AUSTRALIAN PRODUCT INFORMATION

CILATIL®

(tadalafil) film coated tablets

1 NAME OF THE MEDICINE

Tadalafil

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each CILATIL film-coated tablet contains 2.5 mg, 5 mg, 10 mg or 20 mg of tadalafil as the active ingredient.

Excipients of known effect: sugars as lactose.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

2.5 mg: a light yellow, film-coated, round, biconvex tablet debossed with 'M' on one side of the tablet and 'TL over 1' on the other side.

5 mg: a light yellow, film-coated, round, biconvex tablet debossed with 'M' on one side of the tablet and 'TL over 2' on the other side.

10 mg: a light yellow, film-coated, round, biconvex tablet debossed with 'M' on one side of the tablet and 'TL3' on the other side.

20 mg: a light yellow, film-coated, round, biconvex tablet debossed with 'M' on one side of the tablet and 'TL4' on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

CILATIL is indicated for the treatment of:

- erectile dysfunction (ED) in adult males
- moderate to severe lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) in adult males

4.2 DOSE AND METHOD OF ADMINISTRATION

CILATIL is for oral use.

CILATIL can be taken with or without food.

Erectile Dysfunction in Adult Males - on-demand dosing

The recommended dose of CILATIL is either 10 mg or 20 mg, taken prior to anticipated sexual activity. The maximum recommended dose is 20 mg. The maximum recommended dosing frequency is once per day. CILATIL 10 and 20 mg is intended for use prior to anticipated sexual activity and is not for continuous daily use.

Tadalafil has been proven effective up to 36 hours after dosing and, in some patients, as early as 16 minutes after dosing. Patients may initiate sexual activity at varying time points relative to dosing in order to determine their own optimal window of responsiveness.

Erectile Dysfunction in Adult Males - once-a-day dosing

In patients who anticipate a frequent use of tadalafil (i.e. at least twice weekly), a once daily regimen with the lowest dose of CILATIL 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.

Lower Urinary Tract Symptoms Associated with Benign Prostatic Hyperplasia in Adult Males

The recommended dose is 5 mg, taken at approximately the same time every day.

Adult Men with Erectile Dysfunction and Lower Urinary Tract Symptoms Associated with Benign Prostatic Hyperplasia

The recommended dose is 5 mg taken at approximately the same time every day.

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 taking into account any safety concerns and efficacy benefits.

Patients with Renal Impairment

For on-demand dosing for erectile dysfunction, the recommended dose of CILATIL is 10 mg taken prior to anticipated sexual activity and without regard to food for patients with mild or moderate renal impairment. Based on efficacy and tolerability the dose may be increased up to 20 mg. For patients with severe renal impairment 10 mg is the maximum recommended dose.

For once-a-day dosing for erectile dysfunction and/or lower urinary tract symptoms associated with benign prostatic hyperplasia, dosage adjustments are not required in patients with mild or moderate renal impairment. The dose may be decreased to 2.5 mg once a day in these patients based on individual tolerability. Once-a-day dosing of tadalafil is not recommended in patients with severe renal impairment.

Patients with Hepatic Impairment

For on-demand dosing for erectile dysfunction, the recommended dose of CILATIL 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 - PHARMACOKINETICS IN SPECIAL POPULATIONS – Hepatic Impairment)

Once-a-day dosing has not been evaluated in patients with hepatic impairment therefore, if prescribed for erectile dysfunction and/or lower urinary tract symptoms associated with benign prostatic hyperplasia, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician (see Section 5.2 PHARMACOKINETIC PROPERTIES - Pharmacokinetics in Special Populations – Hepatic Impairment). Once-a-day dosing is not recommended for patients with severe hepatic impairment (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Patients with Diabetes

Dosage adjustments are not required in patients with diabetes.

Elderly Patients

Dosage adjustments are not required in elderly patients. If tadalafil is prescribed in this patient group, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician, including an evaluation of concomitant illnesses, any renal impairment and other medications, at treatment initiation and during treatment. (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Use in the Elderly).

Patients Taking Potent CYP3A4 Inhibitors

For once-a-day dosing for erectile dysfunction and/or lower urinary tract symptoms associated with benign prostatic hyperplasia, dosage adjustments are not required in patients taking protease inhibitors (e.g. ritonavir) or other potent CYP3A4 inhibitors (e.g. ketoconazole). The dose may be decreased to 2.5 mg once a day in these patients based on individual tolerability.

Children

Tadalafil has not been studied in subjects under 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 was shown to potentiate the hypotensive effects of both acute and chronic nitrate administration. This is thought to result from the combined effects of nitrates and tadalafil on the nitric oxide/cGMP pathway.

Administration of tadalafil to patients who are using any form of organic nitrate is contraindicated. In a patient prescribed tadalafil where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours in most patients and 4-5 days in the elderly (approximately 4-5 half lives) should have elapsed after the last dose of tadalafil before nitrate administration is considered. In such circumstances, nitrates should only be administered under close medical supervision with appropriate haemodynamic monitoring (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Tadalafil is contraindicated in men for whom sexual intercourse is inadvisable due to unstable cardiovascular disease (e.g. patients with unstable angina and severe congestive heart failure) (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 tadalafil.

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 PDE5 inhibitor exposure (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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

- patients with a 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 should not be used in patients with a known hypersensitivity to tadalafil or to any ingredient of the tablet.

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Before Treatment with Tadalafil

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

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 lower urinary tract symptoms associated with benign prostatic hyperplasia, a medical history and physical examination should be undertaken to rule out the presence of carcinoma of the prostate as well as other potential underlying causes of urinary symptoms and the patient should be carefully assessed for cardiovascular conditions. (Section 4.3 CONTRAINDICATIONS and Section 5.1 PHARMACODYNAMIC PROPERTIES – Clinical Trials).

Cardiovascular

Physicians should consider the potential cardiac risk of sexual activity in patients with pre-existing cardiovascular disease. Patients who experience symptoms upon initiation of sexual activity should be advised to refrain from further sexual activity and should report the episode to their physician.

As with other PDE5 inhibitors, tadalafil has systemic vasodilatory properties that may result in mild and 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 vasodilatory effects. Tadalafil potentiates the hypotensive effect of nitrates. Therefore, coadministration of tadalafil and nitrates is contraindicated (see Section 4.3 CONTRAINDICATIONS). Tadalafil also potentiates the effect of some classes of antihypertensive medications, and this may be clinically important in some individuals. When initiating daily treatment with tadalafil, appropriate clinical considerations should be given to a possible dose adjustment of the antihypertensive therapy (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS – Potential for Tadalafil to Affect Other Drugs – Antihypertensive Agents).

Caution should be exercised when prescribing tadalafil to patients who are taking alpha[1] blockers, such as doxazosin, as simultaneous administration may lead to symptomatic hypotension in some patients. The efficacy of the co-administration of an alpha-blocker and tadalafil for the treatment of BPH has not been adequately studied and therefore not recommended for use (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS – Potential for Tadalafil to Affect Other Drugs).

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.

Hearing

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. These events, which may be

accompanied by tinnitus and dizziness, have been reported in temporal association to the 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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Vision

Visual defects including central serous chorioretinopathy (CSCR) have been reported in connection with the intake of tadalafil and other PDE5 inhibitors. Most cases of CSCR resolved spontaneously after stopping tadalafil. Physicians should advise patients to stop use of all PDE5 inhibitors, including tadalafil, and seek medical attention in the event of sudden visual defect, visual acuity impairment, visual distortion and/or loss of vision in one or both eyes (see Section 4.3 CONTRAINDICATIONS). Such an event may be a sign of non-arteritic anterior ischaemic optic neuropathy (NAION), a cause of decreased vision, including permanent loss of vision that has been reported rarely postmarketing in temporal association with the use of all PDE5 inhibitors. An increased risk of acute NAION has been suggested from analysis of observation data in men with erectile dysfunction within 1 to 4 days of episodic PDE5 inhibitor use (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - Adverse Drug Reactions Identified from Spontaneous Post-marketing Surveillance).

Tadalafil and Other Treatments of Erectile Dysfunction

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.

Priapism and Anatomical Deformation of the Penis

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).

Use with CYP3A4 Inhibitors

Caution should be exercised when prescribing tadalafil to patients using potent CYP3A4 inhibitors (ritonavir, saquinavir, ketoconazole, itraconazole, and erythromycin) as increased tadalafil exposure (AUC) has been observed if the medicinal products are combined.

Lactose

CILATIL tablets contain lactose.

Use in Hepatic Impairment

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

Once-a-day administration either for the treatment of erectile dysfunction or lower urinary tract symptoms associated with 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. Once-a-day dosing is not recommended for patients with severe hepatic impairment.

Use in Renal Impairment

In a clinical pharmacology study, administration of tadalafil 10 mg to patients with moderate renal failure (creatinine clearance = 31 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 (creatinine clearance = 51 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 creatinine clearance < 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.

Use in the Elderly

The number of patients aged 75 years and older who received tadalafil 5 mg for more than 12 weeks is small and therefore the safety and efficacy of long-term use of tadalafil for the treatment of LUTS/BPH for this age group is limited.

In clinical trials with tadalafil 5 mg taken once a day for the treatment of benign prostatic hyperplasia, dizziness and diarrhoea were reported more frequently in patients over 75 years of age. In the clinical pharmacology study LVHN, the mean maximum decrease in standing and supine systolic and diastolic BP at both Day 1 (following a single dose of tadalafil 20 mg) and Day 10, (following once daily dosing with tadalafil 20 mg) was higher in the elderly subjects (70-85 years) compared with younger subjects aged ≤ 60 years. In addition, a higher number of elderly subjects (70-85 years) experienced clinically significant decreases in blood pressure compared with younger subjects. In study LVHS of men with BPH-LUTS on concomitant alpha blockers, a higher proportion of patients aged ≥ 75 years in the tadalafil group had at least one treatment-emergent positive orthostatic test compared with patients aged < 75 years. Based on these data, hypotensive events are a potential risk in patients aged ≥ 75 years treated with tadalafil 5 mg.

If tadalafil is prescribed in this patient group, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician, including an evaluation of concomitant illnesses, any renal impairment and other medications, at treatment initiation and during treatment (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) and Section 5.1 PHARMACODYNAMIC PROPERTIES – Clinical Trials).

Paediatric Use

No data available.

Effects on Laboratory Tests

There are no data available that shows that tadalafil has an effect on laboratory tests.

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 drugs metabolised by CYP450 isoforms. Studies have confirmed that tadalafil does not inhibit or induce CYP450 isoforms, including CYP1A2, CYP3A4, CYP2C9, CYP2C19, CYP2D6 and CYP2E1.

Potential for Other Drugs to Affect Tadalafil

Tadalafil is principally metabolised by CYP3A4. A selective inhibitor of CYP3A4, ketoconazole (400 mg daily), increased tadalafil single-dose exposure (AUC) by 312% and C_{max} by 22%, and ketaconazole (200 mg daily), increased tadalafil single-dose exposure (AUC) by 107%, and C_{max} by 15% relative to the AUC and C_{max} values for tadalafil (10 mg) alone.

Ritonavir (200 mg twice daily), an inhibitor of CYP3A4, 2C9, 2C19, and 2D6, increased tadalafil single dose exposure (AUC) by 124% with no change in C_{max}. Ritonavir (500 mg or 600 mg twice daily)

increased tadalafil (20 mg) single-dose exposure (AUC) by 32% with a 30% reduction 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 should be co-administered with caution because they would be expected to increase plasma concentrations of tadalafil.

A selective CYP3A4 inducer, rifampicin (600 mg daily), reduced tadalafil single-dose exposure (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 phenobarbitone, phenytoin and carbamazepine would also decrease plasma concentrations of tadalafil.

Studies with the CYP3A4 probe substrates midazolam with tadalafil 10 mg and lovastatin with tadalafil 20 mg showed little alteration in the kinetics suggesting that tadalafil is unlikely to have interactions with CYP3A4 substrates.

Antacids (magnesium hydroxide/aluminium hydroxide)

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).

H_2 Antagonists

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

Potential for Tadalafil to Affect Other Drugs

Nitrates

In clinical pharmacology studies, tadalafil 10 mg was shown to potentiate the hypotensive effects of nitrates. Therefore, administration of tadalafil to patients who are using any form of organic nitrate is contraindicated. A placebo-controlled study was conducted to assess the degree of interaction between nitroglycerine and tadalafil. One hundred and fifty subjects received daily doses of tadalafil 20 mg for 7 days. On the 7th day, 0.4 mg sublingual nitroglycerine was given at various times following the daily dose of tadalafil. This interaction lasted for more than 24 hours and was no longer detectable when 48 hours had elapsed (see Section 4.3 CONTRAINDICATIONS)

Recreational Drugs (called “poppers” or “amyl”)

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.

Antihypertensive Agents

Tadalafil has systemic vasodilatory properties and may augment the blood pressure lowering effects of antihypertensive agents. Patients should be advised of this possibility. In a clinical pharmacology study measuring ambulatory blood pressure, when tadalafil (20 mg) was administered to 17 hypertensive patients treated with angiotensin II receptor blockers, ambulatory systolic blood pressure fell by 30 mmHg or more in 9 (53%) subjects on tadalafil treatment and in 5 (29%) subjects on placebo treatment, with a maximum fall of 57 mmHg following tadalafil compared to 37 mmHg following placebo. None of the decreases were associated with any hypotensive symptoms. 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 other clinical pharmacology studies, tadalafil 10 mg was added to angiotensin converting enzyme (ACE) inhibitors (enalapril), beta blockers (metoprolol) or thiazide diuretics (bendrofluazide). Tadalafil 10 mg and 20 mg was added to calcium channel blockers (amlodipine) or alpha-blockers (tamsulosin). In all these studies, tadalafil did not produce a significant additional reduction in mean systolic or diastolic blood pressure. However, potentially significant blood pressure reductions occurred in some individuals. Analysis of phase 3 clinical trial data showed no difference in the overall incidence of adverse events in patients taking tadalafil with or without hypertensive medications.

Human Platelets Contain the PDE5 Enzyme System

Tadalafil, in limited studies, did not affect platelet function in vivo. In in vitro studies tadalafil was shown to potentiate the antiaggregatory effect of sodium nitroprusside (a nitric oxide donor).

Alpha Blockers

In two clinical pharmacology studies, no significant decreases in blood pressure were observed when tadalafil was co-administered to healthy subjects taking the selective alpha[1A]-adrenergic blocker, tamsulosin.

In three clinical pharmacology studies when tadalafil was co-administered to healthy subjects taking doxazosin (4-8 mg daily), an alpha[1]-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 hemodynamic effects from the co-administration of tadalafil 5 mg for once daily use. Subjects had a mean age of 67 years (59% > 65; 25% ≥ 75 years of age). In this study, there was no statistically significant difference in treatment-emergent dizziness.

Caution is advised when PDE5 inhibitors are co-administered with nonselective alpha (α1)-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 (e.g., fainting).

Consideration Should be Given to the Following:

Patients should be stable on alpha-blocker therapy prior to initiating a PDE5 inhibitor. Patients who demonstrate hemodynamic 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.

5-alpha Reductase Inhibitors

In a 26-week clinical trial that compared tadalafil 5 mg co-administered with finasteride 5 mg to placebo plus finasteride 5 mg for the early relief of BPH symptoms, no new adverse reactions were identified. However, as a formal pharmacokinetic drug-drug interaction study evaluating the effects of tadalafil and 5-alpha reductase inhibitors (5-ARIs) has not been performed, caution should be exercised when tadalafil is co-administered with 5-ARIs.

Alcohol

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 20 mg 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.

Aspirin

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

Warfarin

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 an increase or decrease in PT and/or international normalised ratio (INR) should be considered when patients begin taking or cease taking tadalafil.

Ethinylestradiol

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

Theophylline

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

Riociguat

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

Effects on Fertility

There were no effects on fertility, reproductive performance or reproductive organ morphology in male or female rats given oral doses of tadalafil up to 400 mg/kg/day (systemic exposure ca 13 (males) or 25 (females) times that expected at the maximum recommended dose of 20 mg taken once daily, based on AUC for unbound drug at steady state). However, regression of the seminiferous tubular epithelium of the testes resulting in oligospermia or aspermia in the epididymides was observed in dogs treated for 6 or 12 months with oral tadalafil doses ≥ 25 mg/kg/day. The no-observed-effect level for these effects in the 6-month dog study was 10 mg/kg/day. At this dose, systemic exposure to tadalafil, based on unbound drug concentrations,

was similar to that expected in humans taking the maximum recommended dose of 20 mg tadalafil daily. Similar findings were not observed in rats and mice (see section 5.1 Pharmacodynamic Properties).

Use in Pregnancy

Pregnancy category: B1

CILATIL is not intended for use by women.

Studies in rats have shown that tadalafil and/or its metabolites cross the placenta and distribute to the foetus. No evidence of embryofoetal toxicity or teratogenicity was observed in pregnant rats or mice given oral doses of tadalafil up to 1000 mg/kg/day. These doses were associated with systemic exposure to tadalafil ca 12-14-fold that expected at the maximum recommended dose of 20 mg taken once daily, based on AUC for unbound drug at steady state. Increased postnatal pup mortality was observed in rats after oral treatment with tadalafil doses ≥ 60 mg/kg/day during gestation and lactation. The no-effect dose of 30 mg/kg/day was associated with systemic exposure ca 10-fold that expected in humans at the maximum recommended dose of 20 mg tadalafil taken once daily, based on AUC for unbound drug at steady state.

There are no studies of tadalafil in pregnant women.

Use in Lactation

CILATIL is not intended for use by women.

Tadalafil and/or its metabolites are excreted in the milk of lactating rats at concentrations up to 2.4-fold higher than the maximal maternal plasma concentration. Increased postnatal pup mortality was observed in rats after treatment with oral tadalafil doses ≥ 60 mg/kg/day during gestation and lactation (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION - Use in Pregnancy).

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The frequency of reports of dizziness in placebo and tadalafil arms in clinical trials was similar, except in patients over 75 years of age receiving tadalafil 5mg once a day for the treatment of benign prostatic hyperplasia in whom dizziness was reported more frequently. Patients should be aware of how they react to tadalafil before driving or operating machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

An adverse event is defined as any untoward medical occurrence in a patient administered tadalafil that first occurred or worsened in severity after baseline and which does not necessarily have to have a causal relationship with tadalafil treatment. An adverse drug reaction is an adverse event where a causal relationship between tadalafil treatment and an adverse event is at least a reasonable possibility.

Erectile Dysfunction (ED) Clinical Trials

<u>On-Demand Dosing (10mg or 20mg)</u>

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 and 20 mg to over 700 subjects (ages 25 to 80 years). The discontinuation rate due to adverse events in tadalafil-treated patients (2.5%) was not significantly different, although was numerically greater, than placebo-treated patients (1.3%). In these studies, the adverse events 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.

Table 1: Treatment-Emergent Adverse Events Reported by ≥ 2% of Patients Treated with Tadalafil 10 mg or 20 mg 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
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

Adverse Drug Reactions Reported by <2% of Patients Treated with Tadalafil 10 mg or 20 mg in Phase 3 Studies

Frequency estimate: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10,000 to < 1/1000), very rare (< 1/10,000) and not known (events not reported in registration trials cannot be estimated from post-marketing spontaneous reports).

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 (2.5mg or 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 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 Treated with Tadalafil 2.5 mg or 5 mg 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

Adverse Drug Reactions Reported by < 2% of Patients Treated with Tadalafil 2.5 mg or 5 mg in Phase 3 Studies

Frequency estimate: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10,000 to < 1/1000), very rare (< 1/10,000) and not known (events not reported in registration trials cannot be estimated from post-marketing spontaneous reports).

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.

Lower Urinary Tract Symptoms (LUTS) Associated with 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 patients with BPH and

BPH/ED. The discontinuation rate due to adverse events in tadalafil-treated patients (3.1%) was higher than placebo-treated patients (1.5%), with headache being the most frequently reported AE leading to discontinuation in the tadalafil 5 mg group (0.7%). 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 ≥ 1% of Patients Treated with Tadalafil 5 mg and More Frequent on Drug than Placebo in Phase 3 Studies

System Organ Class	Adverse Event	Tadalafil (N = 752) (%)	Placebo (N = 748) (%)
Nervous System Disorders	Headache	3.9	2.0
	Dizziness	1.3	0.8
Musculoskeletal and Connective Tissue Disorders	Back pain	2.4	1.2
	Pain in extremity	1.5	0.0
	Myalgia	1.2	0.5
Gastrointestinal Disorders	Dyspepsia	2.4	0.1
	Diarrhoea	1.3	1.1
	Gastroesophageal Reflux Disease	1.1	0.0
Vascular Disorders	Hypertension	1.6	0.7

Adverse Drug Reactions Reported by < 1% of Patients Treated with Tadalafil 5 mg in Phase 3 Studies

Frequency estimate: very common (≥ 1/10), Common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10,000 to < 1/1000), very rare (< 1/10,000) and not known (events not reported in registration trials cannot be estimated from post-marketing spontaneous reports).

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

Respiratory, Thoracic and Mediastinal Disorders – uncommon: dyspnoea

Elderly

Data in patients over 65 years of age receiving tadalafil in clinical trials, either for the treatment of erectile dysfunction or the treatment of benign prostatic hyperplasia, are limited.

In clinical trials for the treatment of benign prostatic hyperplasia, involving 74 patients aged ≥ 75 years receiving tadalafil 5 mg taken once a day for 12 weeks, dizziness (4.8%) and diarrhoea (7.1%) were reported more frequently in patients aged ≥ 75 years compared with patients aged < 75 years (dizziness, 1.1%; diarrhoea 1.1%). The adverse event rate for patients ≥ 75 years receiving tadalafil was 32.1%, compared to 26.8% in patients < 75 years and 19.4% in patients ≥ 75 years receiving placebo (p = 0.043).

In all BPH studies a total of 62 patients aged ≥ 75 years were exposed to tadalafil 5 mg for ≥ 12 months. Of these 8.8% reported an SAE and 9.8% discontinued due to an adverse event which was more frequent compared to patients < 75 years (3.2% reported an SAE and 6.7% discontinued due to an adverse event) (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS for Use and Section 5.1 PHARMACODYNAMIC PROPERTIES – Clinical Trials).

Adverse Drug Reactions 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[(d)]

Uncommon; palpitations, tachycardia, chest pain

Rare; myocardial infarction

Frequency not known; unstable angina pectoris, ventricular arrhythmia, sudden cardiac death

[(d)] 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 Disorders

Uncommon; hyperhidrosis (sweating)

Eye disorders

Uncommon; blurred vision

Rare; visual field defect

Frequency not known; non-arteritic anterior ischemic optic neuropathy (NAION), retinal vascular occlusion, central serous chorioretinopathy.

Non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported rarely postmarketing in temporal association with the use of phosphodiesterase type 5 (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 Disorders

Rare; prolonged erections

Frequency not known; priapism, spontaneous penile erection

Nervous System Disorders

Very common; headache

Common; dizziness

Rare; stroke[e], migraine, syncope, transient ischemic attacks[e]

Frequency not known; seizures

[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.

Respiratory System Disorders

Uncommon; epistaxis

Ear and Labyrinth Disorders

Very rare; sudden decrease or loss of hearing[f]

[f] 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

Rare; penile haemorrhage, haematospermia

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Single doses of up to 500 mg of tadalafil have been given to healthy subjects and multiple daily doses of 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 information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Tadalafil is a reversible inhibitor of cyclic guanosine monophosphate (cGMP) – specific phosphodiesterase type 5 (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.

Studies in vitro have shown that tadalafil inhibits PDE5 more potently than other PDEs. PDE5 is an enzyme found in the smooth muscle of the corpus cavernosum, prostate, bladder, vascular and visceral smooth muscle, skeletal muscle, platelets, kidney, lung and cerebellum. 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.

Studies of Tadalafil on Vision

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 (see section 4.8 Adverse Effects (Undesirable Effects)).

Studies of Tadalafil on Blood Pressure and Heart Rate

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).

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 or 20 mg of tadalafil compared to placebo.

Study on QT

The effect of a single 100 mg dose of tadalafil on the QT interval was evaluated at the time of peak tadalafil concentration in a randomized, double-blinded, placebo, and active (intravenous ibutilide) -controlled crossover study in 90 healthy males aged 18 to 53 years. The mean change in QTc (Fridericia QT correction) for tadalafil, relative to placebo, was 3.5 milliseconds (two-sided 90% CI = 1.9, 5.1). The mean change in QTc (Individual QT correction) for tadalafil, relative to placebo, was 2.8 milliseconds (two-sided 90% CI = 1.2, 4.4). A 100 mg dose of tadalafil (5 times the highest recommended dose) was chosen because this dose yields exposures covering those observed upon coadministration of tadalafil with potent CYP3A4 inhibitors or those observed in renal impairment. In this study, the mean increase in heart rate associated with a 100 mg dose of tadalafil compared to placebo was 3.1 beats per minute.

Clinical Trials

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 erectile dysfunction (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 significant greater satisfaction with sexual activity compared to partners of patients on placebo.

Tadalafil at doses of 2 to 100 mg has been evaluated in 16 clinical studies involving 3250 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 a 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), etiologies (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% for 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

The diary data from 11 previous efficacy studies in the general ED population was combined to define the period of responsiveness. There were 321, 1143, and 638 patients in the 10 mg, 20 mg tadalafil and placebo group respectively. The response appeared as early as < 1 hour. At 24 hours, 71% & 72% of attempts at sexual intercourse were successful with 10 mg (n = 76) and 20 mg (n = 366) tadalafil respectively. The success rate at 36 hours was 72% and 75% with 10 mg (n = 34) and 20 mg (n = 129) tadalafil respectively. The success rate with placebo was 44% (n = 135) and 47% (n = 46) at 24 and 36 hours post-dose respectively.

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 (ED)

Tadalafil at doses of 2.5, 5, 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. The majority of the patients in these 3 initial studies were responders to previous on-demand treatment with PDE5 inhibitors. 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 two primary efficacy studies of general populations, the mean per-subject proportion of successful intercourse attempts in tadalafil 5-mg-treated patients was 57% and 67% compared to 31% and 37% with placebo.

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

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

Once-a-Day Dosing for the Treatment of Lower Urinary Tract Symptoms (LUTS) Associated with Benign Prostatic Hyperplasia (BPH)

Tadalafil was studied in men with moderate or severe lower urinary tract symptoms associated with benign prostatic hyperplasia in 4 randomised, multi-national, double-blind, placebo-controlled, parallel-design primary efficacy and safety studies of 12 weeks duration enrolling 1500 patients of various ages (range 45-92 years, mean 63.1 years) including 74 patients ≥ 75 years randomised to tadalafil 5 mg for 12 weeks. Patients with unstable angina, myocardial infarction or coronary intervention within 90 days, stroke in past 6 months, current treatment with nitrates, heart failure (New York Heart Association Class 2 or Class 3 or

greater, dependent on study), uncontrolled diabetes (glycosylated HbA1c greater than 9%), or uncontrolled hypertension (systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg) were not enrolled in the LUTS/BPH clinical trials.

Other patients excluded from the studies included:

- infectious, neurological, anatomical or malignant bladder or urethral conditions such as urinary tract infection, interstitial cystitis, urethral stricture or intravesical median lobe, recent urinary retention, Parkinson's disease, multiple sclerosis, and pelvic radiotherapy.
- pelvic surgery or any other pelvic procedure or recent instrumentation of the lower urinary tract such as prostatectomy, penis implant, bowel resection or cystoscopy or prostate biopsy
- lower urinary tract trauma or bladder stones within 6 months of screening
- angina requiring treatment with short or long acting nitrates
- bladder post void residual volume (PVR) ≥ 300ml
- severe renal or hepatic impairment
- receiving androgens, antiandrogens or approved or experimental pharmacologic BPH, overactive bladder (OAB), or ED therapies, including alpha blockers, 5-alpha reductase inhibitors (5-ARIs), antimuscarinics phosphodiesterase type 5 (PDE5) inhibitors, or herbal preparations

The primary efficacy endpoint that evaluated the effect of tadalafil for the signs and symptoms of BPH was the International Prostate Symptom Score (IPSS), a four week recall questionnaire that was administered at the beginning and end of a placebo run-in period and subsequently at follow-up visits after randomization. The IPSS assesses the severity of irritative (frequency, urgency, nocturia) and obstructive symptoms (incomplete emptying, stopping and starting, weak stream, and pushing or straining), with scores ranging from 0 to 35; higher numeric scores representing greater severity. Maximum urinary flow rate (Q_{max}), an objective measure of urine flow, was assessed as a secondary efficacy endpoint in Study LVHJ and as a safety endpoint in Study LVHK.

In each of the individual studies, patients treated with tadalafil 5 mg had 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 LUTS/BPH Studies

Study	**Treatment Arm**	**Severity**	**No. of Patients**	**Total IPSS**		
				Baseline Value (±SD)	**Change from Baseline**	**Difference (95 % CI) vs Placebo**
LVHG	Tadalafil 5 mg	All	205	17.3 (±5.97)	-4.8	-2.6[a] (-3.7, -1.5)
		Moderate	122	14.7 (±3.01)	-4.0	-3.0 (-4.5, -1.5)
		Severe	71	23.7 (±3.40)	-5.6	-2.3 (-4.3, -0.4)
	Placebo	All	205	17.1 (±6.36)	-2.2	

		Moderate	122	14.4 (±2.96)	-1.0	
		Severe	70	24.0 (±3.51)	-3.3	
LVHJ	Tadalafil 5 mg	All	160	17.1 (±6.06)	-5.6	-1.9[b] (-3.2, -0.6)
		Moderate	89	14.7 (±2.84)	-4.4	-1.2 (-3.0, 0.6)
		Severe	61	22.9 (±3.38)	-9.0	-4.0 (-6.2, -1.7)
	Placebo	All	164	16.6 (±5.99)	-3.6	
		Moderate	97	14.3 (±2.90)	-3.2	
		Severe	54	23.4 (±2.85)	-5.1	
LVHR	Tadalafil 5 mg	All	206	18.5 (±5.78)	-6.1	-2.3[a] (-3.5, -1.2)
		Moderate	119	14.9 (±2.63)	-4.6	-1.2 (-2.9, 0.5)
		Severe	83	24.1 (±3.92)	-8.8	-2.9 (-4.8, -1.0)
	Placebo	All	194	18.2 (±5.33)	-3.8	
		Moderate	117	15.2 (±2.98)	-3.5	
		Severe	74	23.6 (±3.26)	-5.9	
LVID	Tadalafil 5 mg	All	171	17.2 (±4.91)	-6.3	-2.1[c] (-3.3, -0.8)
		Moderate	120	15.0 (±2.70)	-6.1	-2.4 (-4.0, -0.8)
		Severe	48	23.5 (±3.07)	-7.4	-1.2 (-3.6, 1.2)
	Placebo	All	172	17.4 (±5.97)	-4.2	
		Moderate	112	14.7 (±2.86)	-3.7	
		Severe	54	24.4 (±4.00)	-6.2	

a p<.001 vs placebo, b p=.004 vs placebo, c p=.001 vs placebo, d p=.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.

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 demonstrated statistical superiority over placebo in improving the BII in each of the 4 studies. No adjustments for multiple comparisons were included in Study LVHG.

In Study LVHJ, the effect of tadalafil 5 mg once daily on maximum urinary flow rate (Q_{max}) was evaluated as a secondary efficacy endpoint. Mean Q_{max} increased from baseline in both the treatment and placebo groups (tadalafil 5 mg: 1.6 mL/sec, placebo: 1.2 mL/sec); however, these changes were not significantly different between groups.

In Study LVHK, the effect of tadalafil 5 mg once daily on Q_{max} was evaluated as a safety endpoint. Mean Q_{max} increased from baseline in both the treatment and placebo groups (tadalafil 5 mg: 1.6 mL/sec, placebo: 1.1 mL/sec); however, these changes were not significantly different between groups.

The number of patients aged 75 years or older who received tadalafil 5 mg for more than 12 weeks in studies supporting the LUTS/BPH indication is limited. In the four primary efficacy and safety studies a total of 74 patients aged ≥ 75 years were exposed to tadalafil 5mg for 12 weeks. In all BPH studies a total of 62 patients aged ≥ 75 years were exposed to tadalafil 5mg for ≥ 12 months.

The change from baseline to endpoint in IPSS for patients aged ≥ 75 years is shown in the table below. In each study, no statistically significant difference was observed between tadalafil 5mg and placebo with respect to baseline to endpoint change in total IPSS among patients aged ≥ 75 years. In addition, in the integrated analysis of the 4 studies, the percentage of patients aged ≥ 75 years achieving at least a 25% decrease in total IPSS was similar on tadalafil 5 mg and placebo (53.6 versus 48.4%) and this difference was not statistically significant (relative benefit of 1.11, 95%CI 0.83, 1.48) (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Table 5: Summary of Results from Individual LUTS/BPH Studies for Patients Aged ≥ 75 Years

Study	Treatment Arm	No. of Patients	Change in IPSS from Baseline (±SD)
LVHG	Tadalafil 5 mg	20	-3.1 (±6.82)
	Placebo	12	-2.8 (±3.90)
LVHJ	Tadalafil 5 mg	30	-5.5 (±7.39)
	Placebo	35	-3.5 (±5.74)
LVHR	Tadalafil 5 mg	21	-6.3 (±6.29)
	Placebo	23	-4.6 (±5.51)
LVID	Tadalafil 5 mg	13	-3.5 (±6.59)
	Placebo	23	-5.0 (±5.47)

Once-a-Day Dosing for the Treatment of Erectile Dysfunction (ED) and the Treatment of Lower Urinary Tract Symptoms (LUTS) Associated with Benign Prostatic Hyperplasia (BPH)

Tadalafil 5 mg once daily resulted in 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; $p < .001$) and for the International Index of Erectile Function Erectile Function (IIEF EF) domain score (mean treatment difference, 4.7; $p <.001$). Patients treated with tadalafil 5 mg had statistically significant improvements versus placebo in both lower urinary tract symptoms and erectile function after 12 weeks of treatment. 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.

In this study, the effect of tadalafil 5 mg once daily on Q_{max} was evaluated as a safety endpoint. Mean Q_{max} increased from baseline in both the treatment and placebo groups (tadalafil 5 mg: 1.6 mL/sec, placebo: 1.2 mL/sec); however, these changes were not significantly different between groups.

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. There is no clinically relevant effect of food on the rate and extent of absorption of tadalafil, thus tadalafil may be taken with or without food. The time of dosing (morning versus evening) has no clinically relevant effects on the rate and extent of absorption. The absolute bioavailability of oral tadalafil has not been established. The mean bioavailability of the tadalafil 20 mg tablet has been estimated to be 88% relative to an oral suspension dosage form.

Distribution

The mean volume of distribution after oral dosing is approximately 63 L. At therapeutic concentrations, 94% of tadalafil in plasma is bound to proteins. Protein binding is not affected by impaired renal function. Less than 0.0005% of the administered dose appears in the semen of healthy subjects.

Metabolism

Tadalafil is metabolised mainly (> 80%) by the cytochrome P450 (CYP) 3A4 isoform, with minor contributions by CYPs 2C8, 2C9, 2C19 and 2D6 (< 20% collectively). 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.

Excretion

The mean oral clearance for tadalafil is 2.5 L/hr 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).

Tadalafil pharmacokinetics in healthy subjects are linear with respect to time and dose. Over a dose range of 2.5 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.

Table 6: Summary of Geometric Mean (CV%) Single Dose Pharmacokinetic Parameters of Tadalafil (20 mg) in Healthy Volunteers

	AUC (µg*h/L)	**C_{max} (µg/L)**	**t_{max} (h)**	**$t_{1/2}$ (h)**
Geometric mean (CV%)	8066 (39.3)	378 (27.6)	2.0 (0.5 to 12.0)[(a)]	17.5 (32.3)

[(a)] Median and range

Pharmacokinetics in Special Populations

Elderly

Healthy elderly subjects (65 years or over) had a lower clearance of tadalafil, resulting in a half-life of 22 hours and 25% higher exposure (AUC), relative to healthy subjects aged 19 to 45 years (half-life of 16-17 hours). This effect does not appear to warrant a dose adjustment (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION – Elderly Patients). The half-life of tadalafil in the elderly increases the period after the last dose of tadalafil during which nitrates should be avoided (see Section 4.3 CONTRAINDICATIONS).

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 (creatinine clearance 51 to 80 mL/min) or moderate (creatinine clearance 31 to 50 ml/min) renal impairment is 10 mg for on-demand dosing for the treatment of erectile dysfunction. For patients with severe (creatinine clearance ≤30 ml/min) renal impairment, 10 mg is the maximum recommended dose for on-demand dosing for the treatment of erectile dysfunction (see SECTION 4.2 DOSE AND METHOD OF ADMINISTRATION).

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.

Hepatic Impairment

Tadalafil exposure (AUC) in subjects with mild and 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). 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. Once a day dosing is not recommended for patients with severe hepatic impairment (see SECTION 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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

Genotoxicity

Tadalafil was not mutagenic or genotoxic in in vitro bacterial and mammalian cell assays, and in in vitro human lymphocytes and in vivo rat micronucleus assays.

Carcinogenicity

Oral administration of tadalafil at doses of 400 mg/kg/day for up to two years in mice resulted in increased development of hepatocellular adenomas in males but not in females. Tadalafil also caused hepatocellular microsomal enzyme induction in rodents and it is possible that this could lead to an increased incidence of hepatocellular neoplasms. However, hepatic microsomal enzyme induction is a common non-genotoxic biologic effect associated with hepatocellular tumour formation in rodents and is not considered relevant to human cancer risk. The no effect dose of 60 mg/kg/day was associated with systemic exposure to tadalafil approximately 5- to 7-fold that expected in men taking the maximum recommended dose of 20 mg daily, based on unbound drug concentrations.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The film coated tablets also contain the following inactive ingredients: povidone, sodium lauryl sulfate, poloxamer, lactose, croscarmellose sodium, microcrystalline cellulose, colloidal anhydrous silica, magnesium stearate and OPADRY II complete film coating system 32K12884 YELLOW (ID 4539).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

2.5 mg: available in PVC/Aclar/Al and PVC/PE/PVDC/Al blister packs of 7 and 28 tablets and in HDPE bottles with polypropylene caps of 28 tablets.

5 mg: available in PVC/Aclar/Al and PVC/PE/PVDC/Al blister packs of 7 and 28 tablets and in HDPE bottles with polypropylene caps of 28 tablets.

10 mg: available in PVC/Aclar/Al and PVC/PE/PVDC/Al blister packs of 2, 4 and 8 tablets.

20 mg: available in PVC/Aclar/Al and PVC/PE/PVDC/Al blister packs of 1, 2, 4 and 8 tablets.

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 215928– CILATIL tadalafil 2.5mg film-coated tablets bottle

AUST R 215924– CILATIL tadalafil 2.5mg film-coated tablets blister pack

AUST R 215930– CILATIL tadalafil 5mg film-coated tablets bottle

AUST R 215923– CILATIL tadalafil 5mg film-coated tablets blister pack

AUST R 215927– CILATIL tadalafil 10mg film-coated tablets blister pack

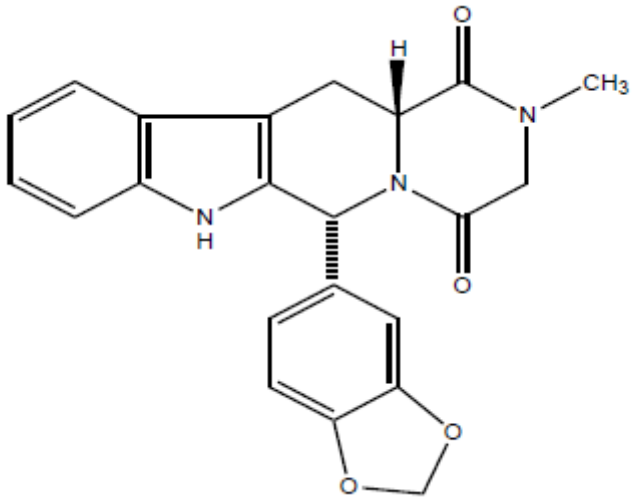
AUST R 215926– CILATIL tadalafil 20mg film-coated tablets blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure



Tadalafil is a crystalline solid that is practically insoluble in water and very slightly soluble in ethanol.

Chemical name: pyrazino[1', 2':1, 6]pyrido[3, 4-b]indole-1, 4-dione, 6-(1, 3-benzodioxol-5-yl)-2, 3, 6, 7, 12, 12a-hexahydro-2-methyl-, (6R, 12aR)-

Molecular formula: $C_{22}H_{19}N_3O_4$

Molecular weight: 389.41

CAS Number

171596-29-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

03/02/2021

10 DATE OF REVISION

13/12/2024

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes
4.4	Addition of safety information regarding the risk of central serous chorioretinipathy (CRCR)
4.8	Addition of central serous chorioretionpathy (CSCR) to post-marketing experience

CILATIL® is a Viatris company trade mark

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