NEW ZEALAND DATA SHEET

1 TADALAFIL LUPIN

Tadalafil Lupin5 mg film-coated tablets.

Tadalafil Lupin10 mg film-coated tablets.

Tadalafil Lupin20 mg film-coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 5 mg, 10 mg or 20 mg tadalafil as the active ingredient.

Excipient with known effect: Tadalafil Lupintablets contain lactose (as monohydrate).

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

3 PHARMACEUTICAL FORM

5 mg: yellow coloured, round shaped, biconvex, film-coated tablets debossed with 'T5' on one side and plain on the other side.

10 mg: yellow coloured, round shaped, biconvex, film-coated tablets debossed with 'T10' on one side and plain on the other side.

20 mg: yellow coloured, round shaped, biconvex, film-coated tablets debossed with 'T20' on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Tadalafil Lupinis indicated for the treatment of:

- erectile dysfunction (ED) in adult men. In order for Tadalafil Lupin to be effective in treating ED, sexual stimulation is required.
- moderate to severe lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) in adult men.
- adult men with co-existing ED and LUTS associated with BPH.

4.2 Dose and Method of Administration

Tadalafil Lupin tablets are for oral use.

Tadalafil Lupincan be taken with or without food.

Tadalafil Lupin does not include 2.5 mg strength. If a patient requires a 2.5 mg dose then other brands of tadalafil are available.

For Erectile Dysfunction in Adult Men - On-demand Dosing

The maximum recommended dose of Tadalafil Lupin is 20 mg, taken prior to anticipated sexual activity. The maximum recommended dosing frequency is once per day. Tadalafil Lupin may be taken between 30 minutes and 36 hours prior to anticipated sexual activity. Patients may initiate sexual activity at varying time points relative to dosing in order to determine their own optimal window of responsiveness. The dose may be lowered to 10 mg based on individual response and tolerability. Tadalafil Lupin may be taken without regard to food. Tadalafil Lupin 10 mg and 20 mg is intended for use prior to anticipated sexual activity and is not for continuous daily use.

For Erectile Dysfunction in Adult Men - Once-a-day Dosing

In patients who anticipate a frequent use of Tadalafil Lupin (ie. at least twice weekly), a once daily regimen with the lowest dose of Tadalafil Lupin might be considered suitable, based on patient choice and the physician's judgement.

In these patients the recommended dose is 5 mg taken once a day at approximately the same time of day. The dose must not exceed 5 mg daily. The dose may be decreased to 2.5 mg once a day based on individual tolerability.

There is insufficient evidence on the maximum duration of treatment. The appropriateness of continued use of the once-a-day regimen should be reassessed periodically.

Benign Prostatic Hyperplasia in Adult Men

The recommended dose is 5 mg, taken at approximately the same time every day. Doses above 5 mg once-a-day are not recommended.

Benign Prostatic Hyperplasia and Erectile Dysfunction in Adult Men

The recommended dose is 5 mg taken at approximately the same time every day. Doses above 5 mg once-a-day are not recommended.

Use in Men With Renal Impairment

For on-demand dosing for erectile dysfunction, the recommended dose of Tadalafil Lupin is 10 mg taken prior to anticipated sexual activity and without regard to food for patients with mild (creatinine clearance 51 mL/min to 80 mL/min) or moderate (creatinine clearance 31 mL/min to 50 mL/min) renal impairment. Based on efficacy and tolerability the dose may be increased up to 20 mg. For patients with severe (creatinine clearance ≤30 mL/min), renal impairment 10 mg is the maximum recommended dose.

A single dose study in 8 men suffering from End Stage Renal Disease who were stable on haemodialysis showed 3-4 fold increase in AUC and 2-2.5 fold increase in C_{max} in tadalafil levels. The half-life of the drug is also prolonged.

For once-a-day dosing for erectile dysfunction and/or benign prostatic hyperplasia, dosage adjustments are not required in patients with mild (creatinine clearance 51 mL/min to 80 mL/min) or moderate

(creatinine clearance 31 mL/min to 50 mL/min) renal impairment. Once-a-day dosing of tadalafil is not recommended in patients with severe (creatinine clearance ≤30 mL/min) renal impairment.

Use in Men With Hepatic Impairment

For on-demand dosing for erectile dysfunction, the recommended dose of Tadalafil Lupin is 10 mg taken prior to anticipated sexual activity with or without food for patients with mild to moderate hepatic impairment (Child-Pugh Class A or B). There are no available data about the administration of doses higher than 10 mg of tadalafil to patients with hepatic impairment. There is limited clinical data on the safety of tadalafil in patients with severe hepatic impairment (Child-Pugh Class C); if prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician (see **Section 5.2 Pharmacokinetic Properties - Characteristics in Specific Groups of Patients: Hepatic Impairment**).

Once-a-day dosing has not been evaluated in patients with hepatic impairment therefore, if prescribed for erectile dysfunction and/or benign prostatic hyperplasia, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician (see **Section 5.2 Pharmacokinetic Properties - Characteristics in Specific Groups of Patients: Hepatic Impairment**).

Use in Men With Diabetes

The presence of diabetes does not require a dose reduction.

Use in Elderly Men

Dosage adjustments are not required in elderly patients. Dosage recommendations described in "*Use in Adult Men*" above apply to elderly men.

Use in Children

Tadalafil Lupin should not be used in individuals below 18 years of age.

4.3 Contraindications

Nitrates and tadalafil must not be used concomitantly. Co-administration of tadalafil 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. In clinical studies, tadalafil (10 mg) was shown to augment the hypotensive effects of nitrates. This is thought to result from the combined effects of nitrates and tadalafil on the nitric oxide/cGMP pathway.

Tadalafil Lupin should not be used in patients with a known hypersensitivity to tadalafil or to any of the excipients.

Agents for the treatment of erectile dysfunction, including tadalafil, must not be used in men with cardiac disease for whom sexual activity is inadvisable. Physicians should consider the potential cardiac risk of sexual activity in patients with pre-existing cardiovascular disease.

The following groups of patients with cardiovascular disease were not included in clinical trials and the use of tadalafil is therefore contraindicated:

- patients with myocardial infarction within the last 90 days;
- patients with unstable angina or angina occurring during sexual intercourse;

- patients with New York Heart Association Class 2 or greater heart failure in the last 6 months;
- patients with uncontrolled arrhythmias, hypotension (<90/50 mmHg), or uncontrolled hypertension;
- patients with a stroke within the last 6 months.

Tadalafil is contraindicated in 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 or not with previous phosphodiesterase type 5 (PDE5) inhibitor exposure (see **Section 4.4 Special Warnings and Precautions for Use** and **Section 4.8 Undesirable Effects - Adverse Events Identified from Spontaneous Post-marketing Surveillance**).

The combination of tadalafil and guanylate cyclase stimulators, such as riociguat, is contraindicated because it may lead to symptomatic hypotension.

4.4 Special Warnings and Precautions for Use

Serious cardiovascular events, including myocardial infarction, sudden cardiac death, unstable angina pectoris, ventricular arrhythmia, stroke, transient ischemic attacks, chest pain, palpitations and tachycardia, have been reported either post marketing and/or in clinical trials. Most of the patients in whom these events have been reported had pre-existing cardiovascular risk factors. However, it is not possible to definitively determine whether these events are related directly to these risk factors, to tadalafil, to sexual activity, or to a combination of these or other factors.

Caution should be exercised when prescribing tadalafil to patients with severe hepatic insufficiency (Child-Pugh Class C) or to those taking CYP3A4 inhibitors or inducers or HIV protease inhibitors.

Once-a-day administration either for the treatment of erectile dysfunction or benign prostatic hyperplasia has not been evaluated extensively in patients with hepatic insufficiency. If tadalafil is prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician.

In a clinical pharmacology study, administration of tadalafil 10 mg to patients with moderate renal failure (Creatinine Clearance (CrCl) = 31 mL/min to 50 mL/min) was determined to be safe but appeared to be less well tolerated in terms of back pain than in patients with mild renal failure (CrCl = 51 mL/min to 80 mL/min) and in healthy subjects.

In a single dose, pharmacodynamic study of 8 patients with End Stage Renal Disease who were stable on haemodialysis, the reported adverse effects included headache, dizziness, and somnolence.

Tadalafil should be prescribed with caution for patients with CrCl <50 mL/min.

Due to increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to influence clearance by dialysis, once-a-day dosing of tadalafil is not recommended in patients with severe renal impairment.

For dosage recommendations in patients with renal impairment, see **Section 4.2 Dose and Method of Administration**.

Priapism has been reported with PDE5 inhibitors, including tadalafil. Patients who experience erections lasting 4 hours or more should be instructed to seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency may result. Tadalafil should be used with caution in patients who have conditions that might predispose them to priapism (such as

sickle cell anaemia, multiple myeloma, or leukaemia), or in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease).

The evaluation of erectile dysfunction should include a determination of potential underlying causes and the identification of appropriate treatment following an appropriate medical assessment.

Prior to initiating treatment with tadalafil for benign prostatic hyperplasia patients should be examined to rule out the presence of carcinoma of the prostate.

The safety and efficacy of combinations of tadalafil and other PDE5 inhibitors or treatments for erectile dysfunction have not been studied. Therefore, the use of such combinations is not recommended.

Caution should be exercised when prescribing tadalafil to patients who are taking alpha1 blockers, such as doxazosin, as simultaneous administration may lead to symptomatic hypotension in some patients.

As with other PDE5 inhibitors, tadalafil has systemic vasodilatory properties that may result in transient decreases in blood pressure. Prior to prescribing tadalafil, physicians should carefully consider whether their patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects.

Physicians should advise patients to stop taking PDE5 inhibitors, including tadalafil, and seek prompt medical attention in the event of sudden decrease or loss of hearing. This may be accompanied by tinnitus, which has been reported in association with the use intake of PDE5 inhibitors, including tadalafil. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors (see **Section 4.8 Undesirable Effects**).

Physicians should advise patients to stop use of all PDE5 inhibitors, including tadalafil, and seek medical attention in the event of a sudden loss of vision in one or both eyes (see **Section 4.3 Contraindications**). Such an event may be a sign of NAION, a cause of decreased vision, including permanent loss of vision that has been reported rarely post-marketing in temporal association with the use of all PDE5 inhibitors. An increased risk of acute NAION has been suggested from analyses of observation data in men with erectile dysfunction within 1 to 4 days of episodic PDE5 inhibitor use (see **Section 4.8 Undesirable Effects - Adverse Events Identified from Spontaneous Post-marketing Surveillance**).

Specific studies examining potential withdrawal effects from daily use have not been conducted. Rebound effects on blood pressure have not been observed after follow-up assessments at 2 weeks and 4 weeks following cessation of up to 1 year of chronic daily treatment of tadalafil. Blood pressure was not specifically monitored leading up to or between the 2 and 4 weeks post-treatment assessments. Based upon the limited clinical data examining withdrawal effects, it is recommended that physicians continue monitoring the cardiovascular status, including blood pressure changes, of their patients after discontinuation of tadalafil.

4.5 Interactions with Other Medicines and Other Forms of Interactions

Tadalafil is not expected to cause clinically significant inhibition or induction of the clearance of medicines metabolised by CYP450 isoforms. Studies have confirmed that tadalafil does not inhibit or induce CYP450 isoforms, including CYP3A4, CYP1A2, CYP2D6, CYP2E1, CYP2C9 and CYP2C19.

Tadalafil is principally metabolised by CYP3A4. A selective inhibitor of CYP3A4, ketoconazole (400 mg daily), increased tadalafil single-dose AUC by 312% and C_{max} by 22%, and ketoconazole (200 mg daily), increased tadalafil single-dose AUC by 107% and C_{max} by 15% relative to the AUC and C_{max} values for tadalafil alone.

Ritonavir (200 mg twice daily), an inhibitor of CYP3A4, 2C9, 2C19, and 2D6, increased tadalafil single-dose AUC by 124% with no change in C_{max}. Although specific interactions have not been studied, other HIV protease inhibitors, such as saquinavir, and other CYP3A4 inhibitors, such as erythromycin, clarithromycin, itraconazole and grapefruit juice would likely increase tadalafil exposure.

A selective CYP3A4 inducer, (rifampicin, 600 mg daily), reduced tadalafil single-dose AUC by 88% and C_{max} by 46%, relative to the AUC and C_{max} values for tadalafil 10 mg alone. This reduced exposure can be anticipated to decrease the efficacy of once-a-day-dosed tadalafil; the magnitude of decreased efficacy is unknown. It can be expected that concomitant administration of other CYP3A4 inducers such as phenobarbital, phenytoin and carbamazepine would also decrease plasma concentrations of tadalafil.

Simultaneous administration of an antacid (magnesium hydroxide/aluminium hydroxide) and tadalafil reduced the apparent rate of absorption of tadalafil without altering exposure (AUC) to tadalafil (10 mg).

An increase in gastric pH resulting from administration of nizatidine, an H_2 antagonist, had no significant effect on tadalafil (10 mg) pharmacokinetics.

In clinical studies, tadalafil (10 mg) was shown to augment the hypotensive effects of nitrates. Therefore, administration of tadalafil to patients who are using any form of organic nitrate is contraindicated (see **Section 4.3 Contraindications**).

In a crossover study, 12 healthy volunteers received a single dose of warfarin 25 mg after taking tadalafil 10 mg or placebo once daily for 6 days. Tadalafil reduced the exposure (AUC) to R- and S-warfarin by 11% and 13% respectively but did not alter the effect of warfarin on prothrombin time. (PT). The clinical implications of these findings are unclear. The possibility of and increase or decrease in PT and/or international normalised ratio (INR) should be considered when patients begin taking or cease taking tadalafil.

Tadalafil has been demonstrated to produce an increase in the oral bioavailability of ethinylestradiol; a similar increase may be expected with oral administration of terbutaline, although the clinical consequence of this is uncertain

Tadalafil (10 mg) did not potentiate the increase in bleeding time caused by acetyl salicylic acid.

Tadalafil has systemic vasodilatory properties and may augment the blood pressure lowering effects of antihypertensive agents. Additionally, in patients taking multiple antihypertensive agents whose hypertension was not well-controlled, greater reductions in blood pressure were observed. These reductions were not associated with hypotensive symptoms in the vast majority of patients. Appropriate clinical advice should be given to patients when they are treated with antihypertensive medications and tadalafil.

When initiating daily treatment with tadalafil, appropriate clinical considerations should be given to a possible dose adjustment of the antihypertensive therapy.

In two clinical pharmacology studies, no significant decreases in blood pressure were observed when tadalafil was co-administered to healthy subjects taking the selective alpha1A-adrenergic blocker, tamsulosin. In three clinical pharmacology studies, when tadalafil was co-administered to healthy subjects taking doxazosin (4-8 mg daily), an alpha1-adrenergic blocker, there was an augmentation of the blood-pressure-lowering effect of doxazosin. The number of patients with potentially clinically significant standing-blood-pressure decreases was greater for the combination. In these clinical pharmacology studies there were symptoms associated with the decrease in blood pressure including syncope.

In patients on a stable dose of alpha-blocker therapy for BPH (tamsulosin, doxazosin, terazosin, alfuzosin or silodosin), a Phase 3 randomised, multicentre, double-blind, placebo-controlled, parallel design, 12 week study assessed the potential for adverse haemodynamic effects from the co-administration of tadalafil 5 mg for once daily use. Subjects had a mean age of 67 years (59% >65 years of age; 25% ≥75 years of age). In this study, there was no statistically significant difference in treatment-emergent adverse events possibly related to hypotension or signs of orthostatic hypotension.

Caution is advised when PDE5 inhibitors are co-administered with nonselective alpha-blockers. PDE5 inhibitors, including tadalafil, 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, which may lead to symptomatic hypotension (eg. 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.

- In those patients who are stable on alpha-blocker therapy, PDE5 inhibitors should be initiated at the lowest recommended dose.

- In those patients already taking an optimised dose of PDE5 inhibitor, 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 when 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.

Tadalafil did not affect alcohol concentrations, and alcohol did not affect tadalafil concentrations. At high doses of alcohol (0.7 g/kg), the addition of tadalafil did not induce statistically significant mean blood pressure decreases. In some subjects, postural dizziness and orthostatic hypotension were observed. When tadalafil was administered with lower doses of alcohol (0.6 g/kg), hypotension was not observed and dizziness occurred with similar frequency to alcohol alone.

Due to the known interaction between tadalafil and nitrates or other nitric oxide donors on nitrogen monoxide/cGMP metabolism, patients must be expressly informed that they should never use recreational drugs called “poppers” or “amyl”, typically taken through inhalation. These drugs represent various alkyl nitrites including amyl nitrite, butyl nitrite and isobutyl nitrite.

Tadalafil (10 mg) had no clinically significant effect on the pharmacokinetics or pharmacodynamics of theophylline, a CYP1A2 substrate. The only pharmadynamic effect was a small (3.5 bpm) increase in heart rate.

Preclinical studies showed an additive systemic blood pressure lowering effect when PDE5 inhibitors were combined with riociguat. In clinical studies, riociguat has been shown to augment the hypotensive effects of PDE5 inhibitors. There was no evidence of favourable clinical effect of the combination in the population studied. Concomitant use of riociguat with PDE5 inhibitors, including tadalafil, is contraindicated as it may potentially lead to symptomatic hypotension (see **Section 4.3 Contraindications**).

4.6 Fertility, Pregnancy and Lactation

Tadalafil is not indicated for use in women.

Use in Pregnancy

There was no evidence of teratogenicity, embryotoxicity or foetotoxicity in rats or mice that received up to 1000 mg/kg/day. In a rat pre- and postnatal development study, the no observed effect dose was 30 mg/kg/day. In the pregnant rat, the AUC for calculated free drug at this dose was approximately 18 times the human AUC at a 20 mg dose. There are no studies of tadalafil in pregnant women (see **Section 5.3 Preclinical Safety Data**).

4.7 Effects on Ability to Drive and Use Machines

Although the frequency of reports of dizziness in placebo and tadalafil arms in clinical trials was similar, patients should be aware of how they react to tadalafil before driving or operating machinery.

4.8 Undesirable Effects

The most commonly reported adverse reactions in patients taking tadalafil for the treatment of ED or BPH were headache, dyspepsia, back pain, and myalgia in which the incidences increase with increasing dose of tadalafil.

Adverse Events Identified from Erectile Dysfunction (ED) Clinical Trials

On-Demand Dosing (10 mg and 20 mg)

In six placebo-controlled Phase 3 clinical trials, five of 12 weeks duration and one of 24 weeks duration, tadalafil was administered in doses of 10 mg and 20 mg to over 700 subjects (aged 25 to 80 years). The discontinuation rate due to adverse effects in tadalafil-treated patients (2.5%) was not significantly different from placebo-treated patients (1.3%). In these studies, the adverse effects reported with tadalafil were generally mild or moderate. In these controlled Phase 3 clinical trials, the following adverse events were reported during 12 weeks of treatment in patients receiving
10 mg and 20 mg doses of tadalafil compared to placebo.

Frequency estimate: 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) and Not Known (events not reported in registration trials cannot be estimated from post- marketing spontaneous reports).

Table 1: Treatment-emergent adverse events reported by ≥2% of patients administered with tadalafil 10-20 mg for the on-demand treatment of ED and more frequent on drug than placebo in Phase 3 Studies

System Organ Class	Adverse Event	Tadalafil (N = 724) (%)	Placebo (N = 379) (%)
Infections and Infestations	Nasopharyngitis	5.5	5.0
Nervous System	Headache	14.8	5.5
	Dizziness	2.2	1.8
Gastrointestinal Disorders	Dyspepsia	10.4	1.6
	Diarrhoea	2.3	1.1
	Upper Abdominal Pain	2.1	0.3

System Organ Class	Adverse Event	Tadalafil (N = 724) (%)	Placebo (N = 379) (%)
Musculoskeletal and Connective Tissue Disorders	Back Pain	6.5	3.2
	Myalgia	3.9	1.6
	Pain in Extremity	3.3	1.3
Respiratory, Thoracic and Mediastinal Disorders	Nasal Congestion	2.8	1.1
Vascular Disorders	Flushing	3.6	1.3

Treatment-emergent Adverse Reactions Reported by <2% of Patients Treated With Tadalafil 10-20 mg in Phase 3 Studies

Nervous System
Rare: Transient amnesia[(a)].

[(a)] Frequency based upon events reported in erectile dysfunction placebo-controlled clinical trials in patients treated with tadalafil on demand and daily dosing with doses within the currently approved dosing range for tadalafil.

Eye Disorders:
Uncommon: Ocular hyperaemia, eye pain, eyelid oedema.
Rare: Changes in colour vision.

Ear and Labyrinth Disorders:
Uncommon: Sudden decrease or loss of hearing[(b)].

[(b)] Sudden decrease or loss of hearing has been reported in a small number of post-marketing and clinical trial cases with the use of all PDE5 inhibitors, including tadalafil. In some of the cases, medical conditions and other factors were reported that may have also played a role in the ear and labyrinth adverse events. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related directly to the use of tadalafil, to the patient's underlying risk factors for hearing loss, a combination of these factors, or to other factors.

Respiratory, Thoracic and Mediastinal Disorders:
Uncommon: Dyspnoea.

Vascular Disorders:
Common: Fatigue.
Uncommon: Oedema peripheral.

Gastrointestinal Disorders:
Common: Nausea, vomiting.

Once-a-Day Dosing (2.5 mg and 5 mg)

In four placebo-controlled, Phase 3 clinical trials, three of 12 weeks duration and one of 24 weeks duration, tadalafil was administered in doses of 2.5 mg and 5 mg to more than 600 subjects (ages 24 to 82 years of age). The discontinuation rate due to adverse events in tadalafil-treated patients (3.55%) was not significantly different from placebo-treated patients (2.52%). The adverse events reported with tadalafil were generally mild or moderate in severity. In these controlled Phase 3 clinical trials, the following adverse events were reported during 12 weeks of treatment in patients receiving 2.5 mg and 5 mg doses of tadalafil compared to placebo:

Table 2: Treatment-emergent adverse events reported by ≥2% of patients administered with tadalafil 2.5-5 mg for the once-a-day treatment of ED and more frequent on drug than placebo in Phase 3 Studies

System Organ Class	Adverse Event	Tadalafil (N = 647) (%)	Placebo (N = 318) (%)
Gastrointestinal Disorders	Dyspepsia	3.9	1.3
Infections and Infestations	Nasopharyngitis	3.4	3.1
	Influenza	2.0	1.9
	Upper Respiratory Tract Infection	2.2	0.9
Musculoskeletal and Connective Tissue Disorders	Back Pain	2.9	1.3
	Myalgia	2.3	0.9

Treatment-emergent Adverse Reactions Reported by <2% of Patients Treated With Tadalafil 2.5-5 mg in Phase 3 Studies

Respiratory, Thoracic and Mediastinal Disorders:
Common: Nasal congestion.
Uncommon: Dyspnoea.

Vascular Disorders:
Common: Flushing.

Nervous System:
Rare: Transient amnesia[(c)].

[(c)] Frequency based upon events reported in erectile dysfunction placebo-controlled clinical trials in patients treated with tadalafil on demand and daily dosing with doses within the currently approved dosing range for tadalafil.

A slightly higher incidence of ECG abnormalities, primarily sinus bradycardia, has been reported in patients treated with tadalafil once-a-day as compared with placebo. Most of these ECG abnormalities were not associated with adverse reactions.

Adverse Events Identified from Benign Prostatic Hyperplasia (BPH) Clinical Trials

In four placebo-controlled, Phase 3 clinical trials of 12 weeks duration enrolling patients of various ages (range 45-92 years), tadalafil was administered in doses of 5 mg to over 700 subjects with BPH and BPH/ED. The discontinuation rate due to adverse events in tadalafil-treated patients (3.1%) was significantly different from placebo-treated patients (1.5%). Headache was the most frequently reported AE leading to discontinuation in the tadalafil 5 mg group (0.7%), and was the only event that was reported by a significantly greater percentage of subjects in the tadalafil group compared with placebo (p=0.025). The adverse events reported with tadalafil were generally mild or moderate in severity. In these controlled Phase 3 clinical trials, the following adverse events were reported in patients receiving 5 mg doses of tadalafil compared to placebo:

Table 3: Treatment-emergent adverse events reported by ≥2% of patients administered with tadalafil 5 mg for the treatment of BPH and more frequent on drug than placebo in Phase 3 studies

System Organ Class	Adverse Event	Tadalafil (N = 647) (%)	Placebo (N = 318) (%)
Nervous System Disorders	Headache	3.9	2.0
Musculoskeletal and Connective Tissue Disorders	Back pain	2.4	1.2
Gastrointestinal Disorders	Dyspepsia	2.4	0.1

Treatment-emergent Adverse Reactions Reported by <2% of Patients Treated With Tadalafil 5 mg in Phase 3 Studies

Musculoskeletal and Connective Tissue Disorders:
Common: Pain in extremity, myalgia.

Gastrointestinal Disorders:
Common: Diarrhoea, gastroesophageal reflux disease.

Nervous System:
Common: Dizziness.
Rare: Transient amnesia[(d)].

[(d)] Frequency based upon events reported in erectile dysfunction placebo-controlled clinical trials in patients treated with tadalafil on demand and daily dosing with doses within the currently approved dosing range for tadalafil.

Respiratory, Thoracic and Mediastinal Disorders:
Uncommon: Dyspnoea.

Vascular Disorders:
Common: Hypertension.

Adverse Events Identified from Spontaneous Post-marketing Surveillance

Body as a Whole
Uncommon: Hypersensitivity reactions including rash and urticaria.
Rare: Facial oedema.
Frequency Not Known: Stevens-Johnson syndrome and exfoliative dermatitis.

Cardiac Disorders[(e)]
Uncommon: Palpitations, tachycardia, chest pain.
Rare: Myocardial infarction.
Frequency Not Known: Unstable angina pectoris, ventricular arrhythmia, sudden cardiac death.

[(e)] Most of the patients in whom these events have been reported had pre-existing cardiovascular risk factors. However, it is not possible to determine whether these events are related directly to these factors, to tadalafil, to sexual activity, or to a combination of these or other factors.

Vascular Disorders
Uncommon: Hypotension (more commonly reported when tadalafil is given to patients who are already taking antihypertensive agents), hypertension.

Gastrointestinal Disorders
Common: Abdominal pain, diarrhoea in the elderly (aged ≥65 years).
Uncommon: Gastroesophageal reflux.

Skin and Subcutaneous Tissue
Uncommon: Hyperhidrosis (sweating).

Special Senses
Uncommon: Blurred vision.
Rare: Visual field defect.
Frequency Not Known: NAION, retinal vascular occlusion.

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 tadalafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for development of NAION, including but not necessarily limited to: 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.

Urogenital System

Rare:	Prolonged erection.
Frequency Not Known:	Priapism, spontaneous penile erection.

Nervous System Disorders

Very common:	Headache.
Common:	Dizziness.
Rare:	Stroke[(f)], migraine, syncope, transient ischemic attacks[(f)].
Frequency not known:	Seizures.

[(f)] Most of the patients in whom these events have been reported had pre-existing cardiovascular risk factors. However, it is not possible to determine whether these events are related directly to these factors, to tadalafil, to sexual activity, or to a combination of these or other factors.

Respiratory System Disorders

Uncommon:	Epistaxis.

Ear and Labyrinth Disorders

Very rare:	Sudden decrease or loss of hearing[(g)].

[(g)] Sudden decrease or loss of hearing has been reported in a small number of post-marketing and clinical trial cases with the use of all PDE5 inhibitors, including tadalafil. In some of the cases, medical conditions and other factors were reported that may have also played a role in the ear and labyrinth adverse events. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related directly to the use of tadalafil, to the patient's underlying risk factors for hearing loss, a combination of these factors, or to other factors.

Immune System Disorders

Rare:	Angioedema.

Reproductive System Disorders

Rare:	Penile haemorrhage and haematospermia.

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

Single doses of up to 500 mg have been given to healthy subjects, and multiple daily doses up to 100 mg have been given to patients. Adverse events were similar to those seen at lower doses. In cases of overdose, standard supportive measures should be adopted as required. Haemodialysis contributes negligibly to tadalafil elimination.

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

Pharmacotherapeutic group: medicines used in erectile dysfunction. ATC code G04BE08.

Mechanism of Action

Tadalafil is a potent, selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific PDE5 in the smooth muscle of the corpus cavernosum, the prostate, the bladder and their vascular supply.

In the corpus cavernosum, when sexual stimulation causes the local release of nitric oxide, inhibition of PDE5 by tadalafil produces increased levels of cGMP. This results in smooth muscle relaxation and inflow of blood into the penile tissues, thereby producing an erection. Tadalafil has no effect in the treatment of erectile dysfunction in the absence of sexual stimulation.

In the smooth muscle of the prostate, bladder and their vascular supply, the effect of PDE5 inhibition on cGMP concentration results in vascular relaxation and increases blood perfusion which may be the mechanism by which symptoms of benign prostatic hyperplasia are reduced. These vascular effects may be complemented by inhibition of bladder afferent nerve activity and smooth muscle relaxation of the prostate and bladder.

Pharmacodynamic Effects

Studies *in vitro* have shown that tadalafil is a selective inhibitor of PDE5. PDE5 is an enzyme found in smooth muscle of the corpus cavernosum, prostate, bladder, vascular and visceral smooth muscle, skeletal muscle, platelets, kidney, lung, and cerebellum. The effect of tadalafil is more potent on PDE5 than on other phosphodiesterases. Tadalafil is >10,000-fold more potent for PDE5 than for PDE1, PDE2, PDE4, and PDE7 enzymes which are found in the heart, brain, blood vessels, liver, leukocytes, skeletal muscle and other organs. Tadalafil is >10,000-fold more potent for PDE5 than for PDE3, an enzyme found in the heart and blood vessels. This selectivity for PDE5 over PDE3 is important because PDE3 is an enzyme involved in cardiac contractility. Additionally, tadalafil is approximately 700-fold more potent for PDE5 than for PDE6, an enzyme which is found in the retina and is responsible for phototransduction. Tadalafil is also >9,000-fold more potent for PDE5 than for PDE8, 9 and 10 and 14-fold more potent for PDE5 than for PDE11. The tissue distribution and physiological effects of the inhibition of PDE8 through PDE11 have not been elucidated.

Tadalafil administered to healthy subjects produced no significant difference compared to placebo in supine systolic and diastolic blood pressure (mean maximal decrease of 1.6/0.8 mmHg, respectively), in standing systolic and diastolic blood pressure (mean maximal decrease of 0.2/4.6 mmHg, respectively), and no significant change in heart rate.

Larger effects were recorded among subjects receiving concomitant nitrates (see **Section 4.3 Contraindications**).

In a study to assess the effects of tadalafil on vision, no impairment of colour discrimination (blue/green) was detected using the Farnsworth-Munsell 100-hue test. This finding is consistent with the low affinity

of tadalafil for PDE6 compared to PDE5. In addition, no effects were observed on visual acuity, electroretinograms, intraocular pressure, or pupillometry. Across all clinical studies, reports of changes in colour vision were rare (<0.1%).

Studies on Spermatogenesis

Three studies were conducted in men to assess the potential effect on spermatogenesis of tadalafil 10 mg (one 6-month study) and 20 mg (one 6-month and one 9-month study) administered daily. There were no adverse effects on sperm morphology or sperm motility in any of the three studies. In the study of 10 mg tadalafil for 6 months and the study of 20 mg tadalafil for 9 months, results showed a decrease in mean sperm concentrations relative to placebo. This effect was not seen in the study of 20 mg tadalafil taken for 6 months. In all 3 studies there were no statistically significant differences between the placebo and tadalafil groups for mean total sperm counts. In addition there was no adverse effect on mean concentrations of reproductive hormones, testosterone, luteinising hormone or follicle stimulating hormone with either 10 mg or 20 mg of tadalafil compared to placebo.

Clinical Efficacy and Safety

On-demand Dosing for the Treatment of Erectile Dysfunction (ED)

Tadalafil, when taken on-demand up to once daily, is effective in improving erectile function in men with ED. In clinical studies assessing patients' ability to engage in successful and satisfying sexual activity, tadalafil demonstrated highly statistically significant improvement compared to placebo. Additionally, partners of patients on tadalafil had statistically significantly greater satisfaction with sexual activity compared to partners of patients on placebo.

Tadalafil at doses of 2 mg to 100 mg has been evaluated in 16 clinical studies involving 3,250 patients. Tadalafil 10 mg and/or 20 mg, taken on-demand up to once daily, was compared to placebo in 6 primary efficacy studies (5 in general ED population, 1 in patients with diabetes). Seven hundred and twenty four (724) patients received tadalafil 10 mg or 20 mg and 379 patients received placebo in these randomised, double-blinded, parallel-group studies. Patients were free to choose the time interval between dose administration and the time of sexual attempts. Food and alcohol intake were not restricted. The studies were designed in this manner in order to allow for convenience and dosing flexibility for the patient and partner.

Several assessment instruments were used to evaluate the effect of tadalafil on erectile function. Global Assessment Questions (GAQ) were asked to determine whether the treatment improved patients' erections. During clinical studies, patients and partners completed sexual encounter profile (SEP) diaries assessing erectile function and sexual satisfaction of each sexual attempt. The International Index of Erectile Function (IIEF), a recall questionnaire, was also completed by patients. The IIEF provides global measures of erectile function and sexual satisfaction, as well as severity of ED.

In all primary efficacy studies, tadalafil demonstrated consistent and statistically significant improvement compared to placebo in all primary and secondary endpoints evaluated. In each primary efficacy study, a significant treatment effect was declared only if there was a statistically significant improvement on all three co-primary measures:

1) the IIEF Erectile Function domain;
2) SEP Question 2 (assessing the ability to penetrate the partner's vagina); and
3) SEP Question 3 (assessing the ability to maintain the erection).

The treatment effect did not diminish over time. Overall, tadalafil consistently showed efficacy in a broad and representative population that included patients with ED of various severities (mild, moderate, severe), aetiologies (including patients with diabetes), ages (21 to 86 years), ethnicities and durations of

ED. In the five primary efficacy studies of general populations, 81% of patients reported that tadalafil 20 mg improved their erections compared to 35% of patients on placebo. Also, patients with ED in all severity categories reported improved erections while taking tadalafil 20 mg (86%, 83% and 72% mild, moderate and severe, respectively) compared to patients on placebo (45%, 42% and 19% for mild, moderate and severe, respectively). Tadalafil showed statistically significant improvement in patients' ability to achieve an erection sufficient for sexual intercourse and maintain the erection for successful intercourse as measured by the SEP diaries. In the primary efficacy studies, 75% of intercourse attempts were successful in patients taking tadalafil 20 mg compared to 32% of patients on placebo. This finding was confirmed by partner SEP responses. Tadalafil also demonstrated statistically significant improvement in erectile function as measured by the IIEF Erectile Function domain. Additionally, in the primary efficacy studies, approximately 60% of patients taking tadalafil 20 mg achieved normal erectile function during treatment. Patients with ED in all severity categories improved into the normal range (defined by IIEF).

Patient Confidence and Sexual Satisfaction

The IIEF also measures patients' confidence that they can attain and keep an erection sufficient for sexual intercourse. Tadalafil statistically significantly improved patient confidence. Analysis of the Intercourse Satisfaction and Overall Satisfaction domains of the IIEF showed that tadalafil treatment provided statistically significant enhancement of sexual satisfaction measured by both domains. Additionally, tadalafil improved the proportion of sexual encounters that were satisfying for both the patient and the partner.

Efficacy in ED Patients with Diabetes Mellitus

Tadalafil is effective in treating ED in patients with diabetes. Patients with diabetes (n=451) were included in all primary efficacy studies, one of which specifically assessed tadalafil only in ED patients with Type 1 or Type 2 diabetes. Tadalafil produced statistically significant improvement in erectile function and sexual satisfaction. In these studies, 68% of patients with diabetes taking tadalafil 20 mg reported improved erections.

Period of Responsiveness

Two clinical studies were conducted in 571 patients in an at-home setting to define the period of responsiveness to tadalafil. One of the two studies specifically assessed the improvement of erectile function at 24 and 36 hours following tadalafil administration. In this study, approximately 60% of sexual attempts at both 24 and 36 hours were successful for patients on tadalafil 20 mg compared to approximately 30% of sexual attempts for patients on placebo.

Therefore, tadalafil demonstrated statistically significant improvement in erectile function and the ability to have successful sexual intercourse up to 36 hours following dosing, as well as patients' ability to attain and maintain erections for successful intercourse compared to placebo as early as 16 minutes following dosing.

Once-a-day Dosing for the Treatment of Erectile Dysfunction

Tadalafil at doses of 2.5 mg, 5 mg and 10 mg taken once a day was initially evaluated in 3 clinical studies involving 853 patients of various ages (range 21-82 years) and ethnicities, with erectile dysfunction of various severities (mild, moderate, severe) and aetiologies. In the two primary efficacy studies of general populations, 76% and 85% of patients reported that tadalafil 5 mg taken once a day improved their erections as compared to 29% and 30% with placebo. Also, patients with erectile dysfunction in all severity categories reported improved erections while taking tadalafil once a day. In the primary efficacy studies, the mean per-subject proportion of successful intercourse attempts in the general population

in tadalafil 5 mg-treated patients was 57% and 67% compared to 31% and 37% with placebo. The majority of the patients in these 3 initial studies were responders to previous on-demand treatment with PDE5 inhibitors.

In a subsequent study, 217 patients who were treatment naive were randomised to tadalafil 5 mg once-a-day vs placebo. The mean per-subject proportion of successful sexual intercourse attempts was 68% in tadalafil 5 mg treated patients compared to 52% for patients on placebo.

Tadalafil 5 mg significantly improves erectile function over the 24-hour period between the doses.

Once-a-day Dosing for the Treatment of Benign Prostatic Hyperplasia (BPH)

Tadalafil was studied in men with signs and symptoms of benign prostatic hyperplasia in 4 randomised, multi-national, double-blind, placebo-controlled, parallel-design primary efficacy and safety studies of 12 weeks duration enrolling over 1,500 patients of various ages (range 45-92 years). In the integrated data from these 4 studies, tadalafil 5 mg (n=742; mean change from baseline of -5.0) demonstrated statistical superiority over placebo (n=735; mean change from baseline of -2.7) in improving the total International Prostate Symptom Score (IPSS; mean treatment difference for tadalafil compared to placebo of -2.3, p<0.001) in the overall benign prostatic hyperplasia population. Similarly, in each of the individual studies, patients treated with tadalafil 5 mg had clinically meaningful improvements in lower urinary tract symptoms with statistically significantly greater decrease in total IPSS as compared to placebo after 12 weeks of treatment. Data for each study are shown below.

Table 4: Summary of results from individual BPH studies

Study	Treatment Arm	No. of Patients	Total IPSS		
			Baseline Value (± SD)	Change from Baseline	Difference (95 % CI) vs Placebo
LVHG	Tadalafil 5 mg	205	17.3 (± 5.97)	-4.8	-2.6[a] (-3.7, -1.5)
	Placebo	205	17.1 (± 6.36)	-2.2	
LVHJ	Tadalafil 5 mg	160	17.1 (± 6.06)	-5.6	-1.9[b] (-3.2, -0.6)
	Placebo	164	16.6 (± 5.99)	-3.6	
LVHR	Tadalafil 5 mg	206	18.5 (± 5.78)	-6.1	-2.3[a] (-3.5, -1.2)
	Placebo	194	18.2 (± 5.33)	-3.8	
LVID	Tadalafil 5 mg	171	17.2 (± 4.91)	-6.3	-2.1[c] (-3.3, -0.8)
	Tamsulosin 0.4 mg	165	16.8 (± 5.31	-5.7	-1.5[d] (-2.8, 0.2)
	Placebo	172	17.4 (± 5.97)	-4.2	

[a] p<0.001 vs placebo.
[b] p=0.004 vs placebo.
[c] p=0.001 vs placebo.
[d] p=0.023 vs placebo.

The improvement in total IPSS in the tadalafil group compared to placebo occurred as early as 1 week in the integrated data from Studies LVHJ and LVID (mean difference of -1.3, p<0.001) and 2 weeks in Study LVHR (mean difference of -1.8, p<0.001).

In the long-term open-label extension phase of the controlled study LVHG, in which patients received tadalafil 5 mg for up to 1 year after the 12-week double-blind treatment period, the improvement in total IPSS induced by tadalafil at week 12 of double-blind treatment was maintained over 1 year.

For the benign prostatic hyperplasia Impact Index (BII), the key secondary efficacy measure, tadalafil 5 mg (n=735; mean change from baseline of -1.6) demonstrated statistical superiority over placebo (n=725; mean change from baseline of -0.9) in improving the BII (mean treatment difference for tadalafil compared to placebo of -0.7, p<0.001) in the integrated data from the 4 studies.

Tadalafil 5 mg once daily resulted in clinically meaningful and statistically significant improvements in both BPH symptoms (as measured by the total IPSS) and erectile function (as measured by the EF domain of the IIEF questionnaire) in patients with both conditions. This was demonstrated in one of the placebo-controlled, double-blind, parallel-arm efficacy and safety studies which specifically assessed the efficacy and safety of tadalafil for once a day use in this population (Study LVHR). In this erectile dysfunction and benign prostatic hyperplasia study, tadalafil 5 mg demonstrated statistical superiority over placebo for total IPSS (mean treatment difference, -2.3; p<0.001) and for the International Index of Erectile Function Erectile Function (IIEF EF) domain score (mean treatment difference, 4.7; p<0.001). The mean per-subject proportion of successful sexual intercourse attempts in this study was 71.9% for tadalafil 5 mg patients compared to 48.3% patients on placebo.

5.2 Pharmacokinetic Properties

Absorption

Tadalafil is rapidly absorbed after oral administration and the mean maximum observed plasma concentration (C_{max}) is achieved at a median time of 2 hours after dosing. Absolute bioavailability of tadalafil following oral dosing has not been determined.

The rate and extent of absorption of tadalafil are not influenced by food, thus tadalafil may be taken with or without food. The time of dosing (morning versus evening) had no clinically relevant effects on the rate and extent of absorption.

Distribution

The mean volume of distribution is approximately 63 litres, indicating that tadalafil is distributed into tissues. At therapeutic concentrations, 94% of tadalafil in plasma is bound to proteins. Protein binding is not affected by impaired renal function.

Samples collected from healthy human subjects approximately 5 hours after dosing indicated that <0.0005% of the total dose of tadalafil is distributed to semen.

Biotransformation

Tadalafil is predominantly metabolised by the cytochrome P450 (CYP) 3A4 isoform. The major circulating metabolite is the methylcatechol glucuronide. This metabolite is at least 13,000-fold less potent than tadalafil for PDE5. Consequently, it is not expected to be clinically active at observed metabolite concentrations.

Elimination

The mean oral clearance for tadalafil is 2.5 L/hour and the mean half-life is 17.5 hours in healthy subjects. Tadalafil is excreted predominantly as inactive metabolites, mainly in the faeces (approximately 61% of the dose) and to a lesser extent in the urine (approximately 36% of the dose).

Linearity/Non-linearity

Tadalafil pharmacokinetics in healthy subjects are linear with respect to time and dose. Over a dose range of 2.5 mg to 20 mg, exposure (AUC) increases proportionally with dose. Steady-state plasma concentrations are attained within 5 days of once-a-day dosing.

Pharmacokinetics determined with a population approach in patients with erectile dysfunction are similar to pharmacokinetics in subjects without erectile dysfunction.

Characteristics in Specific Groups of Patients

Elderly

Healthy elderly subjects (65 years or over), had a lower oral clearance of tadalafil, resulting in 25% higher exposure (AUC) relative to healthy subjects aged 19 to 45 years. This effect of age is not clinically significant and does not warrant a dose adjustment.

Renal Impairment

In subjects with renal insufficiency, including those on haemodialysis, tadalafil exposure (AUC) was higher than in healthy subjects. Therefore, the recommended starting dose of tadalafil in patients with mild or moderate renal impairment is 10 mg for on demand treatment of erectile dysfunction. For patients with severe renal impairment 10 mg is the maximum recommended dose for on-demand treatment of erectile dysfunction (see **Section 4.2 Dose and Method of Administration**). In patients with mild or moderate renal impairment, the recommend dose is 5 mg once-a-day for the treatment of benign prostatic hyperplasia or for the treatment of benign prostatic hyperplasia and erectile dysfunction in men with both conditions. Once-a-day dosing of tadalafil for either the treatment of benign prostatic hyperplasia or erectile dysfunction is not recommended in patients with severe renal impairment.

Hepatic Impairment

Tadalafil exposure (AUC) in subjects with mild or moderate hepatic impairment (Child-Pugh Class A and B) is comparable to exposure in healthy subjects. No controlled data are available in patients with severe hepatic impairment (Child-Pugh Class C) (see **Section 4.4 Special Warnings and Precautions For Use**). Once-a-day administration has not been evaluated in patients with hepatic insufficiency. If tadalafil is prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician.

Patients With Diabetes

Tadalafil exposure (AUC) in patients with diabetes was approximately 19% lower than the AUC value for healthy subjects. This difference in exposure does not warrant a dose adjustment.

5.3 Preclinical Safety Data

Carcinogenicity, Mutagenesis, Impairment of Fertility

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenic potential, and toxicity to reproduction. There was no impairment of fertility in male and female rats. In dogs given tadalafil daily for 6 to 12 months at doses of 25 mg/kg/day and above, there were alterations to the seminiferous tubular epithelium that resulted in a decrease in spermatogenesis in some dogs (see **Section 5.1 Pharmacodynamic Properties**).

6 PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Tadalafil Lupin tablets contain the following excipients: croscarmellose sodium, pregelatinised maize starch, lactose monohydrate, magnesium stearate, microcrystalline cellulose and sodium lauryl sulfate.

Tadalafil Lupin 10 mg and 20 mg tablets are film-coated with OPADRY II complete film-coating system 32K520105 YELLOW (containing lactose monohydrate, hypromellose, triacetin, titanium dioxide (E171), iron oxide yellow (E172), purified talc).

Tadalafil Lupin 5 mg tablets are film-coated with OPADRY II complete film-coating system 32K520094 YELLOW (containing lactose monohydrate, hypromellose, triacetin, titanium dioxide (E171), iron oxide yellow (E172), purified talc).

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

24 months.

6.4 Special Precautions for Storage

Store below 25°C. Store in the original package.

6.5 Nature and Contents of Container

Tadalafil Lupin 5 mg tablets are supplied in PVC/AL and PVC/PCTFE (Aclar)/AL blister packs of 7 or 28 tablets per carton*.

Tadalafil Lupin 10 mg tablets are supplied in PVC/AL and PVC/PCTFE (Aclar)/AL blister packs of 2, 4 or 8 tablets per carton*.

Tadalafil Lupin 20 mg tablets are supplied in PVC/AL and PVC/PCTFE (Aclar)/AL blister packs of 2, 4 or 8 tablets per carton*.

* Not all pack sizes may be marketed.

6.6 Special Precautions for Disposal

No special requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Lupin NZ Limited
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9 DATE OF FIRST APPROVAL

09 October 2025

10 DATE OF REVISION OF THE TEXT

09 October 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of New Information
N/A	