NEW ZEALAND DATA SHEET

1 PRODUCT NAME

LEVITRA® vardenafil (as hydrochloride trihydrate) film coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

LEVITRA 5 mg film-coated tablets (5.926 mg of vardenafil hydrochloride trihydrate).

LEVITRA 10 mg film-coated tablets (11.852 mg of vardenafil hydrochloride trihydrate).

LEVITRA 20 mg film-coated tablets (23.705 mg of vardenafil hydrochloride trihydrate).

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

4 CLINICAL PARTICULARS

4.1 Therapeutic 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.

4.2 Dose and method of administration

The recommended starting dose of LEVITRA is 10 mg, taken orally 25 to 60 minutes before sexual activity. Sexual activity can be initiated as soon as 15 minutes and as long as 4-5 hours after taking LEVITRA. LEVITRA 10 mg orodispersible tablet is not bioequivalent to LEVITRA 10 mg film-coated tablet; therefore, the orodispersible formulation should not be used as an equivalent to LEVITRA 10 mg film-coated tablets.

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 adjustment

Based on efficacy and tolerability, the LEVITRA dose may be increased to one LEVITRA 20 mg film-coated tablet or decreased to one LEVITRA 5 mg film-coated tablet. The maximum daily recommended dose is one LEVITRA 20 mg film-coated tablet.

Elderly (above 65 years)

Dose adjustment is not required in elderly patients.

Children (from birth to 16 years)

LEVITRA is not indicated for use in children.

Hepatic impairment

No dose adjustment is needed 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 10 mg film-coated tablet, based on tolerability and efficacy.

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

Renal impairment

No dose adjustment is needed in patients with mild, CL_{cr} > 50 - 80 mL/min, moderate CL_{cr} > 30 - 50 mL/min, or severe CL_{cr} < 30 mL/min renal impairment.

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

Concomitant use of CYP 3A4 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 Section 4.5 Interaction with other medicines and other forms of interaction).

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

A maximum dose of one LEVITRA 5 mg film-coated tablets should not be exceeded when used in combination with the CYP3A4 inhibitors erythromycin or clarithromycin (see Section 4.5 Interaction with other medicines and other forms of interaction).

Concomitant use with medicinal products containing cobicistat, HIV protease inhibitors such as indinavir and ritonavir, and combinations of these is contraindicated, as they are potent inhibitors of CYP3A4 (see Section 4.3 Contraindications, Section 4.4 Special warnings and precautions for use and Section 4.5 Interaction with other medicines and other forms of interaction).

Table 1: Dosage instructions for concomitant use of LEVITRA film-coated tablets with CYP 3A4 inhibitors

Combination with		**Maximum LEVITRA dose (film-coated tablets)**	**Time interval**
Ketoconazole	> 200 mg daily	Should not be used	
	≤ 200 mg daily	5 mg	within 24 hours
Itraconazole	> 200 mg daily	Should not be used	
	≤ 200 mg daily	5 mg	within 24 hours
Erythromycin		5 mg	within 24 hours
Clarithromycin		5 mg	within 24 hours
Indinavir		Contraindicated	
Ritonavir		Contraindicated	
Cobicistat		Contraindicated	

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 Section 4.5 Interaction with other medicines and other forms of interaction).

In those patients who are stable on alpha-blocker therapy, LEVITRA should be initiated at the lowest recommended starting dose of 5 mg film-coated tablet. 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 is prescribed concomitantly (see Section 4.5 Interaction with other medicines and other forms of interaction).

In those patients already taking an optimised 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.

4.3 Contraindications

LEVITRA is contraindicated in patients with known hypersensitivity to any of the drug's components (active or inactive ingredients).

Nitrates and vardenafil must not be used concomitantly. Co-administration of vardenafil with nitric oxide donors, organic nitrates, or organic nitrites in any form either regularly or intermittently is contraindicated. 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 of LEVITRA with riociguat, a stimulator of soluble guanylate cyclase (sCG), is contraindicated.

LEVITRA is contraindicated in men for whom sexual intercourse is inadvisable due to cardiovascular risk factors (see Section 4.4 Special warnings and precautions for use). The possibility of undiagnosed cardiovascular disorders in men with erectile dysfunction should be considered before prescribing vardenafil.

LEVITRA is contraindicated in patients who have loss of vision in one eye because of non-arteritic anterior ischaemic optic neuropathy (NAION), regardless of whether or not this episode was in connection with previous PDE5 inhibitor exposure (see Section 4.4 Special warnings and precautions for use).

The safety of vardenafil has not been studied in patients with the following conditions and its use in such patients is therefore contraindicated until further information is available: unstable angina; resting or orthostatic hypotension (systolic blood pressure <90 mmHg); uncontrolled hypertension; myocardial infarction, stroke, cardiac ischaemia (except stable angina), or life-threatening arrhythmia within the previous 6 months; uncontrolled arrhythmia; severe hepatic impairment; end-stage renal disease requiring dialysis; known hereditary degenerative retinal disorders such as retinitis pigmentosa.

Concomitant use of LEVITRA with medicinal products containing cobicistat, HIV Protease inhibitors such as indinavir or ritonavir, and combinations of these is contraindicated, as these drugs are potent

inhibitors of CYP 3A4 (see Section 4.2 Dose and method of administration, 4.4 Special warnings and precautions for use and 4.5 Interaction with other medicines and other forms of interaction).

4.4 Special warnings and precautions for use

Cardiovascular Disease

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

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

In a study of the effect of vardenafil on QT interval in 59 healthy males, therapeutic (10 mg) and supratherapeutic (80 mg) doses of vardenafil produced increases in QTc interval. 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 Section 5.3 Preclinical safety data). These observations should be considered in clinical decisions when prescribing vardenafil 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 film-coated tablets.

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 have not been studied. Therefore the use of such combinations is not recommended.

LEVITRA has not been administered to patients with bleeding disorders or significant active peptic ulceration. Therefore, LEVITRA should be given to these patients only after careful benefit-risk assessment. In humans, vardenafil has no effect on bleeding time alone or with aspirin. In vitro studies with human platelets indicate that vardenafil alone did not inhibit platelet aggregation induced by a variety of platelet agonists. With supertherapeutic concentrations of vardenafil a small concentration-dependent enhancement of the antiaggregatory effect of sodium nitroprusside, a 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

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 Section 4.5 Interaction with other medicines 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 of 5 mg 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 film-coated tablets are prescribed concomitantly (see Section 4.5 Interaction with other medicines and other forms of interaction).

In those patients already taking an optimised dose of LEVITRA film-coated tablets, 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 film-coated tablets.

Use with Potent CYP 3A4 Inhibitors

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 vardenafil dose of one LEVITRA 5 mg film-coated tablets should not be exceeded if used in combination with ketoconazole or itraconazole ≤ 200 mg. LEVITRA film-coated tablets must not be taken with dosages of ketoconazole or itraconazole > 200 mg (see Section 4.2 Dose and method of administration and Section 4.5 Interaction with other medicines 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 these drugs are potent inhibitors of CYP 3A4 (see Section 4.2 Dose and method of administration, 4.3 Contraindications and Section 4.5 Interaction with other medicines and other forms of interaction).

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 exploratory study, single doses of riociguat administered to patients with pulmonary arterial hypertension (PAH) treated with sildenafil showed additive haemodynamic 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 Section 4.3 Contraindications).

Non-arteritic anterior ischemic optic neuropathy

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 film-coated tablets. The patient should be advised that in case of sudden vision loss, he should stop taking LEVITRA and consult a physician immediately.

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 post-marketing 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 4.8 Undesirable effects).

Sudden deafness or loss of hearing

Sudden deafness or loss of hearing accompanied by tinnitus and dizziness have 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. Physicians should advise patients to stop taking PDE5 inhibitors, including LEVITRA, and seek prompt medical attention in the event of sudden decrease or loss of hearing.

Use in the elderly

Dose adjustment is not required in elderly patients.

Paediatric use

LEVITRA is not indicated for use in children.

4.5 Interaction with other medicines and other forms of interaction

Nitrates, Nitric Oxide Donors

No potentiation of the blood pressure lowering effect of 0.4 mg of sublingual nitroglycerin was observed when LEVITRA 10 mg film-coated tablets were given at varying time intervals ranging from 24 h down to 1 h, prior to the nitroglycerin dose in a study in 18 healthy male subjects.

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

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 Section 4.3 Contraindications).

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 Section 4.3 Contraindications).

CYP Inhibitors

Vardenafil is metabolised predominantly by hepatic enzymes via CYP 3A4, with some contribution from CYP3A5 and CYP2C isoforms. Therefore, inhibitors of these enzymes may reduce vardenafil clearance (see section 4.2 Dose and method of administration, 4.3 Contraindications and 4.4 Special warnings and precautions for use).

Cimetidine, 400 mg b.i.d., a non-specific P450 inhibitor, had no effect on vardenafil AUC and Cmax when co-administered with LEVITRA 20 mg 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 5 mg 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 5 mg 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.

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 force 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 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 hours after alfuzosin. Two patients, one dosed 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 10 mg and 20 mg film-coated tablets were dosed simultaneously with tamsulosin 0.4 or 0.8 mg 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 5 mg film-coated tablet were dosed simultaneously with terazosin 5 or 10 mg, one of 21 patients experienced symptomatic postural hypotension. Hypotension was not observed when LEVITRA film-coated tablets were 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 of his alpha blocker therapy. In those patients who are stable on alpha-blocker therapy, LEVITRA should be initiated at the lowest recommended starting dose. 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 is prescribed concomitantly (see Section 4.2 Dose and method of administration).

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.

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 an antacid, magnesium hydroxide/aluminium hydroxide, did not affect the AUC or the Cmax of vardenafil.

The bioavailability of LEVITRA 20 mg film-coated tablets was not affected by co-administration of 150 mg b.i.d of the H2 antagonists ranitidine.

LEVITRA 10 mg and 20 mg film-coated tablets did not influence bleeding time when taken alone or in combination with low dose aspirin (2 x 81 mg tablets).

LEVITRA 20 mg did not potentiate the hypotensive effects of ethanol 0.5 g/kg bodyweight. The pharmacokinetics of vardenafil was not altered.

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

No pharmacological, e.g. prothrombin time and clotting factor II, VII and X, interaction was shown when 25 mg of warfarin was co-administered with LEVITRA 20 mg film-coated tablets. Vardenafil pharmacokinetics were not affected by co-administration of warfarin.

No relevant pharmacodynamic or pharmacokinetic interaction was shown when LEVITRA 20 mg film-coated tablets were co-administered with 30 or 60 mg of nifedipine. 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.

4.6 Fertility, pregnancy and lactation

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 0.00012% of the administered dose appeared in the semen of patients.

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

Use in Pregnancy (Category B3)

Vardenafil is not indicated for use by women.

Studies in rats have shown that vardenafil and/or its metabolites cross the placenta and distribute to the foetus. No evidence of embryoofetal 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 foetal 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

4.7 Effects on 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.

4.8 Undesirable effects

All clinical trials (Adverse Drug Reactions)

The frequencies of ADRs reported with LEVITRA are summarised 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).

Table 2: 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	Common	Uncommon	Rare
Immune System Disorders			Allergic oedema and angioedema	Allergic reaction
Infections and Infestations				Conjunctivitis
Psychiatric Disorders			Sleep disorder	
Nervous System Disorders	Headache	Dizziness	Somnolence Paraesthesia and dysesthesia	Syncope Seizure Amnesia
Eye Disorders incl. related Investigations			Visual colour distortions Ocular hyperaemia Eye pain and eye discomfort Photophobia Visual disturbance	Increase in Intraocular pressure
Ear and labyrinth disorders			Tinnitus Vertigo	
Cardiac Disorders incl. related Investigations			Palpitations Tachycardia	Angina pectoris Myocardial infarction Ventricular tachyarrhythmias
Vascular Disorders incl. related Investigations		Vasodilatation		Hypotension
Respiratory, Thoracic and Mediastinal Disorders		Nasal congestion	Dyspnoea Sinus congestion	

System Organ Class	Very Common	Common	Uncommon	Rare
Gastrointestinal Disorders incl. related Investigations		Dyspepsia	Gastrointestinal and abdominal pain Diarrhoea Dry mouth Gastritis Gastrooesophageal reflux disease Vomiting Nausea	
Hepatobiliary System disorder			Increase in transaminases	
Skin and Subcutaneous Tissue Disorders			Rash Erythema	
Musculoskeletal and Connective Tissue Disorders incl. related Investigations			Back pain Myalgia Increase in creatine phosphokinase Increased muscle tone and cramping	
Reproductive System and Breast Disorders			Increase in erection	Priapism
General Disorders and Administration Site Conditions			Feeling unwell	Chest pain

Post-Marketing Experience

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 ischaemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported rarely post-marketing in temporal association with the use of PDE5 inhibitors, including 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 4.4 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 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 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 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 was over 4 weeks were tolerated without producing serious adverse side effects.

When 40 mg of vardenafil was administered twice daily, cases of severe back pain were observed. However, no muscle or neurological toxicity was identified.

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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

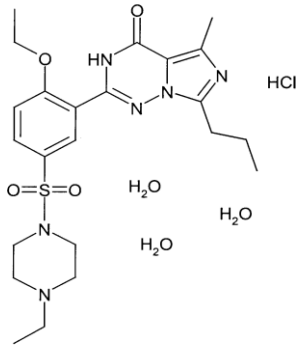
5.1 Pharmacodynamic properties

Physicochemical properties

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

The empirical formula of vardenafil hydrochloride trihydrate is $C_{23}H_{32}N_6O_4S.HCl.3H_2O$ and its molecular weight is 579.1 g/mol. Its chemical structure is shown in Figure 1.

Figure 1: Chemical structure of vardenafil hydrochloride trihydrate.



CAS number: 224785-90-4

Mechanism of action

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.

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

Single oral doses of vardenafil up to 80 mg (four times the maximum recommended daily dose) did not produce clinically relevant effects on the ECGs of healthy volunteers.

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.

Clinical trials

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

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

Across all trials, vardenafil was administered to over 17 000 men with erectile dysfunction ED, many of whom had multiple other medical conditions. Over 2 500 patients were treated with vardenafil for 6 months or longer. Of these, 900 patients have been treated for one year or longer.

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

Table 3: IIEF erectile function domain score and global assessment at Week 12 (Intention-to-treat population).*

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

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

Table 4: Percentage of patients achieving successful penetration and maintenance of erection at Week 12 (Intention-to-treat population).*

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

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

In a randomised, double blind, placebo controlled, fixed dose trial, based on a global assessment question (GAQ), vardenafil, at doses of 5 mg, 10 mg and 20 mg, improved erections in 56%, 77%, and 81% of the patients respectively, at 6 months compared to 28% on placebo.

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

Patients with ED after Radical Prostatectomy

In post-prostatectomy patients, vardenafil demonstrated clinically meaningful and statistically significant improvement in erectile function in a 3 month prospective, fixed dose, placebo-controlled, double blind trial. Erectile function domain score, the rate of obtaining an erection sufficient for penetration, the rate of maintaining an erection sufficient for successful intercourse and hardness were significantly improved compared to placebo for doses of LEVITRA 10 mg and 20 mg film-coated

tablets at all time points. Improved erectile function response rates, as based on GAQ, were 59% on 10 mg, and 65% on LEVITRA 20 mg film-coated tablets compared to 13% on placebo at 3 months. In the subgroup of patients with bilateral nerve-sparing prostatectomy the response rates, as based on GAQ, in patients who completed at 3 months were 60% for LEVITRA 10 mg film-coated tablets and 71% for LEVITRA 20 mg film-coated tablets compared to 12% for placebo.

Patients with ED and Diabetes Mellitus

In patients with diabetes mellitus, vardenafil demonstrated clinically meaningful and statistically significant improvement in erectile function in a 3 month prospective, fixed dose, placebo-controlled, double blind trial. Significant improvements were shown in the erectile function domain score, the rate of obtaining an erection sufficient for penetration, the rate of maintaining an erection sufficient for successful intercourse, and hardness, when 10 mg and 20 mg vardenafil doses were compared to placebo. These improvements were seen at all time points during three months of treatment. In this population, which is typically more resistant to therapy, response rates for improvement of erection, as based on GAQ, were 57% on LEVITRA 10 mg film-coated tablets and 72% for LEVITRA 20 mg film-coated tablets compared to 13% for placebo for patients who completed three months of the trial.

Patients in the active treatment group were continued on blinded active therapy of vardenafil for a total of 6 months. These patients demonstrated response rates of 66% and 74% for LEVITRA 10 mg film-coated tablets and for LEVITRA 20 mg film-coated tablets, respectively.

Patients with Spinal Cord Injury

In patients with ED secondary to traumatic spinal cord injury, LEVITRA film-coated tablets demonstrated clinically meaningful and statistically significant improvement in erectile function in a placebo-controlled, double blind, flexible dose clinical trial. Significant improvements were shown in the erectile function domain score, the ability to obtain and maintain an erection long enough for successful intercourse and penile rigidity compared to placebo. The number of patients who returned to a normal IIEF domain score, ≥ 26, was 53% for LEVITRA film-coated tablets compared to 9% for placebo. The response rates for the ability to obtain and maintain an erection were 76% and 59% on vardenafil compared to 41% and 22% for placebo for patients who completed 3 months treatment which were clinically and statistically significant ($p<0.001$). In this population, which is typically more resistant to therapy, response rates for improvement of erection, as based on GAQ, were 83% for LEVITRA film-coated tablets compared to 26% for placebo for patients who completed 3 months of the trial.

QT prolongation

In a post marketing study of 44 healthy volunteers, single doses of LEVITRA 10 mg film-coated tablets or 50 mg sildenafil were co-administered concomitantly with 400 mg of gatifloxacin, a drug with comparable QT effect. Both vardenafil and sildenafil showed an additive Fridericia QTc effect, vardenafil: 4 msec, sildenafil: 5 msec, when compared to either drug alone. The clinical impact of these QT changes is unknown (see Section 4.4 Special warnings and precautions for use).

Effects on vision

A clinical trial designed to evaluate the possible effects of LEVITRA film-coated tablets using a dose of 40 mg, two times the recommended maximum daily dose, on visual function revealed no effects 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 improved by 6 hours and

no changes were present at 24 hours. The majority of these patients had no subjective visual symptoms.

In a separate double blind placebo controlled clinical trial, at least 15 doses of LEVITRA 20 mg film-coated tablets were administered over 8 weeks versus placebo. Retinal function was measured by ERG and FM-100 test 2, 6 and 24 hours after dosing. Vardenafil did not produce clinically significant retinal effects in healthy men compared to placebo.

In other trials, daily use of LEVITRA film-coated tablets 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 and cardiac parameters

In placebo-controlled clinical pharmacology studies with LEVITRA 10 mg and 20 mg film-coated tablets, the mean maximum decreases in supine systolic and diastolic blood pressure were negligible in comparison to placebo. There was only a small compensatory increase in heartbeat per minute.

Single oral doses of vardenafil up to 80 mg, 4 times the maximum recommended daily dose, did not produce clinically relevant effects on the ECGs of healthy volunteers.

The effect of LEVITRA film-coated tablets, at doses of 10 mg and 80 mg, on QT interval was evaluated in a single-dose, double-blind, randomised, placebo- and active-controlled (moxifloxacin 400 mg) cross-over study in 59 healthy males aged 45-60 years. Sildenafil, a drug in the same class was administered in approximately equipotent therapeutic doses of 50 mg and 400 mg. The QT interval was measured at 1-hour post dose, which approximates the average time of peak vardenafil concentration. The LEVITRA film-coated tablet 80 mg dose, four times the highest recommended dose, was chosen because this dose yielded plasma concentrations similar to those observed upon co-administration of LEVITRA 5 mg film-coated tablets with 600 mg of ritonavir twice daily. Of the CYP3A4 inhibitors studied, ritonavir causes the most significant drug-drug interaction with vardenafil.

The table below summarises the effect on mean uncorrected QT and mean corrected QT interval (QT_C) with different methods of correction, Fridericia and a linear individual correction method, at one 1-hour post-dose. No single correction method is known to be more valid than the other.

Table 5: Mean QT and QT_C changes in msec (90% CI) from baseline relative to placebo at 1 hour post-dose with different methodologies to correct for the effect of heart rate.

Drug/Dose	Heart Rate (bpm)	QT Uncorrected (msec)	Fridericia QT Correction (msec)	Individual QT Correction (msec)
Vardenafil 10 mg	5 (4, 6)	-2 (-4, 0)	8 (6, 9)	4 (3, 6)
Vardenafil 80 mg	6 (5, 7)	-2 (-4, 0)	10 (8, 11)	6 (4, 7)
Moxifloxacin 400 mg	2 (1, 3)	3 (1, 5)	8 (6, 9)	7 (5, 8)
Sildenafil 50 mg	4 (3, 5)	-2 (-4, 0)	6 (5, 8)	4 (2, 5)
Sildenafil 400 mg	5 (4, 6)	-1 (-3, 1)	9 (8, 11)	5 (4, 7)

Moxifloxacin produced the expected 5 – 10 msec prolongation, indicating that the study had the required sensitivity. Therapeutic and supratherapeutic doses of vardenafil and sildenafil produced similar decreases in uncorrected QT but increases in QT_C interval. This study, however, was not designed to make direct statistical comparisons between the drugs or the dose levels. The actual clinical impact of these changes is unknown.

Effects on sperm motility or morphology

Single oral doses of LEVITRA 20 mg film-coated tablets did not produce any effects on sperm motility, morphology or a variety of parameters indicative for male reproductive function.

No clinically relevant effects on sperm concentration, count, motility or morphology were observed in a placebo-controlled study in humans administered LEVITRA 20 mg film-coated tablets for 6 months. Vardenafil had no effect on serum levels of testosterone, luteinizing hormone or follicle stimulating hormone.

5.2 Pharmacokinetic properties

Absorption

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.

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

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

Distribution

The mean steady state volume of distribution (Vss) 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 0.00012% 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.

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 potency of approximately 28% compared to vardenafil, resulting in an efficacy contribution of about 7%.

Excretion

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

Pharmacokinetics in special populations

Elderly (≥ 65 years)

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.

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

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%, following a 10 mg vardenafil dose, 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 AUC was increased by 160% and Cmax was increased by 130%, compared to healthy control subjects. The pharmacokinetics of vardenafil have not been studied in patients with severe hepatic impairment Child-Pugh C) and vardenafil should not be used in this situation.

Renal insufficiency

In patients with mild CLcr > 50 – 80 mL/min to moderate CLcr > 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, CLcr < 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 exposure, AUC and Cmax, 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 and vardenafil should not be used in this situation.

5.3 Preclinical safety data

Carcinogenicity

Vardenafil is not carcinogenic when administered daily for 24 months at 225 or 450 times the maximum recommended human dose of 20 mg in rats and mice, respectively, based on 60 kg/bw in men. The exposure in terms of AUC achieved in male rats and mice was ≥ 360 and ≥ 25 times, respectively, the exposure in men given the maximum recommended human dose of 20 mg.

Genotoxocity

No indication for genotoxic/mutagenic activity of vardenafil was found using the following *in vitro* tests: Ames, HPRT, Cyt. *in vitro* and *in vivo* by MNT testing.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

LEVITRA film-coated tablets also contain the following excipients: crospovidone, magnesium stearate, microcrystalline cellulose, colloidal anhydrous silica, macrogol 400, hypromellose, titanium dioxide (CI77891), iron oxide yellow (CI77492), iron oxide red (CI77491).

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

30 months.

6.4 Special precautions for storage

Store below 25 °C.

6.5 Nature and contents of container

LEVITRA is available in blister packs of 4 and 8 tablets (not all pack sizes may be marketed).

6.6 Special precautions for disposal

No special requirements. Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

27 February 2003

10 DATE OF REVISION OF THE TEXT

10 December 2019

SUMMARY TABLE OF CHANGES

Section Changed	**Summary of New Information**
Section 4.4 *Special warnings and precautions for use* and Section 4.8 *Undesirable effects*	Addition of information regarding the risk of non-arteritic anterior ischemic optic neuropathy.
Section 4.2 Dose and method of administration, Section 4.3 *Contraindications*, Section 4.4 *Special warnings and precautions for use* and Section 4.5 *Interaction with other medicines and other forms of interactions*	Minor correction to ritonavir and indinavir contraindications. Inclusion of co-administration with cobicistat as a contraindication. Inclusion of potential effects of vardenafil on P-gp substrates more sensitive than digoxin.

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