}O and its molecular weight is 579.1 g/mol. Its chemical structure is shown in Figure 1. (CAS number: 224785-90-4)

Figure 1.

DESCRIPTION
Levitra orodispersible tablet is a white round tablet without tablet markings. Each tablet contains 10 mg of vardenafil (as 11.852 mg of vardenafil hydrochloride trihydrate).

Levitra orodispersible tablets contain the following excipients: aspartame, peppermint flavour 290017, magnesium stearate, crospovidone, mannitol, silicon dioxide and sorbitol.

PHARMACOLOGY
The pharmacodynamic studies described below were conducted using vardenafil film-coated tablets.

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

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

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

In vitro assays have shown that vardenafil is a selective inhibitor of PDE5, with an IC$_{50}$ of 0.7 nM for human platelet PDE5.

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

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

**Effects on Visual Perception**

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

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

**Effects on Blood Pressure**

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

**Effects on Cardiac Parameters**

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

**Effects on Exercise Performance in Patients with Coronary Artery Disease**

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

**Pharmacokinetics**

**Absorption**

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

Bioavailability studies have shown that Levitra 10 mg orodispersible tablet is not bioequivalent to Levitra 10 mg film-coated tablet. The bioavailability (AUC) from the 10 mg orodispersible tablet is 21 to 29% higher in patients and 44% higher in healthy subjects than from the Levitra 10 mg film-coated tablet. Therefore, Levitra 10 mg orodispersible tablets should not be used as an equivalent to Levitra 10 mg film-coated tablets.

**Distribution**

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

Vardenafil and its major circulating metabolite (M1) are highly bound to plasma proteins (about 95% for parent drug or M1). This protein binding is reversible and independent of total drug concentrations.
Based upon measurements of vardenafil in semen of healthy subjects 90 minutes after dosing, not more than 0.0002% of the administered dose may appear in the semen of patients.

**Metabolism**

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

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

The mean terminal half life of vardenafil in patients receiving Levitra orodispersible tablets varied between about 4 – 6 hours. The elimination half life of the metabolite M1 is approximately 3 hours.

**Excretion**

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

**Pharmacokinetics in special populations**

**Elderly**

Vardenafil AUC and C<sub>max</sub> in elderly patients (65 years or over) taking Levitra orodispersible tablets 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 65 years or over following once-daily dosing of Levitra 10 mg orodispersible tablet over ten days.

**Renal insufficiency**

In patients with mild (CL<sub>cr</sub> > 50 – 80 mL/min) to moderate (CL<sub>cr</sub> > 30 – 50 mL/min) renal impairment vardenafil pharmacokinetics were similar to that of a normal renal function control group following a vardenafil 20 mg film-coated tablet dose. In volunteers with severe renal impairment (CL<sub>cr</sub> < 30 mL/min) the mean AUC was increased by 21% and the mean C<sub>max</sub> decreased by 23%, compared to volunteers with no renal impairment. No statistically significant correlation between creatinine clearance and vardenafil plasma exposure (AUC and C<sub>max</sub>) was observed. Based on this data, no dose adjustment is needed in patients with impaired renal function.

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

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

In patients with mild hepatic impairment (Child-Pugh A), vardenafil AUC and $C_{\text{max}}$ were increased 1.2-fold (AUC by 17% and $C_{\text{max}}$ by 22%) following a vardenafil 10 mg film-coated tablet dose, compared to healthy control subjects. The pharmacokinetics of vardenafil ODT have not been studied in subjects with mild hepatic impairment (Child-Pugh A). An estimated ceiling of 1.7-fold and 1.4-fold increase in AUC and $C_{\text{max}}$ respectively can be expected following a vardenafil 10 mg orodispersible tablet dose in subjects with mild hepatic impairment, compared to vardenafil 10 mg film-coated tablet dose in healthy control subject.

In patients with moderate hepatic impairment (Child-Pugh B), vardenafil AUC was increased 2.6-fold (an increase of 160%) and $C_{\text{max}}$ was increased 2.3-fold (an increase of 130%), compared to healthy control subjects. Treatment in patients with mild hepatic impairment should not be initiated with Levitra 10 mg orodispersible tablets. In these patients, vardenafil 5 mg film-coated tablet should be used as a starting dose, which may subsequently be increased to vardenafil 10 mg and 20 mg film-coated tablet or Levitra 10 mg orodispersible tablets based on tolerability and efficacy.

Levitra orodispersible tablet 10 mg should not be used in patients with moderate hepatic impairment. The pharmacokinetics of vardenafil have not been studied in patients with severe hepatic impairment (Child-Pugh C). Levitra should not be used in this population (see CONTRAINDICATIONS).

CLINICAL TRIALS

Efficacy and safety of Levitra orodispersible tablets was separately demonstrated in a broad population in two studies totalling 701 patients (placebo 343; Levitra orodispersible tablets 358) who were randomised to receive treatment for 12 weeks. Patient subgroups analysed in these studies included elderly patients (51%), patients with history of diabetes mellitus (29%), dyslipidemia (39%) and hypertension (40%).

Primary efficacy assessment was by means of the Erectile Function (EF) Domain score of the International Index of Erectile Function (IIEF) Questionnaire and two questions from the Sexual Encounter Profile (SEP) dealing with the ability to achieve vaginal penetration (SEP2; “Were you able to insert your penis into your partner’s vagina?”), and the ability to maintain an erection long enough for successful intercourse (SEP3, “Did your erection last long enough for you to have successful intercourse?”). The International Index of Erectile Function (IIEF) is a validated self-report instrument assessing male sexual function over a period of 4 weeks. The EF domain is comprised of 6 questions focusing on erection problems.

Pooled data from the two trials demonstrate International Index of Erectile Function – Erectile Function (IIEF-EF) domain scores were significantly higher with Levitra orodispersible tablet compared to placebo.

A percentage of 71% of all sexual attempts reported had successful penetration compared to 44% of all attempts in the placebo group. These results were also reflected in
subgroups, in elderly patients (67%), in patients with history of diabetes mellitus (63%), patients with history of dyslipidemia (66%) and hypertension (70%) of all sexual attempts reported had successful penetration.

About 63% of all reported sexual attempts with Levitra orodispersible tablets were successful in terms of erection maintenance compared to about 26% of all placebo-controlled sexual attempts. In the predefined subgroups 57% (elderly patients), 56% (patients with history of diabetes mellitus), 59% (patients with history of dyslipidemia) and 60% (patients with history of hypertension) of all reported attempts with Levitra orodispersible tablet were successful in terms of maintenance of erection.

The efficacy of Levitra orodispersible tablets was demonstrated regardless of baseline erectile dysfunction severity, etiology (organic, psychogenic, and mixed), duration of ED, ethnicity and age.

Table 1. IIEF erectile function domain score (Intention-to-treat population, means). ‡

<table>
<thead>
<tr>
<th>Study Population</th>
<th>IIEF erectile function domain score</th>
<th>Placebo</th>
<th>Levitra ODT 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Baseline</td>
<td>Wk 12</td>
</tr>
<tr>
<td>General</td>
<td>332</td>
<td>12.8</td>
<td>14.2</td>
</tr>
<tr>
<td>&lt; 65 years</td>
<td>160</td>
<td>13.3</td>
<td>15.2</td>
</tr>
<tr>
<td>≥ 65 years</td>
<td>172</td>
<td>12.4</td>
<td>13.3</td>
</tr>
<tr>
<td>Diabetic</td>
<td>84</td>
<td>11.7</td>
<td>13.3</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>109</td>
<td>12.7</td>
<td>13.3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>148</td>
<td>12.0</td>
<td>12.9</td>
</tr>
</tbody>
</table>

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

Table 2. Percentage of patients achieving successful penetration (Intention-to-treat population, means). ‡

<table>
<thead>
<tr>
<th>Study Population</th>
<th>Success rates (%) ‘Penetration’</th>
<th>Placebo</th>
<th>Levitra ODT 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Baseline</td>
<td>Wk 12</td>
</tr>
<tr>
<td>General</td>
<td>330</td>
<td>38.3</td>
<td>43.8</td>
</tr>
<tr>
<td>&lt; 65 years</td>
<td>160</td>
<td>43.6</td>
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<tr>
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<td>170</td>
<td>33.3</td>
<td>39.3</td>
</tr>
<tr>
<td>Diabetic</td>
<td>84</td>
<td>31.3</td>
<td>39.2</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>108</td>
<td>40.8</td>
<td>41.9</td>
</tr>
<tr>
<td>Hypertension</td>
<td>146</td>
<td>38.6</td>
<td>40.0</td>
</tr>
</tbody>
</table>

‡ overall success rates under treatment up to 12 weeks or last available visit.
Table 3. Percentage of patients achieving successful maintenance of erection (Intention-to-treat population, means). ‡

<table>
<thead>
<tr>
<th>Study Population</th>
<th>Success rates (%) ‘Maintenance’</th>
<th>Placebo</th>
<th>Levitra ODT 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Baseline</td>
<td>Wk 12</td>
</tr>
<tr>
<td>General</td>
<td>324</td>
<td>15.0</td>
<td>26.7</td>
</tr>
<tr>
<td>&lt; 65 years</td>
<td>159</td>
<td>15.0</td>
<td>30.2</td>
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<tr>
<td>≥ 65 years</td>
<td>165</td>
<td>15.0</td>
<td>23.2</td>
</tr>
<tr>
<td>Diabetic</td>
<td>83</td>
<td>12.7</td>
<td>23.1</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>108</td>
<td>14.7</td>
<td>22.6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>144</td>
<td>13.1</td>
<td>23.1</td>
</tr>
</tbody>
</table>

‡ overall success rates under treatment up to 12 weeks or last available visit.

INDICATIONS

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

Levitra is not indicated for use by women.

CONTRAINDICATIONS

- Patients with known hypersensitivity to the active substance or to any of the excipients.

- Co-administration with nitrates, nitric oxide donors or organic nitrates in any form either regularly or intermittently. Drugs which must not be used concomitantly include, but are not limited to glyceryl trinitrate (injection, tablets, sprays or patches), isosorbide salts, sodium nitroprusside, amyl nitrite, nicorandil or organic nitrates in any form. Consistent with the effects of PDE inhibition on the nitric oxide/cGMP – pathway, PDE5 inhibitors may potentiate the hypotensive effects of nitrates.

- Concomitant use with moderate inhibitors (e.g. erythromycin) and potent inhibitors (e.g. clarithromycin, ketoconazole, itraconazole and HIV Protease inhibitors such as indinavir or ritonavir) of CYP 3A4

- Patients who have loss of vision in one eye because of non-arteritic anterior ischaemic optic neuropathy (NAION), regardless of whether this episode was in connection with previous exposure to PDE5 inhibitor.

- Known hereditary degenerative retinal disorders such as retinitis pigmentosa.

- Patients in whom sexual intercourse is inadvisable due to cardiovascular risk factors (see PRECAUTIONS). The possibility of undiagnosed cardiovascular
disorders in men with erectile dysfunction should be considered before prescribing the medicine.

- Patients with following cardiac conditions: unstable angina, resting or orthostatic hypotension (systolic blood pressure < 90 mmHg), uncontrolled hypertension, myocardial infarction, stroke, cardiac ischaemia (except stable angina), life-threatening arrhythmia within the previous 6 months and uncontrolled arrhythmia.

- Moderate and severe hepatic impairment.

- End-stage renal disease requiring dialysis.

PRECAUTIONS

Cardiovascular Disease

Prior to initiating any treatment for erectile dysfunction, physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity. Vardenafil has vasodilator properties which may result in mild and transient decreases in blood pressure. Patients with left ventricular outflow obstruction, e.g., aortic stenosis and idiopathic hypertrophic subaortic stenosis, can be sensitive to the action of vasodilators including Type 5 phosphodiesterase inhibitors.

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

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

Other Pre-existing Medical Conditions

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

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

Vardenafil has not been administered to patients with bleeding disorders or significant active peptic ulceration. Therefore vardenafil should be given to these patients only after
careful benefit-risk assessment. In humans, vardenafil has no effect on bleeding time alone or with aspirin. *In vitro* studies with human platelets indicate that vardenafil alone did not inhibit platelet aggregation induced by a variety of platelet agonists. With supratherapeutic 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.

**Use with alpha-blockers**

Patients taking alpha-blockers should not initiate vardenafil therapy with Levitra orodispersible tablets. Patients treated with alpha-blockers who have previously used vardenafil film-coated tablets may be switched to Levitra orodispersible tablets. Caution is advised when PDE5 inhibitors are co-administered with alpha blockers. PDE5 inhibitors, including Levitra orodispersible tablets and alpha-adrenergic blocking agents are both vasodilators with blood-pressure lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. In some patients, concomitant use of these two drug classes can lower blood pressure significantly (see INTERACTIONS WITH OTHER MEDICINES) leading to symptomatic hypotension (e.g. fainting). Consideration should be given to the following:

- Patients should be stable on alpha-blocker therapy prior to initiating a PDE5 inhibitor. Patients who demonstrate haemodynamic instability on alpha-blocker therapy alone are at increased risk of symptomatic hypotension with concomitant use of PDE5 inhibitors.

- Patients treated with alpha-blockers should not be initiated on vardenafil therapy with Levitra orodispersible tablets. In those patients who are stable on alpha-blocker therapy, vardenafil should be initiated at the lowest recommended starting dose of 5 mg film-coated tablets. Patients may subsequently be switched to Levitra 10 mg orodispersible tablets.

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

- Safety of combined use of PDE5 inhibitors and alpha-blockers may be affected by other variables, including intravascular volume depletion and other anti-hypertensive drugs.

**Use with CYP 3A4 Inhibitors**

Concomitant use of moderate (e.g. erythromycin) or potent cytochrome P450 3A4 (CYP 3A4) inhibitors (e.g. clarithromycin, ketoconazole, itraconazole or HIV protease inhibitors such as indinavir or ritonavir) can be expected to produce markedly increased vardenafil plasma levels. Concomitant use with ketoconazole, itraconazole, erythromycin, clarithromycin, indinavir or ritonavir is contraindicated. (See CONTRAINDICATIONS and INTERACTIONS WITH OTHER MEDICINES).
NAION

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

Sudden decrease or loss of hearing

Physicians should advise patients to stop taking PDE5 inhibitors, including vardenafil, and seek prompt medical attention in the event of sudden decrease or loss of hearing. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors, including vardenafil. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors (see ADVERSE EFFECTS).

Other

Aspartame: Levitra orodispersible tablet contains aspartame, a source of phenylalanine which may be harmful for people with phenylketonuria.

Sorbitol: Levitra orodispersible tablet contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take Levitra orodispersible tablets.

Ability to Drive and Use Machines

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

Carcinogenicity

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

Genotoxicity

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

Impairment of Fertility

In a specific clinical trial, single oral doses of 20 mg of vardenafil did not produce any effects on sperm motility or morphology or a variety of parameters indicative for male reproductive function. Based upon measurements of vardenafil in semen of healthy subjects 90 minutes after dosing, not more than 0.0002% of the administered dose appeared in the semen of patients.
Studies in rats showed no effects on fertility, reproductive performance or reproductive organ morphology in males or females given oral doses of vardenafil up to 100 mg/kg/day (systemic exposure > 200 times that expected at the maximum recommended dose of 20 mg, based on AUC).

**Other vardenafil formulations**

Levitra 10 mg orodispersible tablet is not bioequivalent to Levitra 10 mg film-coated tablets (see DOSAGE AND ADMINISTRATION).

**Use in Pregnancy (Category B3)**

Vardenafil is not indicated for use by women.

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

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

There are no studies of vardenafil in pregnant women.

**Use in Lactation**

Vardenafil is not indicated for use by women.

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

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

**INTERACTIONS WITH OTHER MEDICINES**

The studies described in this section were conducted using vardenafil film-coated tablets.

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 enzymes may reduce vardenafil clearance.

**Demonstrated Interactions**
**Macrolide Antibiotics**

Erythromycin (500 mg three times a day), a CYP3A4 inhibitor, caused a 4-fold increase in vardenafil AUC and a 3-fold increase in $C_{\text{max}}$ when co-administered with vardenafil (5 mg) to healthy volunteers. Levitra orodispersible tablets should not be used in combination with erythromycin or clarithromycin (see CONTRAINDICATIONS).

**Potent CYP 3A4 inhibitors**

**Ketoconazole**

Ketoconazole (200 mg), which is a potent CYP3A4 inhibitor, caused a 10-fold increase in vardenafil AUC and a 4-fold increase in $C_{\text{max}}$ when co-administered with vardenafil 5 mg to healthy volunteers. Levitra orodispersible tablets should not be used in combination with ketoconazole (see DOSAGE AND ADMINISTRATION).

**Indinavir**

Indinavir is a potent CYP3A4 inhibitor. Co-administration of vardenafil film-coated tablet (10 mg) with the HIV protease inhibitor indinavir (800 mg three times a day) resulted in a 16-fold increase in vardenafil AUC and a 7-fold increase in vardenafil $C_{\text{max}}$. At 24 hours after co-administration, the plasma levels of vardenafil were approximately 4% of the maximum vardenafil plasma level ($C_{\text{max}}$). Concomitant use of indinavir and Levitra orodispersible tablets is therefore contraindicated.

**Ritonavir**

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

**Potential Interactions**

**Other CYP 3A4 Inhibitors**

Concomitant use of other moderate or potent CYP 3A4 inhibitors (such as clarithromycin, itraconazole, other HIV protease inhibitors) can also be expected to produce markedly increased vardenafil plasma levels (See Demonstrated Interactions). Levitra orodispersible tablets should not be used in combination with other moderate or potent CYP3A4 inhibitors such as clarithromycin, itraconazole and other HIV protease inhibitors.

**Nitrates, Nitric Oxide Donors**

There is limited information on the potential hypotensive effects of vardenafil when given in combination with nitrates. Based on experience with other PDE5 inhibitors, some patients may experience clinically significant hypotension if vardenafil and nitrates are coadministered and concomitant use is therefore contraindicated (see CONTRAINDICATIONS).
Nitrates should not be administered for at least 24 hours (approximately 5 half-lives) after the last dose of vardenafil. A longer washout period should be observed if the patient has been taking concomitant drugs, such as CYP3A4 inhibitors, which impair vardenafil metabolism.

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

**Antihypertensive agents**

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

**Alpha-blockers**

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

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

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

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

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

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

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

When Levitra 5 mg film-coated tablets were dosed simultaneously with 5 or 10 mg of terazosin, 1 out of 21 patients experienced symptomatic postural hypotension. Hypotension was not observed when vardenafil was dosed 6 hours after terazosin. This should be considered when deciding about a time separation of dosing between Levitra and terazosin. There was no case of syncope in this study or in the earlier alfuzosin or terazosin studies.
Figure 2: Mean change from baseline in standing systolic blood pressure (mmHg) over 6 hour interval following simultaneous or 6 hr separation administration of vardenafil 5 mg or placebo with stable dose tamsulosin 0.4 mg in normotensive BPH patients.

![Figure 2](image)

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

![Figure 3](image)

Concomitant treatment should be initiated only if the patient is stable on his alpha-blocker therapy. In patients who are stable on alpha-blocker therapy, vardenafil should be initiated
at a starting dose of 5 mg film-coated tablets. Patients treated with alpha-blockers should not use Levitra 10 mg orodispersible tablets to initiate therapy.

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

**Interactions shown not to exist**

The studies described in this section were conducted using vardenafil film-coated tablets.

**Glibenclamide**

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

**Warfarin**

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

**Nifedipine**

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

**Digoxin**

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

**Antacids**

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

**Ranitidine, Cimetidine**

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

**Aspirin**
Vardenafil (10 mg) administered as film-coated tablets did not influence bleeding time when taken alone or in combination with low dose aspirin (2 x 81 mg tablets).

**Ethanol**

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

**Other Drugs**

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

**ADVERSE EFFECTS**

Safety of Levitra orodispersible tablets was evaluated in two identical multi-national, randomised double-blind, placebo-controlled trials. In both pivotal studies, enrolment was stratified so that approximately 50% of patients were ≥ 65 years old. An integrated analysis of both studies included a total of 335 subjects that received Levitra orodispersible tablets compared to 340 subjects that received placebo (mean age was 61.7, range 21.0 to 88.0. 68% White, 5% Black, 6% Asian, 11% Hispanic and 11% Other). The discontinuation rates due to adverse reactions were 1.4% for Levitra orodispersible tablet compared to 0.4% for placebo.
### Table 4: Adverse events reported by ≥ 1% of patients treated with Levitra orodispersible tablet in controlled trials

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Preferred Term (PT)</th>
<th>Levitra ODT (N = 355)</th>
<th>Placebo (N = 340)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td>Bundle Branch Block Right</td>
<td>0.0%</td>
<td>1.2%</td>
</tr>
<tr>
<td></td>
<td>Supraventricular extrasystoles</td>
<td>1.1%</td>
<td>0.9%</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td>Diarrhoea</td>
<td>1.7%</td>
<td>0.9%</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
<td>2.8%</td>
<td>0.0%</td>
</tr>
<tr>
<td><strong>Infections and Infestations</strong></td>
<td>Nasopharyngitis</td>
<td>0.6%</td>
<td>1.2%</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td>Back pain</td>
<td>2.0%</td>
<td>0.3%</td>
</tr>
<tr>
<td></td>
<td>Muscle spasms</td>
<td>1.1%</td>
<td>0.6%</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td>Dizziness</td>
<td>2.3%</td>
<td>0.0%</td>
</tr>
<tr>
<td></td>
<td>Dysgeusia</td>
<td>1.1%</td>
<td>1.2%</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>14.4%</td>
<td>1.8%</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td>Nasal congestion</td>
<td>3.1%</td>
<td>0.3%</td>
</tr>
<tr>
<td><strong>Social Circumstances</strong></td>
<td>Pharmaceutical Product Complaint</td>
<td>0.0%</td>
<td>1.2%</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td>Flushing</td>
<td>7.6%</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

The number of subjects in all placebo-controlled clinical trials for vardenafil is vardenafil n = 9155; placebo n = 5500. Vardenafil was generally very well tolerated. Adverse events were generally transient and mild to moderate in nature.

**All vardenafil clinical trials**

Levitra orodispersible tablets and vardenafil film-coated tablets have been administered to 17 748 men during controlled and uncontrolled clinical trials worldwide. The number of patients treated for 6 months or longer was 3357, and 1350 patients were treated for at least 1 year. When vardenafil film-coated tablet or Levitra orodispersible tablet was taken as recommended, the following adverse drug reactions were reported in all clinical trials.
Table 5: Adverse drug reactions reported in patients in all clinical trials for vardenafil worldwide which are either reported as drug-related in ≥ 0.1% of the patients or rare and considered serious in nature.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very Common ≥ 10%</th>
<th>Common &gt; 1% to &lt;10%</th>
<th>Uncommon &gt;0.1% to &lt;1%</th>
<th>Rare &gt;0.01% to &lt; 0.1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune System Disorders</td>
<td></td>
<td>Allergic oedema and angioedema</td>
<td></td>
<td>Allergic reaction</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td></td>
<td></td>
<td></td>
<td>Conjunctivitis</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td></td>
<td>Sleep disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Headache</td>
<td>Dizziness*</td>
<td>Somnolence</td>
<td>Syncope</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Paraesthesia and dysesthesia</td>
<td>Amnesia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Seizure</td>
</tr>
<tr>
<td>Eye Disorders incl. related Investigations</td>
<td></td>
<td>Visual disturbance</td>
<td>Visual colour distortions</td>
<td>Increase in intraocular pressure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ocular hyperaemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Eye pain and eye discomfort</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Photophobia</td>
<td></td>
</tr>
<tr>
<td>Ear and Labyrinth Disorders</td>
<td></td>
<td>Tinnitus</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Vertigo</td>
<td></td>
</tr>
<tr>
<td>Cardiac Disorders incl. related Investigations</td>
<td></td>
<td>Palpitations</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Tachycardia</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Angina pectoris</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ventricular tachyarrhythmias</td>
</tr>
<tr>
<td>Vascular Disorders incl. related Investigations</td>
<td></td>
<td>Vasodilatation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hypotension</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td>Nasal congestion</td>
<td>Dyspnoea</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sinus congestion</td>
<td></td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Very Common ≥ 10%</td>
<td>Common &gt; 1% to &lt;10%</td>
<td>Uncommon &gt;0.1% to &lt;1%</td>
<td>Rare &gt;0.01% to &lt;0.1%</td>
</tr>
<tr>
<td>--------------------</td>
<td>-------------------</td>
<td>---------------------</td>
<td>-----------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Gastrointestinal Disorders incl. related Investigations</td>
<td>Dyspepsia</td>
<td>Gastrointestinal and abdominal pain</td>
<td>Diarrhoea</td>
<td>Dry mouth</td>
</tr>
<tr>
<td>Hepatobiliary System Disorder</td>
<td>Increase in transaminases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>Rash</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Erythema</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders incl. related Investigations</td>
<td>Back pain</td>
<td>Myalgia</td>
<td>Increase in creatine kinase</td>
<td>Increased muscle tone and cramping</td>
</tr>
<tr>
<td>Reproductive System and Breast Disorders</td>
<td>Increase in erection</td>
<td></td>
<td></td>
<td>Priapism</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>Feeling unwell</td>
<td></td>
<td></td>
<td>Chest pain</td>
</tr>
</tbody>
</table>

*In a pooled analysis of placebo-controlled fix-dose studies comparing 5 mg, 10 mg and 20 mg of vardenafil film-coated tablets a higher rate of dizziness was seen in elderly subjects (≥ 65 years) with doses of 10 mg or higher than in younger subjects (4.2% vs. 1.2%). Dizziness was usually mild and resolved without any further action. Due to the vasodilatory properties of PDE 5 inhibitors, concomitant use with alpha-blockers may contribute to dizziness.*
Myocardial infarction (MI) has been reported in temporal association with the use of vardenafil and sexual activity, but it was not possible to determine whether MI is related directly to vardenafil, or to sexual activity, to the patient's underlying cardiovascular disease, or to a combination of these factors.

Non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported rarely post-marketing in temporal association with the use of PDE inhibitors, including vardenafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for development of NAION, including: low cup to disc ratio (“crowded disc”), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient’s underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors.

Visual disturbances including vision loss (temporary or permanent) have been reported rarely post-marketing in temporal association with the use of PDE5 inhibitors, including vardenafil. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient’s underlying vascular risk factors or to other factors.

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

**DOSAGE AND ADMINISTRATION**

The recommended dose is one Levitra orodispersible tablet, taken orally 60 minutes before sexual activity. Sexual activity can be initiated as soon as 15 minutes and as long as 4 – 5 hours after taking Levitra orodispersible tablet. Sexual stimulation is required for a natural response to treatment.

The maximum recommended dose is one Levitra orodispersible tablet per day.

Levitra orodispersible tablet can be taken under fed or fasted conditions. (see PHARMACOKINETICS, Absorption)

Levitra orodispersible tablet should be taken without liquid immediately upon removal from the blister. It should be placed on the tongue. Manipulate the tablet with the tongue against the palate and swallow with saliva once it has disintegrated. Do not chew the tablet. Do not bite on the disintegrated particles.

**Dose Range**

Based on efficacy and tolerability, the vardenafil dose may be increased to 20 mg (one 20 mg film-coated tablet) or decreased to 5 mg (one 5 mg film-coated tablet). Levitra 10 mg orodispersible tablet is not bioequivalent to Levitra 10 mg film-coated tablet. Levitra 10 mg orodispersible tablets have 21 to 44% higher bioavailability compared to Levitra 10 mg film-coated tablets. For patients requiring a higher or lower dose, vardenafil film-coated
tablets should be considered. Depending on co-morbidities and concomitant medications, it may be necessary to commence on a lower dose of 5 mg film-coated tablet.

**Elderly (above 65 years)**

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

**Children (from birth to 18 years)**

Levitra orodispersible tablet is not indicated for use in children.

**Hepatic impairment**

In patients with mild hepatic impairment (Child-Pugh A), vardenafil 5 mg should be used as a starting dose, which may subsequently be increased to one Levitra orodispersible tablet. Levitra orodispersible tablet is not indicated as a starting dose in patients with mild hepatic impairment. There is limited clinical data in patients with mild hepatic impairment on Levitra orodispersible tablets.

Vardenafil clearance is reduced in patients with moderate hepatic impairment (Child-Pugh B). The pharmacokinetics of vardenafil have not been studied in patients with severe hepatic impairment (Child-Pugh C). Levitra orodispersible tablet should not be used in patients with moderate or severe hepatic impairment (see CONTRAINDICATIONS).

**Renal impairment**

No dose adjustment is needed in patients with mild ($\text{CL}_{\text{cr}} > 50-80$ mL/min), moderate ($\text{CL}_{\text{cr}} > 30-50$ mL/min), or severe ($\text{CL}_{\text{cr}} < 30$ mL/min) renal impairment.

The pharmacokinetics of vardenafil have not been studied in patients requiring dialysis, therefore vardenafil should not be used in these patients (see Pharmacokinetics).

**Concomitant Alpha-blockers**

Patients treated with alpha-blockers should not be initiated on vardenafil therapy with Levitra orodispersible tablets.

In those patients who are stable on alpha-blocker therapy, 5 mg vardenafil film-coated tablets should be used as initial therapy (see PRECAUTIONS and INTERACTIONS WITH OTHER MEDICINES). Patients may subsequently be switched to Levitra orodispersible tablets.

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

**OVERDOSAGE**
The maximum dose of vardenafil for which human data are available is a single 120 mg dose of the film-coated tablets administered to eight healthy male volunteers. The majority of these subjects experienced reversible back pain/myalgia and/or “abnormal vision”.

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

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

Contact Poisons Information Centre 131126 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

Levitra orodispersible tablet is available in blister packs of 1 (sample pack), 4 and 8. Each orodispersible tablet contains vardenafil hydrochloride trihydrate equivalent to 10 mg of vardenafil. Store in original container.

Store below 30 °C.

NAME AND ADDRESS OF THE SPONSOR

BAYER AUSTRALIA LIMITED
ABN 22 000 138 714
875 Pacific Highway
PYMBLE NSW 2073

POISON SCHEDULE OF THE MEDICINE

PRESCRIPTION ONLY MEDICINE

DATE OF FIRST INCLUSION IN THE ARTG

27 January 2011

DATE OF MOST RECENT AMENDMENT

12 March 2013

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