Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Tadalafil

Proprietary Product Name: Adcirca

Sponsor: Eli Lilly Australia Pty Ltd

September 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
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About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission:	Extension of Indications and Additional Trade Name
Decision:	Approved
Date of Decision:	5 August 2011
Active ingredient(s):	Tadalafil
Product Name(s):	Adcirca
Sponsor's Name and Address:	Eli Lilly Australia Pty Ltd 112 Wharf Rd West Ryde NSW 2114
Dose form(s):	Tablet
Strength(s):	20 mg
Container(s):	Blister pack
Pack size(s):	14, 28 or 56 tablets
Approved Therapeutic use:	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.
Route(s) of administration:	Oral
Dosage:	The recommended dose is 40 mg (2 x 20 mg) taken once daily with or without food.
ARTG Number:	172882

Product Background

Tadalafil is a reversible inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase type 5 (PDE5). Pulmonary arterial hypertension (PAH) 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.

PAH is a rare, progressive and life threatening disease with the incidence of 1-2 per million in Western countries. There are a number of treatments available for PAH in adults including PDE5 inhibitors such as sildenafil, endothelin receptor antagonists and prostanoids.

This AusPAR describes the evaluation of an application by Eli Lilly Australia Pty Ltd (the sponsor) to extend the indications of Cialis (tadalafil) and to include an additional trade name (Adcirca) for treatment of PAH.

The following indication was proposed by the sponsor:

Adcirca is indicated 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.

The recommended dosage is 40 mg (2 x 20 mg) taken once daily with or without food with modifications for renal and hepatic impairment.

Regulatory Status

Tadalafil is currently registered in Australia as Cialis tablets 2.5, 5, 10 and 20 mg and was approved for its current indications on 15 October 2002. Adcirca (tadalafil) was designated as an Orphan Drug by the TGA on 21 April 2010 for the treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability.

A similar application was submitted to the European Union (EU) on 18 October 2008. The application was approved on 30 November 2009 with the following indication:

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.

A similar application was submitted to Canada on 31 October 2008. The application was approved on 25 November 2009 with the following indication:

Adcirca (tadalafil) is indicated for the treatment of idiopathic ("primary") pulmonary arterial hypertension (PAH) or PAH associated with connective tissue disease, congenital heart disease or anorexigen use in patients with WHO Functional Class II or III who have not responded to conventional therapy.

A similar application was submitted to the USA on 23 July 2008. The application was approved on 22 May 2009 with the following indication:

Adcirca is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

Tadalafil tablets containing 2.5, 5, 10 and 20 mg of tadalafil are already registered under the tradename of Cialis for the treatment of erectile dysfunction.

This submission is to register a similar 20 mg tadalafil tablet for the treatment of pulmonary arterial hypertension under the tradename of Adcirca.

There are no compendial monographs for the drug substance or the dosage form containing this drug substance.

All details relating to the tadalafil drug substance are as for the previously registered products. The particle size distribution for this practically insoluble drug substance is controlled with limits.

Drug Product

The product is to be manufactured by Lilly del Caribe Inc., Puerto Rico (one of the three manufacturers used for the 20 mg Cialis tablet).

Compared to the 20 mg Cialis tablet, the 20 mg Adcirca has the same core but a different film coat: orange rather than yellow caused by the addition of a small amount of iron oxide red.

The specifications of the product are based on those for the 20 mg Cialis tablet and have acceptable expiry limits.

The proposed product is stable and no changes were observed on storage. Stability data was provided that supported a shelf life of 3 years when stored below 25°C in PVC/PE/PCFTE \ Al blister packs. The condition 'store in original container' will also be used.

Biopharmaceutics

Clinical Background

The Phase III clinical efficacy studies were performed using the registered tadalafil Cialis 20 mg tablets.

Studies Evaluated

One new bioavailability study was provided in this submission. Study H6D-EW-LVHO was a single dose, two way crossover study to determine the affect of food on the bioavailability of tadalafil at a dose of 40 mg (as proposed in the PI). Though Cialis 20 mg tablets were used, it is accepted that this study is relevant. The results (Tables 1 and 2, Figure 1) indicate food has no affect.

Table 1: Pharmacokinetic parameters for tadalafil fed and fasted

	Treatment	
Parameter	40 mg tadalafil (fed) (N=13)	40 mg tadalafil (fasted) (N=14)
AUC(0-24) (ng.h/mL)	8986 (21.2)	8336 (21.5)
AUC(0-t_{last}) (ng.h/mL)	16184 (34.6)	14589 (31.4)
AUC(0-∞) (ng.h/mL)	17386 (41.9)	15404 (36.8)
C_{max} (ng/mL)	586 (18.0)	553 (22.3)
t_{max} (h) [a]	3.00 (1.00-6.00)	2.00 (1.00-6.00)
$t_{1/2}$ (h)	20.7 (38.6)	20.2 (34.3)
CL/F (L/h)	2.31 (41.6)	2.59 (37.0)
V_z/F (L)	68.8 (20.2)	75.6 (19.5)

[a] Median (min-max) data

Figure 1: Comparison of plasma concentration of tadalafil fed and fasted

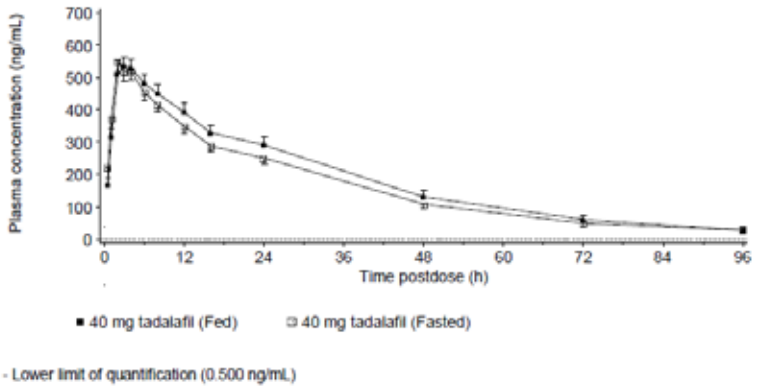


Table 2: Comparison of pharmacokinetic parameters of tadalafil fed and fasted including confidence intervals

Parameter	Geometric Least Squares Means (GLSM)		Ratio of GLSM (Fed:Fasted)	90% CI for the ratio (Fed:Fasted)		Within subject CV%
	40 mg tadalafil (Fed)	40 mg tadalafil (Fasted)		Lower	Upper	
$AUC_{(0-t)}$ (ng.h/mL)	15938	14303	1.11	**1.04**	**1.19**	9.02
$AUC_{(0-\infty)}$ (ng.h/mL)	17118	15079	1.14	**1.05**	**1.22**	9.92
C_{max} (ng/mL)	584	547	1.07	**0.994**	**1.15**	9.73
	Medians		**Median difference**	**90% CI for the difference (Fed:Fasted)**		
	40 mg tadalafil (Fed)	**40 mg tadalafil (Fasted)**		**Lower**	**Upper**	
T_{max} (h)	3.00	2.00	0.500	**-0.00833**	**2.00**	

Justification for Not Providing Bioavailability Data

No data were provided comparing the proposed tablets to the registered tadalafil Cialis 20 mg tablets. However given that the difference in formulation was only the addition of a small amount of iron oxide red to the film coat and this did not affect the dissolution profile, it was accepted that this was not required and that the food effect study using the registered tadalafil Cialis 20 mg tablets was relevant.

Advisory Committee Consideration

Given that the proposed product is very similar to a registered products and the only bioavailability study provided was not controversial, the advice of the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM) was not sought.

Quality Summary and Conclusions

Approval of this submission was recommended with respect to the chemistry and quality.

Food did not affect the bioavailability of tadalafil at a dose of 40 mg (the usual dose proposed in the Product Information [PI]). However the results for the maximum plasma concentration (T_{max}) in this study (2-3 hours) were less than cited in the PI (4 hours).

III. Nonclinical Findings

Introduction

No new nonclinical safety data were submitted with this application. Thus, the assessment of the safety of tadalafil for the indicated population will rely primarily on nonclinical studies performed in support of the original registration application for tadalafil (Cialis). One new *in vivo* pharmacology study and two *in vitro* pharmacokinetic studies have been submitted as part of the current application.

Pharmacology (Efficacy)

The rationale for the use of tadalafil for the treatment of PAH is that it is a selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5); inhibition of PDE5 increases

cGMP concentrations, resulting in relaxation of the pulmonary vascular smooth muscle cell and vasodilation of the pulmonary vascular bed.

An *in vivo* efficacy study was submitted which investigated the effects of monocrotaline (MCT) induced PAH in rats, a well established model of the human disease. The study was designed to measure the effects of tadalafil on PAH progression during development of PAH and to measure the effects after PAH is established. Sildenafil was used as a comparator. Within three weeks of administration, MCT treatment in rats resulted in clinical like PAH effects including increased mean pulmonary arterial pressure (MPAP), increased systolic right ventricular pressure (SRVP), reduced heart rate and blood pressure and evidence of right ventricular hypertrophy (increased body weight-relative weight; histopathology analysis was not conducted). Marked decreases in survival rate (by up to 60%) and blood oxygenation (pO_2 and $\%SpO_2$) were observed 3-6 weeks following MCT treatment.

Tadalafil treatment (0.5, 2.5 and 10 mg/kg/day orally [PO]) for three weeks immediately following MCT injection appeared to delay the progression of PAH in this model. Improvement in haemodynamic parameters was observed at all doses, with MPAP similar to that of untreated rats at the highest dose where the extrapolated area under the plasma concentration time curve (AUC) for unbound tadalafil was similar to exposure at the maximum clinical dose. Right ventricle weights partially returned towards untreated (no MCT) values at the high dose (HD), although it was unknown whether this correlated with improved pathology. Sildenafil (25 mg/kg/day) had slightly greater effects on MPAP and SRVP and significantly greater effects on right ventricular weights than tadalafil (10 mg/kg/day).

A dose related increase in survival time was observed with tadalafil treatment during the PAH phase of the rat model (3-6 weeks following MCT treatment), with 70% survival at the HD (compared with 40% survival of MCT treated rats and 100% survival of untreated rats). Slight improvements in right ventricular weights, pO_2 and $\%SpO_2$ levels were observed at the highest dose, with slight effects on blood gases at lower doses. In addition, relative weights of the left ventricle and septum were increased at the high dose; the significance of this finding was unclear in the absence of histopathology analysis. MPAP and other haemodynamic parameters were not measured in this experiment. The observed effects at the high dose were generally similar to those seen with sildenafil treatment.

Consistent with inhibition of PDE5, generally dose related increases in levels of cGMP in plasma and lungs were also observed in both experiments, although usually to a lesser extent than with sildenafil treatment (25 mg/kg/day PO). Tadalafil treatment did not appear to alter the effect on MCT related reductions in body weight gain at either phase of PAH.

Pharmacokinetics

Two *in vitro* studies were submitted, investigating the potential for pharmacokinetic drug interactions with tadalafil. In the first study, tadalafil (1-20 μM) was shown to be a mechanism based inhibitor of cytochrome P450 (CYP) 3A4 activity, based on time and concentration dependent inhibition of metabolism of a CYP3A4 substrate (midazolam) *in vitro*. Tadalafil was less potent than other known mechanism based CYP3A4 inhibitors, with an inactivation clearance (Cl_{inact}) value of 17 min^{-1} mM^{-1}, compared with 327 min^{-1} mM^{-1} for diltiazem and 59 min^{-1} mM^{-1} for erythromycin. The sponsor reported that clinical studies did not identify an effect on the clearance of two CYP3A4 substrates, midazolam or lovastatin. Thus, tadalafil was not considered to be a clinically significant inhibitor of CYP3A4.

Tadalafil was shown to be a substrate of the P-glycoprotein (P-gp) transporter system in MDCK canine kidney cells *in vitro*, with transport in the basolateral to apical direction favoured by approximately five fold. However, transport of tadalafil remained relatively high in the presence of P-gp inhibitors, indicative of passive transport of tadalafil. Tadalafil also inhibited P-gp activity *in vitro*, with a median inhibitory concentration (IC_{50}) value of 11.5 µM (compared with a clinical C_{max} of 698 ng/mL or 1.8 µM). Thus, drug interactions due to inhibition of P-gp are unlikely to adversely affect the metabolism of tadalafil.

Relative exposure

As the recommended daily clinical dose of tadalafil for PAH patients (40 mg/day) exceeds the maximum recommended clinical dose for erectile dysfunction (20 mg on demand), re-calculation of relative exposure (AUC and the maximal plasma concentration [C_{max}]) in nonclinical toxicity studies is required. The sponsor calculated relative exposure based on clinical pharmacokinetic parameters measured in healthy subjects, however comparisons with the indicated patient population were considered preferable.

Pharmacokinetic data were calculated for PAH patients in one clinical trial with tadalafil (Study H6D-MC-LVGY), including data collected at the recommended daily dose of 40 mg. These data were predicted by population pharmacokinetic modelling of sparse data points in a large number of patients, rather than direct calculation following determination of tadalafil plasma concentration time profiles. This approach may be limited by many factors, such as interindividual variability, extent of existing knowledge, complexity of the data analysis techniques, potential for introduction of bias and study design (for example, timing of sampling in relation to actual C_{max} and the minimum plasma concentration [C_{min}]).[1,2] Therefore, the predicted pharmacokinetic parameters are considered to be relatively broad estimates only. However, predicted AUC based exposure in PAH patients at 40 mg/day (13.7 µg.h/mL) was similar to that seen in conventional studies in healthy subjects (for example, the area under the plasma concentration time curve from time zero to 24 hours [$AUC_{0\text{-}24\,h}$] at 40 mg/day in Study H6D-MC-LVHM was 12.5 µg.h/mL), suggesting that the use of the AUC value from PAH patients was considered appropriate.

Toxicokinetic data from long term studies in rats and dogs were considered to be most relevant and were used for calculating relative exposure compared with PAH patients. AUC and C_{max} based exposure in dogs was highly variable, possibly due to emesis in some animals and values were generally reported as ranges. AUC based exposure was measured for different time periods in different species; however, concentration time profiles were generally similar and direct comparison of AUC values was considered appropriate. Exposure margins were also adjusted to account for differences in plasma protein binding of tadalafil in mice, dogs and humans, expressed as free (unbound) tadalafil AUC values. Respective unbound fractions of tadalafil were 0.15 (mice), 0.08 (rats), 0.13 (dog) and 0.06 (human). No Observable Adverse Effect Levels (NOAELs) were calculated for all species but NOAELs were not established in male dogs due to reproductive tract toxicity observed at all doses.

Toxicology (Safety)

No new nonclinical toxicity studies for tadalafil were submitted. The previous nonclinical data for tadalafil were originally assessed for safety on the basis of intermittent use (erectile dysfunction) in a male population at a maximum dose of 20 mg daily. The current submission requires reassessment of these data taking into account the following changes:

[1] Lavé T et al. Challenges and opportunities with modelling and simulation in drug discovery and drug development. Xenobiotica 2007; 37: 1295-1310.

[2] Jackson KA, Rosenbaum SE. The application of population pharmacokinetics to the drug development process. Drug Dev Ind Pharm 1998; 24: 1155-1162.

chronic instead of intermittent use, use in both males and females and an increase in maximum daily dose from 20 mg to 40 mg.

In the original submission for tadalafil, repeat dose PO toxicity studies of up to 6 months duration were conducted in rats and 12 months duration in dogs. Adequate exposure margins (based on AUC and C_{max} for unbound tadalafil) and NOAELs were established for all toxicity findings except for adverse effects on male reproductive tissues in 6 and 12 month dog studies (discussed below). Tadalafil was generally well tolerated in rats, with a low incidence of liver arteritis only observed at a relative exposure margin 7-18 times greater than the exposure at the maximum recommended human dose (MRHD) of 40 mg/day.

Male reproductive tissues, primarily the testes and epididymis, were identified as a major target organ for toxicity in dog studies of ≥3 months in duration and in the 2 year carcinogenicity studies in mice at drug exposure levels similar to that expected at the MRHD. Pathological examination revealed marked tissue atrophy, resulting in oligospermia/aspermia, which was only slowly reversible in some cases. There was no evidence for irreversible necrotic changes.

In its *Nonclinical Overview*, the sponsor provided the following arguments to support the view that that the effects of tadalafil on the male reproductive system observed in dogs are of limited relevance to humans:

The effects of tadalafil on the testes were species specific; testes of rats and mice of the repeat dose studies were unaffected. No impairment of fertility or effects on other male reproductive parameters (including histopathology of the testes) was noted at tadalafil doses as high as 400 mg/kg. Furthermore, there were no adverse effects on sperm morphology in 3 clinical studies conducted in men to assess the potential effect on sperm characteristics of tadalafil 10 mg (one 6 month study) and 20 mg (one 6 month and one 9 month study) administered daily. In 2 of the 3 studies, a decrease in mean sperm concentrations relative to placebo was noted; however, these differences were not clinically meaningful. Finally, there was no adverse effect on mean concentrations of reproductive hormones, testosterone, luteinizing hormone, or follicle stimulating hormone with either 10 or 20 mg of tadalafil compared to placebo.

The opening statement concerning species specificity is incorrect as testicular atrophy and epididymidal oligospermia/aspermia were noted at relative exposure margins of around 3 to 6 (AUC) in the mouse 2 year carcinogenicity study. Thus, the nonclinical data for tadalafil have shown male reproductive toxicity in a rodent and a non-rodent species following chronic exposure to tadalafil at relative exposure levels (AUC) similar to, or just above, that anticipated at the MRHD for PAH. Therefore, while the available clinical data for tadalafil might provide some reassurance for a lack of a clinically meaningful signal in humans, it was nevertheless recommended that the sponsor specifically targets the potential for male reproductive toxicity in its postmarket reporting.

Use in women

The new PAH indication includes females in the target population, which raises the issue of the potential reproductive toxicity of tadalafil in women. There is little cause for clinical concern as there was no evidence of teratogenicity, embryofetal toxicity or effects on fertility in rats and mice in previous studies at exposures of unbound tadalafil 7 to 9 fold greater than exposure (AUC) at the MRHD. However, TGA evaluation of two previously submitted pre/postnatal development studies in rats revealed conflicting results that have not been discussed by the sponsor in its *Nonclinical Overview*. While reduced pup survival, particularly between post natal days (PND) 1–4, was observed in one study at maternal doses ≥ 60 mg/kg/day PO (extrapolated relative exposure ≥8 based on AUC), a follow up

study of similar design found reduced pup survival at 30 mg/kg/day PO (relative exposure about 5), but not at 200 mg/kg/day (relative exposure about 9*)*. Despite such inconsistencies, it would appear that exposure margins at all relevant doses were adequate and that the proposed Product Information statements (Use in Pregnancy, Use in Lactation) suitably address this issue.

Pregnancy classification

The current pregnancy category for tadalafil (B1) was considered appropriate for the PAH indication.

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.

Nonclinical Summary and Conclusions

Tadalafil delayed the development of PAH in a monocrotaline induced model of the disease in rats, with a dose related improvement in mean pulmonary arterial pressure, heart rate, blood pressure and right ventricular hypertrophy when administered orally for three weeks immediately following induction of PAH (AUC based exposures were less than or equal to the predicted exposure at the recommended clinical dose). When tadalafil was administered to rats with active PAH (3-6 weeks post induction) it improved survival time and right ventricular hypertrophy, although the latter occurred to a lesser extent than during the induction phase. Results in both phases were similar to that of sildenafil treatment and were characterised by broadly dose related increases in cGMP in plasma and lungs, consistent with inhibition of PDE5.

In vitro pharmacokinetic drug interactions studies identified tadalafil as a mechanism based inhibitor of CYP3A4 activity, based on time and concentration dependent inhibition of metabolism of a CYP3A4 substrate (midazolam; the Cl_{inact} value was 17 min^{-1} mM^{-1}, compared with 327 min^{-1} mM^{-1} and 59 min^{-1} mM^{-1} for positive controls diltiazem and erythromycin). However, this was considered unlikely to be clinically relevant. Tadalafil was also identified as a P-glycoprotein substrate *in vitro* but passive transport of tadalafil appeared to be the predominant mechanism for cellular uptake. Tadalafil inhibited P-glycoprotein activity *in vitro*, with a mean IC_{50} value of 11.5 μM (compared with a clinical C_{max} of 698 ng/mL or 1.8 μM). Thus, drug interactions due to inhibition of P-gp are unlikely to adversely affect the metabolism of tadalafil.

No new nonclinical studies investigating the safety of tadalafil were submitted. The previous nonclinical data submitted for tadalafil were originally assessed for safety on the basis of intermittent use (erectile dysfunction) in a male population at a maximum dose of 20 mg daily. This data was reassessed in the light of chronic use in both male and female populations at a maximum dose of 40 mg (double the previous maximum dose).

The primary toxicity identified in previous PO repeat dose toxicity studies with tadalafil (up to 6 months duration in rats and 12 months in dogs) was an effect on the male reproductive tract in dogs, including atrophy of the testes and epididymides and oligospermia/aspermia, which occurred at potentially clinically relevant doses (exposure

margins 0.3-3) following chronic administration of tadalafil. While clinical studies noted in the Product Information failed to find effects of tadalafil on spermatogenesis and male reproductive hormones, the potential for chronic tadalafil administration to cause toxicity to the male reproductive tract should still be targeted in postmarket monitoring reports.

Oral tadalafil doses of 400 mg/kg/day (exposure margins 2-3) for up to two years in mice resulted in increased development of hepatocellular adenomas in males but not in females. This was probably related to hepatic microsomal enzyme induction, which is common in rodents and is not considered relevant to human cancer risk.

There were no effects on fertility, reproductive performance or reproductive organ morphology in rats at exposures sixfold (males) or 17 fold (females) that expected at the recommended clinical dose. Effects on the male reproductive system in dogs are discussed above. No evidence of teratogenicity or embryofetal toxicity in rats and mice was seen in previous studies at exposure margins of ≥7. Increased postnatal pup mortality was observed in rats after oral tadalafil treatment during gestation and lactation. Exposure at the no effect dose was about fivefold that expected in humans.

There were no nonclinical objections to the registration of tadalafil for the proposed indication.

IV. Clinical Findings

Introduction

The application is based on a single pivotal study, LVGY, and the subsequent extension phase of this study, LVGX, some additional pharmacokinetic studies because of the higher recommended dose for PAH (40 mg/day) compared to erectile dysfunction (up to 20 mg/day) and some additional interaction studies. The pivotal study was performed in North America, Europe and Japan and in adherence to Good Clinical Practice and in keeping with the patient protections outlined in the Declaration of Helsinki.

Pharmacokinetics

Introduction

In addition to the Cialis for erectile dysfunction (ED) submission, the following additional clinical pharmacology studies were conducted specifically for this submission: LVHC (pharmacokinetics in Japanese subjects), LVHO (food effect), LVGZ (bosentan interaction), LVHL (digoxin interaction) and LVHM (oral contraceptive interaction).

Absorption, distribution, metabolism and excretion (ADME) profile

The ADME profile of tadalafil was adequately established in the previous Cialis for ED submission and is summarised below.

Tadalafil is rapidly absorbed after oral administration and the mean maximum 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. The absolute bioavailability of oral tadalafil has not been established. The mean bioavailability of a 20 mg tablet has been estimated to be 88% relative to an oral suspension dosage form.

The mean volume of distribution after oral dosing is approximately 77 L at steady state. At therapeutic concentrations, 94% of tadalafil in plasma in bound to proteins.

Tadalafil is metabolised mainly (>80%) by CYP3A4, with minor contributions by CYPs 2C8, 2C9, 2C19 and 2D6 (<20% collectively). The major metabolite is the methylcatechol glucuronide. This metabolite is at least 13,000 fold less potent than tadalafil for PDE5. The mean oral clearance for tadalafil is 3.4 L/hr at steady state and the mean terminal half life

is 16 hours in healthy subjects. Tadalafil is excreted predominantly as inactive metabolites mainly in the faeces.

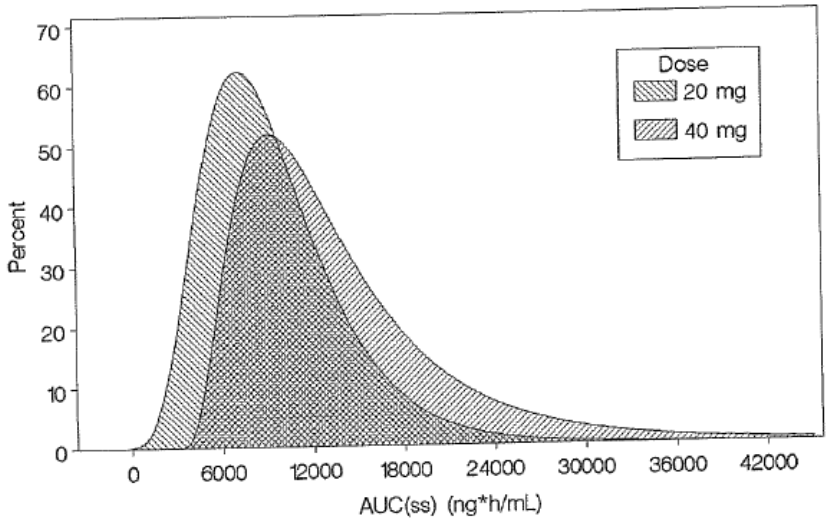
For this PAH submission additional information on population kinetics in PAH patients was obtained and is discussed below. A further study of the effect of food on the absorption of tadalafil was included in this submission. Study LVHO was an open label randomised, two way crossover study evaluating the effect of a high fat meal on the pharmacokinetics of tadalafil administered as a single oral dose of 40 mg in 12 healthy subjects. Tadalafil was administered in the fasting state and within 30 minutes of a FDA-defined high fat breakfast.[3] At least 7 days separated each dosing period. This study was also discussed in *Section II*. Administrations of tadalafil with a high fat meal lead to an 11% to 14% increase in systemic exposure (AUC) for tadalafil. C_{max} was not affected by food. Statistical analysis indicated that AUC and C_{max} were equivalent in the fasted and fed states with the 90% confidence intervals overlapping (within the accepted bioequivalence values of 80%-125%) (Table 2). The results of this study support the statement in the PI that tadalafil may be taken with or without food.

Dose Proportionality

Dose proportionality was studied as part of the population pharmacokinetics that was included in the pivotal efficacy study LVGY. The parameter estimate for the relative bioavailability of the 40 mg dose was 0.65, indicating a reduction in bioavailability of 35% (95% confidence intervals (CI): 28.6%, 42.0%) for the 40 mg dose when compared to the lower doses (2.5, 10, and 20 mg) studied in this trial. Furthermore, a bioequivalence assessment of the individual area under the plasma concentration time curve at steady state (AUC_{ss}) values comparing the 40 mg to the 20 mg dose group reveals a geometric mean ratio (90% CI) of 1.48 (1.30, 1.68) (Figure 2). Additionally, approximately 81% of the observed tadalafil AUC_{ss} predicted following 40 mg once daily administration were within the 5th to 95th percentiles of those estimated following 20 mg. Due to the lack of dose proportionality between 20 mg and 40 mg, it appears that the 40 mg dose would provide exposures approximating a 30 mg (90% CI: 26, 34 mg) dose.

[3] The test meal was the high fat, high calorie meal recommended by the FDA guideline, which contains approximately 800 to 1000 calories and approximately 50% of fat in the total caloric content. The meal consisted of 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes and 8 ounces of whole milk.

Figure 2: Probability distributions of individual predicted tadalafil AUC_{ss} for subjects administered 20 mg and 40 mg tadalafil



Source: LVGY Population PK/PD Report, Figure LVGY.9.7

Pharmacokinetics in target populations

Population pharmacokinetics were evaluated in the pivotal study LVGY. The pharmacokinetics of tadalafil were evaluated in 305 subjects (69 male and 236 female) with pulmonary arterial hypertension, receiving once daily doses of tadalafil 2.5 mg, 10 mg, 20 mg, 40 mg or placebo for 16 weeks; plasma samples were collected at Weeks 4, 8, 12 and 16. The pharmacokinetic (PK) analysis included 1102 concentration records from 305 subjects (69 male and 236 female) administered tadalafil 2.5 mg (n = 77), 10 mg (n = 77), 20 mg (n = 77) or 40 mg (n = 74) once daily. This included data from 22 Japanese subjects having 246 observations and 241 Caucasian subjects with 2676 observations. The pharmacokinetic data was best described by a one compartment model with a rapid first order absorption rate (0.84 h-1). The typical estimate (percentage standard error [%SEE]) for the apparent clearance (CL/F) was 1.59 L/h (5.0%) for subjects not receiving concomitant bosentan with an apparent volume of distribution (V/F) of 79.7 L (6.7%). Systemic exposure to tadalafil was not influenced by cardiovascular conditions, gender and ethnicity, PAH history or duration, creatinine clearance, total serum protein, weight, or concomitant warfarin or digoxin use, thereby suggesting that tadalafil can be administered without regard to these factors. In the present LVGY evaluation, only the covariate of dose (40 mg) was found to be a predictor of bioavailability (F) and concomitant bosentan use significantly influenced CL/F. To compare the pharmacokinetics of tadalafil following once daily administration to subjects with ED and those with PAH, the final population PK parameters from this study (LVGY) and those from Study LVFP were used. The typical CL/F estimates from Studies LVFP and LVGY were broadly similar with any difference being <20% and unlikely to be clinically relevant. Further, the 95% confidence intervals demonstrated considerable overlap resulting in comparable tadalafil plasma concentration time profiles.

Special Populations

Study LVHC evaluated the pharmacokinetics of tadalafil 40 mg in healthy adult Japanese subjects following multiple oral administrations in 24 subjects (male and female) who were randomised to either placebo or tadalafil 40 mg/day for 10 days. Tadalafil exposures (the area under the plasma concentration time curve for a dosing period τ

[AUC_τ] and C_{max}) were comparable across Days 5 and 10; similarly the apparent clearance at steady state (CL_{ss}/F) appeared stationary between Days 5 and 10, indicating an absence of time dependent tadalafil PK. To compare the tadalafil PK of Japanese and non-Japanese subjects following 40 mg once daily multiple dose administration, results from the present study (LVHC) and those from a non-Japanese trial (H6D-MC-LVGZ) were assessed. Notably, Study LVGZ included only non-Japanese male subjects (N=15; approximately 80% Caucasian) receiving once daily multiple dose 40 mg tadalafil; however, demographic and baseline characteristics of all subjects, irrespective of ethnicity, were generally similar. As expected, the median weight of subjects in LVHC was greater (25%) than Japanese subjects, although overlap between the groups was evident. The results indicated that tadalafil plasma concentration time profiles following 40 mg per day were comparable in both Japanese and non-Japanese subjects.

No further studies were submitted in special populations although this was extensively studied in the previous Cialis submission and all details are included in the proposed Adcirca PI.

Interactions

Bosentan interaction study

Study LVGZ was a single centre, open label, randomised, three period crossover study to investigate the interaction of tadalafil and bosentan. Bosentan is an endothelin antagonist approved for use in PAH and 51% of the patients in the pivotal efficacy study were taking concomitant bosentan. Study LVGZ enrolled 13 healthy males and studied tadalafil 40 mg/day and bosentan 125 mg twice per day. Each treatment period was 10 days with a 7 day washout period in between.

Compared to administration of tadalafil alone, concomitant single dose bosentan did not alter tadalafil or metabolite exposure (AUC and C_{max}) or the rate of absorption. However after 10 days of concomitant multiple dose exposure tadalafil clearance increased by approximately 70% with a corresponding decrease in AUC of 42% and C_{max} by 27%. The exposure of the tadalafil metabolite was unchanged.

Concomitant treatment with tadalafil did not appear to have any effect on the pharmacokinetics of bosentan.

Oral contraceptive interaction study

Study LVHM investigated the effects of tadalafil on the oral contraceptive (OC) (levonorgestrel + ethinyloestradiol [Microgynon]) pharmacokinetics in healthy female subjects. This was a double blind, placebo controlled, three period, two sequence, randomised, crossover study in 30 subjects. Microgynon was administered daily for 21 days in each of the 3 periods and tadalafil or placebo in the first and third periods .There was a 7 day washout between periods.

At steady state, tadalafil increased ethinyloestradiol exposure (AUC) by 26% and C_{max} by 70% relative to the OC alone. There was no statistically significant effect of tadalafil on levonorgestrel. The effect on ethinyloestradiol is possibly due to inhibition of gut sulphation by tadalafil.

Digoxin interaction study

Study LVHL investigated the effect of tadalafil on the steady state pharmacokinetics of digoxin in healthy subjects. This open label single sequence study enrolled 20 subjects. Digoxin was administered as a loading dose of 1 mg on Day 1 then 0.25 mg on Days 2 to 17. Tadalafil 40 mg was administered from Days 8 to 17. There was no statistically significant effect of multiple dose tadalafil on the steady state pharmacokinetics of digoxin.

Evaluator's overall comments on pharmacokinetic interactions.

The most significant interactions of tadalafil are those described previously in the ED submission, including the potential of 3A4 inhibitors to increase tadalafil plasma levels and exposure, the contraindication with nitrates and the interaction with some antihypertensives (the vasodilatory effect of tadalafil may augment the effect of some antihypertensives). In this submission, bosentan, a moderate inducer of CYP3A4, was shown to reduce systemic exposure to tadalafil (AUC by 42% and C_{max} by 27%). Tadalafil had no effect on bosentan levels.

Tadalafil had no significant effect on the pharmacokinetics of digoxin.

Concomitant use of tadalafil with an oral contraceptive led to increased ethinyloestradiol exposure (AUC by 26% and C_{max} by 70%).

The possible pharmacokinetic interactions are adequately described in the proposed PI.

Evaluator's overall conclusions on pharmacokinetics.

The pharmacokinetic profile of tadalafil was well established for the ED indication. In this submission the kinetics in the PAH population were explored in a population PK study. In patients with PAH not receiving concomitant bosentan, the average tadalafil exposure at steady state following 40 mg/day was 26% higher when compared to healthy volunteers. There were no significant differences in C_{max} compared to healthy volunteers. The results suggest a lower clearance in PAH patients compared to healthy volunteers. The kinetics of tadalafil are linear from 2.5 mg to 20 mg but they are less than proportional from 20 mg to 40 mg.

There is a pharmacokinetic interaction between tadalafil and bosentan such that the clearance of tadalafil is increased (and AUC and C_{max} decreased) by concomitant administration.

There is no significant interaction between tadalafil and digoxin or a representative oral contraceptive.

Pharmacodynamics

Tadalafil is a potent and selective inhibitor of phosphodiesterase type 5 (PDE5), the enzyme responsible for the degradation of cGMP. Pulmonary arterial hypertension is associated with the impaired release of nitric oxide by the vascular endothelium and the consequent reduction of cGMP concentrations within the pulmonary vascular smooth muscle. Inhibition of PDE5 by tadalafil increases the concentrations of cGMP resulting in relaxation of the pulmonary vascular smooth muscle cells and vasodilation of the pulmonary vascular bed. The pharmacodynamics of tadalafil were well described in the ED submission. No additional information was provided in this submission for use of tadalafil for PAH.

Efficacy

Introduction

Efficacy was assessed in one pivotal study LVGY and a follow on extension study LVGX.

Pivotal study LVGY

LVGY was a pivotal, multicentre, randomised, double blind, placebo controlled study which evaluated the safety and efficacy of tadalafil (2.5, 10, 20 and 40 mg given orally once daily for 16 weeks) in approximately 400 patients with PAH at 82 centres in North America, Europe and Japan.

The primary efficacy endpoint was the six minute walk (6-MW) distance change from baseline to Week 16.

Secondary endpoints included:

1. WHO Functional Class change from baseline to Week 16.
2. Time to first occurrence of clinical worsening, defined as any of the following: death, lung transplantation, atrial septostomy, hospitalisation due to worsening of PAH or initiation of new PAH therapy.
3. Borg Dyspnoea Scale change from baseline to Week 16.[4]
4. In a subset of patients, cardiopulmonary haemodynamics (including mean pulmonary artery pressure (MPAP), pulmonary vascular resistance (PVR), mean right atrial pressure, cardiac index (CI), cardiac output (CO), pulse capillary wedge pressure, mean arterial pressure (MAP), mixed venous oxygen saturation and systemic vascular resistance (SVR) changes from baseline to Week 16.

   Quality of Life (QoL) as measured by SF36v2 and European Quality of Life (EuroQoL) Questionnaire scores at baseline and end of treatment (Week 16).[5,6]

Subjects who met the eligibility criteria were stratified by PAH aetiology, bosentan use, and 6-MW distance. Subjects were then randomly assigned to one of five treatment groups (placebo, 2.5 mg, 10 mg, 20 mg or 40 mg tadalafil) on a 1:1:1:1:1 basis. For PAH aetiology groups were stratified by idiopathic PAH versus other aetiologies. Baseline 6-MW was categorised as ≤325 m and >325 m. Bosentan use was stratified as yes/no. Randomisation was performed by a computerised interactive voice response system (IVRS) system at a central location for all sites.

The "intent to treat" (ITT) population for the primary analysis included all patients who were randomised to treatment and received at least one dose of the study drug. The null hypothesis of no difference between each of the tadalafil treatment groups and placebo was tested using a permutation based procedure similar to the Mann-Whitney test stratified by PAH aetiology, bosentan use, and baseline 6-MW distance (≤325, >325 metres). For the efficacy analysis, multiplicity was an issue because each tadalafil treatment group (2.5, 10, 20 or 40 mg) was compared with placebo for the primary endpoint as well as for key secondary endpoints. The 2-dimensional multiplicity adjustment (multiple doses and endpoints) was addressed statistically using step down testing as follows:

· Testing began with tadalafil 40 mg versus placebo for the primary endpoint (change from baseline in 6-MW distance);

[4] Borg Dyspnoea Scale is a subject-perceived level of dyspnoea at the end of treatment after the 6-MW test.

[5] The SF-36 is a multi-purpose, short-form health survey with only 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. It measures eight domains of health: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. It yields scale scores for each of these eight health domains, and two summary measures of physical and mental health. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. The SF-36 is available for two recall periods: standard (4-week recall) and acute (1-week recall).

[6] Developed by EuroQol, EQ-5D is a standardised instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status.

- If it was significant at the α-level (two-sided) of 0.01, testing of secondary endpoints at this dose proceeded. The order that the secondary endpoints were tested was as follows:
    - improvement in WHO Functional Class,
    - time to clinical worsening, and
    - change from baseline in Borg Dyspnoea Score.

If improvement in WHO Functional Class was significant at the α-level (two-sided) of 0.05, testing of the time to clinical worsening was done and so forth. Testing of the primary endpoint for tadalafil 20 mg compared to placebo was conducted only if the tadalafil 40 mg compared to placebo primary comparison was significant.

The testing level of significance for the primary and secondary endpoints was 2-sided 0.01 and 2-sided 0.05, respectively.

Diagnosis and Inclusion Criteria

Subjects were at least 12 years old and had a diagnosis of PAH that was idiopathic, related to collagen disease, related to anorexigen use, related to HIV infection, associated with atrial septal defect or associated with surgical repair of at least 1 year duration of a congenital systemic to pulmonary shunt. The diagnosis was established by a resting MPAP >25 mmHg, pulmonary wedge pressure <15 mmHg and PVR≥ 3 Wood units via right heart catheterisation.

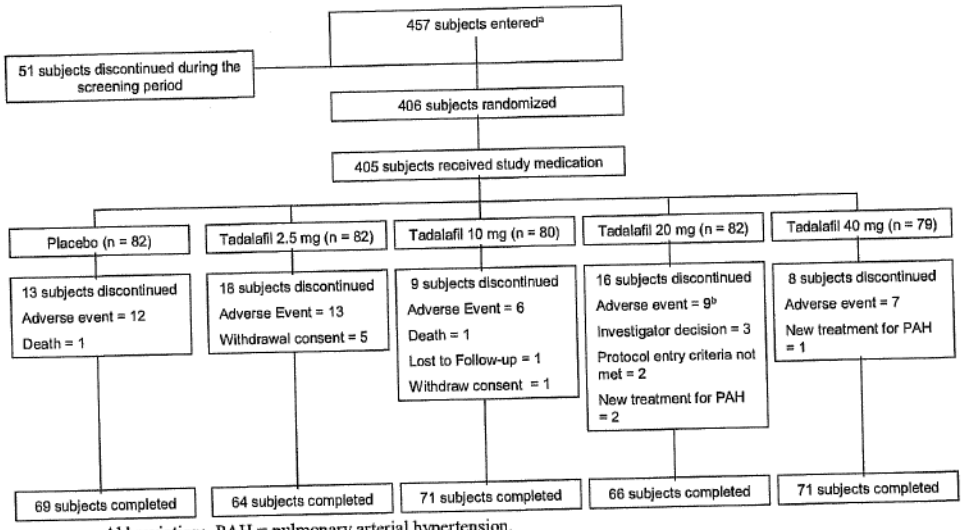
The mean exclusion criteria were nursing or pregnant, PAH not related to inclusion criteria, arterial oxygen saturation <88%, history of left sided heart failure or atrial septostomy, severe hepatic impairment, severe renal insufficiency (on dialysis or creatinine clearance <30 mL/min), blood pressure (BP)>160/90 or diastolic >100 or <50 mmHg, nitrate treatment for angina, experimental treatment for PAH within 4 weeks, treatment with HIV protease inhibitors, ketoconazole or itraconazole.

The inclusion/exclusion criteria represent a real life population of PAH patients who would be eligible for tadalafil treatment.

Enrolment, Patient Characteristics and Compliance

Overall, 406 patients were randomised to treatment, 82 on placebo and 342 on tadalafil. A total of 341 patients completed 16 weeks treatment: 69 on placebo and 272 on tadalafil (Figure 3).

Figure 3: Illustration of subject disposition in Study H6D-MC-LVGY



Abbreviation: PAH = pulmonary arterial hypertension.

a Subjects were allowed to screen more than once but were only counted as entered into the study once.

b One tadalafil 20-mg treated subject discontinued the study due to an adverse event and then later died due to the adverse event. The death was considered to have occurred during the study.

The mean age of all subjects was 54 years with the majority being Caucasian and female. Pulmonary arterial hypertension aetiologies were predominantly idiopathic PAH and related to collagen vascular disease. Slightly more than half (53%) were receiving bosentan therapy. The majority had a WHO Functional Class II (n=130, 32%) or III (n=265, 65%).

The baseline characteristics of the five treatment groups were well balanced. Compliance was also similar across all groups.

There were 9 protocol violations: 7 of these were due use of a prohibited concomitant medication. Two patients did not fit the entry criteria. These small numbers are unlikely to have any significant influence on the results.

Efficacy Results

Primary Endpoint

Patients receiving tadalafil 40 mg once daily had a statistically and clinically significant improvement in 6-MW distance compared to subjects receiving placebo after 16 weeks of treatment. Median change from baseline to Week 16 was 12, 17, 30, 32 and 35 metres in placebo, tadalafil 2.5 mg, 10 mg, 20 mg and 40 mg groups, respectively. Although 10, 20 and 40 mg produced statistically significant improvements over placebo, 40 mg produced the most significant improvement (Table 3).

The analysis of covariance (ANCOVA) placebo adjusted least square means (LSM) treatment difference between tadalafil 40 mg and placebo was 32.8 metres (95% CI = 15.2 to 50.3 metres). The improvement in 6-MW reached significance after 8 weeks and was maintained for the study duration of 16 weeks.

Secondary Endpoints

In the secondary protocol specified step down analyses, there were no significant differences (the protocol specified level of statistical significance was not reached) between subjects receiving tadalafil 40 mg compared to placebo in incidences of WHO Functional Class 'improvement, no change or worsening' (Table 3). Since there were no statistically significant treatment differences from placebo in WHO Functional Class, the

descriptive statistics and inferential tests on all other secondary variables were presented as additional information for the primary endpoint. Although the time to clinical worsening was statistically significantly greater in the tadalafil 40 mg group compared to placebo (p=0.041), this should be interpreted with caution due to high variability of the results. The probability of subjects not having a clinically worsening event at Week 16 was higher for the tadalafil 40 mg group (94%, 95% CI: 85% to 98%) compared to the placebo group (84%, 95% CI: 74% to 90%). However, there was considerable overlap of the 95% confidence interval between the two groups.

Table 3: Study LVGY, Summary of primary and secondary efficacy endpoints (change from baseline to Week 16)

			Tadalafil			
		Placebo (N=82)	2.5mg (N=82)	10mg (N=80)	20mg (N=82)	40mg (N=79)
6-minute walk Distance (meters)	n	79	79	78	80	76
	Median	12.20	17.00	30.50	32.00	35.05
	Mean (SD)	9.21(59.96)	21.79(60.83)	28.60(62.17)	36.23(47.53)	41.14(49.39)
	95% C.I.*a	-4.22,22.65	8.17,35.42	14.58,42.61	25.65,46.81	29.85,52.42
	p-value*b		0.4023	0.0466	0.0278	0.0004
	Trt difference*c		10.00	16.10	21.90	26.00
WHO Functional Class	n	82	82	80	82	79
	Improved (1-2 class)	17(20.73)	21(25.61)	19(23.75)	30(36.59)	18(22.78)
	No change	52(63.41)	43(52.44)	50(62.50)	37(45.12)	53(67.09)
	Worsen	13(15.85)	18(21.95)	11(13.75)	15(18.29)	8(10.13)
	p-value*d		0.9720	0.5758	0.1694	0.3630
Clinical Worsening	n	82	82	80	82	79
No. of Subjects had worsening, n (%)		13(15.85)	10(12.20)	7(8.75)	8(9.76)	4(5.06)
Time to Worsening	Mean (SD)	100.79(27.94)	102.91(25.09)	105.80(23.83)	103.23(27.79)	106.24(24.16)
	p-value*e		0.5591	0.1955	0.3018	0.0410
Borg Dyspnea Score	n	79	79	78	78	76
	Median	0.00	-0.50	0.00	-0.25	-0.50
	Mean (SD)	0.41(1.89)	-0.68(1.76)	-0.36(1.92	-0.29(2.08)	-0.70(1.75)
	95% C.I.*a	-0.02,0.83	-1.07,-0.28	-0.79,0.07	-0.76,0.17	-1.10,-0.30
	p-value*b		0.0103	0.1483	0.1581	0.0679
	Trt difference*c		-1.00	-1.00	-1.00	-1.00

N = number of randomized subjects who have received study medication; n = number of subject with nonmissing data at baseline and endpoint; trt = study treatment.
*a 95% confidence interval (C.I) is calculated based on t Distribution.
*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.
*c Treatment difference compared to Placebo are estimated using the methodology of Hodges-Lehmann.
*d Cochran-Mantel-Haenszel (CMH) test stratified by PAH etiology, bosentan use, and baseline 6-minutes walk distance compared to placebo.
*e Permutation test stratified by PAH etiology, bosentan use, and baseline 6-minute walk distance (<= 325 m and >325 m) on log-rank score.

Source: EFFN02GY, EFFN71GY, EFFN04GY, EFFN01GY

There were no significant differences between any tadalafil group compared to the placebo group in the Borg dyspnoea score. However the Borg dyspnoea score was reduced in all tadalafil groups with the largest reduction seen in the 40 mg group.

Several cardiopulmonary hemodynamic parameters were significantly improved compared to baseline in the tadalafil groups. The tadalafil 40 mg group had statistically significant improvements in mPAP, PVR, CI, and CO ($p<0.05$).

Improvement in SF-36v2 was seen in almost all 8 domains of QoL in the tadalafil groups compared to placebo with the 40 mg group having significant improvement in 6 domains ($p<0.05$). Significant improvement in EuroQoL was also seen in all tadalafil groups compared to placebo in the index score (both US and UK; $p<0.05$). Only the tadalafil 40 mg group achieved a significant improvement in the health state visual analog scale (VAS) (p=0.0215).

Long term efficacy

LVGX Extension was a long term extension study of LVGY to determine the long term safety and durability of response to tadalafil when used for treatment of PAH.

Study Design

Part 1 of LVGX was a double blind extension of LVGY to evaluate the safety and efficacy of tadalafil 20 and 40 mg daily for 52 weeks. Patients were to receive tadalafil 20 or 40 mg

depending on their response in the pivotal study LVGY. All patients were to receive tadalafil 40 mg/day except patients who responded well to 20 mg per day in LVGY.

Part 2 was an open label extension to Part 1 to provide patient access.

Objectives

The primary objective of Part 1 of the study was to evaluate the long term safety of tadalafil: safety was measured by adverse event (AE) reporting, physical exams, electrocardiograms (ECGs) and laboratory tests. The secondary objective of Part 1 of the study was to determine the durability of efficacy observed in LVGY by evaluation of the 6-MW test and WHO Functional Class. Patients were eligible to continue in LVGX if they had no clinical worsening in LVGY and also those who had clinical worsening on doses less than 40 mg per day of tadalafil.

Results

A total of 77 of the original 82 sites participated in the extension study: 357 patients entered LVGX, 63 received tadalafil 20 mg and 294 received tadalafil 40 mg per day.

Overall, 293 patients completed Part 1, 52 on tadalafil 20 mg and 241 on tadalafil 40 mg.

Subjects receiving unchanged treatment with tadalafil 20 mg from Study LVGY had a baseline 6-MW distance of 397.74 metres. At the end of LVGX their mean 6-MW distance had increased slightly to 401.52 metres.

For subjects receiving unchanged treatment with tadalafil 40 mg, the mean baseline was 403.31 metres and at the end of LVGX their mean was 400.26 metres.

For subjects with a dose change from placebo to 40 mg, the 6-MW distance increased from baseline of 361.27 metres to 377.9 metres at the end of LVGX.

For subjects changing their tadalafil dosage from 2.5, 10 or 20 mg to 40 mg, the change in mean 6-MW distance was from 368.97 metres to 371.21 metres.

The majority of patients taking tadalafil 20 mg (80.65%) and 40 mg (91.04%) showed either no change or an improvement in their WHO Functional Class status. The highest incidence of improvement was seen in patients who went from placebo in LVGY to 40 mg in LVGX.

Only minimal changes were observed in the Borg Dyspnoea Score after 52 weeks of therapy.

The fact that 6-MW was stable or increased over the one year period suggests that efficacy is maintained. However, it was considered surprising that the lower dose groups who were changed to 40 mg/day did not show a greater increase.

Clinical studies in special populations

Due to the potential differences in response in subjects based upon the stratification factors used for randomization, subgroup analysis was conducted for the primary and key secondary efficacy endpoints:

- bosentan use (yes, no);
- PAH aetiology (idiopathic and anorexigen use, others) and
- baseline 6-MW distance ($\leq$325 metres, $\geq$325 metres).

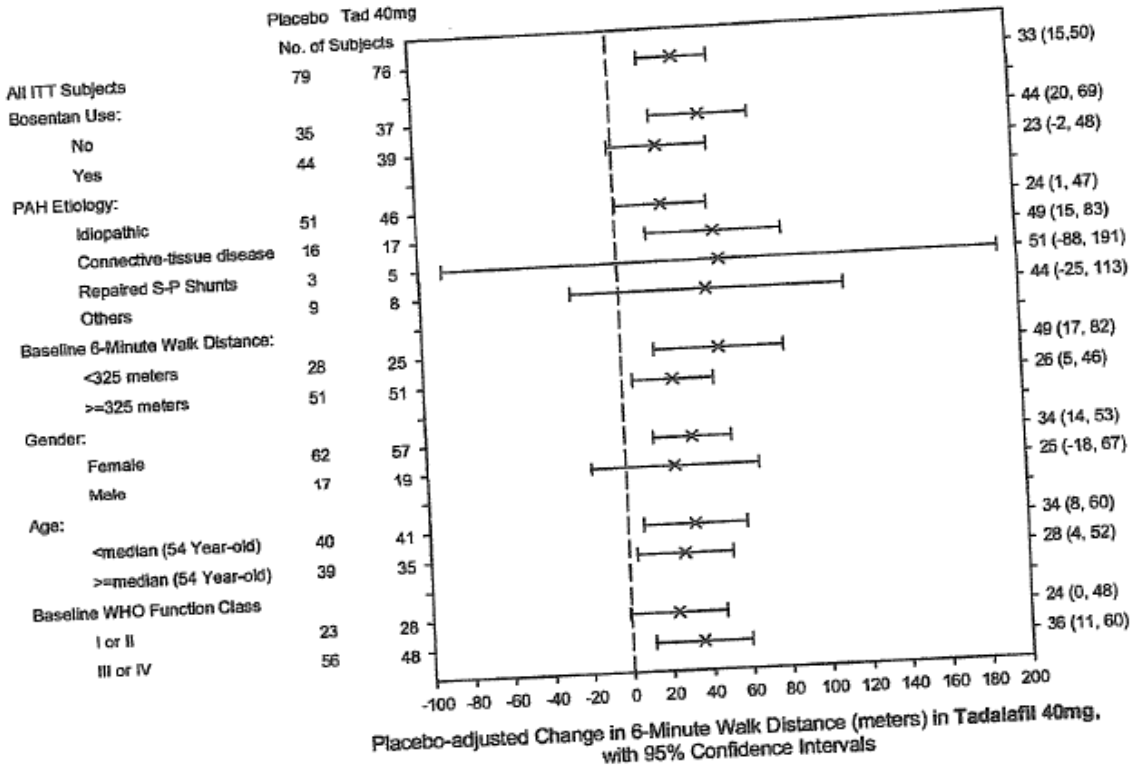
The 6-MW distance was analysed by the following subgroups:

- PAH aetiology (idiopathic, connective tissue disease [collagen vascular disease], repaired congenital systemic to pulmonary shunt, others),

- gender (male, female),
- age category (<median age, ≥median age) and
- WHO Functional Class (combined Class I and II, combined Class III and IV).

In the pivotal study LVGY, there was consistent improvement in 6-MW distance at 16 weeks in the 40 mg group compared to placebo in almost all populations (bosentan use, PAH aetiology, baseline 6-MW distance, gender, age category and baseline WHO Functional Class) (Figure 4).

Figure 4: Tadalafil 40 mg placebo adjusted change from baseline in 6-MW distance by study population – mean (95% CI)



Abbreviations: ITT = intent to treat; Tad = tadalafil; WHO = World Health Organization.

Bosentan use

Differences in baseline characteristics between bosentan and non-bosentan subjects were observed in age group, duration of PAH, and PAH aetiology. Bosentan subjects were slightly younger than non-bosentan subjects (mean age = 51 versus 57 years) with 20.8% bosentan subjects versus 35.4% of non-bosentan subjects in the ≥65 age group. Bosentan subjects were less likely to have PAH duration <2 years (37.0% versus 76.2%) than non-bosentan subjects but were more likely to have PAH duration ≥2 to >4 years (31.5% versus 4.7%) and also ≥4 years (31.5% versus 19.1%). Bosentan subjects were less likely to have idiopathic PAH aetiology than non-bosentan subjects (57.4% versus 65.1%) but

were more likely to have PAH related to collagen vascular disease (25.9% versus 20.6%). While both bosentan and non-bosentan subjects had similar increases in 6-MW distance, the non-bosentan subjects had larger placebo adjusted treatment difference increases in 6-MW distance, especially in the tadalafil 40 mg treatment group. In bosentan treated subjects, there was no significant treatment effect for any tadalafil treatment group compared to placebo (p=0.0907). The maximum placebo adjusted treatment difference for 6-MW distance was in the tadalafil 40 mg treatment group (22.7 metres; 95% CI: -2.4, 47.8). However, the tadalafil 40 mg subgroup that did not receive bosentan concomitantly had a significantly improved placebo adjusted treatment difference of 44.3 metres in 6-MW distance. Hence, the improvement in 6-MW reached statistical significance in the tadalafil without bosentan group but was borderline in the concomitant bosentan group. The sponsor notes in the PI that "the efficacy of tadalafil in patients already on bosentan has not been conclusively shown".

Pulmonary artery aetiology

Subjects who were randomized and stratified by PAH aetiology were initially evaluated by Idiopathic/Anorexigen Use (n=263) and other (included related to collagen vascular Disease) [n=142]. For subjects whose PAH was idiopathic (n=242), the placebo treatment group median 6-MW distance from baseline to end of treatment increased by 18.0 metres (mean 15.6 metres). For all tadalafil treated subjects with idiopathic PAH, the median change in 6-MW distance from baseline to end of treatment was numerically higher compared to placebo (median range: 16.5 to 35.1 metres; mean range: 19.9 to 39.8 metres). The tadalafil 10 and 40 mg treatment groups were significantly improved compared to placebo ($p<0.05$).

For subjects whose PAH was related to collagen vascular disease (n=89), the placebo treatment group median 6-MW distance from baseline to end of treatment increased by 1.3 metres (mean -17.3 metres). For all tadalafil treated subjects whose PAH was related to collagen vascular disease, the median change in 6-MW distance from baseline to end of treatment was numerically higher compared to placebo (median range: 4.1 to 27.0 metres; mean range: 2.6 to 31.7 metres) with the proposed tadalafil 40 mg treatment group reaching significance ($p<0.05$). The other aetiology subgroups had very few patients and results were very variable as evident from Figure 4.

Hence, efficacy of the proposed dose of 40 mg tadalafil was shown in the subgroups of patients with idiopathic PAH and PAH due to collagen vascular disease.

Baseline 6MW distance (≤ or >325metres)

For subjects whose baseline 6-MW distance was >325 metres (n=260), the placebo treatment group median 6-MW distance from baseline to end of treatment increased by12.0 metres (mean: 7.5 metres). For all tadalafil treatment groups, the median change from baseline to end of treatment in 6-MW distance were numerically higher compared to placebo (median range: 18.0 to 32.5 metres; mean range: 22.0 to 35.6 metres). The tadalafil 20 mg (median: 32.5 metres; mean: 35.6 metres; $p<0.05$) and 40 mg (median: 25.0 metres, mean: 33.3 metres; $p<0.05$) treatment groups had 6-MW distances that were significantly improved compared with placebo.

For subjects whose baseline 6-MW distance was ≤325 metres (n=145), the placebo treatment group median 6-MW distance from baseline to end of treatment increased by 13.6 metres (mean: 12.3 metres). All tadalafil treated subjects' median change from baseline to end of treatment in 6-MW distance was numerically higher compared with placebo (median range: 9.2 to 52.0 metres; mean range: 19.2 to 57.2 metres). The tadalafil 40 mg treatment group (median: 52.0 metres; mean: 57.2 metres; $p<0.05$) had 6-MW distance that was significantly improved compared with placebo.

Baseline WHO Functional Class

For WHO Functional Class I and II subjects (n=134), the placebo treatment group median 6-MW distance from baseline to end of treatment increased by 12.8 metres (mean: 10.8 metres). Across all tadalafil treatment groups, median change in 6-MW distance from baseline to end of treatment was numerically higher than placebo (median range: 22.5 to 36.7 metres; mean range: 32.2 to 40.7 metres). The tadalafil 40 mg treatment group (median: 36.7; mean: 37.5 metres; $p<0.05$) had 6-MW distance that was significantly improved compared with placebo.

For WHO Functional Class III and IV subjects (n=271), the placebo treatment group median 6-MW distance from baseline to end of treatment increased by 4.8 metres (mean: 8.6 metres). Across all tadalafil treatment groups, median change in 6-MW distance from baseline to end of treatment was numerically higher than placebo (median range: 13.0 to 33.0 metres; mean range: 11.4 to 43.3 metres). The tadalafil 20 mg (median: 32.5 metres; mean: 38.3 metres; $p<0.05$) and 40 mg (median 33.0 metres, mean 43.3 metres; $p<0.05$) treatment groups had 6-MW distance that was significantly improved compared with placebo.

A majority of the patients had WHO class II or III at baseline: only 4 patients had baseline WHO Class I (0.99%) and 7 patients belonged to WHO Class IV (1.73%). Hence, efficacy was shown in patients with WHO class II and III, which is also the specific indication proposed for tadalafil.

Evaluator's overall conclusions on clinical efficacy

The efficacy studies were well conducted for this orphan indication. Approval for PAH has already been obtained in the EU, USA and Canada.

The optimal dose is 40 mg per day with a 20 mg starting dose for some special populations.

The results are clinically and statistically significant and the outcome measures used such as 6-MW and QoL are both standard and clinically meaningful. The studies are compliant with the EU guidelines for drugs for PAH which recommend exercise capacity (6-MW) and change in Functional Class and QoL as endpoints (tadalafil is already approved in the EU for PAH).

Efficacy did not appear to be affected by race, gender and age. Furthermore, long term efficacy was maintained over one year.

There will undoubtedly be a desire to add tadalafil to the therapy of patients who are responding inadequately to bosentan. Tadalafil does appear to add benefit when added to bosentan but this did not reach clear statistical significance. This is noted in the Adcirca PI. The combination appears to be reasonably well tolerated.

Safety

Introduction

Approximately 500 patients have been treated in the tadalafil PAH program, including both efficacy and clinical pharmacology studies. This is composed of 406 patients randomised to treatment in the efficacy studies (342 to tadalafil and 82 to placebo and 90 patients/healthy subjects included in the clinical pharmacology studies). Overall, 18,400 patients have been exposed to tadalafil in clinical studies of ED and PAH. As of September 2007 approximately 12.9 million patients had been exposed to tadalafil worldwide.

Safety was examined in the Study LVGY and LVGX using AEs, vital signs and clinical laboratory data. Ophthalmologic exams were conducted at baseline and at the study

endpoints. ECGs were performed at baseline and the study endpoint for LVGY. Serum chemistry and haematology were assessed at baseline, 4, 8, 12 and 16 weeks with the regular investigator visits.

Patient exposure

Approximately 400 patients participated in the PAH efficacy studies. Some 12.9 million people have been exposed to tadalafil until September 2007.

Of the 406 randomised to treatment in LVGY (342 to tadalafil and 82 to placebo), 341 patients completed 16 weeks treatment (272 on tadalafil and 69 on placebo). A total of 357 patients commenced treatment in LVGX and 293 completed one year of treatment with tadalafil 20 or 40 mg/day.

Adverse events

The most commonly reported treatment emergent adverse events (TEAEs) in study LVGY were similar to the most commonly reported AEs with tadalafil for the treatment of ED with the addition of a number of AEs related to the PAH disease state. The most frequently reported AEs were headache, diarrhoea, nausea, back pain, dizziness, dyspepsia, flushing, myalgia and nasopharyngitis (Table 4). However menorrhagia and or vaginal haemorrhage were reported in 8 subjects in study LVGY (placebo: 0, T2.5 mg: 0, T10 mg: 1, T20 mg: 3, T40 mg: 4). The sponsor suggested that as menorrhagia is common and the incidence in the study low a relationship to tadalafil can neither be defined nor ruled out. Menorrhagia is included in the PI.

Table 4: Summary of TEAEs occurring in at least 5% of placebo or tadalafil treated subjects (in any treatment group) by preferred term in descending order of incidence in the combined tadalafil group – Study LVGY (N=405)

Preferred Term	Placebo (N=82) n	(%)	T2.5mg (N=82) n	(%)	T10mg (N=80) n	(%)	T20mg (N=82) n	(%)	T40mg (N=79) n	(%)	All tadalafil (N=323) n	(%)
Patients with >= 1 TEAE	65	(79.3)	72	(87.8)	72	(90.0)	69	(84.1)	75	(94.9)	288	(89.2)
Headache	12	(14.6)	15	(18.3)	30	(37.5)	26	(31.7)	33	(41.8)	104	(32.2)
Diarrhoea	8	(9.8)	9	(11.0)	9	(11.3)	6	(7.3)	9	(11.4)	33	(10.2)
Nausea	5	(6.1)	6	(7.3)	7	(8.8)	8	(9.8)	9	(11.4)	30	(9.3)
Back pain	5	(6.1)	5	(6.1)	5	(6.3)	10	(12.2)	8	(10.1)	28	(8.7)
Dizziness	7	(8.5)	9	(11.0)	8	(10.0)	5	(6.1)	6	(7.6)	28	(8.7)
Dyspepsia	2	(2.4)	4	(4.9)	2	(2.5)	11	(13.4)	8	(10.1)	25	(7.7)
Oedema peripheral	7	(8.5)	7	(8.5)	6	(7.5)	7	(8.5)	5	(6.3)	25	(7.7)
Pulmonary hypertension	7	(8.5)	7	(8.5)	5	(6.3)	7	(8.5)	6	(7.6)	25	(7.7)
Flushing	2	(2.4)	3	(3.7)	5	(6.3)	5	(6.1)	10	(12.7)	23	(7.1)
Myalgia	3	(3.7)	2	(2.4)	3	(3.8)	7	(8.5)	11	(13.9)	23	(7.1)
Nasopharyngitis	6	(7.3)	4	(4.9)	6	(7.5)	2	(2.4)	10	(12.7)	22	(6.8)
Dyspnoea	3	(3.7)	8	(9.8)	4	(5.0)	4	(4.9)	5	(6.3)	21	(6.5)
Pain in extremity	2	(2.4)	3	(3.7)	4	(5.0)	4	(4.9)	9	(11.4)	20	(6.2)
Muscle spasms	2	(2.4)	4	(4.9)	8	(10.0)	5	(6.1)	2	(2.5)	19	(5.9)
Upper respiratory tract infection	3	(3.7)	5	(6.1)	5	(6.3)	4	(4.9)	5	(6.3)	19	(5.9)
Epistaxis	3	(3.7)	6	(7.3)	4	(5.0)	5	(6.1)	3	(3.8)	18	(5.6)
Cough	7	(8.5)	2	(2.4)	6	(7.5)	2	(2.4)	7	(8.9)	17	(5.3)
Palpitations	2	(2.4)	5	(6.1)	7	(8.8)	3	(3.7)	1	(1.3)	16	(5.0)
Arthralgia	1	(1.2)	4	(4.9)	7	(8.8)	2	(2.4)	2	(2.5)	15	(4.6)
Chest pain	1	(1.2)	4	(4.9)	1	(1.3)	5	(6.1)	5	(6.3)	15	(4.6)
Vomiting	1	(1.2)	2	(2.4)	2	(2.5)	6	(7.3)	5	(6.3)	15	(4.6)

Approximately 70% of patients in pivotal study LVGY had a TEAE with most being mild to moderate in intensity. The proportion of patients with severe AEs was similar in the various treatment groups: placebo; 19.5%, tadalafil 2.5 mg; 19.5%, tadalafil 10 mg; 22.5%, tadalafil 20 mg; 19.5%, tadalafil 40 mg; 13.9%.

In the long term extension study, LVGX, the most commonly reported AEs (>3% of subjects) which were considered to be possibly treatment related by the investigator were

headache (15%), flushing (5.6%), dizziness (5%), dyspepsia (3.6%), diarrhoea (3.6%), nasal congestion (3-6%), back pain (3.4%) and nausea (3.1%) (Table 5).

Table 5: TEAEs occurring in ≥3% of subjects by preferred term in descending order of incidence – Study LVGX

	T20 (N=63)		T40 P:Pla (N=75)		T40 P:T2.5-20 (N=150)		T40 P:T40 (N=69)		All T40 (N=294)		TOTAL (N=357)	
Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients with >= 1 TEAE	57	(90.5)	69	(92.0)	139	(92.7)	64	(92.8)	272	(92.5)	329	(92.2)
HEADACHE	9	(14.3)	21	(28.0)	38	(25.3)	11	(15.9)	70	(23.8)	79	(22.1)
DIARRHOEA	7	(11.1)	7	(9.3)	21	(14.0)	11	(15.9)	39	(13.3)	46	(12.9)
BACK PAIN	3	(4.8)	12	(16.0)	19	(12.7)	7	(10.1)	38	(12.9)	41	(11.5)
OEDEMA PERIPHERAL	6	(9.5)	7	(9.3)	22	(14.7)	6	(8.7)	35	(11.9)	41	(11.5)
UPPER RESPIRATORY TRACT INFECTION	7	(11.1)	9	(12.0)	15	(10.0)	10	(14.5)	34	(11.6)	41	(11.5)
DIZZINESS	4	(6.3)	9	(12.0)	24	(16.0)	3	(4.3)	36	(12.2)	40	(11.2)
PALPITATIONS	5	(7.9)	5	(6.7)	21	(14.0)	7	(10.1)	33	(11.2)	38	(10.6)
NASOPHARYNGITIS	5	(7.9)	10	(13.3)	13	(8.7)	9	(13.0)	32	(10.9)	37	(10.4)
DYSPNOEA	5	(7.9)	6	(8.0)	15	(10.0)	10	(14.5)	31	(10.5)	36	(10.1)
FATIGUE	3	(4.8)	4	(5.3)	10	(6.7)	12	(17.4)	26	(8.8)	29	(8.1)
PULMONARY ARTERIAL HYPERTENSION	3	(4.8)	5	(6.7)	13	(8.7)	8	(11.6)	26	(8.8)	29	(8.1)
COUGH	5	(7.9)	8	(10.7)	8	(5.3)	7	(10.1)	23	(7.8)	28	(7.8)
PAIN IN EXTREMITY	6	(9.5)	7	(9.3)	10	(6.7)	4	(5.8)	21	(7.1)	27	(7.6)
EPISTAXIS	6	(9.5)	6	(8.0)	11	(7.3)	3	(4.3)	20	(6.8)	26	(7.3)
DYSPEPSIA	5	(7.9)	5	(6.7)	12	(8.0)	3	(4.3)	20	(6.8)	25	(7.0)
NAUSEA	3	(4.8)	4	(5.3)	11	(7.3)	7	(10.1)	22	(7.5)	25	(7.0)
INSOMNIA	4	(6.3)	5	(6.7)	9	(6.0)	5	(7.2)	19	(6.5)	23	(6.4)
CHEST PAIN	4	(6.3)	3	(4.0)	8	(5.3)	7	(10.1)	18	(6.1)	22	(6.2)
FLUSHING	3	(4.8)	9	(12.0)	6	(4.0)	4	(5.8)	19	(6.5)	22	(6.2)
ANAEMIA	3	(4.8)	3	(4.0)	14	(9.3)	1	(1.4)	18	(6.1)	21	(5.9)
BRONCHITIS	2	(3.2)	6	(8.0)	8	(5.3)	4	(5.8)	18	(6.1)	20	(5.6)
MYALGIA	5	(7.9)	6	(8.0)	4	(2.7)	4	(5.8)	14	(4.8)	19	(5.3)
RASH	4	(6.3)	5	(6.7)	4	(2.7)	6	(8.7)	15	(5.1)	19	(5.3)
ARTHRALGIA	1	(1.6)	4	(5.3)	12	(8.0)	1	(1.4)	17	(5.8)	18	(5.0)
NASAL CONGESTION	1	(1.6)	5	(6.7)	6	(4.0)	6	(8.7)	17	(5.8)	18	(5.0)
VISION BLURRED	5	(7.9)	4	(5.3)	7	(4.7)	2	(2.9)	13	(4.4)	18	(5.0)
MUSCLE SPASMS	3	(4.8)	2	(2.7)	9	(6.0)	2	(2.9)	13	(4.4)	16	(4.5)
URINARY TRACT INFECTION	1	(1.6)	6	(8.0)	6	(4.0)	3	(4.3)	15	(5.1)	16	(4.5)
DEPRESSION	3	(4.8)	4	(5.3)	4	(2.7)	4	(5.8)	12	(4.1)	15	(4.2)
SINUSITIS	2	(3.2)	2	(2.7)	6	(4.0)	5	(7.2)	13	(4.4)	15	(4.2)
INFLUENZA	3	(4.8)	2	(2.7)	8	(5.3)	1	(1.4)	11	(3.7)	14	(3.9)
HYPOKALAEMIA	1	(1.6)	3	(4.0)	5	(3.3)	4	(5.8)	12	(4.1)	13	(3.6)
RIGHT VENTRICULAR FAILURE	1	(1.6)	6	(8.0)	5	(3.3)	1	(1.4)	12	(4.1)	13	(3.6)
MUSCULOSKELETAL PAIN	4	(6.3)	4	(5.3)	3	(2.0)	1	(1.4)	8	(2.7)	12	(3.4)
OEDEMA	3	(4.8)	0	(0.0)	6	(4.0)	3	(4.3)	9	(3.1)	12	(3.4)
WEIGHT INCREASED	3	(4.8)	1	(1.3)	4	(2.7)	4	(5.8)	9	(3.1)	12	(3.4)
ANXIETY	1	(1.6)	3	(4.0)	5	(3.3)	2	(2.9)	10	(3.4)	11	(3.1)
ASTHENIA	1	(1.6)	3	(4.0)	7	(4.7)	0	(0.0)	10	(3.4)	11	(3.1)
GASTROOESOPHAGEAL REFLUX DISEASE	1	(1.6)	6	(8.0)	2	(1.3)	2	(2.9)	10	(3.4)	11	(3.1)
PNEUMONIA	0	(0.0)	2	(2.7)	7	(4.7)	2	(2.9)	11	(3.7)	11	(3.1)

Abbreviations: N = number of entered subjects who have received study medication, n = number of subjects with at least one TEAE, TEAE = treatment- emergent adverse event, Prev = Actual received study treatment in previous placebo-control double-blind study, P = Prev, T2.5-20 = Tadalafil 2.5-20mg, T20 = Tadalafil 20mg, T40= Tadalafil 40mg

* Subjects may be counted in more than one category. Baseline is the run-in period (Visit 1-2) prior to randomization in the previous placebo-control double-blind study.

Serious adverse events and deaths

In the pivotal study LVGY, incidences of subjects who experienced at least one serious adverse event (SAE) were similar in the placebo and all tadalafil groups. The only SAEs to occur in more than one subject in any tadalafil group were pulmonary hypertension, right ventricular failure and anaemia. The nonfatal SAEs considered by the investigator to be treatment related in all tadalafil subjects were dyspnoea, priapism, oesophageal varices, haemorrhage, hypotension, gastritis, menorrhagia, headache and drug hypersensitivity.

Overall, 54 patients in study LVGY had at least one SAE. More common SAEs were anaemia (3), pulmonary hypertension (10) and right ventricular failure (6 - distributed across the dosage groups).

There were 3 deaths reported in pivotal study LVGY (1 each in the placebo, tadalafil 10 and 20 mg groups). In the extension study LVGX, 11 deaths were reported. Many of these were from recognised causes of death associated with PAH.

Serious AEs resulting in death included worsening PAH (placebo), sudden death (tadalafil 10 mg) and histiocytosis haematophagic (tadalafil 20 mg). Only one subject (receiving

tadalafil 20 mg) died due to an SAE (histiocytosis haematophagic syndrome) that was considered by the investigator to be treatment related.

Laboratory Findings

Haematology, coagulation (including International Normalised Ratio [INR]), urinalysis and serum chemistry panel were assessed. For each parameter there were minimal mean differences across groups and over time. There was a low number of subjects with >3 times the upper limit of normal for serum alanine transferase (placebo: 2, T2.5: 1, T10:1, T20:1) and similarly for aspartate transferase. There were small numbers of patients in each treatment group with low platelet counts.

Overall there were minimal changes in clinical laboratory values.

Safety in special populations

Subgroup analyses were performed to assess the relationship between demographic characteristics and concomitant medication and safety outcomes that include age, gender, tadalafil exposure >90th percentile in AUC or C_{max}, renal impairment, bosentan use, CYP3A4 inhibitor use and synthetic oestrogen use.

No new AEs associated with tadalafil use were identified based on the analyses above and no increased incidence in any of the special populations. The number of patients over 75 years was limited.

Safety related to drug-drug interactions and other interactions

The drug interactions of tadalafil had been investigated for the ED submission. Important ones from the ED submission include the 3A4 interactions and the concurrent nitrate contraindication. In this submission the interaction with bosentan (used by >50% in the pivotal study) was investigated and concurrent use does not appear to be a safety risk. There did not appear to be a significant interaction with digoxin or a representative oral contraceptive.

Discontinuation due to Adverse Events

In study LVGY 49 patients had an AE leading to discontinuation including the deaths mentioned above. The rate of discontinuation did not increase with increasing dose and the most common AE leading to discontinuation was pulmonary hypertension. Incidences of subjects who experienced at least 1 AE that lead to discontinuation from the study were similar across the placebo and tadalafil groups. The only AEs that lead to subject discontinuation in more than one subject were pulmonary hypertension, dyspnoea, back pain and right ventricular failure.

Thirty subjects discontinued due to an adverse event (including death) during treatment in long term study LVGX. The most common causes of discontinuation were pulmonary hypertension and right ventricular failure. Within the tadalafil 40 mg group, the highest number of discontinuations occurred in those subjects who increased their dose to 40 mg in study LVGX from tadalafil 2.5-20 mg in LVGY; however, the lowest number of discontinuations occurred within the tadalafil 40 mg group of patients who had previously been on placebo in study LVGY. Discontinuations were similar in the groups of subjects who remained on a stable 20 or 40 mg dose from study LVGY through to LVGX.

Evaluator's overall conclusions on clinical safety

The safety profile of tadalafil in PAH does not differ greatly from its known profile in ED.

The most common AEs are headache, diarrhoea, nausea, back pain, dizziness, dyspepsia, flushing, myalgia and nasopharyngitis. There are a number of PAH symptoms also added with this submission.

Withdrawals (49 patients) in the 2 efficacy studies were mostly related to progressive PAH. The most common causes of withdrawal were pulmonary hypertension and right ventricular failure. Deaths also were mostly related to the underlying disease.

A 'new' AE in this submission, compared to male patient predominance in the ED submissions, was menorrhagia. The incidence of bleeding disorders was however similar across placebo and treatment groups.

Overall tadalafil is a reasonably well tolerated therapy for PAH.

List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a List of Questions to the sponsor is generated. The only question was one on the proposed PI which is beyond the scope of this AusPAR.

Clinical Summary and Conclusions

Clinical aspects

Clinical Pharmacology

The pharmacokinetic profile of tadalafil was well established for the ED submission. In this submission the kinetics in the PAH population were explored in a population PK study. In patients with PAH not receiving concomitant bosentan, the average tadalafil exposure at steady state following 40 mg/day was 26% higher when compared to healthy volunteers. There were no significant differences in C_{max} compared to healthy volunteers. The results suggest a lower clearance in PAH patients compared to healthy volunteers.

The pharmacokinetics of tadalafil are linear from 2.5 mg to 20 mg but they are less than proportional from 20 mg to 40 mg.

There is a pharmacokinetic interaction between tadalafil and bosentan such that the clearance of tadalafil is increased (and AUC and C_{max} decreased) by concomitant administration. There was no significant interaction between tadalafil and digoxin or a representative oral contraceptive.

Efficacy

The efficacy studies were well conducted for this indication. The optimal dose is 40 mg per day with a starting dose of 20 mg per day for some special populations. The results are clinically and statistically significant and the outcome measures used such as 6-MW distance and QoL were both standard and clinically meaningful. Efficacy was not affected by race, gender and age. Long term efficacy was maintained for one year of treatment.

Safety

The safety profile of tadalafil in PAH does not differ greatly from its known profile in ED. The most common AEs were headache, diarrhoea, nausea, back pain, dizziness, dyspepsia, flushing, myalgia and nasopharyngitis. In this submission, there were a number of PAH symptoms reported as adverse events as would be expected.

Withdrawals (49 patients) in the two efficacy studies were mostly related to progressive PAH. The most common causes of withdrawal were pulmonary hypertension and right ventricular failure. Deaths were most commonly due to the underlying disease.

A 'new' AE in this submission, compared to the male patient predominance in ED, was menorrhagia. The incidence of bleeding disorders was however similar across placebo and treatment groups.

Overall tadalafil is a reasonably tolerated therapy for PAH.

Benefit risk assessment

Benefits

There is a sound pharmacological rationale for the use of PDE5 inhibitors for PAH.

The efficacy of tadalafil, as measured by change in 6-MW distance, has been demonstrated in patients with WHO class II and III PAH. The pivotal study LVGY included a range of the likely real world patients. Efficacy was demonstrated in patients with idiopathic PAH and PAH related to connective tissue disorders. There was a trend to further improvement in 6-MW in patients on bosentan that did not reach statistical significance. The combination was well tolerated.

The recommended dosage for most patients is 40 mg once daily. Some special groups should start on 20 mg per day. These include patients with mild to moderate renal impairment where a starting dose of 20 mg once per day is recommended and patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A and B) where following a single dose of 10 mg, a starting dose of 20 mg/day may be considered.

Maintenance of efficacy after one year of therapy was supported by extension study LVGX.

No new safety issues for tadalafil were identified in the PAH submission. The adverse event profile is similar to that seen in erectile dysfunction. AEs did not increase disproportionately in the elderly (there were few patients older than 75years in the studies however).

Risks

The number of patients treated in this orphan indication (400) is limited. However a much larger number (12 million) have been treated for ED. The most common AEs are well known from ED including headache, flushing, nasopharyngitis, myalgia and priapism. Epistaxis/menorrhagia has also been reported. In considering risks the possible interactions with 3A4 inhibitors and nitrates should also be remembered. These are included in the PI.

The more serious AEs and deaths reported in the PAH clinical studies were mostly associated with progression of the underlying disease (most common were pulmonary hypertension and right heart failure).

Balance

Tadalafil is a useful addition to the medications for the treatment of PAH. It has useful efficacy as measured by 6-MW distance and QoL measures. The safety profile is reasonable in relation to the severity of the disease.

Tadalafil provides additional efficacy and QoL improvement in PAH with a tolerable adverse event profile.

Conclusions

The overall risk benefit balance is favourable and approval was recommended for tadalafil 40 mg once daily for the proposed indication of 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.

V. Pharmacovigilance Findings

Risk Management Plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

Safety Specification

The summary of the ongoing safety concerns as specified by the sponsor is shown in Table 6.

Table 6: Ongoing safety concerns for tadalafil

Important Identified Risks	• Priapism • Hypotension/Increased Hypotensive Effect
Important Potential Risks	General Tadalafil Use: • Sudden hearing loss • Non-arterial anterior ischemic optic neuropathy (NAION) Pulmonary Arterial Hypertension (PAH)-Related: • Increased Uterine Bleeding Erectile Dysfunction (ED) once-daily dosing: • Characterization of safety and tolerability in the elderly population

Following review of both the nonclinical and clinical aspects of the safety specification, the above summary of the ongoing safety concerns was acceptable to the OPR reviewer.

However, it was noted that the safety specification identifies the following populations not studied in the pre-authorisation phase:

- women who were nursing or pregnant
- paediatric patients <12 years of age
- patients with severe renal impairment
- patients with severe hepatic cirrhosis (Child-Pugh Class C)
- The following groups of patients with cardiovascular disease:
    - patients with clinically significant aortic and mitral valve disease
    - patients with pericardial constriction
    - patients with restrictive or congestive cardiomyopathy
    - patients with significant left ventricle dysfunction
    - patients with life threatening arrhythmias
    - patients with symptomatic coronary artery disease
    - patients with hypotension (< 90/50 mm Hg), or uncontrolled hypertension

The proposed Australian PI states the use of tadalafil in these patient groups is not recommended, although not strictly contraindicated. Dosage modifications are recommended in the context of renal and hepatic impairment. Consequently it was suggested that these patient groups be included as important missing information in the summary of ongoing safety concerns.

Pharmacovigilance Plan

The sponsor proposed routine pharmacovigilance activities to monitor all the specified ongoing safety concerns.[7]

In addition the sponsor proposed to further monitor all the specified ongoing safety concerns by following up specific AEs that have been identified as significant (targeted surveillance terms) by using specifically designed follow up forms/questionnaires.

Furthermore for the important potential risk: 'Non-arteritic anterior ischemic optic neuropathy (NAION)', the sponsor proposes to conduct a Phase IV, outpatient, observational, non-interventional, multicentre, prospective, case crossover study to evaluate the possible association between the use of phosphodiesterase type 5 (PDE5) inhibitors and the risk of acute NAION in adult males (Study H6D-MC-LVHQ).

In principle the OPR reviewer had no objection to the sponsor implementing additional pharmacovigilance activities to further monitor all of the specified ongoing safety concerns.

Risk Minimisation Activities

The sponsor proposed only routine risk minimisation activities for all the specified ongoing safety concerns, as the sponsor claims the safety profile of tadalafil is well described and consistent with the information presented in the current labelling.[8] No additional risk minimisation activities are planned.

The OPR reviewer noted that the sponsor's proposed routine risk minimisation activities appeared to be reasonable.

In conclusion, the OPR reviewer noted that in addition to the ongoing safety concerns as specified by the sponsor it was recommended that the populations identified in the safety specification as not studied in the pre-authorisation phase be included as important missing information. It was acknowledged that routine risk minimisation has already been proposed for these ongoing safety concerns. The reviewer also recommended revisions to the proposed PI but these are beyond the scope of this AusPAR.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

All details relating to the tadalafil drug substance are as for the previously registered products. Compared to the 20 mg Cialis tablet, the 20 mg Adcirca tablet has the same core but a different film coat. The latter is orange rather than yellow due to the addition of a small amount of iron oxide red. The specifications of the product are based on those for the 20 mg Cialis tablet and have been found by the quality evaluator to have acceptable

[7] Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

[8] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

expiry limits. The proposed product is stable and no changes were observed on storage. Stability data was provided that supported a shelf life of 3 years when stored below 25°C. Approval of the submission was therefore recommended by the pharmaceutical chemistry evaluator with respect to chemistry and quality control.

In relation to bioavailability, the pharmaceutical chemistry evaluator noted the following:

The Phase III clinical studies were performed using the registered tadalafil, Cialis 20 mg tablets. As noted above, the latter only differed from the proposed tadalafil Adcirca 20 mg tablets in that a yellow film coat was used rather than an orange film coat. It was accepted that the two tablets would be bioequivalent.

There was one new bioavailability study in the submission. This was Study H6D-EW-LVHO which was a single dose, two way, crossover study to determine the effect of food on the bioavailability of tadalafil at a dose of 40 mg. The dose recommended in the PI is 40 mg (2 x 20 mg) taken once daily with or without food. The results indicated that food had no effect on the bioavailability of tadalafil. The quality evaluator did note that the result of 2-3 hours for T_{max} in this study was less than that cited in the proposed PI, namely 4 hours. *The sponsor was asked to comment on this discrepancy.*

Nonclinical

Tadalafil delayed the development of pulmonary arterial hypertension (PAH) in a monocrotaline induced model of the disease in rats, with dose related improvements in mean pulmonary arterial pressure, heart rate, blood pressure and right ventricular hypertrophy when administered orally for 3 weeks following induction of PAH. When tadalafil was administered to rats with active PAH (3-6 weeks after induction), it improved survival time and right ventricular hypertrophy. Results in both phases were similar to that following sildenafil treatment and were characterised broadly by dose related increases in cGMP in plasma and lungs, consistent with inhibition of PDE5.

In vitro pharmacokinetic drug interaction studies identified tadalafil as a mechanism-based inhibitor of CYP3A4 activity, based on time and concentration dependent inhibition of metabolism of midazolam, a CYP3A4 substrate. However, the degree of inhibition was considered unlikely to be clinically relevant. Tadalafil was also identified as a P-glycoprotein substrate *in vitro* but passive transport of tadalafil appeared to be the predominant mechanism for cellular uptake. Therefore drug interactions due to the inhibition of P-gp were considered as unlikely to adversely affect the metabolism of tadalafil.

No new nonclinical studies investigating the safety of tadalafil were submitted. The previous nonclinical data submitted was originally assessed for safety on the basis of intermittent use for the indication of erectile dysfunction in a male population at a maximum dose of 20 mg daily. This data was reassessed in the light of the proposed chronic use in both male and female populations at a maximum dose of 40 mg which is double the maximum dose recommended for erectile dysfunction.

As noted by the nonclinical evaluator, the primary toxicities identified in the previous oral repeat dose toxicity studies with tadalafil (up to 6 months duration in rats and 12 months in dogs) were effects on the male reproductive tract in dogs. These effects included atrophy of the testes and epididymides and oligospermia/aspermia, both of which occurred at potentially clinically relevant doses (exposure margins 0.3-3) following chronic administration of tadalafil. The nonclinical evaluator also noted that, while clinical studies reported in the currently approved PI under Pharmacodynamics failed to find effects of tadalafil on spermatogenesis and male reproductive hormones, the potential for

chronic tadalafil administration to cause toxicity to the male reproductive tract should still be targeted in any reports monitoring the postmarket experience.

Oral tadalafil doses of 400 mg/kg/day (exposure margins 2-3) for up to 2 years in mice resulted in increased development of hepatocellular adenomas in males but not in females. This was probably related to hepatic microsomal enzyme induction which is common in rodents and is not considered relevant to human cancer risk.

There were no effects on fertility, reproductive performance or reproductive organ morphology in rats at exposures sixfold (males) or 17 fold (females) that expected at the recommended clinical dose. No evidence of teratogenicity or embryofetal toxicity in rats and mice was seen in previous studies at exposure margins of ≥ 7 fold. Increased post-natal pup mortality was observed in rats after oral tadalafil treatment during gestation and lactation. Exposure at the no effect dose was approximately fivefold that expected in humans.

The nonclinical evaluator was of the opinion that there were no nonclinical objections to the registration of tadalafil for the proposed indication.

The sponsor provided a response to the nonclinical evaluation report which discussed the issue of tadalafil related effects on the testis which were believed to have occurred in a 3 month study in male beagle dogs. The sponsor argued that the observed testicular and epididymal changes were not significant because (i) there was no clear dose relationship in treated dogs, (ii) effects were not qualitatively different from controls and (iii) many of the dogs used in the study were sexually immature.

The nonclinical evaluator noted that the age of the male beagle dogs at the commencement of the study was 13-18 months old, an age which is well beyond the point at which this species achieves normal sexual maturation in the testis and epididymides. Therefore, the doubling of the incidence of testes hypo/aspermatogenesis and epididymal oligospermia/aspermia (from 1 to 2 out of 4 animals) and the doubling of the incidence of degeneration of seminiferous epithelium (from 2 to 4 out of 4 animals) observed at 10 mg/kg/day tadalafil compared with controls is unlikely to be an artefact of immaturity. The nonclinical evaluator also observed a strong trend of increasing incidence with dose in the 3 month study. The evaluator also noted that the latter should be considered in the context of study findings in the same tissues from 6 and 12 month studies and that this was the second dog study for which the sponsor claims artefactual changes in the testis and epididymis. The first was another 6 month dog study. The overall conclusion of the nonclinical evaluator was that the consistent testicular and epididymal changes with increasing dose across multiple studies makes it inappropriate to dismiss the dog 3 month study findings from the PI. The Delegate agreed strongly with the position adopted by the nonclinical evaluator and requested the sponsor to amend the proposed statement about Effects on Fertility in line with the statement proposed by the nonclinical evaluator.

Clinical

Clinical Evaluation

The clinical evaluator recommended approval and was of the opinion that the overall risk benefit balance was favourable and recommended approval for tadalafil 40 mg once daily for the indication as proposed.

Pharmacology

As noted by the clinical evaluator the ADME profile of tadalafil was established in the Cialis submission. The profile can be summarised as follows:

- Tadalafil is rapidly absorbed after oral administration and the mean 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
- The absolute bioavailability of oral tadalafil has not been established. The mean bioavailability of a 20 mg tablet has been estimated to be 88% relative to an oral suspension dosage form.
- 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
- Tadalafil is metabolised mainly (> 80%) by CYP3A4 isoform and the major metabolite is the methylcatechol glucuronide
- The mean terminal half-life is 16 hours in healthy subjects

Administration with a high fat meal led to an increase in systemic exposure (AUC) for tadalafil of between 11% and 14% with no change in C_{max}. Statistical analysis indicated that both AUC and C_{max} in the fasted and fed states had 90% CIs which were within the accepted bioequivalence endpoints of 80%-125%.

The pharmacokinetics of tadalafil were evaluated in 305 subjects with PAH, receiving once daily tadalafil 2.5 mg, 10 mg, 20 mg or 40 mg or placebo for 16 weeks. The PK data was best described by a one compartment model with rapid first order absorption. Systemic exposure to tadalafil was not influenced by cardiovascular state, gender, ethnicity, PAH history or duration, creatinine clearance, total serum protein, body weight or concomitant warfarin or digoxin use. Only the covariate of dose (40 mg) was found to be a predictor of bioavailability (F). Also concomitant bosentan use significantly influenced CL/F. In patients with PAH not receiving concomitant bosentan, the average tadalafil exposure at steady-state following 40 mg daily was 26% higher than when compared to healthy volunteers. As noted by the clinical evaluator, these results suggest a lower clearance in PAH patients compared to healthy volunteers.

The pharmacokinetics of tadalafil were linear from 2.5 mg to 20 mg but were less than proportional from 20 mg to 40 mg. It appeared that a dose of 40 mg would yield exposures approximating those of a 30 mg dose.

Tadalafil plasma concentration vs time profiles following 40 mg per day were comparable in both Japanese and non-Japanese subjects.

Compared to the administration of tadalafil alone, concomitant single dose bosentan did not alter tadalafil or metabolite exposure or the rate of absorption (AUC or C_{max}). However, after 10 days of concomitant multiple dose exposure, tadalafil clearance increased by approximately 70% with corresponding decreases in AUC and C_{max} of 42% and 27%, respectively. There was no effect on the PK parameters of the tadalafil metabolite. Concomitant treatment with tadalafil did not appear to have any effect on the pharmacokinetics of bosentan.

At steady state, tadalafil increased ethinyloestradiol exposure (AUC) by 26% and C_{max} by 70% relative to the OCP alone. There was no statistically significant effect of tadalafil on levonorgestrel.

There was no statistically significant effect of multiple dose tadalafil on the steady state pharmacokinetics of digoxin.

Efficacy

LVGY was a pivotal, multicentre, randomised, double blind, placebo controlled study which evaluated the efficacy and safety of tadalafil (2.5, 10, 20 and 40 mg orally once daily for 16 weeks) in approximately 400 patients with PAH at 82 centres in North America,

Europe and Japan. The primary efficacy endpoint was the change from baseline to Week 16 in the 6-minute walking distance (6-MW). The secondary efficacy endpoints included:

- Change from baseline to Week 16 in WHO Functional Class
- Time to first occurrence of clinical worsening
- Change from baseline to Week 16 in the Borg Dyspnoea Scale
- Various cardiopulmonary haemodynamic parameters and QoL measures in a subset of patients

Overall, patients receiving tadalafil 40 mg once daily had a statistically and clinically significant improvement in 6-MW distance compared to subjects receiving placebo after 16 weeks of treatment. Median changes from baseline to Week 16 were 12, 17, 30, 32 and 35 metres in the placebo, tadalafil 2.5, 10, 20 and 40 mg groups, respectively. The ANCOVA placebo adjusted LSM treatment difference between tadalafil 40 mg and placebo was 32.8 metres (95% CI [15.2, 50.3]). A summary of the primary and secondary efficacy results is displayed in Table 3. The table appears to show a placebo subtracted treatment difference for the 40 mg tadalafil dose of 26.0 metres rather than the 32.8 metres reported in the evaluation report. *The sponsor was requested to clarify the apparent discrepancy.*

There was no significant difference between tadalafil 40 mg and placebo for the first of the specified secondary endpoints, the change in WHO Functional Class, the p-value being 0.3630. Given the nature of the step down analysis of the secondary endpoints specified in the study protocol, no remaining results could be regarded as being of statistical significance. However, all secondary endpoint results were supportive of the primary endpoint in a descriptive sense.

Part 1 of **LVGX Extension** was a double blind extension of LVGY to evaluate the safety and efficacy of tadalafil 20 and 40 mg daily for 52 weeks. All patients were to receive tadalafil 40 mg/day except patients who responded well to 20 mg per day in LVGY. Part 2 was an open label extension to Part 1 in order to provide access to the drug for patients. Overall, 293 patients completed Part 1, 52 on tadalafil 20 mg and 241 on tadalafil 40 mg. For the clinical evaluator, the fact that the 6-MW test was stable or increased over the one year period suggests that efficacy was maintained. However, as also noted by the evaluator, subjects in the lower dose groups who were changed to 40 mg/day only showed minimal changes (for subjects changing their tadalafil dose from 2.5, 10 or 20 mg to 40 mg, the change in mean 6-MW distance was from 368.97 metres to 371.21 metres). There were no tables of these results in the evaluation report. *The sponsor was requested to report the full analyses of the changes in mean and median 6-MW test at Week 52 for each of the patient groups 2.5, 10 and 20 mg when changed to 40 mg (that is, for each group separately).*

The improvement in the 6-MW test was shown to be statistically significant in the group of subjects who took tadalafil alone (without concomitant bosentan) but was only of borderline statistical significance in the group of subjects who took both medicines. *The sponsor was asked to clarify whether the study was actually powered to determine statistical significance in the results with and without concomitant bosentan.*

Efficacy of the proposed dose of 40 mg of tadalafil was shown in the two largest subgroups of patients with PAH, those with idiopathic PAH and those with PAH due to collagen vascular disease.

Subjects were stratified according to whether the baseline 6-minute walk distance was ≤ 325 m or > 325 m. There was a statistically significant change from baseline to Week 16 in the 6-MW distance in both groups for subjects taking tadalafil 40 mg once daily. There

was a greater treatment difference observed for those whose baseline 6-MW distance was ≤ 325 m compared with those whose baseline 6-MW distance was > 325 m. However, there was no formal, direct comparison between these latter two groups.

Efficacy was demonstrated at a statistically significant level for tadalafil 40 mg once daily for the group of subjects composed of those whose baseline WHO Functional Class was either I or II and also for the group of subjects composed of those whose baseline WHO Functional Class was either III or IV. However, of the 134 subjects in the combined I and II group, there were only 4 subjects (1%) who belonged to WHO Functional Class I at baseline and of the 271 subjects in the combined III and IV group, there were only 7 subjects (< 2%) who belonged to WHO Functional Class IV at baseline. Thus, there were effectively only two groups, those belonging to WHO Functional Class II and those belonging to WHO Functional Class III.

The efficacy studies were well designed with appropriate endpoints. Efficacy was demonstrated at the 40 mg once daily dose level for those with PAH of the idiopathic type and with PAH secondary to collagen vascular disease. It was also demonstrated in those with PAH of baseline WHO Functional Classes II or III. Clearly there was a large overlap between those with PAH of the two aetiological types and those with PAH of either WHO Functional Class II or III.

Safety

Of the 406 randomised to treatment in the pivotal study LVGY (342 to tadalafil and 82 to placebo), 341 patients completed 16 weeks of treatment (272 on tadalafil and 69 on placebo). In the extension study LVGX, there were 357 patients who commenced treatment and of these 293 completed one year of treatment on either tadalafil 20 mg or 40 mg once daily.

The most commonly reported TEAEs in study LVGY were similar to those reported with the use of tadalafil in the treatment of erectile dysfunction with the addition of a number of adverse events related to pulmonary arterial hypertension. The most frequently reported adverse events were headache, diarrhoea, nausea, back pain, dizziness, dyspepsia, flushing, myalgia and nasopharyngitis. Of interest menorrhagia and/or vaginal haemorrhage were reported in 8 subjects in the pivotal study (all on tadalafil with a possible dose response (1 on tadalafil 10 mg, 3 on tadalafil 20 mg and 4 on tadalafil 40 mg). *The sponsor was asked to comment on the significance of this finding, including a comment on its biological plausibility.*

The only serious adverse events to occur in more than one subject in any tadalafil group were pulmonary hypertension, right ventricular failure and anaemia, that is, events not uncommonly associated with the underlying disease. The non-fatal serious adverse events considered by the investigator to be treatment related in all tadalafil subjects were dyspnoea, priapism, oesophageal varices, haemorrhage, hypotension, gastritis, menorrhagia, headache and drug hypersensitivity. Serious adverse events resulting in death included worsening of PAH (placebo), sudden death (tadalafil 10 mg) and histiocytosis haematophagic syndrome (20 mg). The latter was the only fatal serious adverse event considered by the investigator to be treatment related.

There were minimal changes in clinical laboratory values. There were no new signals of associations between adverse events and baseline demographic, concomitant medication or other factors (for example, age, gender, tadalafil exposure > 90th percentile for AUC or C_{max}, renal impairment, bosentan use, CYP3A4 inhibitor use or synthetic oestrogen use).

The rates of discontinuation from the pivotal study did not increase with increasing dose and the most common adverse event leading to discontinuation was pulmonary

hypertension. Incidences of subjects who experienced at least one adverse event that led to discontinuation from the study were similar across the placebo and tadalafil groups.

As noted by the clinical evaluator, the safety profile of tadalafil in PAH does not differ markedly from its known profile when used in the treatment of erectile dysfunction. Withdrawals (49 patients) in the two efficacy studies were mostly related to progressive PAH. Overall, tadalafil was well tolerated by the patients with PAH.

Risk Management Plan

The Office of Product Review has evaluated the Risk Management Plan for Adcirca identified as version 1.3, dated 15 October 2009. The RMP evaluator in OPR informed the Delegate that the only outstanding issue was the sponsor's reluctance to include certain populations as important missing information in future updates of the RMP. The RMP evaluator commented that these populations were identified in the Safety Specification of the RMP as not studied in the pre-authorisation phase. The RMP evaluator considered that these patient groups are relevant to the PAH patient population and should be monitored by routine pharmacovigilance activities and also was strongly of the opinion that the Pharmacovigilance Plan of the RMP should be amended accordingly

It seemed clear to the Delegate that, if the populations referred to were identified in the Safety Specification of the RMP as not having been studied in the pre-authorisation phase, then it is a simple matter of logic that each of these populations therefore constitutes important missing information with regard to that RMP. The Delegate therefore proposed the following as a specific condition of registration to be implemented with any approval for registration:

The Risk Management Plan Version 1.3, dated 15 October 2009 and updated according to the sponsor's letter of 23 March 2011, is to be implemented. In addition the following safety concerns are to be included as important missing information:

- Women who are nursing mothers or who are pregnant
- Patients with severe renal impairment
- Patients with severe hepatic cirrhosis (Child-Pugh Class C)

Risk-Benefit Analysis

Delegate Considerations

Most of the issues which make up the risk/benefit balance for the use of tadalafil in the management of pulmonary arterial hypertension have been soundly canvassed in the clinical evaluation report. There is a sound pharmacological rationale for the use of PDE 5 inhibitors for PAH. Efficacy of tadalafil 40 mg once daily and as measured by the change from baseline over 16 weeks has been demonstrated in patients with PAH of WHO Functional Classes II and III, as well as in patients with idiopathic PAH and PAH related to collagen vascular disease. There was broad overlap between the functional classes and the two aetiologies in that the great majority of patients in the study were covered by these classifications. Overall, tadalafil was well tolerated by the patients with PAH, with the more serious adverse events and deaths reported in the clinical efficacy/safety studies having been associated with progression of the underlying disease.

There were no subjects in the pivotal clinical trial below the age of 14 years and the Delegate was of the opinion that the indications should reflect that fact. It was therefore proposes to recommend the adoption of the EU wording which includes the phrase, '*in adults*'. *Both the sponsor and the ACPM were asked for comment on this issue.*

What was not clear to the Delegate was the exact basis upon which the dosage regimens in subjects with mild to moderate renal impairment and in subjects with mild to moderate

hepatic cirrhosis have been determined. Was there actual clinical trial evidence of the use of tadalafil in PAH in such subjects? The Delegate noted that exclusion criteria included severe hepatic impairment and severe renal insufficiency. Therefore it is possible that there were subjects with either mild to moderate hepatic impairment or mild to moderate renal impairment not only enrolled in the pivotal study but randomised across the various treatment arms. The Delegate was not aware of any data which details the numbers/percentages of patients with these impairments in the treatment arms nor of any efficacy/safety outcomes stratified by the presence or absence of these impairments. *The sponsor was asked to provide, in its pre-ACPM response, a summary of whatever relevant information there is which will help clarify this issue.*

The sponsor was requested to provide some background information and a brief comment on the significance of the fatal case of histiocytosis haematophagic syndrome and the syndrome itself.

The Delegate also questioned the ACPM as to whether it was of the opinion that there is sufficient evidence in the submission evaluated and in the pre-ACPM response to permit approval of the dosage regimens in subjects with mild to moderate renal impairment and in subjects with mild to moderate hepatic cirrhosis?

The Delegate proposed to approve this submission for the indication:

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.

Response from Sponsor

The sponsor agreed with the restricted indication suggested by the Delegate and addressed each of the issues raised by the Delegate.

T_{max}

The 4 hour T_{max} cited in the proposed PI was taken from Study LVGZ, which assessed the pharmacokinetic interaction between a 40 mg daily dose of tadalafil and twice daily dosing of 125 mg bosentan in healthy males. The median T_{max} of tadalafil was 4 hours (range: 3.00-4.07 hours) after the first dose on Day 1 and was also 4 hours (range: 2.00-4.07 hours) on Day 10 at steady state during multiple dosing. Data from LVGZ are appropriate for labeling since in this study tadalafil was dosed to steady state at a regimen of 40 mg once daily. The median T_{max} in Study LVHO was 2-3 hours, however tadalafil pharmacokinetics were only studied following a single dose of 40 mg and steady state was not achieved in this study.

However the difference in the various estimates of T_{max} is clinically unimportant in the setting of once daily dosing. What is important is the overall exposure as indicated by $AUC_{0\text{-}24\,h}$, which based on single dose data is nearly identical between studies.

Placebo subtracted treatment difference

The analyses specified in the LVGY statistical analysis plan, which was finalized and approved prior to database lock, included computing both Hodges-Lehmann median estimates and simple population mean estimates of the differences in 6-MW distance between treatment groups (placebo-subtracted treatment effects). Because a higher than expected percentage of subjects used bosentan concomitantly during the study, these unadjusted estimates of the treatment effect were supplemented with LSM estimates of placebo subtracted treatment differences derived from ANCOVA models with terms for the centred baseline of 6-MW distance, PAH aetiology and bosentan use. This adjusted ANCOVA model was consistent with the stratified permutation test used as the pre-

specified primary inferential analysis method. The conclusion based on the ANCOVA analysis of the primary endpoint (treatment with tadalafil 40 mg significantly improves 6-MW distance compared to placebo; p=0.0004) was consistent with the conclusion of the primary inferential analysis. As such, the point estimate of the placebo subtracted treatment difference based on the adjusted ANCOVA LS mean (32.8 metres) is considered a more valid estimate of the true treatment effect than the unadjusted Hodges-Lehmann estimate (26.00 metres).

Full analyses of the changes in mean and median 6-MW test at Week 52 for each of the patient groups

The sponsor provided the requested analysis. The 7 patients who escalated to 40 mg from tadalafil 20 mg in LVGY represent patients who had clinical worsening in Study LVGY.

Pivotal study power

The sponsor indicated that the pivotal study was not powered to determine statistical significance for each of the special populations.

Menorrhagia and/or vaginal haemorrhage

The sponsor indicated that a plausible mechanism for the role of PDE5 inhibitors in the occurrence of menorrhagia/vaginal bleeding has not been identified. However, several cases of increased uterine bleeding (including menorrhagia and/or vaginal haemorrhage) have been reported in tadalafil studies involving female patients. The incidence rate across the combined tadalafil treatment groups was 1.9%; this event has been found to occur more often in patients on tadalafil compared to placebo and therefore the sponsor has identified uterine bleeding as an adverse drug reaction (ADR) in the proposed Australian PI. It should be noted that 4 of the 8 cases of menorrhagia and/or vaginal haemorrhage resolved spontaneously with no specific therapy and did not recur through Study LVGY or LVGX.

The incidence of menorrhagia worldwide in an otherwise healthy population is 9% to 14% (Hallberg et al. 1966).[9] However, only 40% to 50% of women complaining of heavy bleeding suffer from menorrhagia (Fraser et al. 1984).[10] About 30% of women complain of heavy menses and annually about 5% of women seek medical care for increased menstrual bleeding. In about 50% of cases, no organic pathology is determined and dysfunctional uterine bleeding is diagnosed (Oehler and Rees 2003).[11] Increased menstrual bleeding has several adverse effects including anaemia, iron deficiency, reduced quality of life and increased cost of healthcare (Pitkin 2007).[12] However, infrequent episodes of menorrhagia usually do not carry severe risks to women's general health.

Toxicology and preclinical and clinical pharmacology studies performed to date to evaluate the effect of tadalafil on platelet aggregation and bleeding time, as well as drug interaction studies with warfarin and aspirin, have not revealed a potential role of PDE5 inhibitors on bleeding events including increased uterine bleeding (including menorrhagia or vaginal haemorrhage).

Phosphodiesterase type 5 (PDE5) is expressed in the smooth muscle of the corpora cavernosal of the vagina (D'Amati et al. 2002) and within the myometrium of the uterine

[9] Hallberg L, Hogdahl A, Nilsson L, Rybo G. Menstrual blood loss--a population study. Variation at different ages and attempts to define normality. Acta Obstet Gynecol Scand 1966; 45: 320-351.
[10] Fraser IS, McCarron G, Markham R. A preliminary study of factors influencing perception of menstrual blood loss volume. Am J Obstet Gynecol 1984; 149: 788-793.
[11] Oehler MK, Rees MC. Menorrhagia: an update. Acta Obstet Gynecol Scand 2003; 82: 405-422.
[12] Pitkin J. Dysfunctional uterine bleeding. BMJ 2007; 334: 1110-1114.

wall (Rybalkin et al. 2002; Dolci et al. 2006).[13,14,15] At least 5 PDE types are expressed within human myometrial cells, of these, PDE5 and PDE1C represent the 2 major cGMP hydrolysing enzymes (Rybalkin et al. 2002).[14] In comparing the expression of PDE5 in quiescent versus proliferating myometrial cells, Dolci et al. (2006) showed expression of PDE5 was up regulated in quiescent myometrial cells and reduced in proliferating myometrial cells.[15] In addition, treatment of proliferating myometrial cells with a PDE5 inhibitor (sildenafil) did not affect proliferation rates (Dolci et al. 2006). The relationship between PDE5 expression within myometrial cells and the occurrence of increased uterine bleeding (menorrhagia/vaginal haemorrhage) is currently unknown.

In summary, biological plausibility for an association between menorrhagia and/or vaginal haemorrhage and PDE5 inhibitors does not currently exist.

The fatal case of histiocytosis haematophagic syndrome

The sponsor described this case in detail. She was suspected to have developed thrombotic thrombocytopenic purpura (TTP) and haemophagocytic syndrome (HPS) and died of suspected HPS. At autopsy the cause of the death was considered to be the underlying pulmonary hypertension and cardiac failure. In the opinion of the investigator, the study drug could not be the direct cause of HPS but a possibility could not be ruled out that the study drug led to it because the patient was suspected to have developed HPS about two weeks after the study drug had started. He considered the events were unrelated to protocol procedures.

The association of both TTP and HPS conditions with systemic lupus erythematosus (the patient's underlying condition) is, whilst rare, well described and many of the features of the case are similar to those described in the literature (Hamasaki et al. 2003; Lambotte et al. 2006).[16,17] Further, the sponsor had seen no similar cases in the large clinical trial database and the extensive postmarketing surveillance for tadalafil.

TTP is a rare but life threatening disorder characterised by pyrexia, microangiopathic haemolytic anaemia, thrombocytopenia, fluctuating neurological signs and renal involvement. Infection, drugs and pregnancy are known to trigger TTP, but its aetiology remains unclear. The association of TTP with SLE has been well described in the literature. A review of the literature by Hamasaki et al. (2003) revealed 56 case reports of SLE complicated by TTP.[16] The overall mortality was 34%. This mortality rose to 40.5% in those cases where the diagnosis of SLE preceded the TTP.

HPS occurs mainly in the setting of serious infections and lymphomas. However, it can also occur in the course of 2 active systemic diseases without simultaneous infection: adult Still disease and SLE. The number of case reports of HPS associated with SLE is less than with TTP. However, a retrospective review of 15 cases was performed by Lambotte et al. (2006).[17] All patients were febrile with most having greater than or equal to 2 cytopenias. The common features associated with the HPS were a high frequency of cardiac

[13] D'Amati G, DiGioia CRT, Bologna M et al. Type 5 phosphodiesterase expression in the human vagina. Urology 2002; 60: 191-195.
[14] Rybalkin SD, Rybalkina IG, Feil R, Hofmann F, Beavor JA. Regulation of cGMP-specific phosphodiesterase (PDE5) phosphorylation in smooth muscle cells. JBC 2002; 277: 3310-3317.
[15] Dolci S, Belmonte A, Santone R et al. Subcellular localization and regulation of type-1C and type-5 phosphodiesterases. BBRC 2006; 341: 837-846.
[16] Hamasaki S, Mimura T, Kanda H et al. Systemic lupus erythematosus and thrombotic thrombocytopenic purpura: a case report and literature review. Clin Rheumatol. 2003; 22: 355-358.
[17] Lambotte O, Khellaf M, Harmouche H et al. Characteristics and long-term outcome of 15 episodes of systemic lupus erythematosus-associated hemophagocytic syndrome. Medicine (Baltimore) 2006; 85: 169-182.

involvement, a low C-reactive protein, cutaneous mucous symptoms and arthritis. In none of the cases was an infectious agent identified.

The authors found 23 more case reports in the literature of HPS associated with SLE all describing similar features to those described.

The sponsor believed that it was unlikely that this rare event was associated with tadalafil, however bleeding events in general are considered as targeted surveillance term in the pharmacovigilance plan and such events are closely monitored through routine pharmacovigilance activities.

Dosage regimens in subjects with renal impairment and hepatic cirrhosis

The sponsor indicated that in clinical pharmacology studies using single dose tadalafil (5 to 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. Population analyses across four Phase III ED studies and the pivotal PAH Phase III study consistently identified no subject specific factors, including renal function, that warranted consideration of dosing regimen adjustments. However, the limited clinical experience, across all indications, in patients with impaired renal function at doses exceeding 20 mg and the comparable predicted PK between subjects with impaired renal function receiving tadalafil 20 mg and those with normal renal function receiving tadalafil 40 mg resulted in the proposed dosing recommendations.

When compared with the overall population in Study LVGY, and with each other, the TEAE profile for subjects with normal (no), mild and moderate renal impairment was similar. Thus, the incidence of TEAEs reported overall did not appear to be affected by renal impairment. Worsening of WHO Functional Class was the leading cause for discontinuation and the incidence of discontinuation for this reason (and others) showed no evidence of an effect by renal status.

The results of the analysis of 6-MW distance indicated improved response with tadalafil over placebo in all renal impairment categories. There was also evidence of dose response within each subgroup with better response in the higher doses (20 and 40 mg tadalafil). Although the patient numbers are small, the mean differences for the 40 mg tadalafil group in each renal category is similar to the overall mean response (32.8 metres) reported for the primary endpoint.

In the clinical pharmacology study (LVAK), tadalafil exposure (AUC) in subjects with mild or moderate hepatic cirrhosis (Child-Pugh Class A or B) was comparable to exposure in healthy subjects when a single oral dose of 10 mg was administered. From the study it was concluded that overall no consistent PK difference was observed with increasing hepatic impairment with tadalafil. Child-Pugh data were not collected in Study LVGY, therefore, patient enrolment information cannot be provided. The dosing recommendations in patients with mild to moderate hepatic cirrhosis was proposed, in the absence of robust data, to allow the physician the opportunity to make a patient specific risk/benefit evaluation in this life threatening disease state.

Testicular and epididymal changes

The sponsor acknowledged the nonclinical evaluator's request to include the 3 month dog study and indicated it would update the product information accordingly.

Risk Management Plan

The sponsor indicated it would include the nominated issues as important missing information in the next updated version of the Risk Management Plan for Adcirca in Australia.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended approval of the submission as an additional trade name and an extension of indications for that trade name only to include:

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.

In making this recommendation, the ACPM considered there is a sound pharmacological rationale for the use of PDE 5 inhibitors for Pulmonary Arterial Hypertension (PAH). Efficacy of tadalafil treatment up to one year has been demonstrated in patients with PAH of WHO Functional Classes II and III, in patients with idiopathic PAH and in PAH related to collagen vascular disease. The ACPM agreed with the Delegate that the indications should be limited to adults due to the lack of data in patients less than 18 years. Tadalafil was well tolerated with the more serious adverse events and deaths reported having been associated with progression of the underlying disease.

The ACPM, taking into account the submitted evidence of pharmaceutical quality, safety and efficacy, considered there is a favourable benefit risk profile for this product.

The ACPM also recommended changes to the proposed PI and Consumer Medicines Information (CMI) but these are beyond the scope of this AusPAR.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Adcirca containing tadalafil 20 mg, indicated for:

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.

Among specific conditions of registration was the following:

The Risk Management Plan Version 1.3, dated 15 October 2009 and updated according to the sponsor's letter of 23 March 2011, is to be implemented. In addition the following safety concerns are to be included as important missing information:

- Women who are nursing mothers or who are pregnant
- Patients with severe renal impairment
- Patients with severe hepatic cirrhosis (Child-Pugh Class C)

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

ADCIRCA®

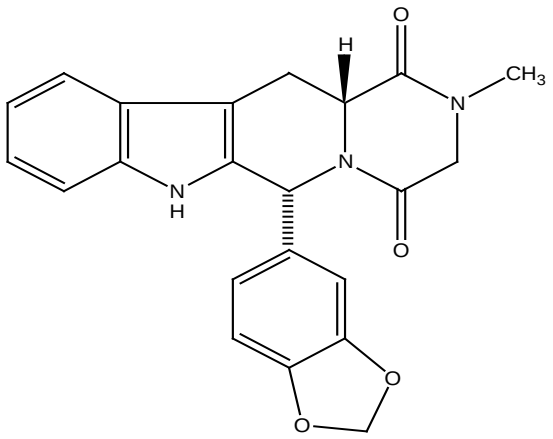
(tadalafil)

NAME OF THE MEDICINE

ADCIRCA® (tadalafil).

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

Tadalafil has the following structural formula:



DESCRIPTION

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

PHARMACOLOGY

PharmacodynamicsTadalafil 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 ADVERSE 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 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.

Pharmacokinetics

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.

Elimination
The mean oral clearance for tadalafil is 3.4 L/hr at steady state 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 DOSAGE AND 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 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.

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 enrollment.

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 1). In the ADCIRCA 40 mg treatment group, the placebo-adjusted mean change increase in 6-MWD was 33 meters (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).

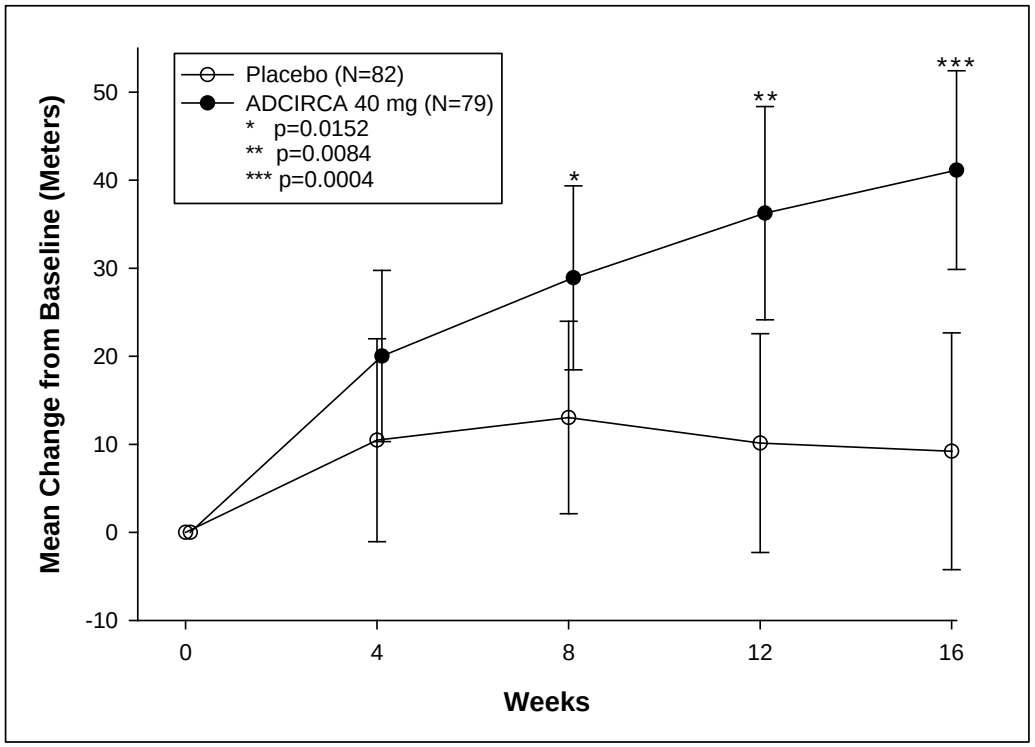


Figure 1: 6-Minute Walk Distance (metres) Mean Change from Baseline, with 95% Confidence Intervals

Table 1 – 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 meters ($p<0.01$). In patients taking ADCIRCA 40 mg and concomitant bosentan therapy, the placebo adjusted mean change in 6-MWD was 23 meters ($p>0.05$).

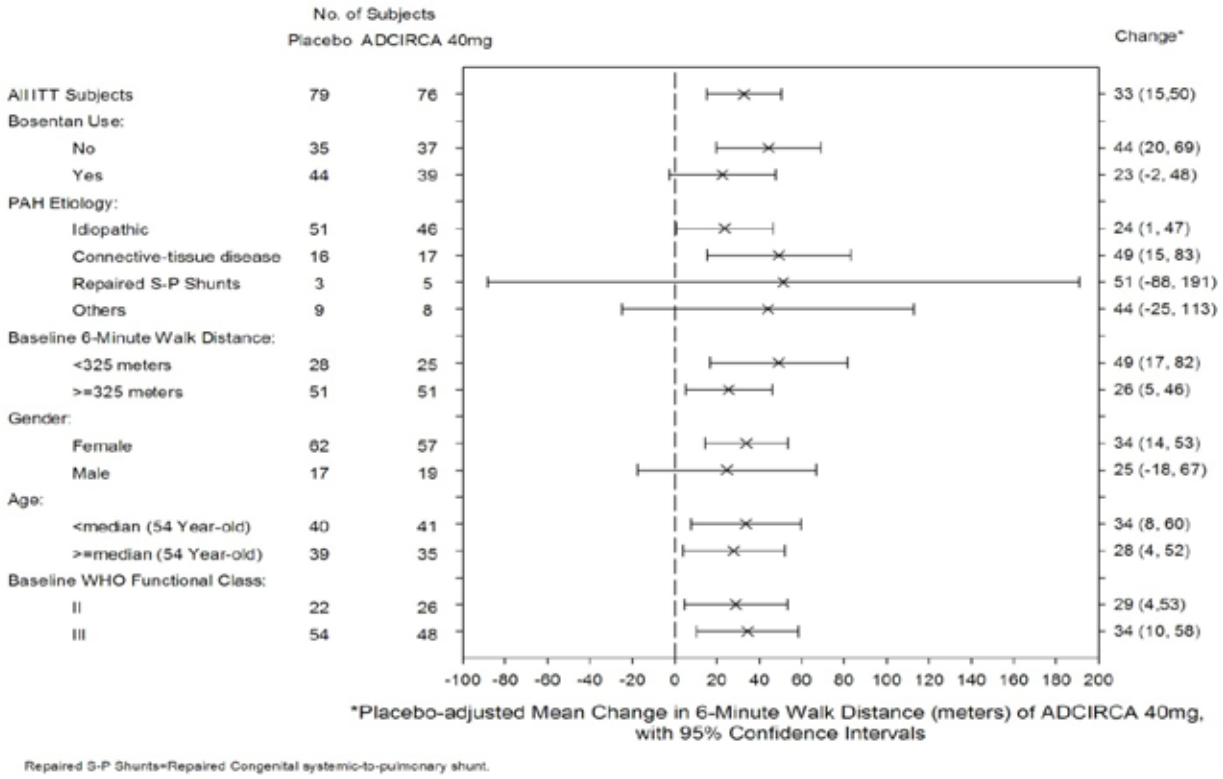


Figure 2: Placebo-adjusted Mean Change in 6-Minute Walk Distance (metres) of ADCIRCA 40 mg, with 95% Confidence Intervals

The secondary endpoints were tested in a sequential order specified in the protocol, which is the order listed in Table 2, 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 2 - 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.

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.

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 PRECAUTIONS- Interactions with Other Drugs).

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 PRECAUTIONS).

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

- patients with acute 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.

PRECAUTIONS

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 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 PRECAUTIONS – Potential for ADCIRCA to Affect Other Drugs – 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. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake 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 ADVERSE 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 PRECAUTIONS – Potential for ADCIRCA to Affect Other Drugs).

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

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.

For patients chronically taking potent inducers of CYP3A4, such as rifampicin, the use of tadalafil is not recommended (see PRECAUTIONS – Interactions with Other Medicines).

For patients taking concomitant potent inhibitors of CYP3A4, such as ketoconazole or ritonavir, the use of tadalafil is not recommended (see PRECAUTIONS – Interactions with Other Medicines).

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 PRECAUTIONS – Interactions with Other Medicines and 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 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. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. 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.

<u>Effects on Fertility</u>

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 unkown.

Use in Pregnancy

Pregnancy category B1.

Studies in rats have shown that tadalafil and/or its metabolites cross the placenta and distribute to the fetus. No evidence of embryofetal toxicity or teratogenicity was observed in pregnant rats or 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 of40 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 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.

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.

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.

Interactions with Other Medicines

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 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 ketaconazole (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 PRECAUTIONS and 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 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 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 mm Hg or more in 9 (53%) subjects on tadalafil treatment and in 5 (29%) subjects on placebo treatment, with a maximum fall of 57 mm Hg following tadalafil compared to 37 mm Hg 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 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 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.

Effects on Ability to Drive and Operate Machinery
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.

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

ADVERSE 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 3 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 3. 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 Mediastrinal 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

The table 4 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 (≥□/10), Common (≥□/100 to <□/10), Uncommon (≥□/1000 to <□/100), Rare (≥□/10,000 to <□/1000), Very Rare (<□/10,000) and Not known.

Table 4. Treatment Emergent Adverse Reactions Reported by Patients Receiving ADCIRCA 40 mg

Very common (≥□/10)	**Common** (≥□/100 to <□/10)	**Uncommon** (≥□/1000 to <□/100)	**Rare** (≥□/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 hemorrhage.

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 postmarketing 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, 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: priapism and prolonged erection

DOSAGE AND 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 Precautions and Pharmacokinetics).

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 Precautions and Pharmacokinetics).

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.

OVERDOSAGE

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. In case of overdose, immediately contact the Poisons Information Centre (in Australia, call 13 11 26; in New Zealand call 0800 764 766) for advice.

PRESENTATION AND STORAGE CONDITIONS

ADCIRCA 20 mg tablets are presented in blister packs of 14*, 28** and 56 tablets per carton.
* only available as a starter pack
**not currently available

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

NAME AND ADDRESS OF THE SPONSOR

Eli Lilly Australia Pty. Limited
112 Wharf Road,
West Ryde NSW 2114

POISON SCHEDULE OF THE MEDICINE

S4

DATE OF APPROVAL

TGA Approval

05 August 2011

Therapeutic Goods Administration

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