# AUSTRALIAN PRODUCT INFORMATION

# ADCIRCA® (TADALAFIL) TABLETS

## 1. NAME OF THE MEDICINE

Tadalafil

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tadalafil 20 mg.

Excipients with known effect: lactose.

For the full list of excipients, see section **6.1 List of excipients**

## 3. PHARMACEUTICAL FORM

ADCIRCA 20 mg tablets are orange, almond shaped tablets, for oral administration, marked "4467" on one side. The active ingredient in ADCIRCA tablets is tadalafil.

## 4. CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

ADCIRCA is indicated in adults for the treatment of pulmonary arterial hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity. Efficacy has been shown in idiopathic PAH (IPAH) and in PAH related to collagen vascular disease.

### 4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment should only be initiated and monitored by a physician experienced in the treatment of PAH.

The recommended dose is 40 mg (2 x 20 mg) taken once daily with or without food.

**Use in patients with renal impairment:**

In patients with mild to moderate renal impairment a starting dose of 20 mg once per day is recommended based on data from clinical pharmacology studies. Although clinical pharmacology studies in patients with renal impairment have not been performed with 40mg the dose may be increased to 40 mg once per day, based on individual efficacy and tolerability. In patients with severe renal impairment the use of ADCIRCA is not recommended due to limited clinical experience in these patients. (see section **4.4 Special Warnings and Precautions for Use, Use in renal impairment** and section **5.2 Pharmacokinetic properties**).

**Use in patients with hepatic impairment:**

Based on data obtained in a clinical pharmacology study performed using single doses of 10 mg in patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A and B), a starting dose of 20 mg once per day may be considered. If tadalafil is prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician. Patients with severe hepatic cirrhosis (Child-Pugh Class C) have not been studied and therefore dosing of tadalafil is not recommended. (see section **4.4 Special Warnings and Precautions for Use, Use in hepatic impairment** and section **5.2 Pharmacokinetic properties**)).

**Use in children and adolescents**

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

**Elderly Patients**

Dosage adjustments are not required in elderly patients.

## 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 ADCIRCA 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 ADCIRCA 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 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 severe hypotension (<90/50 mm Hg)
- patients with unstable angina
- patients with uncontrolled arrhythmias
- patients with 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.

Guanylate Cyclase Stimulators - 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

The following groups of patients with cardiovascular disease were not included in PAH clinical trials:

- Patients with clinically significant aortic and mitral valve disease
- Patients with pericardial constriction
- Patients with restrictive or congestive cardiomyopathy
- Patients with significant left ventricular dysfunction
- Patients with life-threatening arrhythmias
- Patients with symptomatic coronary artery disease

Since there are no clinical data on the safety of tadalafil in these patients, the use of tadalafil is not recommended.

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Since there are no clinical data on administration of tadalafil to patients with veno-occlusive disease, administration of tadalafil to such patients is not recommended. Should signs of pulmonary oedema occur when tadalafil is administered, the possibility of associated PVOD should be considered.

As with other PDE5 inhibitors, tadalafil has systemic vasodilatory properties that may result in mild and transient decreases in blood pressure. Prior to prescribing ADCIRCA, physicians should carefully consider whether their patients with underlying conditions, such as severe left ventricular outflow obstruction, fluid depletion, autonomic hypotension or patients with resting hypotension, could be adversely affected by vasodilatory effects.

Tadalafil potentiates the hypotensive effect of nitrates. Therefore, coadministration of ADCIRCA 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 ADCIRCA to Affect Other Medicines - Antihypertensive agents**).

Physicians should advise patients to stop taking PDE5 inhibitors, including ADCIRCA, 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 of PDE5

inhibitors, including ADCIRCA. 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)**).

Caution should be exercised when prescribing ADCIRCA to patients who are taking alpha[1] blockers, such as doxazosin, as simultaneous administration may lead to symptomatic hypotension in some patients (see section **4.5 Interactions with other medicines and other forms of interactions, Potential for ADCIRCA to Affect Other Medicines**).

For patients chronically taking potent inducers of CYP3A4, such as rifampicin, the use of tadalafil is not recommended (see section **4.5 Interactions with other medicines and other forms of interactions**).

For patients taking concomitant potent inhibitors of CYP3A4, such as ketoconazole or ritonavir, the use of tadalafil is not recommended (see section **4.5 Interactions with other medicines and other forms of interactions**).

The efficacy and safety of tadalafil co-administered with prostacyclin or its analogues has not been studied in controlled clinical trials. Therefore, caution is recommended in case of co-administration.

The efficacy of tadalafil in patients already on bosentan therapy has not been conclusively demonstrated (see section **4.5 Interactions with other medicines and other forms of interactions** and section **5.1 Pharmacodynamic properties, Clinical trials**).

The safety and efficacy of combinations of ADCIRCA and other PDE5 inhibitors or other treatments for erectile dysfunction have not been studied. Therefore patients should be informed not to take ADCIRCA with these medications.

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).

Physicians should advise patients to stop use of all PDE5 inhibitors, including ADCIRCA, and seek medical attention in the event of any sudden visual defect including 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 analyses of observational data in men with erectile dysfunction within 1 to 4 days of episodic PDE5 inhibitor use. Patients with known hereditary degenerative retinal disorders, including retinitis pigmentosa, were not included in the clinical trials, and use in these patients is not recommended.

ADCIRCA tablets contain lactose.

**Use in hepatic impairment**

Patients with severe hepatic cirrhosis (Child-Pugh Class C) have not been studied and therefore dosing of ADCIRCA is not recommended.

**Use in renal impairment**

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

**Use in the Elderly**

No data available.

**Paediatric Use**

No data available.

**Effects on Laboratory Tests**

No data available.

## 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 Medicines to Affect ADCIRCA**

*Cytochrome P450 Inhibitors*

*Azole Antifungals (e.g. ketoconazole)*

Tadalafil is principally metabolised by CYP3A4. A selective inhibitor of CYP3A4, ketoconazole (400 mg daily), increased tadalafil (20 mg) single-dose exposure (AUC) by 312% and $C_{max}$ by 22%, and ketoconazole (200 mg daily), increased tadalafil (10 mg) single-dose exposure (AUC) by 107%, and $C_{max}$ by 15% relative to the AUC and $C_{max}$ values.

*Protease inhibitors (e.g. ritonavir)*

Ritonavir (200 mg twice daily), an inhibitor of CYP3A4, 2C9, 2C19, and 2D6, increased tadalafil (20 mg) 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% and decreased $C_{max}$ by 30%. 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.

*Cytochrome P450 Inducers*

*Endothelin-1 receptor antagonists (e.g. bosentan)*

Bosentan (125 mg twice daily), a substrate of CYP2C9 and CYP3A4 and a moderate inducer of CYP3A4, CYP2C9 and possibly CYP2C19, reduced tadalafil (40 mg once per day) systemic

exposure by 42% and $C_{max}$ by 27% following multiple dose co-administration. The efficacy of tadalafil in patients already on bosentan therapy has not been conclusively demonstrated (see section **4.4 Special warnings and precautions for use** and section **5.1 Pharmacodynamic properties, Clinical trials** ). Tadalafil did not affect the exposure (AUC and $C_{max}$) of bosentan or its metabolites. The safety and efficacy of combinations of ADCIRCA and other endothelin-1 receptor antagonists have not been studied.

*Antimicrobial agents (e.g. rifampicin)*

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.

*Cytochrome P450 Substrates*

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 ADCIRCA to Affect Other Medicines**

*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 7$^{th}$ 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 compared to subjects whose blood pressure was 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 ADCIRCA.

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.

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.

Caution is advised when PDE5 inhibitors are coadministered with nonselective alpha (α1)-blockers. PDE5 inhibitors, including ADCIRCA, 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 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 optimized 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.

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).

*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*

When administered in combination with aspirin, tadalafil 20 mg did not prolong bleeding time, relative to aspirin alone. ADCIRCA has not been administered to patients with bleeding disorders or significant active peptic ulceration. Although ADCIRCA has not been shown to increase bleeding times in healthy subjects, use in patients with bleeding disorders or significant active peptic ulceration should be based upon a careful risk-benefit assessment.

*P-glycoprotein substrates (e.g. digoxin)*

Tadalafil (40 mg once per day) had no clinically significant effect on the pharmacokinetics of digoxin.

*CYP2C9 substrates (e.g.R-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.

*Oral Contraceptive Pill*

At steady-state, tadalafil (40 mg once per day) increased ethinylestradiol exposure (AUC) by 26% and $C_{max}$ by 70% relative to oral contraceptive administered with placebo. There was no statistically significant effect of tadalafil on levonorgestrel which suggests the effect of ethinylestradiol is due to inhibition of gut sulphation by tadalafil. The clinical relevance of this finding is uncertain.

*CYP1A2 substrates (e.g. 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.

*Terbutaline*

A similar increase in AUC and $C_{max}$ seen with ethinylestradiol may be expected with oral administration of terbutaline, probably due to inhibition of gut sulphation by tadalafil. The clinical relevance of this finding is uncertain

*Other PDE5 inhibitors*

The safety and efficacy of combinations of ADCIRCA and other PDE5 inhibitors have not been studied. Therefore, the use of such combinations is not recommended.

*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 ( a dose producing AUCs for unbound tadalafil of 7-fold for males or 18-fold for females the exposures at the recommended human dose of 40 mg). However, regression of the seminiferous tubular epithelium of the testes resulting in oligospermia or aspermia in the epididymides was observed in dogs treated for 3, 6 or 12 months with oral tadalafil doses ≥ 10 mg/kg/day. AUC-based exposure approximately 0.3 to 3-fold the exposure at the recommended human dose of 40 mg). A no-effect level for these effects in dogs was not established. Similar findings were not observed in mice in a carcinogenicity study at AUC-based exposures similar to exposure at the recommended human dose of 40 mg. The potential relevance of the male reproductive-toxicity findings to humans treated chronically with tadalafil is unknown.

**Use in pregnancy**

Pregnancy category B1.

Studies in rats have shown that tadalafil and/or its metabolites cross the placenta and distribute to the foetus. No evidence of embryofetal 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* 7-8-fold that expected at the recommended dose of 40 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* 5-fold that expected in humans at the recommended dose of 40 mg tadalafil taken once daily, based on AUC for unbound drug at steady state. There are no studies of tadalafil in pregnant women. Because animal reproduction studies are not always predictive of human response, tadalafil should be used during pregnancy only if clearly needed.

**Use in lactation**

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. Because many drugs are excreted in human milk, caution should be exercised when ADCIRCA is administered to a nursing woman.

## 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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

In the pivotal placebo-controlled study of ADCIRCA for the treatment of PAH, a total of 323 patients were treated with ADCIRCA at doses ranging from 2.5 mg to 40 mg once daily and 82 patients were treated with placebo. The duration of treatment was 16 weeks. The overall frequency of discontinuation due to adverse events was low (ADCIRCA 11%, placebo 16%). Three hundred and fifty seven (357) subjects who completed the pivotal study entered a long-term extension study. Doses studied were 20 mg and 40 mg once daily.

**Table 1** below lists the adverse events reported in greater than or equal to 4% of patients taking ADCIRCA 40 mg during the placebo-controlled clinical trial. Please note that some of these adverse events occurred more often in patients receiving placebo and may not necessarily be causally related to ADCIRCA use.

**Table 1. Treatment Emergent Adverse Events Reported by ≥4% of Patients Receiving ADCIRCA 40 mg**

| ADVERSE EVENT | Placebo (%) (N=82) | Tadalafil 40 mg (%) (N=79) |
|---|---|---|
| Infections and Infestations | | |
| Nasopharyngitis | 7 | 13 |
| Respiratory Tract Infection (Upper and Lower) | 6 | 13 |
| Bronchitis | 0 | 5 |
| Urinary Tract Infection | 0 | 4 |
| Psychiatric disorders | | |
| Insomnia | 2 | 4 |
| Nervous System Disorders | | |
| Headache | 15 | 42 |
| Dizziness | 9 | 8 |
| Vascular disorders | | |
| Flushing | 2 | 13 |
| Hot Flush | 2 | 4 |
| Respiratory Tract, Thoracic and Mediastinal Disorders | | |

| | | |
|---|---|---|
| Cough | 9 | 9 |
| Nasal Congestion (including sinus congestion) | 1 | 9 |
| Pulmonary hypertension | 9 | 8 |
| Dyspnoea | 4 | 6 |
| Upper Respiratory Tract Infection | 4 | 6 |
| Respiratory tract infection | 3 | 5 |
| Epistaxis | 4 | 4 |
| Gastrointestinal Disorders | | |
| Diarrhoea | 10 | 11 |
| Nausea | 6 | 11 |
| Dyspepsia | 2 | 10 |
| Vomiting | 1 | 6 |
| Gastroesophageal Reflux Disease | 4 | 5 |
| Constipation | 1 | 4 |
| Skin and subcutaneous tissue disorders | | |
| Rash | 3 | 5 |
| Musculoskeletal and Connective Tissue Disorders | | |
| Myalgia | 4 | 14 |
| Pain in Extremity | 2 | 11 |
| Back Pain | 6 | 10 |
| Musculoskeletal Stiffness | 0 | 4 |
| Reproductive system and breast disorders | | |
| Menorrhagia (including increased uterine bleeding[a)] | 0 | 4 |
| General Disorders and Administration Site Conditions | | |
| Oedema peripheral | 9 | 6 |
| Fatigue | 4 | 6 |
| Chest Pain | 1 | 6 |
| Oedema | 1 | 5 |
| Non-Cardiac Chest Pain | 0 | 4 |
| Therapeutic response unexpected | 0 | 4 |

[a]Clinical non-MedDRA term to include reports of abnormal/excessive menstrual bleeding conditions such as menorrhagia, metrorrhagia, menometrorrhagia, or vaginal haemorrhage.

The **Table 2** below lists the adverse reactions reported during the placebo-controlled clinical trial in patients with PAH treated with ADCIRCA. These adverse reactions have been found to occur more often in patients receiving ADCIRCA compared to placebo and are considered to be causally related to ADCIRCA use. The adverse reactions reported were transient, and generally mild or moderate. At the beginning of therapy headache may occur; and decreases over time even if treatment is continued. Adverse reaction data are limited in patients over 75 years of age. Also included in the table are some adverse events/reactions which have been reported in clinical trials and/or post marketing with tadalafil in the treatment of male erectile dysfunction.

The most frequently noted adverse reactions in the pivotal study were headache, nausea, back pain, pain in extremity, dyspepsia, flushing, myalgia and nasopharyngitis.

## Adverse reactions

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.

**Table 2. Treatment Emergent Adverse Reactions Reported by Patients Receiving ADCIRCA 40 mg**

| Very common (≥1/10) | Common (≥1/100 to <1/10) | Uncommon (≥1/1000 to <1/100) | Rare (≥1/10,000 to < 1/1000) |
|---|---|---|---|
| Nervous System disorders | | | |
| Headache | | | |
| Eye disorders | | | |
| | Blurred vision | | |
| Vascular disorders | | | |
| Flushing | Hypotension | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Nasopharyngitis (including nasal congestion, sinus congestion and rhinitis) | Epistaxis | | |
| Gastrointestinal disorders | | | |
| Nausea, Dyspepsia (including abdominal pain/discomfort[1]) | Vomiting | | |
| Musculoskeletal, connective tissue and bone disorders | | | |
| Myalgia, Back pain Pain in extremity (including limb discomfort) | | | |
| Reproductive system and breast disorders | | | |
| | Increased uterine Bleeding[2] | | |

[1] Actual MedDRA terms included are abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and stomach discomfort.

[2] Clinical non-MedDRA term to include reports of abnormal/excessive menstrual bleeding conditions such as menorrhagia, metrorrhagia, menometrorrhagia, or vaginal haemorrhage.

## Adverse reactions identified from spontaneous post marketing surveillance

The following adverse reactions have been identified during post approval use of tadalafil, in which tadalafil was authorized for the treatment of erectile dysfunction. These events have been chosen for inclusion either due to their seriousness, reporting frequency, lack of clear alternative causation, or a combination of these factors. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

**Body as a whole**: hypersensitivity reactions including rash, urticaria, and facial edema.

**Cardiovascular and cerebrovascular:** serious cardiovascular events, including myocardial infarction, sudden cardiac death, stroke, chest pain, palpitations, and tachycardia, have been reported post marketing in temporal association with the use of tadalafil. 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.

Hypotension (more commonly reported when tadalafil is given to patients who are already taking antihypertensive agents), hypertension, and syncope.

**Ear and labyrinth disorders**: sudden hearing loss.

**Skin and subcutaneous tissues**: hyperhidrosis (sweating), Stevens-Johnson syndrome, and exfoliative dermatitis.

**Nervous system:** migraine seizure and transient amnesia.

**Respiratory system:** epistaxis.

**Special senses**: blurred vision, retinal vein occlusion, visual field defect, non-arteritic anterior ischemic optic neuropathy.

Non-arteritic anterior ischemic optic neuropathy, a cause of decreased vision including permanent loss of vision, has been reported rarely post-marketing in temporal association with the use of phosphodiesterase type 5 (PDE5) inhibitors, including CIALIS. 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, hyperlipidaemia, 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**: priapism and prolonged erection

**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 http://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 male patients with erectile dysfunction. 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). Pulmonary arterial hypertension is associated with impaired release of nitric oxide by the vascular endothelium and consequent reduction of cGMP concentrations within the pulmonary vascular smooth muscle. PDE5 is the predominant phosphodiesterase in the pulmonary vasculature. Inhibition of PDE5 by tadalafil increases the concentrations of cGMP resulting in relaxation of the pulmonary vascular smooth muscle cell and vasodilation of the pulmonary vascular bed.

Studies *in vitro* have shown that tadalafil inhibits PDE5 more potently than other PDEs. PDE5 is an enzyme found in the corpus cavernosum smooth muscle, 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.

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)**).

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 mm Hg, respectively), in standing systolic and diastolic blood pressure (mean maximal decrease of 0.2/4.6 mm Hg, respectively) and no significant change in heart rate. Larger effects were recorded among subjects receiving concomitant nitrates (see section **4.3 Contraindications**).

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.

**Clinical trials**

A randomized, double-blind, 16 week placebo-controlled study was conducted in 405 patients with pulmonary arterial hypertension, defined as a resting mean pulmonary artery pressure (mPAP) ≥25 mm Hg, pulmonary capillary wedge pressure (PCWP) ≤15 mm Hg, and pulmonary vascular resistance (PVR) ≥3 Wood units via right heart catheterization. Allowed background therapy included bosentan (maintenance dosing up to 125 mg twice daily) and chronic anticoagulation. The use of prostacyclin or analogue, L-arginine, phosphodiesterase inhibitor, or other chronic PAH medications were not permitted.

Subjects were randomly assigned to 1 of 5 treatment groups (tadalafil 2.5, 10, 20, 40 mg, or placebo) in a 1:1:1:1:1 ratio. Subjects had to be at least 12 years of age and had a diagnosis of PAH that was idiopathic, related to collagen vascular disease, anorexigen use, human immunodeficiency virus (HIV) infection, associated with an atrial-septal defect, or associated with surgical repair of a congenital systemic-to-pulmonary shunt of least 1 year in duration (for example, ventricular septal defect, patent ductus arteriosus). Patients with a history of left-sided heart disease, severe renal insufficiency, or pulmonary hypertension related to conditions other than specified in the inclusion criteria were not eligible for enrolment.

The mean age of all subjects was 54 years (range 14 - 90 years) with the majority of subjects being Caucasian (81%) and female (78%). PAH etiologies were predominantly idiopathic PAH (61%) and related to collagen vascular disease (23%). More than half (53%) of the subjects in the study were receiving concomitant bosentan therapy. The majority of subjects had a World Health Organization (WHO) Functional Class III (65%) or II (32%). The mean baseline 6-minute walk distance (6-MWD) was 344 meters. Of the 405 subjects, 341 completed the study.

The primary efficacy endpoint was the change from baseline at week 16 in 6-MWD (see **Figure 1, Table 3**). In the ADCIRCA 40 mg treatment group, the placebo-adjusted mean change increase in 6-MWD was 33 metres (95% C.I. 15-50 meters; p=0.0004). The improvement in 6-MWD was apparent at 8 weeks of treatment and then maintained at week 12 and week 16 ($p<0.05$).

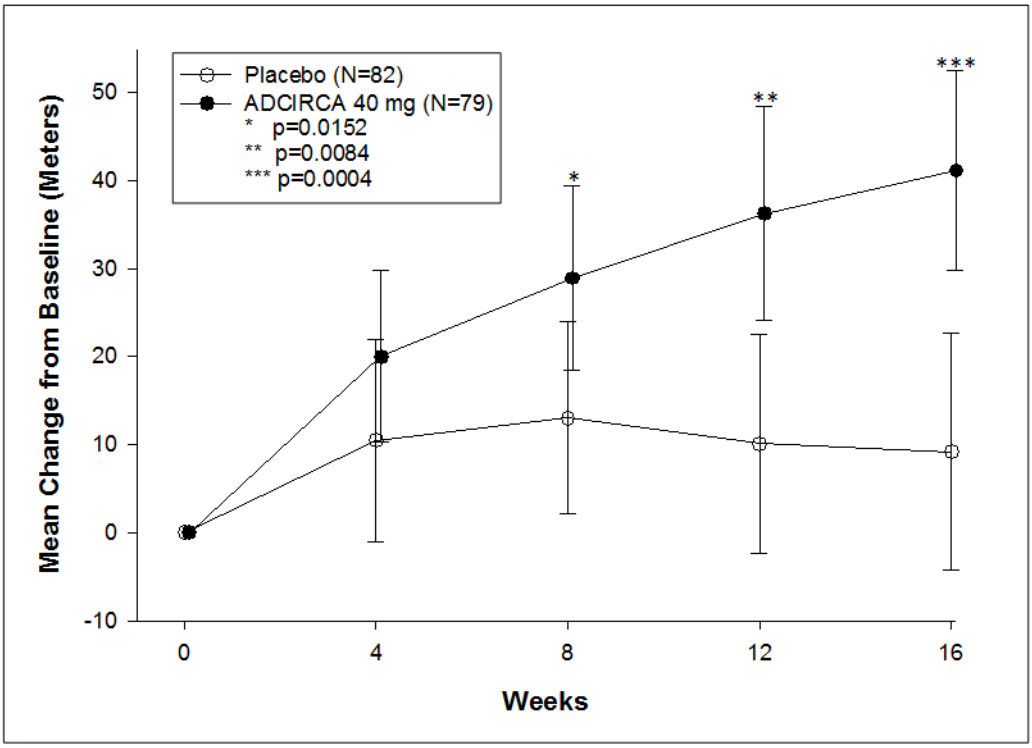



**Figure 1. 6-Minute Walk Distance (metres) Mean Change from Baseline, with 95% Confidence Intervals**

**Table 3. 6-Minute Walk Distance (metres) Mean Change from Baseline to Endpoint**

| | **Placebo (N=82)** | **Tadalafil 10 mg (N=80)** | **Tadalafil 20 mg (N=82)** | **Tadalafil 40 mg (N=79)** |
|---|---|---|---|---|
| Mean (SD) | 9.21 (59.96) | 28.60 (62.17) | 36.23 (47.53) | 41.14 (49.39) |
| Treatment difference[a] | | 19.9 | 27.5 | 32.8 |
| 95% C.I.[a] | | 0.9, 38.8 | 10.6, 44.3 | 15.2, 50.3 |
| p-value[b] | | 0.0466 | 0.0278 | 0.0004 |

[a] ANCOVA model with Type II sum of squares including the centered baseline of 6-MW distance (cont.), PAH etiology, and bosentan use. Treatment difference is the Active Least Square mean subtract Placebo Least Square mean.

[b] Permutation test stratified by PAH etiology, bosentan use, and baseline 6-minute walk distance (<= 325 m and >325 m) on rank compared to placebo.

Placebo-adjusted changes in 6-MWD at 16 weeks were evaluated in subgroups (see **Figure 2**), although the study was not powered to demonstrate statistical significance within subgroups. In patients taking only ADCIRCA 40 mg (i.e., without concomitant bosentan), the placebo-adjusted mean change in 6-MWD was 44 metres ($p<0.01$). In patients taking ADCIRCA 40 mg and concomitant bosentan therapy, the placebo adjusted mean change in 6-MWD was 23 meters ($p>0.05$).

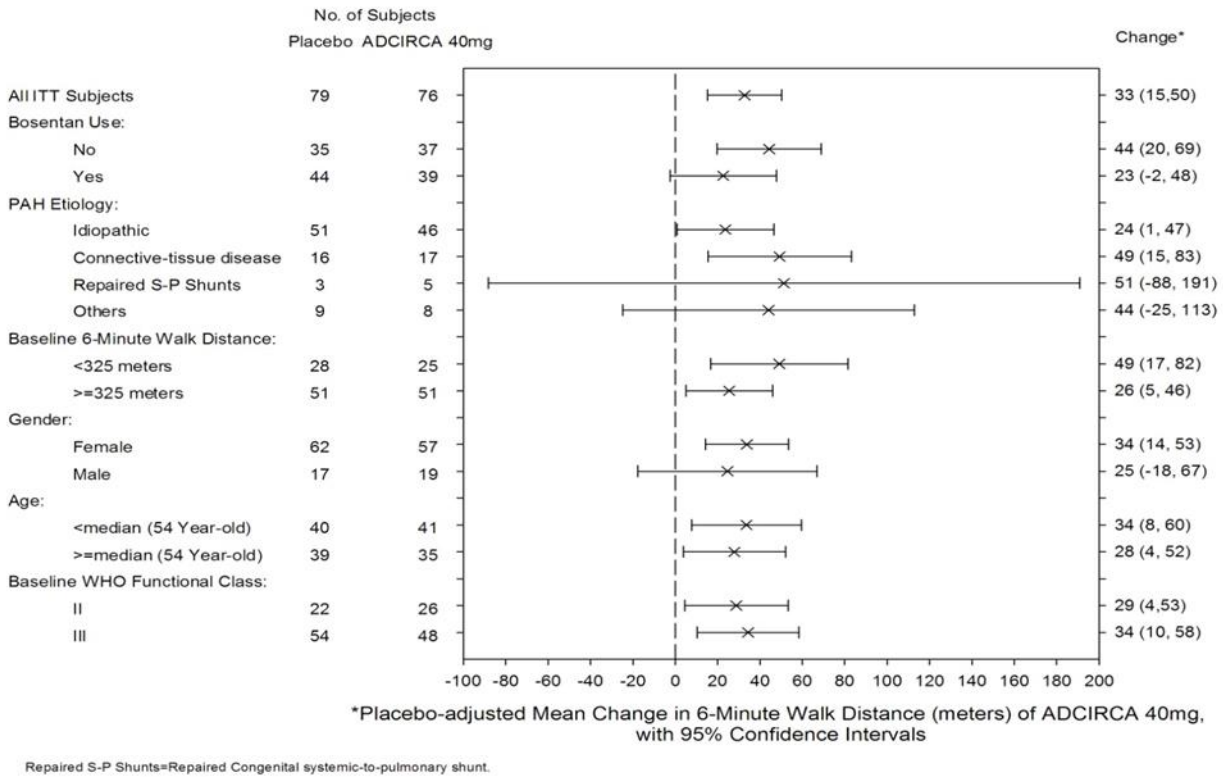



**Figure 2. Placebo-adjusted Mean Change in 6-Minute Walk Distance (metres) of ADCIRCA 40 mg, with 95% Confidence Intervals**

The secondary endpoints were tested in a sequential order specified in the protocol, which is the order listed in **Table 4**, with no further inferential testing once a statistically non-significant result was reached. Inferential testing did not proceed beyond WHO functional Class since this comparison was statistically non-significant.

**Table 4. Secondary Endpoints (Change from Baseline to End of Treatment – Week 16)**

| | **Placebo (N=82)** | **Tadalafil 10 mg (N=80)** | **Tadalafil 20 mg (N=82)** | **Tadalafil 40 mg (N=79)** |
|---|---|---|---|---|
| **Change in WHO Functional Class No. (%)** | | | | |
| Improved | 17 (20.7) | 19 (23.8) | 30 (36.6) | 18 (22.8) |
| No Change | 52 (63.4) | 50 (62.5) | 37 (45.1) | 53 (67.1) |
| Worsen | 13 (15.9) | 11 (13.75) | 15 (18.3) | 8 (10.1) |
| P-value | | 0.5758 | 0.1694 | 0.3630 |
| **Clinical Worsening[a]** | | | | |
| Probability of No Clinical Worsening at Week 16 (95% C.I.) | 0.84 (0.74, 0.90) | 0.91 (0.82,0.95) | 0.90 (0.80, 0.95) | 0.94 (0.85, 0.98) |
| No. of patients (%) with Clinical Worsening | 13 (15.9) | 7 (8.8) | 8 (9.8) | 4 (5.1) |
| **Change in Borg Dyspnea[b] Score** | | | | |
| Mean (SD) | 0.41 (1.89) | -0.36 (1.92) | -0.29 (2.08) | -0.70 (1.75) |

[a] Clinical worsening was defined as death, lung transplantation, atrial septostomy, hospitalization due to worsening PAH, initiation of new PAH therapy, and worsening WHO functional class.

[b] A positive change in Borg-Dyspnea score represents a worsening of patient perceived breathlessness during the 6 minute walk.

A statistically significant ($p<0.05$) increase in quality of life, compared to placebo, was demonstrated in the tadalafil 40 mg group in 6 of the 8 SF36 domains (physical functioning, role physical, bodily pain, general health, vitality and social functioning) and in all questions of EuroQoL.

*Long-term treatment*

357 patients from the placebo-controlled study entered a long-term extension study. Of these, 311 patients had been treated with tadalafil for at least 6 months and 293 for 1 year (median exposure 365 days; range 2 days to 415 days). For those patients for which there are data, the survival rate at 1 year is 96.4%. Additionally, 6 minute walk distance and WHO functional class status appeared to be stable in those treated with tadalafil for 1 year.

## 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 4 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 after a single 10 mg administration) 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 77 L at steady state. 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 3.4 L/hr and the mean terminal half-life is 16 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**

Over a dose range of 2.5 to 20 mg, tadalafil exposure (AUC) increases proportionally with dose in healthy subjects. Between 20 mg to 40 mg, a less than proportional increase in exposure is observed. During tadalafil 20 mg and 40 mg once daily dosing, steady-state plasma concentrations are attained within 5 days, and exposure is approximately 1.5 fold of that after a single dose.

**Population pharmacokinetics**

In patients with pulmonary hypertension not receiving concomitant bosentan, the average tadalafil exposure at steady-state following 40 mg was 26% higher when compared to those of healthy volunteers. There were no clinically relevant differences in $C_{max}$ compared to healthy volunteers. The results suggest a lower clearance of tadalafil in patients with pulmonary hypertension compared to healthy volunteers.

**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 after a 10 mg dose (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 ADCIRCA during which nitrates should be avoided (see section **4.3 Contraindications**).

*Renal Impairment*

In clinical pharmacology studies using single-dose tadalafil (5-20 mg), tadalafil exposure (AUC) approximately doubled in subjects with mild (creatinine clearance 51 to 80 mL/min) or moderate (creatinine clearance 31 to 50 mL/min) renal impairment and in subjects with end-stage renal disease on dialysis. In haemodialysis patients in these studies, $C_{max}$ was 41% higher than that observed in healthy subjects. Haemodialysis contributed negligibly to tadalafil elimination.

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

*Hepatic Impairment*

A clinical pharmacology study was conducted using a single 10-mg dose of tadalafil to investigate the effect of hepatic impairment on the pharmacokinetics of tadalafil in subjects with hepatic dysfunction as defined by the Child-Pugh classification. Tadalafil exposure (AUC) in subjects with mild and moderate hepatic impairment (Child-Pugh Class A and B) was comparable to exposure in healthy subjects after a 10-mg dose. There are no available data about the administration of doses higher than 10 mg of tadalafil to patients with hepatic impairment. No controlled data are available in patients with severe hepatic impairment (Child-Pugh Class C) and therefore dosing of tadalafil in these patients is not recommended. 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 after a 10 mg dose. This difference in exposure does not warrant a dose adjustment.

*Race*

Pharmacokinetic studies have included subjects and patients from different ethnic groups, and no differences in the typical exposure to tadalafil have been identified. No dose adjustment is warranted.

*Gender*

In healthy female and male subjects following single and multiple-doses of tadalafil, no clinically relevant differences in exposure were observed. No dose adjustment is warranted.

### 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 2 to 3- fold that expected in humans taking the recommended dose of 40 mg daily, based on unbound drug concentrations.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 LIST OF EXCIPIENTS

ADCIRCA tablets also contain the following excipients: croscarmellose sodium, hyprolose, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, purified talc, titanium dioxide, triacetin, iron oxide yellow and iron oxide red.

### 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. Store in the original package.

## 6.5 NATURE AND CONTENTS OF CONTAINER

ADCIRCA 20 mg tablets are presented in PVC/Al or PVC/PE/PCTFE (Aclar)/Al blister packs of 14*, 28** and 56 tablets per carton.

*only available as a starter pack

**not currently available.

## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

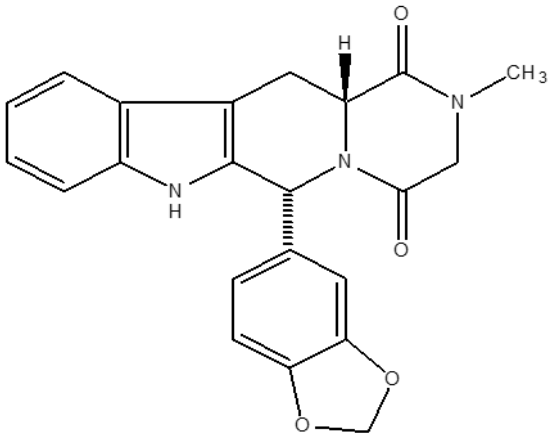
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

## 6.7 PHYSICOCHEMICAL PROPERTIES

### Chemical structure

Chemically, tadalafil is 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)-. Tadalafil has the empirical formula $C_{22}H_{19}N_3O_4$ representing a molecular weight of 389.41. Tadalafil is a crystalline solid that is practically insoluble in water and very slightly soluble in ethanol.

Tadalafil has the following structural formula:




### CAS number

The CAS number for tadalafil is 171596-29-5.

# 7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 - Prescription only Medicine

## 8. SPONSOR

Eli Lilly Australia Pty Ltd
Level 9, 60 Margaret Street, Sydney, NSW 2000
AUSTRALIA
1800 454 559

## 9. DATE OF FIRST APPROVAL

10 August 2011

## 10. DATE OF REVISION

14 July 2023

**SUMMARY TABLE OF CHANGES**

| Section changed | Summary of new information |
|---|---|
| 6.5 | Additional blister material added |
| 8 | Sponsor address update |

ADCIRCA® is a registered trademark of Eli Lilly and Company