

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ADCIRCA 20 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 20 mg tadalafil.

Excipient with known effect

Each film-coated tablet contains 233 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Orange and almond shaped film-coated tablets of 12.09 mm x 7.37 mm, marked "4467" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults

Treatment of pulmonary arterial hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity (see section 5.1).

Efficacy has been shown in idiopathic PAH (IPAH) and in PAH related to collagen vascular disease.

Paediatric population

Treatment of paediatric patients aged 2 years and above with pulmonary arterial hypertension (PAH) classified as WHO functional class II and III.

4.2 Posology and method of administration

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

Posology

Adults

The recommended dose is 40 mg (two x 20 mg film-coated tablets) taken once daily.

Paediatric population (age 2 years to 17 years)

The recommended once daily doses based on age and weight categories in paediatric patients are shown below.

Paediatric patient's age and/or weight	Recommended daily dose and dosing regimen
Age \geq 2 years old Body weight \geq 40 kg Body weight $<$ 40 kg	40 mg (two 20 mg tablets) once daily 20 mg (one 20 mg tablet or 10 mL of oral suspension (OS), 2 mg/mL tadalafil*) once daily

* Oral suspension is available for administration to paediatric patients who require 20 mg and are not able to swallow tablets.

For patients $<$ 2 years old no PK or efficacy data are available from clinical trials. The most appropriate dose of ADCIRCA in children aged between 6 months to $<$ 2 years has not been established. Therefore, ADCIRCA is not recommended in this age subset.

Delayed dose, missed dose, or vomiting

If there is a delay in the administration of ADCIRCA, but yet within the same day, the dose should be taken with no changes to the subsequent dose schedules. Patients should not take an extra dose if a dose is missed.

Patients should not take an extra dose if vomiting occurs.

Special populations

Elderly patients

Dose adjustments are not required in elderly patients.

Renal impairment

Adults and paediatric population (2 to 17 years, weighing at least 40 kg)

In patients with mild to moderate renal impairment a starting dose of 20 mg once per day is recommended. 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 tadalafil is not recommended (see sections 4.4 and 5.2).

Paediatric population (2 to 17 years, weighing less than 40 kg)

In patients $<$ 40 kg and with mild to moderate renal impairment a starting dose of 10 mg once per day is recommended. The dose may be increased to 20 mg once per day, based on individual efficacy and tolerability. In patients with severe renal impairment the use of tadalafil is not recommended (see sections 4.4 and 5.2).

Hepatic impairment

Adults and paediatric population (2 to 17 years, weighing at least 40 kg)

Due to limited clinical experience 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.

Paediatric population (2 to 17 years, weighing less than 40 kg)

In patients $<$ 40 kg and with mild to moderate hepatic impairment, a starting dose of 10 mg once per day may be considered.

For patients of all ages, if tadalafil is prescribed, a careful individual benefit/risk assessment 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 sections 4.4 and 5.2).

Paediatric population (age $<$ 2 years)

Dosing and efficacy of ADCIRCA has not been established for children aged $<$ 2 years. Currently available data are described in sections 4.8 and 5.1.

Method of administration

ADCIRCA is for oral use.

The film-coated tablets should be swallowed whole with water, with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Acute myocardial infarction within the last 90 days.

Severe hypotension (< 90/50 mm Hg).

In clinical trials, tadalafil was shown to augment the hypotensive effects of nitrates. This is thought to result from the combined effects of nitrates and tadalafil on the nitric oxide/cGMP pathway. Therefore, administration of tadalafil to patients who are using any form of organic nitrate is contraindicated (see section 4.5).

The co-administration of phosphodiesterase type 5 (PDE5) inhibitors, including tadalafil, with guanylate cyclase stimulators, such as riociguat, is contraindicated as it may potentially lead to symptomatic hypotension (see section 4.5).

Patients who have loss of vision in one eye because of non-arteritic anterior ischemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous PDE5 inhibitor exposure (see section 4.4).

4.4 Special warnings and precautions for use

Cardiovascular diseases

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
- Patients with uncontrolled hypertension.

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.

Tadalafil has systemic vasodilatory properties that may result in transient decreases in blood pressure. Physicians should carefully consider whether their patients with certain underlying conditions, such as severe left ventricular outflow obstruction, fluid depletion, autonomic hypotension or patients with resting hypotension, could be adversely affected by such vasodilatory effects.

In patients who are taking alpha₁ blockers concomitant administration of tadalafil may lead to symptomatic hypotension in some patients (see section 4.5). Therefore, the combination of tadalafil and doxazosin is not recommended.

Vision

Visual defects, including Central Serous Chorioretinopathy (CSCR), and cases of NAION have been reported in connection with the intake of tadalafil and other PDE5 inhibitors. Most cases of CSCR resolved spontaneously after stopping tadalafil. Regarding NAION, analyses of observational data suggest an increased risk of acute NAION in men with erectile dysfunction following exposure to tadalafil or other PDE5 inhibitors. As this may be relevant for all patients exposed to tadalafil, the patient should be advised that in case of sudden visual defect, visual acuity impairment and/or visual distortion, he should stop taking ADCIRCA and consult a physician immediately (see section 4.3). 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.

Decreased or sudden hearing loss

Cases of sudden hearing loss have been reported after the use of tadalafil. Although other risk factors were present in some cases (such as age, diabetes, hypertension, previous hearing loss history and associated connective tissue diseases) patients should be advised to seek prompt medical attention in the event of sudden decrease or loss of hearing.

Renal and hepatic impairment

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

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

Priapism and anatomical deformation of the penis

Priapism has been reported in men treated with PDE5 inhibitors. 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 with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease), or in patients who have conditions which may predispose them to priapism (such as sickle cell anaemia, multiple myeloma or leukaemia).

Use with CYP3A4 inducers or inhibitors

For patients chronically taking potent inducers of CYP3A4, such as rifampicin, the use of tadalafil is not recommended (see section 4.5).

For patients taking concomitant potent inhibitors of CYP3A4, such as ketoconazole or ritonavir, the use of tadalafil is not recommended (see section 4.5).

Treatments for erectile dysfunction

The safety and efficacy of combinations of tadalafil and other PDE5 inhibitors or other treatments for erectile dysfunction have not been studied. Patients should be informed not to take ADCIRCA with these medicinal products.

Prostacyclin and its analogues

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.

Bosentan

The efficacy of tadalafil in patients already on bosentan therapy has not been conclusively demonstrated (see sections 4.5 and 5.1).

Lactose

ADCIRCA contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on tadalafil

Cytochrome P450 inhibitors

Azole antifungals (e.g. ketoconazole)

Ketoconazole (200 mg daily), increased tadalafil (10 mg) single dose exposure (AUC) 2-fold and C_{max} by 15 %, relative to the AUC and C_{max} values for tadalafil alone. Ketoconazole (400 mg daily) increased tadalafil (20 mg) single dose exposure (AUC) 4-fold and C_{max} by 22 %.

Protease inhibitors (e.g. ritonavir)

Ritonavir (200 mg twice daily), which is an inhibitor of CYP3A4, CYP2C9, CYP2C19, and CYP2D6, increased tadalafil (20 mg) single dose exposure (AUC) 2-fold 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 %.

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 sections 4.4 and 5.1). Tadalafil did not affect the exposure (AUC and C_{max}) of bosentan or its metabolites. The safety and efficacy of combinations of tadalafil and other endothelin-1 receptor antagonists have not been studied.

Antimycobacterials (e.g. rifampicin)

A CYP3A4 inducer, rifampicin (600 mg daily), reduced tadalafil AUC by 88 % and C_{max} by 46 %, relative to the AUC and C_{max} values for tadalafil alone (10 mg).

Effects of tadalafil on other medicinal products

Nitrates

In clinical trials, tadalafil (5, 10 and 20 mg) was shown to augment the hypotensive effects of nitrates. This interaction lasted for more than 24 hours and was no longer detectable when 48 hours had elapsed after the last tadalafil dose. Therefore, administration of tadalafil to patients who are using any form of organic nitrate is contraindicated (see section 4.3).

Anti-hypertensives (including Calcium channel blockers)

The co-administration of doxazosin (4 and 8 mg daily) and tadalafil (5 mg daily dose and 20 mg as a single dose) increases the blood pressure-lowering effect of this alpha-blocker in a significant manner. This effect lasts at least twelve hours and may be symptomatic, including syncope. Therefore, this combination is not recommended (see section 4.4).

In interaction studies performed in a limited number of healthy volunteers, these effects were not reported with alfuzosin or tamsulosin.

In clinical pharmacology studies, the potential for tadalafil (10 and 20 mg) to augment the hypotensive effects of antihypertensive medicinal products was examined. Major classes of antihypertensive medicinal products were studied either as monotherapy or as part of combination therapy. In patients taking multiple antihypertensive medicinal products whose hypertension was not well controlled, greater reductions in blood pressure were observed compared to patients whose blood pressure was well controlled, where the reduction was minimal and similar to that in healthy subjects. In patients receiving concomitant antihypertensive medicinal products, tadalafil 20 mg may induce a blood pressure decrease, which (with the exception of doxazosin -see above) is, in general, minor and not likely to be clinically relevant.

Riociguat

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

CYP1A2 substrates (e.g. theophylline)

When tadalafil 10 mg was administered with theophylline (a non-selective phosphodiesterase inhibitor) there was no pharmacokinetic interaction. The only pharmacodynamic effect was a small (3.5 beats per minutes [bpm]) increase in heart rate.

CYP2C9 substrates (e.g. R-warfarin)

Tadalafil (10 mg and 20 mg) had no clinically significant effect on exposure (AUC) to S-warfarin or R-warfarin (CYP2C9 substrate), nor did tadalafil affect changes in prothrombin time induced by warfarin.

Acetylsalicylic acid

Tadalafil (10 mg and 20 mg) did not potentiate the increase in bleeding time caused by acetyl salicylic acid.

P-glycoprotein substrates (e.g. digoxin)

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

Oral contraceptive

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 intestinal sulphation by tadalafil. The clinical relevance of this finding is uncertain.

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 intestinal sulphation by tadalafil. The clinical relevance of this finding is uncertain.

Alcohol

Alcohol concentrations were not affected by co-administration with tadalafil (10 mg or 20 mg). In addition, no changes in tadalafil concentrations were seen after co-administration with alcohol. Tadalafil (20 mg) did not augment the mean blood pressure decrease produced by alcohol (0.7 g/kg or approximately 180 mL of 40 % alcohol [vodka] in an 80 kg male), but in some subjects, postural dizziness and orthostatic hypotension were observed. The effect of alcohol on cognitive function was not augmented by tadalafil (10 mg).

Paediatric population

Interaction studies have only been performed in adults.

Based upon population PK analysis, the estimates of apparent clearance (CL/F) and the effect of bosentan on CL/F in paediatric patients are similar to those in adult patients with PAH. No dose adjustment is considered necessary for tadalafil with bosentan use.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data from the use of tadalafil in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). As a precautionary measure, it is preferable to avoid the use of tadalafil during pregnancy.

Breast-feeding

Available pharmacodynamic/toxicological data in animals have shown excretion of tadalafil in milk. A risk to the breastfed child cannot be excluded. ADCIRCA should not be used during breast feeding.

Fertility

Effects were seen in dogs that might indicate impairment of fertility. Two subsequent clinical trials suggest that this effect is unlikely in humans, although a decrease in sperm concentration was seen in some men (see sections 5.1 and 5.3).

4.7 Effects on ability to drive and use machines

ADCIRCA has negligible influence on the ability to drive or use machines. Although the frequency of reports of dizziness in placebo and tadalafil arms in clinical trials was similar, patients should be aware of how they react to ADCIRCA, before driving or operating machinery.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions, occurring in $\geq 10\%$ of patients in the tadalafil 40 mg treatment arm, were headache, nausea, back pain, dyspepsia, flushing, myalgia, nasopharyngitis and pain in extremity. The adverse reactions reported were transient, and generally mild or moderate. Adverse reaction data are limited in patients over 75 years of age.

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) patients who completed the pivotal study entered a long-term extension study. Doses studied were 20 mg and 40 mg once daily.

Tabulated list of adverse reactions

The table below lists the adverse reactions reported during the placebo-controlled clinical trial in patients with PAH treated with ADCIRCA. Also included in the table are some adverse reactions which have been reported in clinical trials and/or post-marketing with tadalafil in the treatment of male erectile dysfunction. These events have either been assigned a frequency of “Not known,” as the frequency in PAH patients cannot be estimated from the available data or assigned a frequency based on the clinical trial data from the pivotal placebo-controlled study of ADCIRCA.

Frequency estimate: Very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1\,000$ to $< 1/100$), rare ($\geq 1/10\,000$ to $< 1/1\,000$), very rare ($< 1/10\,000$) and not known (cannot be estimated from the available data).

System Organ Class	Very common	Common	Uncommon	Rare	Not known¹
Immune system disorders		Hypersensitivity reactions ⁵			Angioedema
Nervous system disorders	Headache ⁶	Syncope, Migraine ⁵	Seizures ⁵ , Transient amnesia ⁵		Stroke ² (including haemorrhagic events)
Eye disorders		Blurred vision			Non-arteritic anterior ischemic optic neuropathy (NAION), Retinal vascular occlusion, Visual field defect, Central serous chorioretinopathy
Ear and labyrinth disorders			Tinnitus		Sudden hearing loss
Cardiac disorders		Palpitations ^{2, 5}	Sudden cardiac death ^{2, 5} , Tachycardia ^{2, 5}		Unstable angina pectoris, Ventricular arrhythmia, Myocardial Infarction ²
Vascular disorders	Flushing	Hypotension	Hypertension		
Respiratory, thoracic and mediastinal disorders	Nasopharyngitis (including nasal congestion, sinus congestion and rhinitis)	Epistaxis			

Gastrointestinal disorders	Nausea, Dyspepsia (including abdominal pain/discomfort ³)	Vomiting, Gastroesophageal reflux			
Skin and subcutaneous tissue disorders		Rash	Urticaria ⁵ , Hyperhidrosis (sweating) ⁵		Stevens-Johnson Syndrome, Exfoliative dermatitis
Musculoskeletal, connective tissue and bone disorders	Myalgia, Back pain Pain in extremity (including limb discomfort)				
Renal and urinary disorders			Haematuria		
Reproductive system and breast disorders		Increased uterine bleeding ⁴	Priapism ⁵ , Penile haemorrhage, Haemospermia		Prolonged erections
General disorders and administration site conditions		Facial oedema, Chest pain ²			

(1) Events not reported in registration trials and cannot be estimated from the available data. The adverse reactions have been included in the table as a result of post-marketing or clinical trial data from the use of tadalafil in the treatment of erectile dysfunction.

(2) Most of the patients in whom these events have been reported had pre-existing cardiovascular risk factors.

(3) Actual MedDRA terms included are abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and stomach discomfort.

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

(5) The adverse reactions have been included in the table as a result of post-marketing or clinical trial data from the use of tadalafil in the treatment of erectile dysfunction; and in addition, the frequency estimates are based on only 1 or 2 patients experiencing the adverse reaction in the pivotal placebo-controlled study of ADCIRCA.

(6) Headache was the most commonly reported adverse reaction. Headache may occur at the beginning of therapy; and decreases over time even if treatment is continued.

Paediatric population

A total of 51 paediatric patients aged from 2.5 to 17 years with PAH were treated with tadalafil in clinical trials (H6D-MC-LVHV, H6D-MC-LVIG). A total of 391 paediatric patients with PAH, from new-born to < 18 years, were treated with tadalafil in an observational post-marketing study (H6D-JE-TD01). Following tadalafil administration, the frequency, type and severity of adverse reactions in children and adolescents were similar to that seen for adults. Due to differences in study design, sample size, gender, age range, and doses, safety findings from these trials are detailed separately below.

Placebo-controlled clinical trial in paediatric patients (H6D-MC-LVHV)

In a randomised, placebo-controlled study in 35 patients aged 6.2 to 17.9 years (median age of 14.2 years) with PAH, a total of 17 patients were treated once daily with ADCIRCA 20 mg (middle-weight cohort, ≥ 25 kg to < 40 kg) or 40 mg (heavy-weight cohort, ≥ 40 kg), and 18 patients

were treated with placebo, for 24 weeks. The most common AEs, occurring in ≥ 2 patients treated with tadalafil, were headache (29.4 %), upper respiratory tract infection and influenza (17.6 % each), and arthralgia and epistaxis (11.8 % each). No deaths or SAEs were reported. Of the 35 paediatric patients treated in the short-term, placebo-controlled study, 32 entered the 24 month long-term open-label extension and 26 patients completed the follow-up. No new safety signals were observed.

Uncontrolled pharmacokinetic study in paediatric patients (H6D-MC-LVIG)

In a paediatric multiple ascending dose study, 19 patients with a median age of 10.9 years [range 2.5 - 17 years] received once daily ADCIRCA, for an open-label treatment duration of 10 weeks (Period 1) and for up to a further 24 months in an extension (Period 2). SAEs were reported in 8 patients (42.1 %). These were pulmonary hypertension (21.0 %), viral infection (10.5 %), and cardiac failure, gastritis, pyrexia, type 1 diabetes mellitus, febrile convulsion, presyncope, seizure, and ovarian cyst (5.3 % each). No patient was discontinued due to AEs. TEAEs were reported in 18 patients (94.7 %) and the most frequent TEAEs (occurring in ≥ 5 patients) were headache, pyrexia, viral upper respiratory tract infection, and vomiting. Two deaths were reported.

Post-marketing study in paediatric patients (H6D-JE-TD01)

Safety data were collected during an observational post-marketing study in Japan including 391 paediatric PAH patients (2 years maximum observational period). The mean age of patients in the study was 5.7 ± 5.3 years, including 79 patients aged < 1 year, 41 aged 1 to < 2 years, 122 aged 2 to 6 years, 110 aged 7 to 14 years, and 39 aged 15 to 17 years. AEs were reported in 123 patients (31.5 %). The incidences of AEs (≥ 5 patients) were pulmonary hypertension (3.6 %); headache (2.8 %); heart failure and decreased platelet count (2.0 % each); epistaxis and upper respiratory tract infection (1.8 % each); bronchitis, diarrhoea, and abnormal hepatic function (1.5 % each); and gastroenteritis, protein losing gastroenteropathy, and increased aspartate aminotransferase (1.3 % each). The incidence of SAEs was 12.0 % (≥ 3 patients), including pulmonary hypertension (3.6 %), heart failure (1.5 %), and pneumonia (0.8 %). Sixteen deaths (4.1 %) were reported; none were related to tadalafil.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via [the national reporting system listed in Appendix V](#).

4.9 Overdose

Single doses of up to 500 mg have been given to healthy subjects, and multiple daily doses up to 100 mg have been given to patients with erectile dysfunction. Adverse reactions 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urologicals, drugs used in erectile dysfunction, ATC code: G04BE08.

Mechanism of action

Tadalafil is a potent and selective inhibitor of PDE5, the enzyme responsible for the degradation of cyclic guanosine monophosphate (cGMP). 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.

Pharmacodynamic effects

Studies *in vitro* have shown that tadalafil is a selective inhibitor of PDE5. PDE5 is an enzyme found in corpus cavernosum smooth muscle, vascular and visceral smooth muscle, skeletal muscle, platelets, kidney, lung, and cerebellum. The effect of tadalafil is more potent on PDE5 than on other phosphodiesterases. Tadalafil is > 10 000-fold more potent for PDE5 than for PDE1, PDE2, and PDE4, enzymes which are found in the heart, brain, blood vessels, liver, 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 > 10 000-fold more potent for PDE5 than for PDE7 through PDE10.

Clinical efficacy and safety

Pulmonary arterial hypertension in adults

A randomised, double-blind, placebo-controlled study was conducted in 405 patients with pulmonary arterial hypertension. Allowed background therapy included bosentan (stable maintenance dose up to 125 mg twice daily) and chronic anticoagulation, digoxin, diuretics and oxygen. More than half (53.3 %) of the patients in the study were receiving concomitant bosentan therapy.

Patients were randomised to one of five treatment groups (tadalafil 2.5 mg, 10 mg, 20 mg, 40 mg, or placebo). Patients were at least 12 years of age and had a diagnosis of PAH that was idiopathic, related to collagen disease, related to anorexigen use, related to human immunodeficiency virus (HIV) infection, associated with an atrial-septal defect, or associated with surgical repair of at least 1 year in duration of a congenital systemic-to-pulmonary shunt (for example, ventricular septal defect, patent ductus arteriosus). The mean age of all patients was 54 years (range 14 to 90 years) with the majority of patients being Caucasian (80.5 %) and female (78.3 %). Pulmonary arterial hypertension (PAH) aetiologies were predominantly idiopathic PAH (61.0 %) and related to collagen vascular disease (23.5 %). The majority of patients had a World Health Organization (WHO) Functional Class III (65.2 %) or II (32.1 %). The mean baseline 6-minute-walk-distance (6MWD) was 343.6 meters.

The primary efficacy endpoint was the change from baseline at week 16 in 6-minute walk distance (6MWD). Only tadalafil 40 mg achieved the protocol defined level of significance with a placebo-adjusted median increase in 6MWD of 26 metres ($p = 0.0004$; 95 % CI: 9.5, 44.0; Pre-specified Hodges-Lehman method) (mean 33 metres, 95 % CI: 15.2, 50.3). The improvement in walk distance was apparent from 8 weeks of treatment. Significant improvement ($p < 0.01$) in the 6MWD was demonstrated at week 12 when the patients were asked to delay taking study medicinal product in order to reflect trough active substance concentration. Results were generally consistent in subgroups according to age, gender, PAH aetiology and baseline WHO functional class and 6MWD. The placebo-adjusted median increase in 6MWD was 17 metres ($p = 0.09$; 95 % CI: -7.1, 43.0; Pre-specified Hodges-Lehman method) (mean 23 metres, 95 % CI: -2.4, 47.8) in those patients who received tadalafil 40 mg in addition to their concomitant bosentan ($n = 39$), and was 39 metres ($p < 0.01$, 95 % CI: 13.0, 66.0; Pre-specified Hodges-Lehman method) (mean 44 metres, 95 % CI: 19.7, 69.0) in those patients who received tadalafil 40 mg alone ($n = 37$).

The proportion of patients with improvement in WHO functional class by week 16 was similar in the tadalafil 40 mg and placebo groups (23 % vs. 21 %). The incidence of clinical worsening by week 16 in patients treated with tadalafil 40 mg (5 %; 4 of 79 patients) was less than placebo (16 %; 13 of 82 patients). Changes in the Borg dyspnoea score were small and non-significant with both placebo and tadalafil 40 mg.

Additionally, improvements compared to placebo were observed with tadalafil 40 mg in the physical functioning, role-physical, bodily pain, general health, vitality and social functioning domains of the SF 36. No improvements were observed in the role emotional and mental health domains of the SF-36. Improvements compared to placebo were observed with tadalafil 40 mg in the EuroQol (EQ 5D) US and UK index scores comprising mobility, self-care, usual activities, pain/discomfort, anxiety/depression components, and in the visual analogue scale (VAS).

Cardiopulmonary haemodynamics was performed in 93 patients. Tadalafil 40 mg increased cardiac output (0.6 L/min) and reduced pulmonary artery pressures (-4.3 mmHg) and pulmonary vascular resistance (-209 dyn.s/cm⁵) compared to baseline ($p < 0.05$). However, post hoc analyses demonstrated that changes from baseline in cardiopulmonary haemodynamic parameters for the tadalafil 40 mg treatment group were not significantly different compared to placebo.

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.

Tadalafil 20 mg 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.

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. Across all clinical trials, reports of changes in colour vision were rare ($< 0.1\%$).

Three trials 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. In two of these trials decreases were observed in sperm count and concentration related to tadalafil treatment of unlikely clinical relevance. These effects were not associated with changes in other parameters such as motility, morphology and FSH.

Paediatric population

Pulmonary arterial hypertension in children

A total of 35 paediatric patients with PAH aged 6 to < 18 years were treated in a 2-period add-on (in addition to patient's current endothelin receptor antagonist) study (H6D-MC-LVHV) to evaluate tadalafil efficacy, safety, and PK. In the 6-month double-blind period (Period 1), 17 patients received tadalafil and 18 patients received placebo.

Tadalafil dose was administered based on patient's weight at the screening visit. The majority of patients (25 [71.4 %]) were ≥ 40 kg and received 40 mg, with the remainder (10 [28.6 %]) weighing ≥ 25 kg to < 40 kg and receiving 20 mg. There were 16 male and 19 female patients in this study; the median age for the overall population was 14.2 years (ranged from 6.2 to 17.9 years). No patient aged < 6 years was enrolled in the study. Pulmonary arterial hypertension aetiologies were predominantly IPAH (74.3 %) and PAH associated with persisting or recurrent pulmonary hypertension after repair of a congenital systemic to pulmonary shunt (25.7 %). The majority of patients were in WHO functional Class II (80 %).

The primary objective of period 1 was to evaluate the efficacy of tadalafil compared with placebo in improving 6MWD from baseline to Week 24, as assessed in patients ≥ 6 to < 18 years of age who were developmentally capable of performing a 6MW test. For the primary analysis (MMRM), the LS

mean (Standard Error: SE) change from baseline to 24 weeks in 6MWD was 60 (SE: 20.4) metres for tadalafil and 37 (SE: 20.8) metres for placebo.

Additionally, in paediatric patients with PAH aged ≥ 2 to < 18 years, an exposure-response (ER) model was used to predict 6MWD based upon paediatric exposure following 20 or 40 mg daily doses estimated using a Population PK model and an established adult ER model (H6D-MC-LVGY). The model demonstrated similarity of response between model-predicted and the actual observed 6MWD in paediatric patients aged 6 to < 18 years from Study H6D-MC-LVHV.

There were no confirmed cases of clinical worsening in either treatment group during period 1. The proportion of patients with improvement in WHO functional class from baseline to week 24 was 40 % in the tadalafil group compared to 20 % in the placebo group. Additionally, a positive trend of potential efficacy in tadalafil versus placebo group was also observed in measurements like NT-Pro-BNP (treatment difference: -127.4, 95 % CI, -247.05 to -7.80), echocardiographic parameters (TAPSE: treatment difference 0.43, 95 % CI, 0.14 to 0.71; left ventricular EI-systolic: treatment difference -0.40, 95 % CI, -0.87 to 0.07; left ventricular EI-diastolic: treatment difference -0.17, 95 % CI, -0.43 to 0.09; 2 patients with reported pericardial effusion from placebo group and none from tadalafil group), and CGI-I (improved in tadalafil 64.3 %, placebo 46.7 %).

Long term extension data

A total of 32 patients from the placebo-controlled study (H6D-MC-LVHV) entered the open-label 2-year extension period (period 2) during which all patients received tadalafil at their appropriate weight cohort-related dose. The primary objective of period 2 was to evaluate the long-term safety of tadalafil.

In total, 26 patients completed the follow-up, during which time no new safety signals were observed. Clinical worsening was experienced in 5 patients; 1 had new onset syncope, 2 had an increase in endothelin receptor antagonist dose, 1 had addition of new PAH-specific concomitant therapy and 1 was hospitalized for PAH progression. WHO functional class was maintained or improved in the majority of patients at the end of period 2.

Pharmacodynamic effects in children aged < 6 years

Due to limited availability of pharmacodynamic measures and lack of a suitable and approved clinical endpoint in children younger than age 6 years, efficacy is extrapolated in this population based upon exposure-matching to the adult efficacious dose range.

Dosing and efficacy of ADCIRCA has not been established for children aged less than 2 years.

Duchenne muscular dystrophy

A single study has been performed in paediatric patients with Duchenne Muscular Dystrophy (DMD) in which no evidence of efficacy was seen. The randomised, double-blind, placebo-controlled, parallel, 3-arm study of tadalafil was conducted in 331 boys aged 7-14 years with DMD receiving concurrent corticosteroid therapy. The study included a 48-week double-blind period where patients were randomised to tadalafil 0.3 mg/kg, tadalafil 0.6 mg/kg, or placebo daily. Tadalafil did not show efficacy in slowing the decline in ambulation as measured by the primary 6-minute walk distance (6MWD) endpoint: least squares (LS) mean change in 6MWD at 48 weeks was -51.0 meters (m) in the placebo group, compared with -64.7 m in the tadalafil 0.3 mg/kg group ($p = 0.307$) and -59.1 m in the tadalafil 0.6 mg/kg group ($p = 0.538$). In addition, there was no evidence of efficacy from any of the secondary analyses performed in this study. The overall safety results from this study were generally consistent with the known safety profile of tadalafil and with adverse events (AEs) expected in a paediatric DMD population receiving corticosteroids.

5.2 Pharmacokinetic properties

Pharmacokinetic studies have shown that ADCIRCA tablets and oral suspension are bioequivalent based upon AUC(0- ∞) in the fasted state. The t_{\max} of the oral suspension is approximately 1 hour later than the tablets, however the difference was not considered clinically relevant. While the tablets may

be taken with or without food, the oral suspension should be taken on an empty stomach at least 1 hour before or 2 hours after a meal.

Absorption

Tadalafil is readily absorbed after oral administration and the mean maximum observed plasma concentration (C_{\max}) is achieved at a median time of 4 hours after dosing. Pharmacokinetic studies have shown that ADCIRCA tablets and oral suspension are bioequivalent based upon AUC(0- ∞). Absolute bioavailability of tadalafil following oral dosing has not been determined.

The rate and extent of absorption of tadalafil film-coated tablets are not influenced by food, thus ADCIRCA tablets may be taken with or without food. The effect of food on the rate and extent of absorption with the tadalafil oral suspension has not been investigated; therefore, tadalafil suspension should be taken on an empty stomach at least 1 hour before or 2 hours after a meal. The time of dosing (morning versus evening after a single 10 mg administration) had no clinically relevant effects on the rate and extent of absorption. For children, tadalafil was dosed in clinical trials and post-marketing trials without regard to food with no safety concerns.

Distribution

The mean volume of distribution is approximately 77 L at steady state, indicating that tadalafil is distributed into tissues. At therapeutic concentrations, 94 % of tadalafil in plasma is bound to proteins. Protein binding is not affected by impaired renal function.

Less than 0.0005 % of the administered dose appeared in the semen of healthy subjects.

Biotransformation

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

Elimination

The mean oral clearance for tadalafil is 3.4 L/h 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 oral clearance of tadalafil, resulting in 25 % higher exposure (AUC) relative to healthy subjects aged 19 to 45 years after a 10 mg dose. This effect of age is not clinically significant and does not warrant a dose adjustment.

Renal impairment

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 and in subjects with end-stage renal disease on dialysis. In haemodialysis patients, C_{\max} was 41 % higher than that observed in healthy subjects. Haemodialysis contributes 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

Tadalafil exposure (AUC) in subjects with mild and moderate hepatic impairment (Child-Pugh Class A and B) is comparable to exposure in healthy subjects when a dose of 10 mg is administered. If tadalafil is prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician. There are no available data about the administration of doses higher than 10 mg of tadalafil to patients with hepatic impairment.

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

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.

Paediatric population

Based on data from 36 paediatric patients with PAH aged 2 to < 18 years, body weight did not have an impact on the clearance of tadalafil; the AUC values in all paediatric weight groups are similar to those in adult patients at the same dose. Body weight was shown to be a predictor of peak exposure in children; due to this weight effect, the dose is 20 mg daily for paediatric patients ≥ 2 years and weighing < 40 kg, and the C_{\max} is expected to be similar to paediatric patients weighing ≥ 40 kg taking 40 mg daily. T_{\max} for the tablet formulation was estimated at approximately 4 hours and was independent of body weight. Tadalafil half-life values were estimated to range from 13.6 to 24.2 hours for a range of 10 to 80 kg of body weight and did not show any clinically relevant differences.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional trials of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction.

There was no evidence of teratogenicity, embryotoxicity or foetotoxicity in rats or mice that received up to 1 000 mg/kg/day tadalafil. In a rat prenatal and postnatal development study, the no observed effect dose was 30 mg/kg/day. In the pregnant rat the AUC for calculated free active substance at this dose was approximately 18 times the human AUC at a 20 mg dose.

There was no impairment of fertility in male and female rats. In dogs given tadalafil daily for 6 to 12 months at doses of 25 mg/kg/day (resulting in at least a 3-fold greater exposure [range 3.7 – 18.6] than seen in humans given a single 20 mg dose) and above, there was regression of the seminiferous tubular epithelium that resulted in a decrease in spermatogenesis in some dogs. See also section 5.1.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate
Croscarmellose sodium
Hydroxypropylcellulose
Microcrystalline cellulose
Sodium laurilsulfate
Magnesium stearate

Film-coat

Lactose monohydrate
Hypromellose
Triacetin
Titanium dioxide (E171)
Iron oxide yellow (E172)
Iron oxide red (E172)
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture. Do not store above 30 °C.

6.5 Nature and contents of container

Aluminium/PVC/PE/PCTFE blisters in cartons of 28 and 56 film-coated tablets.

Not all packs sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/476/005-006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1 October 2008
Date of latest renewal: 22 May 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

1. NAME OF THE MEDICINAL PRODUCT

ADCIRCA 2 mg/mL oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of oral suspension contains 2 mg tadalafil.

Excipient with known effect

Each mL of oral suspension contains:

2.1 mg sodium benzoate (E211)

110.25 mg sorbitol (E420)

3.1 mg propylene glycol (E1520)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral suspension

White to practically white suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults

Treatment of pulmonary arterial hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity (see section 5.1).

Efficacy has been shown in idiopathic PAH (IPAH) and in PAH related to collagen vascular disease.

Paediatric population

Treatment of paediatric patients aged 2 years and above with pulmonary arterial hypertension (PAH) classified as WHO functional class II and III.

4.2 Posology and method of administration

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

Posology

Adults

The recommended dose is 40 mg (two x 20 mg film-coated tablets) taken once daily.

Paediatric population (age 2 years to 17 years)

The recommended once daily doses based on age and weight categories in paediatric patients are shown below.

Paediatric patient's age and/or weight	Recommended daily dose and dosing regimen
Age \geq 2 years old Body weight \geq 40 kg Body weight $<$ 40 kg	40 mg (two 20 mg tablets*) once daily 20 mg (one 20 mg tablet or 10 mL of oral suspension (OS), 2 mg/mL tadalafil*) once daily

* Tablets are available for patients able to swallow them and taking a 20 or 40 mg dose.

For patients $<$ 2 years old no PK or efficacy data are available from clinical trials. The most appropriate dose of ADCIRCA in children aged between 6 months to $<$ 2 years has not been established. Therefore, ADCIRCA is not recommended in this age subset.

Delayed dose, missed dose, or vomiting

If there is a delay in the administration of ADCIRCA, but yet within the same day, the dose should be taken with no changes to the subsequent dose schedules. Patients should not take an extra dose if a dose is missed.

Patients should not take an extra dose if vomiting occurs.

Special populations

Elderly patients

Dose adjustments are not required in elderly patients.

Renal impairment

Adults and paediatric population (2 to 17 years, weighing at least 40 kg)

In patients with mild to moderate renal impairment a starting dose of 20 mg once per day is recommended. 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 tadalafil is not recommended (see sections 4.4 and 5.2).

Paediatric Population (2 to 17 years, weighing less than 40 kg)

In patients $<$ 40 kg and with mild to moderate renal impairment a starting dose of 10 mg once per day is recommended. The dose may be increased to 20 mg once per day, based on individual efficacy and tolerability. In patients with severe renal impairment the use of tadalafil is not recommended (see sections 4.4 and 5.2).

Hepatic impairment

Adults and paediatric population (2 to 17 years, weighing at least 40 kg)

Due to limited clinical experience 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.

Paediatric population (2 to 17 years, weighing less than 40 kg)

In patients $<$ 40 kg and with mild to moderate hepatic impairment, a starting dose of 10 mg once per day may be considered.

For patients of all ages, if tadalafil is prescribed, a careful individual benefit/risk assessment 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 sections 4.4 and 5.2).

Paediatric population (age $<$ 2 years)

Dosing and efficacy of ADCIRCA in children aged $<$ 2 years has not been established. Currently available data are described in sections 4.8 and 5.1.

Method of administration

Oral use.

The oral suspension should be taken on an empty stomach at least 1 hour before or 2 hours after a meal.

For instructions on preparation of the medicinal product before administration, see section 6.6.

The prescribed dose of ADCIRCA oral suspension can be administered via nasogastric (NG) tube. Follow the manufacturer's instructions for the NG tube to administer the medicinal product. To ensure adequate dosing, after administration of the oral suspension, the enteral feeding tube must be flushed with at least 3 mL of water or sodium chloride 9 mg/ml (0.9 %) solution for infusion.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Acute myocardial infarction within the last 90 days.

Severe hypotension (< 90/50 mm Hg).

In clinical trials, tadalafil was shown to augment the hypotensive effects of nitrates. This is thought to result from the combined effects of nitrates and tadalafil on the nitric oxide/cGMP pathway. Therefore, administration of tadalafil to patients who are using any form of organic nitrate is contraindicated (see section 4.5).

The co-administration of phosphodiesterase type 5 (PDE5) inhibitors, including tadalafil, with guanylate cyclase stimulators, such as riociguat, is contraindicated as it may potentially lead to symptomatic hypotension (see section 4.5).

Patients who have loss of vision in one eye because of non-arteritic anterior ischemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous PDE5 inhibitor exposure (see section 4.4).

4.4 Special warnings and precautions for use

Cardiovascular diseases

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
- Patients with uncontrolled hypertension.

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.

Tadalafil has systemic vasodilatory properties that may result in transient decreases in blood pressure. Physicians should carefully consider whether their patients with certain underlying conditions, such as severe left ventricular outflow obstruction, fluid depletion, autonomic hypotension or patients with resting hypotension, could be adversely affected by such vasodilatory effects.

In patients who are taking α_1 blockers concomitant administration of tadalafil may lead to symptomatic hypotension in some patients (see section 4.5). Therefore, the combination of tadalafil and doxazosin is not recommended.

Vision

Visual defects, including Central Serous Chorioretinopathy (CSCR), and cases of NAION have been reported in connection with the intake of tadalafil and other PDE5 inhibitors. Most cases of CSCR resolved spontaneously after stopping tadalafil. Regarding NAION, analyses of observational data suggest an increased risk of acute NAION in men with erectile dysfunction following exposure to tadalafil or other PDE5 inhibitors. As this may be relevant for all patients exposed to tadalafil, the patient should be advised that in case of sudden visual defect, visual acuity impairment and/or visual distortion, he should stop taking ADCIRCA and consult a physician immediately (see section 4.3). 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.

Decreased or sudden hearing loss

Cases of sudden hearing loss have been reported after the use of tadalafil. Although other risk factors were present in some cases (such as age, diabetes, hypertension, previous hearing loss history and associated connective tissue diseases) patients should be advised to seek prompt medical attention in the event of sudden decrease or loss of hearing.

Renal and hepatic impairment

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

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

Priapism and anatomical deformation of the penis

Priapism has been reported in men treated with PDE5 inhibitors. 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 with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease), or in patients who have conditions which may predispose them to priapism (such as sickle cell anaemia, multiple myeloma or leukaemia).

Use with CYP3A4 inducers or inhibitors

For patients chronically taking potent inducers of CYP3A4, such as rifampicin, the use of tadalafil is not recommended (see section 4.5).

For patients taking concomitant potent inhibitors of CYP3A4, such as ketoconazole or ritonavir, the use of tadalafil is not recommended (see section 4.5).

Treatments for erectile dysfunction

The safety and efficacy of combinations of tadalafil and other PDE5 inhibitors or other treatments for erectile dysfunction have not been studied. Patients should be informed not to take ADCIRCA with these medicinal products.

Prostacyclin and its analogues

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.

Bosentan

The efficacy of tadalafil in patients already on bosentan therapy has not been conclusively demonstrated (see sections 4.5 and 5.1).

Excipients

Sodium benzoate

This medicinal product contains 2.1 mg sodium benzoate in each mL of oral suspension.

Sorbitol

This medicinal product contains 110.25 mg sorbitol in each mL. Sorbitol is a source of fructose. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account. Patients with hereditary fructose intolerance (HFI) must not be given this medicine unless strictly necessary.

Propylene glycol

This medicinal product contains 3.1 mg propylene glycol in each mL.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per 1 mL, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on tadalafil

Cytochrome P450 inhibitors

Azole antifungals (e.g. ketoconazole)

Ketoconazole (200 mg daily), increased tadalafil (10 mg) single dose exposure (AUC) 2-fold and C_{max} by 15 %, relative to the AUC and C_{max} values for tadalafil alone. Ketoconazole (400 mg daily) increased tadalafil (20 mg) single dose exposure (AUC) 4-fold and C_{max} by 22 %.

Protease inhibitors (e.g. ritonavir)

Ritonavir (200 mg twice daily), which is an inhibitor of CYP3A4, CYP2C9, CYP2C19, and CYP2D6, increased tadalafil (20 mg) single dose exposure (AUC) 2-fold 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 %.

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 sections 4.4 and 5.1). Tadalafil did not affect the exposure (AUC and C_{\max}) of bosentan or its metabolites. The safety and efficacy of combinations of tadalafil and other endothelin-1 receptor antagonists have not been studied.

Antimycobacterials (e.g. rifampicin)

A CYP3A4 inducer, rifampicin (600 mg daily), reduced tadalafil AUC by 88 % and C_{\max} by 46 %, relative to the AUC and C_{\max} values for tadalafil alone (10 mg).

Effects of tadalafil on other medicinal products

Nitrates

In clinical trials, tadalafil (5, 10 and 20 mg) was shown to augment the hypotensive effects of nitrates. This interaction lasted for more than 24 hours and was no longer detectable when 48 hours had elapsed after the last tadalafil dose. Therefore, administration of tadalafil to patients who are using any form of organic nitrate is contraindicated (see section 4.3).

Anti-hypertensives (including Calcium channel blockers)

The co-administration of doxazosin (4 and 8 mg daily) and tadalafil (5 mg daily dose and 20 mg as a single dose) increases the blood pressure-lowering effect of this alpha-blocker in a significant manner. This effect lasts at least twelve hours and may be symptomatic, including syncope. Therefore, this combination is not recommended (see section 4.4).

In interaction studies performed in a limited number of healthy volunteers, these effects were not reported with alfuzosin or tamsulosin.

In clinical pharmacology trials, the potential for tadalafil (10 and 20 mg) to augment the hypotensive effects of antihypertensive medicinal products was examined. Major classes of antihypertensive medicinal products were studied either as monotherapy or as part of combination therapy. In patients taking multiple antihypertensive medicinal products whose hypertension was not well controlled, greater reductions in blood pressure were observed compared to patients whose blood pressure was well controlled, where the reduction was minimal and similar to that in healthy subjects. In patients receiving concomitant antihypertensive medicinal products, tadalafil 20 mg may induce a blood pressure decrease, which (with the exception of doxazosin -see above) is, in general, minor and not likely to be clinically relevant.

Riociguat

Preclinical trials showed an additive systemic blood pressure lowering effect when PDE5 inhibitors were combined with riociguat. In clinical trials, riociguat has been shown to augment the hypotensive effects of PDE5 inhibitors. There was no evidence of favourable clinical effect of the combination in the population studied. Concomitant use of riociguat with PDE5 inhibitors, including tadalafil, is contraindicated (see section 4.3).

CYP1A2 substrates (e.g. theophylline)

When tadalafil 10 mg was administered with theophylline (a non-selective phosphodiesterase inhibitor) there was no pharmacokinetic interaction. The only pharmacodynamic effect was a small (3.5 beats per minute [bpm]) increase in heart rate.

CYP2C9 substrates (e.g. R-warfarin)

Tadalafil (10 mg and 20 mg) had no clinically significant effect on exposure (AUC) to S-warfarin or R-warfarin (CYP2C9 substrate), nor did tadalafil affect changes in prothrombin time induced by warfarin.

Acetylsalicylic acid

Tadalafil (10 mg and 20 mg) did not potentiate the increase in bleeding time caused by acetyl salicylic acid.

P-glycoprotein substrates (e.g. digoxin)

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

Oral contraceptive

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 intestinal sulphation by tadalafil. The clinical relevance of this finding is uncertain.

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 intestinal sulphation by tadalafil. The clinical relevance of this finding is uncertain.

Alcohol

Alcohol concentrations were not affected by co-administration with tadalafil (10 mg or 20 mg). In addition, no changes in tadalafil concentrations were seen after co-administration with alcohol. Tadalafil (20 mg) did not augment the mean blood pressure decrease produced by alcohol (0.7 g/kg or approximately 180 mL of 40 % alcohol [vodka] in an 80 kg male), but in some subjects, postural dizziness and orthostatic hypotension were observed. The effect of alcohol on cognitive function was not augmented by tadalafil (10 mg).

Paediatric population

Interaction studies have only been performed in adults.

Based upon population PK analysis, the estimates of apparent clearance (CL/F) and the effect of bosentan on CL/F in paediatric patients are similar to those in adult patients with PAH. No dose adjustment is considered necessary for tadalafil with bosentan use.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data from the use of tadalafil in pregnant women. Animal trials do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). As a precautionary measure, it is preferable to avoid the use of tadalafil during pregnancy.

Breast-feeding

Available pharmacodynamic/toxicological data in animals have shown excretion of tadalafil in milk. A risk to the breastfed child cannot be excluded. ADCIRCA should not be used during breast feeding.

Fertility

Effects were seen in dogs that might indicate impairment of fertility. Two subsequent clinical trials suggest that this effect is unlikely in humans, although a decrease in sperm concentration was seen in some men (see sections 5.1 and 5.3).

4.7 Effects on ability to drive and use machines

ADCIRCA has negligible influence on the ability to drive or use machines. Although the frequency of reports of dizziness in placebo and tadalafil arms in clinical trials was similar, patients should be aware of how they react to ADCIRCA, before driving or operating machinery.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions, occurring in $\geq 10\%$ of patients in the tadalafil 40 mg treatment arm, were headache, nausea, back pain, dyspepsia, flushing, myalgia, nasopharyngitis and pain in extremity. The adverse reactions reported were transient, and generally mild or moderate. Adverse reaction data are limited in patients over 75 years of age.

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) patients who completed the pivotal study entered a long-term extension study. Doses studied were 20 mg and 40 mg once daily.

Tabulated list of adverse reactions

The table below lists the adverse reactions reported during the placebo-controlled clinical trial in patients with PAH treated with ADCIRCA. Also included in the table are some adverse reactions which have been reported in clinical trials and/or post-marketing with tadalafil in the treatment of male erectile dysfunction. These events have either been assigned a frequency of "Not known," as the frequency in PAH patients cannot be estimated from the available data or assigned a frequency based on the clinical trial data from the pivotal placebo-controlled study of ADCIRCA.

Frequency estimate: Very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1\,000$ to $< 1/100$), rare ($\geq 1/10\,000$ to $< 1/1\,000$), very rare ($< 1/10\,000$) and not known (cannot be estimated from the available data).

System Organ Class	Very common	Common	Uncommon	Rare	Not known ¹
Immune system disorders		Hypersensitivity reactions ⁵			Angioedema
Nervous system disorders	Headache ⁶	Syncope, Migraine ⁵	Seizures ⁵ , Transient amnesia ⁵		Stroke ² (including haemorrhagic events)
Eye disorders		Blurred vision			Non-arteritic anterior ischemic optic neuropathy (NAION), Retinal vascular occlusion, Visual field defect, Central serous chorioretinopathy
Ear and labyrinth disorders			Tinnitus		Sudden hearing loss
Cardiac disorders		Palpitations ^{2, 5}	Sudden cardiac death ^{2, 5} , Tachycardia ^{2, 5}		Unstable angina pectoris, Ventricular arrhythmia, Myocardial Infarction ²
Vascular disorders	Flushing	Hypotension	Hypertension		

Respiratory, thoracic and mediastinal disorders	Nasopharyngitis (including nasal congestion, sinus congestion and rhinitis)	Epistaxis			
Gastrointestinal disorders	Nausea, Dyspepsia (including abdominal pain/discomfort ³)	Vomiting, Gastroesophageal reflux			
Skin and subcutaneous tissue disorders		Rash	Urticaria ⁵ , Hyperhidrosis (sweating) ⁵		Stevens-Johnson Syndrome, Exfoliative dermatitis
Musculoskeletal, connective tissue and bone disorders	Myalgia, Back pain Pain in extremity (including limb discomfort)				
Renal and urinary disorders			Haematuria		
Reproductive system and breast disorders		Increased uterine bleeding ⁴	Priapism ⁵ , Penile haemorrhage, Haemospermia		Prolonged erections
General disorders and administration site conditions		Facial oedema, Chest pain ²			

(1) Events not reported in registration trials and cannot be estimated from the available data. The adverse reactions have been included in the table as a result of post-marketing or clinical trial data from the use of tadalafil in the treatment of erectile dysfunction.

(2) Most of the patients in whom these events have been reported had pre-existing cardiovascular risk factors.

(3) Actual MedDRA terms included are abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and stomach discomfort.

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

(5) The adverse reactions have been included in the table as a result of post-marketing or clinical trial data from the use of tadalafil in the treatment of erectile dysfunction; and in addition, the frequency estimates are based on only 1 or 2 patients experiencing the adverse reaction in the pivotal placebo-controlled study of ADCIRCA.

(6) Headache was the most commonly reported adverse reaction. Headache may occur at the beginning of therapy; and decreases over time even if treatment is continued.

Paediatric population

A total of 51 paediatric patients aged from 2.5 to 17 years with PAH were treated with tadalafil in clinical trials (H6D-MC-LVHV, H6D-MC-LVIG). A total of 391 paediatric patients with PAH, from new-born to < 18 years, were treated with tadalafil in an observational post-marketing study (H6D-JE-TD01). Following tadalafil administration, the frequency, type and severity of adverse reactions in children and adolescents were similar to that seen for adults. Due to differences in study design, sample size, gender, age range, and doses, safety findings from these trials are detailed separately below.

Placebo-controlled clinical trial in paediatric patients (H6D-MC-LVHV)

In a randomised, placebo-controlled study in 35 patients aged 6.2 to 17.9 years (median age of 14.2 years) with PAH, a total of 17 patients were treated once daily with ADCIRCA 20 mg (middle-

weight cohort, ≥ 25 kg to < 40 kg) or 40 mg (heavy-weight cohort, ≥ 40 kg), and 18 patients were treated with placebo, for 24 weeks. The most common AEs, occurring in ≥ 2 patients treated with tadalafil, were headache (29.4 %), upper respiratory tract infection and influenza (17.6 % each), and arthralgia and epistaxis (11.8 % each). No deaths or SAEs were reported. Of the 35 paediatric patients treated in the short-term, placebo-controlled study, 32 entered the 24 month long-term open-label extension and 26 patients completed the follow-up. No new safety signals were observed.

Uncontrolled pharmacokinetic study in paediatric patients (H6D-MC-LVIG)

In a paediatric multiple ascending dose study, 19 patients with a median age of 10.9 years [range 2.5 – 17 years] received once daily ADCIRCA, for an open-label treatment duration of 10 weeks (Period 1) and for up to a further 24 months in an extension (Period 2). SAEs were reported in 8 patients (42.1 %). These were pulmonary hypertension (21.0 %), viral infection (10.5 %), and cardiac failure, gastritis, pyrexia, type 1 diabetes mellitus, febrile convulsion, presyncope, seizure, and ovarian cyst (5.3 % each). No patient was discontinued due to AEs. TEAEs were reported in 18 patients (94.7 %) and the most frequent TEAEs (occurring in ≥ 5 patients) were headache, pyrexia, viral upper respiratory tract infection, and vomiting. Two deaths were reported.

Post-marketing study in paediatric patients (H6D-JE-TD01)

Safety data were collected during an observational post-marketing study in Japan including 391 paediatric PAH patients (2 years maximum observational period). The mean age of patients in the study was 5.7 ± 5.3 years, including 79 patients aged < 1 year, 41 aged 1 to < 2 years, 122 aged 2 to 6 years, 110 aged 7 to 14 years, and 39 aged 15 to 17 years. AEs were reported in 123 patients (31.5 %). The incidences of AEs (≥ 5 patients) were pulmonary hypertension (3.6 %); headache (2.8 %); heart failure and decreased platelet count (2.0 % each); epistaxis and upper respiratory tract infection (1.8 % each); bronchitis, diarrhoea, and abnormal hepatic function (1.5 % each); and gastroenteritis, protein losing gastroenteropathy, and increased aspartate aminotransferase (1.3 % each). The incidence of SAEs was 12.0 % (≥ 3 patients), including pulmonary hypertension (3.6 %), heart failure (1.5 %), and pneumonia (0.8 %). Sixteen deaths (4.1 %) were reported; none were related to tadalafil.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Single doses of up to 500 mg have been given to healthy subjects, and multiple daily doses up to 100 mg have been given to patients with erectile dysfunction. Adverse reactions 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urologicals, drugs used in erectile dysfunction, ATC code: G04BE08.

Mechanism of action

Tadalafil is a potent and selective inhibitor of PDE5, the enzyme responsible for the degradation of cyclic guanosine monophosphate (cGMP). 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.

Pharmacodynamic effects

Studies *in vitro* have shown that tadalafil is a selective inhibitor of PDE5. PDE5 is an enzyme found in corpus cavernosum smooth muscle, vascular and visceral smooth muscle, skeletal muscle, platelets, kidney, lung, and cerebellum. The effect of tadalafil is more potent on PDE5 than on other phosphodiesterases. Tadalafil is > 10 000-fold more potent for PDE5 than for PDE1, PDE2, and PDE4, enzymes which are found in the heart, brain, blood vessels, liver, 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 > 10 000-fold more potent for PDE5 than for PDE7 through PDE10.

Clinical efficacy and safety

Pulmonary arterial hypertension in adults

A randomised, double-blind, placebo-controlled study was conducted in 405 patients with pulmonary arterial hypertension. Allowed background therapy included bosentan (stable maintenance dose up to 125 mg twice daily) and chronic anticoagulation, digoxin, diuretics and oxygen. More than half (53.3 %) of the patients in the study were receiving concomitant bosentan therapy.

Patients were randomised to one of five treatment groups (tadalafil 2.5 mg, 10 mg, 20 mg, 40 mg, or placebo). Patients were at least 12 years of age and had a diagnosis of PAH that was idiopathic, related to collagen disease, related to anorexigen use, related to human immunodeficiency virus (HIV) infection, associated with an atrial-septal defect, or associated with surgical repair of at least 1 year in duration of a congenital systemic-to-pulmonary shunt (for example, ventricular septal defect, patent ductus arteriosus). The mean age of all patients was 54 years (range 14 to 90 years) with the majority of patients being Caucasian (80.5 %) and female (78.3 %). Pulmonary arterial hypertension (PAH) aetiologies were predominantly idiopathic PAH (61.0 %) and related to collagen vascular disease (23.5 %). The majority of patients had a World Health Organization (WHO) Functional Class III (65.2 %) or II (32.1 %). The mean baseline 6-minute-walk-distance (6MWD) was 343.6 meters.

The primary efficacy endpoint was the change from baseline at week 16 in 6-minute walk distance (6MWD). Only tadalafil 40 mg achieved the protocol defined level of significance with a placebo-adjusted median increase in 6MWD of 26 metres ($p = 0.0004$; 95 % CI: 9.5, 44.0; Pre-specified Hodges-Lehman method) (mean 33 metres, 95 % CI: 15.2, 50.3). The improvement in walk distance was apparent from 8 weeks of treatment. Significant improvement ($p < 0.01$) in the 6MWD was demonstrated at week 12 when the patients were asked to delay taking study medicinal product in order to reflect trough active substance concentration. Results were generally consistent in subgroups according to age, gender, PAH aetiology and baseline WHO functional class and 6MWD. The placebo-adjusted median increase in 6MWD was 17 metres ($p = 0.09$; 95 % CI: -7.1, 43.0; Pre-specified Hodges-Lehman method) (mean 23 metres, 95 % CI: -2.4, 47.8) in those patients who received tadalafil 40 mg in addition to their concomitant bosentan ($n = 39$), and was 39 metres ($p < 0.01$, 95 % CI: 13.0, 66.0; Pre-specified Hodges-Lehman method) (mean 44 metres, 95 % CI: 19.7, 69.0) in those patients who received tadalafil 40 mg alone ($n = 37$).

The proportion of patients with improvement in WHO functional class by week 16 was similar in the tadalafil 40 mg and placebo groups (23 % vs. 21 %). The incidence of clinical worsening by week 16 in patients treated with tadalafil 40 mg (5 %; 4 of 79 patients) was less than placebo (16 %; 13 of 82 patients). Changes in the Borg dyspnoea score were small and non-significant with both placebo and tadalafil 40 mg.

Additionally, improvements compared to placebo were observed with tadalafil 40 mg in the physical functioning, role-physical, bodily pain, general health, vitality and social functioning domains of the SF-36. No improvements were observed in the role emotional and mental health domains of the SF-36. Improvements compared to placebo were observed with tadalafil 40 mg in the EuroQol (EQ-5D) US and UK index scores comprising mobility, self-care, usual activities, pain/discomfort, anxiety/depression components, and in the visual analogue scale (VAS).

Cardiopulmonary haemodynamics was performed in 93 patients. Tadalafil 40 mg increased cardiac output (0.6 L/min) and reduced pulmonary artery pressures (-4.3 mmHg) and pulmonary vascular resistance (-209 dyn.s/cm⁵) compared to baseline ($p < 0.05$). However, post hoc analyses demonstrated that changes from baseline in cardiopulmonary haemodynamic parameters for the tadalafil 40 mg treatment group were not significantly different compared to placebo.

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.

Tadalafil 20 mg 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.

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. Across all clinical trials, reports of changes in colour vision were rare (< 0.1 %).

Three trials 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. In two of these trials decreases were observed in sperm count and concentration related to tadalafil treatment of unlikely clinical relevance. These effects were not associated with changes in other parameters such as motility, morphology and FSH.

Paediatric population

Pulmonary arterial hypertension in children

A total of 35 paediatric patients with PAH aged 6 to < 18 years were treated in a 2-period add-on (in addition to patient's current endothelin receptor antagonist) study (H6D-MC-LVHV) to evaluate tadalafil efficacy, safety, and PK. In the 6-month double-blind period (Period 1), 17 patients received tadalafil and 18 patients received placebo.

Tadalafil dose was administered based on patient's weight at the screening visit. The majority of patients (25 [71.4 %]) were ≥ 40 kg and received 40 mg, with the remainder (10 [28.6 %]) weighing ≥ 25 kg to < 40 kg and receiving 20 mg. There were 16 male and 19 female patients in this study; the median age for the overall population was 14.2 years (ranged from 6.2 to 17.9 years). No patient aged < 6 years was enrolled in the study. Pulmonary arterial hypertension aetiologies were predominantly IPAH (74.3 %) and PAH associated with persisting or recurrent pulmonary hypertension after repair of a congenital systemic to pulmonary shunt (25.7 %). The majority of patients were in WHO functional Class II (80 %).

The primary objective of period 1 was to evaluate the efficacy of tadalafil compared with placebo in improving 6MWD from baseline to Week 24, as assessed in patients ≥ 6 to < 18 years of age who were developmentally capable of performing a 6MW test. For the primary analysis (MMRM), the LS

mean (Standard Error; SE) change from baseline to 24 weeks in 6MWD was 60 (SE: 20.4) metres for tadalafil and 37 (SE: 20.8) metres for placebo.

Additionally, in paediatric patients with PAH aged ≥ 2 to < 18 years, an exposure-response (ER) model was used to predict 6MWD based upon paediatric exposure following 20 or 40 mg daily doses estimated using a Population PK model and an established adult ER model (H6D-MC-LVGY). The model demonstrated similarity of response between model-predicted and the actual observed 6MWD in paediatric patients aged 6 to < 18 years from Study H6D-MC-LVHV.

There were no confirmed cases of clinical worsening in either treatment group during period 1. The proportion of patients with improvement in WHO functional class from baseline to week 24 was 40% in the tadalafil group compared to 20% in the placebo group. Additionally, a positive trend of potential efficacy in tadalafil versus placebo group was also observed in measurements like NT-Pro-BNP (treatment difference: -127.4, 95 % CI, -247.05 to -7.80), echocardiographic parameters (TAPSE: treatment difference 0.43, 95 % CI, 0.14 to 0.71; left ventricular EI-systolic: treatment difference -0.40, 95 % CI, -0.87 to 0.07; left ventricular EI-diastolic: treatment difference -0.17, 95 % CI, -0.43 to 0.09; 2 patients with reported pericardial effusion from placebo group and none from tadalafil group), and CGI-I (improved in tadalafil 64.3 %, placebo 46.7 %).

Long term extension data

A total of 32 patients from the placebo-controlled study (H6D-MC-LVHV) entered the open-label 2-year extension period (period 2) during which all patients received tadalafil at their appropriate weight cohort-related dose. The primary objective of period 2 was to evaluate the long-term safety of tadalafil.

In total, 26 patients completed the follow-up, during which time no new safety signals were observed. Clinical worsening was experienced in 5 patients; 1 had new onset syncope, 2 had an increase in endothelin receptor antagonist dose, 1 had addition of new PAH-specific concomitant therapy and 1 was hospitalized for PAH progression. WHO functional class was maintained or improved in the majority of patients at the end of period 2.

Pharmacodynamic effects in children aged < 6 years

Due to limited availability of pharmacodynamic measures and lack of a suitable and approved clinical endpoint in children younger than age 6 years, efficacy is extrapolated in this population based upon exposure-matching to the adult efficacious dose range.

Dosing and efficacy of ADCIRCA has not been established for children aged less than 2 years.

Duchenne muscular dystrophy

A single study has been performed in paediatric patients with Duchenne Muscular Dystrophy (DMD) in which no evidence of efficacy was seen. The randomised, double-blind, placebo-controlled, parallel, 3-arm study of tadalafil was conducted in 331 boys aged 7-14 years with DMD receiving concurrent corticosteroid therapy. The study included a 48-week double-blind period where patients were randomised to tadalafil 0.3 mg/kg, tadalafil 0.6 mg/kg, or placebo daily. Tadalafil did not show efficacy in slowing the decline in ambulation as measured by the primary 6-minute walk distance (6MWD) endpoint: least squares (LS) mean change in 6MWD at 48 weeks was -51.0 meters (m) in the placebo group, compared with -64.7 m in the tadalafil 0.3 mg/kg group ($p = 0.307$) and -59.1 m in the tadalafil 0.6 mg/kg group ($p = 0.538$). In addition, there was no evidence of efficacy from any of the secondary analyses performed in this study. The overall safety results from this study were generally consistent with the known safety profile of tadalafil and with adverse events (AEs) expected in a paediatric DMD population receiving corticosteroids.

5.2 Pharmacokinetic properties

Pharmacokinetic studies have shown that ADCIRCA tablets and oral suspension are bioequivalent based upon AUC(0- ∞) in the fasted state. The t_{\max} of the oral suspension is approximately 1 hour later than the tablets, however the difference was not considered clinically relevant. While the tablets may

be taken with or without food, the oral suspension should be taken on an empty stomach at least 1 hour before or 2 hours after a meal.

Absorption

Tadalafil is readily absorbed after oral administration and the mean maximum observed plasma concentration (C_{\max}) is achieved at a median time of 4 hours after dosing. Pharmacokinetic studies have shown that ADCIRCA tablets and oral suspension are bioequivalent based upon $AUC(0-\infty)$. Absolute bioavailability of tadalafil following oral dosing has not been determined.

The rate and extent of absorption of tadalafil film-coated tablets are not influenced by food, thus ADCIRCA tablets may be taken with or without food. The effect of food on the rate and extent of absorption with the tadalafil oral suspension has not been investigated; therefore, tadalafil suspension should be taken on an empty stomach at least 1 hour before or 2 hours after a meal. The time of dosing (morning versus evening after a single 10 mg administration) had no clinically relevant effects on the rate and extent of absorption. For children, tadalafil was dosed in clinical trials and post-marketing studies without regard to food with no safety concerns.

Distribution

The mean volume of distribution is approximately 77 L at steady state, indicating that tadalafil is distributed into tissues. At therapeutic concentrations, 94 % of tadalafil in plasma is bound to proteins. Protein binding is not affected by impaired renal function.

Less than 0.0005 % of the administered dose appeared in the semen of healthy subjects.

Biotransformation

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

Elimination

The mean oral clearance for tadalafil is 3.4 L/h 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 oral clearance of tadalafil, resulting in 25 % higher exposure (AUC) relative to healthy subjects aged 19 to 45 years after a 10 mg dose. This effect of age is not clinically significant and does not warrant a dose adjustment.

Renal impairment

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 and in subjects with end-stage renal disease on dialysis. In haemodialysis patients, C_{max} was 41 % higher than that observed in healthy subjects. Haemodialysis contributes 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

Tadalafil exposure (AUC) in subjects with mild and moderate hepatic impairment (Child-Pugh Class A and B) is comparable to exposure in healthy subjects when a dose of 10 mg is administered. If tadalafil is prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician. There are no available data about the administration of doses higher than 10 mg of tadalafil to patients with hepatic impairment.

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

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.

Paediatric population

Based on data from 36 paediatric patients with PAH aged 2 to < 18 years, body weight did not have an impact on the clearance of tadalafil; the AUC values in all paediatric weight groups are similar to those in adult patients at the same dose. Body weight was shown to be a predictor of peak exposure in children; due to this weight effect, the dose is 20 mg daily for paediatric patients ≥ 2 years and weighing < 40 kg, and the C_{max} is expected to be similar to paediatric patients weighing ≥ 40 kg taking 40 mg daily. T_{max} for the tablet formulation was estimated at approximately 4 hours and was independent of body weight. Tadalafil half-life values were estimated to range from 13.6 to 24.2 hours for a range of 10 to 80 kg of body weight and did not show any clinically relevant differences.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional trials of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction.

There was no evidence of teratogenicity, embryotoxicity or foetotoxicity in rats or mice that received up to 1 000 mg/kg/day tadalafil. In a rat prenatal and postnatal development study, the no observed effect dose was 30 mg/kg/day. In the pregnant rat the AUC for calculated free active substance at this dose was approximately 18 times the human AUC at a 20 mg dose.

There was no impairment of fertility in male and female rats. In dogs given tadalafil daily for 6 to 12 months at doses of 25 mg/kg/day (resulting in at least a 3-fold greater exposure [range 3.7 – 18.6] than seen in humans given a single 20 mg dose) and above, there was regression of the seminiferous tubular epithelium that resulted in a decrease in spermatogenesis in some dogs. See also section 5.1.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Xanthan gum
Microcrystalline cellulose
Carmellose sodium
Citric acid
Sodium citrate
Sodium benzoate (E211)
Silica, colloidal anhydrous
Sorbitol (E420), liquid (crystallising)
Polysorbate 80
Sucralose
Simethicone emulsion, 30 % (containing simethicone, methylcellulose, sorbic acid, purified water)
Artificial cherry flavour (contains propylene glycol (E1520))
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.
After initial bottle opening: 110 days

6.4 Special precautions for storage

Store the bottle upright. This medicinal product does not require any special storage conditions. For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Polyethylene terephthalate (PET) bottle with a peelable seal and child-resistant polypropylene (PP) closure containing 220 mL of oral suspension, inside a carton.

Each carton contains one bottle, and a low-density polyethylene (LDPE) 10 mL graduated syringe with 1 mL graduations and an LDPE press-in-bottle adaptor.

6.6 Special precautions for disposal and other handling

Preparation: The press-in-bottle adaptor (PIBA) which is supplied in the product carton should be inserted firmly into the neck of the bottle before first use and remain in place for the duration of the usage of the bottle. Shake bottle well for at least 10 seconds before each use. Shake again if the bottle sits longer than 15 minutes. The dosing syringe should be inserted into the PIBA and the dose

withdrawn from the inverted bottle aligning the mL graduation mark with the bottom of the flange. The cap should be replaced after each use. Rinse syringe by placing water in a cup and filling syringe with water and pushing the water out.

Dose recovery of tadalafil was achieved with nasogastric (NG) tubes made of silicone and polyurethane at 60 cm in length and tube size of 8 Fr. To ensure adequate dosing, after administration of the oral suspension, the NG tube must be flushed at least 3 mL of water or sodium chloride 9 mg/ml (0.9 %) solution for infusion.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/476/007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1 October 2008

Date of latest renewal: 22 May 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Lilly S.A.
Avda de la Industria 30
28108 Alcobendas (Madrid)
Spain

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING – FILM-COATED TABLETS
OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

ADCIRCA 20 mg film-coated tablets
tadalafil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 20 mg tadalafil

3. LIST OF EXCIPIENTS

lactose

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

film-coated tablet

28 film-coated tablets

56 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture. Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
--

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/1/08/476/005-006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADCIRCA 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
--

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

ADCIRCA 20 mg tablets
tadalafil

2. NAME OF THE MARKETING AUTHORISATION HOLDER
--

Lilly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Mon.
Tue.
Wed.
Thu.
Fri.
Sat.
Sun.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING – ORAL SUSPENSION

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

ADCIRCA 2 mg/mL oral suspension
tadalafil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of oral suspension contains 2 mg of tadalafil

3. LIST OF EXCIPIENTS

sodium benzoate (E211); sorbitol (E420), liquid (crystallising); propylene glycol (E1520). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

oral suspension.

220 mL

Each carton contains 1 bottle, 1 syringe and 1 press-in-bottle adaptor.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Shake the medicine bottle well for at least 10 seconds before each use to fully mix the suspension.

Shake again if the bottle sits longer than 15 minutes

Once daily.

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After initial opening: use within 110 days. Open date: _____

9. SPECIAL STORAGE CONDITIONS

Store the bottle upright.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/476/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

ADCIRCA 2 mg/mL

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING – ORAL SUSPENSION
BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

ADCIRCA 2 mg/mL oral suspension
tadalafil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of oral suspension contains 2 mg of tadalafil.

3. LIST OF EXCIPIENTS

sodium benzoate (E211); sorbitol (E420), liquid (crystallising); propylene glycol (E1520). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral suspension
220 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Shake well for 10 seconds before use.
Once daily.
Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
After initial opening: use within 110 days.

9. SPECIAL STORAGE CONDITIONS

Store the bottle upright.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/476/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the user

ADCIRCA 20 mg film-coated tablets tadalafil

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any of the side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See Section 4.

What is in this leaflet

1. What ADCIRCA is and what it is used for
2. What you need to know before you take ADCIRCA
3. How to take ADCIRCA
4. Possible side effects
5. How to store ADCIRCA
6. Contents of the pack and other information

1. What ADCIRCA is and what it is used for

ADCIRCA contains the active substance tadalafil.

ADCIRCA is a treatment for pulmonary arterial hypertension in adults and in children aged 2 years and above.

It belongs to a group of medicines called phosphodiesterase type 5 (PDE5) inhibitors which work by helping the blood vessels around your lungs relax, improving the flow of blood into your lungs. The result of this is an improved ability to do physical activity.

2. What you need to know before you take ADCIRCA

Do not take ADCIRCA

- if you are allergic to tadalafil or any of the other ingredients (see section 6).
- if you are taking any form of nitrates such as amyl nitrite, used in the treatment of chest pain. ADCIRCA has been shown to increase the effects of these medicines. If you are taking any form of nitrate or are unsure tell your doctor.
- if you have ever had loss of vision – a condition described as “stroke of the eye” (non-arteritic anterior ischemic optic neuropathy - NAION).
- if you have had a heart attack in the last 3 months.
- if you have low blood pressure.
- if you are taking riociguat. This medicine is used to treat pulmonary arterial hypertension (i.e., high blood pressure in the lungs) and chronic thromboembolic pulmonary hypertension (i.e., high blood pressure in the lungs secondary to blood clots). PDE5 inhibitors, such as ADCIRCA, have been shown to increase the hypotensive effects of this medicine. If you are taking riociguat or are unsure tell your doctor.

Warnings and precautions

Talk to your doctor before taking ADCIRCA.

Before taking the tablets, tell your doctor if you have:

- any heart problems other than your pulmonary hypertension
- problems with your blood pressure

- any hereditary eye disease
- an abnormality of red blood cells (sickle cell anaemia)
- cancer of the bone marrow (multiple myeloma)
- cancer of the blood cells (leukaemia)
- any deformation of your penis, or unwanted or persistent erections lasting more than 4 hours
- a serious liver problem
- a serious kidney problem.

If you experience sudden decrease or loss of vision or your vision is distorted, dimmed while you are taking ADCIRCA, stop taking ADCIRCA and contact your doctor immediately.

Decreased or sudden hearing loss has been noted in some patients taking tadalafil. Although it is not known if the event is directly related to tadalafil, if you experience decreased or sudden hearing loss, contact your doctor immediately.

Children and adolescents

ADCIRCA is not recommended for the treatment of pulmonary arterial hypertension in children under 2 years of age because it has not been studied in this age group.

Other medicines and ADCIRCA

Tell your doctor if you are taking, have recently taken or might take any other medicines.

Do NOT take these tablets if you are already taking nitrates.

Some medicines may be affected by ADCIRCA or they may affect how well ADCIRCA will work.

Tell your doctor or pharmacist if you are already taking:

- bosentan (another treatment for pulmonary arterial hypertension)
- nitrates (for chest pain)
- alpha blockers used to treat high blood pressure or prostate problems
- riociguat
- rifampicin (to treat bacterial infections)
- ketoconazole tablets (to treat fungal infections)
- ritonavir (for HIV treatment)
- tablets for erectile dysfunction (PDE5 inhibitors).

ADCIRCA with alcohol

Drinking alcohol may temporarily lower your blood pressure. If you have taken or are planning to take ADCIRCA, avoid excessive drinking (over 5 units of alcohol), since this may increase the risk of dizziness when standing up.

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. Do not take ADCIRCA when pregnant, unless it is strictly necessary and you have discussed this with your doctor.

Do not breast-feed while taking these tablets as it is not known if the medicine passes into human breast milk. Ask your doctor or pharmacist for advice before taking any medicine while pregnant or breast-feeding.

When dogs were treated there was reduced sperm development in the testes. A reduction in sperm was seen in some men. These effects are unlikely to lead to a lack of fertility.

Driving and using machines

Dizziness has been reported. Check carefully how you react to this medicine before driving or using any machinery.

ADCIRCA contains lactose

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

ADCIRCA contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take ADCIRCA

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

ADCIRCA is supplied as a 20 mg tablet. Swallow the tablet(s) whole with a drink of water. The tablet(s) can be taken with or without food.

Pulmonary arterial hypertension in adults

The usual dose is two 20 mg tablets taken once a day. You should take both tablets at the same time, one after the other. If you have a mild or moderate liver or kidney problem, your doctor may advise you to take only one 20 mg tablet per day.

Pulmonary arterial hypertension in children (age 2 years and above) weighing at least 40 kg

The recommended dose is two 20 mg tablets taken once a day. Both tablets should be taken at the same time, one after the other. If you have a mild or moderate liver or kidney problem, your doctor may advise you to take only one 20 mg tablet per day.

Pulmonary arterial hypertension in children (age 2 years and above) weighing less than 40 kg

The recommended dose is one 20 mg tablet taken once a day. If you have a mild or moderate liver or kidney problem, your doctor may advise you to take 10 mg once per day.

Other form(s) of this medicine may be more suitable for children; ask your doctor or pharmacist.

If you take more ADCIRCA than you should

If you or anyone else takes more tablets than they should, tell your doctor or go to a hospital immediately, taking the medicine or pack with you. You may experience any of the side effects described in section 4.

If you forget to take ADCIRCA

Take your dose as soon as you remember if it is within 8 hours of when you should have taken your dose. Do NOT take a double dose to make up for the one that you have forgotten.

If you stop taking ADCIRCA

Do not stop taking your tablets, unless advised otherwise by your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. These effects are normally mild to moderate in nature.

If you experience any of the following side effects stop using the medicine and seek medical help immediately:

- allergic reactions including skin rashes (frequency common).
- chest pain - do not use nitrates, but seek immediate medical assistance (frequency common).

- priapism, a prolonged and possibly painful erection after taking ADCIRCA (frequency uncommon). If you have such an erection, which lasts continuously for more than 4 hours you should contact a doctor immediately.
- sudden loss of vision (rarely reported), distorted, dimmed, blurred central vision or sudden decrease of vision (frequency not known).

The following side effects have been very commonly reported in patients taking ADCIRCA (may affect more than 1 in 10 people): headache, flushing, nasal and sinus congestion (blocked nose), nausea, indigestion (including abdominal pain or discomfort), muscle aches, back pain and pain in the extremity (including limb discomfort)

Other side effects have been reported:

Common (may affect up to 1 in 10 people)

- blurred vision, low blood pressure, nosebleed, vomiting, increased or abnormal uterine bleeding, swelling of the face, acid reflux, migraine, irregular heartbeat and fainting.

Uncommon (may affect up to 1 in 100 people)

- seizures, passing memory loss, hives, excessive sweating, penile bleeding, presence of blood in semen and/or urine, high blood pressure, fast heart rate, sudden cardiac death and ringing in the ears.

PDE5 inhibitors are also used for the treatment of erectile dysfunction in men. Some side effects have been rarely reported:

- Partial, temporary or permanent decrease or loss of vision in one or both eyes and serious allergic reaction which causes swelling of the face or throat. Sudden decrease or loss of hearing has also been reported.

Some side effects have been reported in men taking tadalafil for the treatment of erectile dysfunction. These events were not seen in clinical trials for pulmonary arterial hypertension and therefore frequency is unknown:

- swelling of the eyelids, eye pain, red eyes, heart attack and stroke.

Some additional rare side effects have been reported in men taking tadalafil that were not seen in clinical trials. These include:

- distorted, dimmed, blurred central vision or sudden decrease of vision (frequency not known).

Most but not all of those men reporting fast heart rate, irregular heartbeat, heart attack, stroke and sudden cardiac death had known heart problems before taking tadalafil. It is not possible to determine whether these events were related directly to tadalafil.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store ADCIRCA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after 'EXP'. The expiry date refers to the last day of that month.

Store in the original package in order to protect from moisture. Do not store above 30°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What ADCIRCA contains

The active substance is tadalafil. Each tablet contains 20 mg of tadalafil.

The other ingredients are:

Tablet core: lactose monohydrate, croscarmellose sodium, hydroxypropylcellulose, microcrystalline cellulose, sodium laurilsulfate, magnesium stearate, see section 2 "ADCIRCA contains lactose" and "ADCIRCA contains sodium".

Film-coat: lactose monohydrate, hypromellose, triacetin, titanium dioxide (E171), iron oxide yellow (E172), iron oxide red (E172), talc.

What ADCIRCA looks like and contents of the pack

ADCIRCA 20 mg comes as orange film-coated tablets (tablets). They are in the shape of almonds and have "4467" marked on one side.

ADCIRCA 20 mg is available in blister packs containing 28 or 56 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: Eli Lilly Nederland B.V., Papendorpseweg 83, 3528 BJ Utrecht, The Netherlands

Manufacturer: Lilly S.A., Avda. de la Industria 30, 28108 Alcobendas, Madrid, Spain

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

Belgique/België/Belgien

Eli Lilly Benelux S.A./N.V.
Tél/Tel: + 32-(0)2 548 84 84

Lietuva

Eli Lilly Lietuva
Tel. +370 (5) 2649600

България

ТП "Ели Лили Недерланд" Б.В. - България
тел. + 359 2 491 41 40

Luxembourg/Luxemburg

Eli Lilly Benelux S.A./N.V.
Tél/Tel: + 32-(0)2 548 84 84

Česká republika

ELI LILLY ČR, s.r.o.
Tel: + 420 234 664 111

Magyarország

Lilly Hungária Kft.
Tel: + 36 1 328 5100

Danmark

Eli Lilly Danmark A/S
Tlf: +45 45 26 60 00

Malta

Charles de Giorgio Ltd.
Tel: + 356 25600 500

Deutschland

Lilly Deutschland GmbH
Tel. + 49-(0) 6172 273 2222

Nederland

Eli Lilly Nederland B.V.
Tel: + 31-(0) 30 60 25 800

Eesti

Eli Lilly Nederland B.V.
Tel: +372 6 817 280

Norge

Eli Lilly Norge A.S.
Tlf: + 47 22 88 18 00

Ελλάδα

ΦΑΡΜΑΣΕΡΒ-ΛΙΛΛΥ Α.Ε.Β.Ε.
Τηλ: +30 210 629 4600

España

Lilly S.A.
Tel: +34-91 663 50 00

France

Lilly France
Tél: +33-(0) 1 55 49 34 34

Hrvatska

Eli Lilly Hrvatska d.o.o.
Tel: +385 1 2350 999

Ireland

Eli Lilly and Company (Ireland) Limited
Tel: +353-(0) 1 661 4377

Ísland

Icepharma hf.
Sími: + 354 540 8000

Italia

Eli Lilly Italia S.p.A.
Tel: +39- 055 42571

Κύπρος

Phadisco Ltd
Τηλ: +357 22 715000

Latvija

Eli Lilly (Suisse) S.A Pārstāvniecība Latvijā
Tel: +371 67364000

Österreich

Eli Lilly Ges.m.b.H.
Tel: +43-(0) 1 711 780

Polska

Eli Lilly Polska Sp. z o.o.
Tel: +48 22 440 33 00

Portugal

Lilly Portugal Produtos Farmacêuticos, Lda
Tel: +351-21-4126600

România

Eli Lilly România S.R.L.
Tel: +40 21 4023000

Slovenija

Eli Lilly farmacevtska družba, d.o.o.
Tel: +386 (0)1 580 00 10

Slovenská republika

Eli Lilly Slovakia s.r.o.
Tel: +421 220 663 111

Suomi/Finland

Oy Eli Lilly Finland Ab
Puh/Tel: +358-(0) 9 85 45 250

Sverige

Eli Lilly Sweden AB
Tel: +46-(0) 8 7378800

United Kingdom (Northern Ireland)

Eli Lilly and Company (Ireland) Limited
Tel: +353-(0) 1 661 4377

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>

Package leaflet: Information for the user

ADCIRCA 2 mg/mL oral suspension tadalafil

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any of the side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See Section 4.

What is in this leaflet

1. What ADCIRCA is and what it is used for
2. What you need to know before you take ADCIRCA
3. How to take ADCIRCA
4. Possible side effects
5. How to store ADCIRCA
6. Contents of the pack and other information

1. What ADCIRCA is and what it is used for

ADCIRCA contains the active substance tadalafil.

ADCIRCA is a treatment for pulmonary arterial hypertension in adults and in children aged 2 years and above. The oral suspension is intended for paediatric patients who are not able to swallow tablets and whose dose is 20 mg.

It belongs to a group of medicines called phosphodiesterase type 5 (PDE5) inhibitors which work by helping the blood vessels around your lungs relax, improving the flow of blood into your lungs. The result of this is an improved ability to do physical activity.

2. What you need to know before you take ADCIRCA

Do not take ADCIRCA

- if you are allergic to tadalafil or any of the other ingredients (see section 6).
- if you are taking any form of nitrates such as amyl nitrite, used in the treatment of chest pain. ADCIRCA has been shown to increase the effects of these medicines. If you are taking any form of nitrate or are unsure tell your doctor.
- if you have ever had loss of vision – a condition described as “stroke of the eye” (non-arteritic anterior ischemic optic neuropathy - NAION).
- if you have had a heart attack in the last 3 months.
- if you have low blood pressure.
- if you are taking riociguat. This medicine is used to treat pulmonary arterial hypertension (i.e., high blood pressure in the lungs) and chronic thromboembolic pulmonary hypertension (i.e., high blood pressure in the lungs secondary to blood clots). PDE5 inhibitors, such as ADCIRCA, have been shown to increase the hypotensive effects of this medicine. If you are taking riociguat or are unsure tell your doctor.

Warnings and precautions

Talk to your doctor before taking ADCIRCA.

Before taking ADCIRCA, tell your doctor if you have:

- any heart problems other than your pulmonary hypertension
- problems with your blood pressure
- any hereditary eye disease
- an abnormality of red blood cells (sickle cell anaemia)
- cancer of the bone marrow (multiple myeloma)
- cancer of the blood cells (leukaemia)
- any deformation of your penis, or unwanted or persistent erections lasting more than 4 hours
- a serious liver problem
- a serious kidney problem.

If you experience sudden decrease or loss of vision or your vision is distorted, dimmed while you are taking ADCIRCA, stop taking ADCIRCA and contact your doctor immediately.

Decreased or sudden hearing loss has been noted in some patients taking tadalafil. Although it is not known if the event is directly related to tadalafil, if you experience decreased or sudden hearing loss, contact your doctor immediately.

Children and adolescents

ADCIRCA is not recommended for the treatment of pulmonary arterial hypertension in children under 2 years of age because it has not been studied in this age group.

Other medicines and ADCIRCA

Tell your doctor if you are taking, have recently taken or might take any other medicines.

Do NOT take this oral suspension if you are already taking nitrates.

Some medicines may be affected by ADCIRCA or they may affect how well ADCIRCA will work.

Tell your doctor or pharmacist if you are already taking:

- bosentan (another treatment for pulmonary arterial hypertension)
- nitrates (for chest pain)
- alpha blockers used to treat high blood pressure or prostate problems
- riociguat
- rifampicin (to treat bacterial infections)
- ketoconazole tablets (to treat fungal infections)
- ritonavir (for HIV treatment)
- tablets for erectile dysfunction (PDE5 inhibitors).

ADCIRCA with alcohol

Drinking alcohol may temporarily lower your blood pressure. If you have taken or are planning to take ADCIRCA, avoid excessive drinking (over 5 units of alcohol), since this may increase the risk of dizziness when standing up.

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. Do not take ADCIRCA when pregnant, unless it is strictly necessary and you have discussed this with your doctor.

Do not breast-feed while taking the oral suspension as it is not known if the medicine passes into human breast milk. Ask your doctor or pharmacist for advice before taking any medicine while pregnant or breast-feeding.

When dogs were treated there was reduced sperm development in the testes. A reduction in sperm was seen in some men. These effects are unlikely to lead to a lack of fertility.

Driving and using machines

Dizziness has been reported. Check carefully how you react to this medicine before driving or using any machinery.

ADCIRCA contains sodium benzoate (E211)

This medicine contains 2.1 mg sodium benzoate in each mL.

ADCIRCA contains sorbitol (E420)

This medicine contains 110.25 mg sorbitol in each mL. Sorbitol is a source of fructose. If your doctor has told you that you (or your child) have an intolerance to some sugars or if you have been diagnosed with hereditary fructose intolerance (HFI), a rare genetic disorder in which a person cannot break down fructose, talk to your doctor before you (or your child) take or receive this medicine.

ADCIRCA contains propylene glycol (E1520)

This medicine contains 3.1 mg propylene glycol in each mL.

ADCIRCA contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per 1 mL, that is to say essentially 'sodium-free'.

3. How to take ADCIRCA

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

ADCIRCA oral suspension is supplied in a bottle. This is part of a pack which also includes a dosing device containing a 10 mL oral syringe marked in 1 mL increments and a press-in-bottle adaptor. Read the instructions for use booklet, which is included in the carton for instructions on how to use the adaptor and the syringe.

The recommended dose is 10mL of oral suspension once daily for children aged 2 years and above and weighing less than 40kg.

If you have a mild or moderate liver or kidney problem, your doctor may prescribe a lower dose.

The oral suspension should be taken on an empty stomach at least 1 hour before or 2 hours after a meal.

If you take more ADCIRCA than you should

If you or anyone else takes more suspension than they should, tell your doctor or go to a hospital immediately, taking the medicine bottle with you. You may experience any of the side effects described in section 4.

If you forget to take ADCIRCA

Take your dose as soon as you remember if it is within 8 hours of when you should have taken your dose. Do NOT take a double dose to make up for the one that you have forgotten.

If you stop taking ADCIRCA

Do not stop taking your medicine, unless advised otherwise by your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. These effects are normally mild to moderate in nature.

If you experience any of the following side effects stop using the medicine and seek medical help immediately:

- allergic reactions including skin rashes (frequency common).
- chest pain - do not use nitrates, but seek immediate medical assistance (frequency common).
- priapism, a prolonged and possibly painful erection after taking ADCIRCA (frequency uncommon). If you have such an erection, which lasts continuously for more than 4 hours you should contact a doctor immediately.
- sudden loss of vision (rarely reported), distorted, dimmed, blurred central vision or sudden decrease of vision (frequency not known).

The following side effects have been very commonly reported in patients taking ADCIRCA (may affect more than 1 in 10 people): headache, flushing, nasal and sinus congestion (blocked nose), nausea, indigestion (including abdominal pain or discomfort), muscle aches, back pain and pain in the extremity (including limb discomfort)

Other side effects have been reported:

Common (may affect up to 1 in 10 people)

- blurred vision, low blood pressure, nosebleed, vomiting, increased or abnormal uterine bleeding, swelling of the face, acid reflux, migraine, irregular heartbeat and fainting.

Uncommon (may affect up to 1 in 100 people)

- seizures, passing memory loss, hives, excessive sweating, penile bleeding, presence of blood in semen and/or urine, high blood pressure, fast heart rate, sudden cardiac death and ringing in the ears.

PDE5 inhibitors are also used for the treatment of erectile dysfunction in men. Some side effects have been rarely reported:

- Partial, temporary or permanent decrease or loss of vision in one or both eyes and serious allergic reaction which causes swelling of the face or throat. Sudden decrease or loss of hearing has also been reported.

Some side effects have been reported in men taking tadalafil for the treatment of erectile dysfunction. These events were not seen in clinical trials for pulmonary arterial hypertension and therefore frequency is unknown:

- swelling of the eyelids, eye pain, red eyes, heart attack and stroke.

Some additional rare side effects have been reported in men taking tadalafil that were not seen in clinical trials. These include:

- distorted, dimmed, blurred central vision or sudden decrease of vision (frequency not known).

Most but not all of those men reporting fast heart rate, irregular heartbeat, heart attack, stroke and sudden cardiac death had known heart problems before taking tadalafil. It is not possible to determine whether these events were related directly to tadalafil.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via **the national reporting system** listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store ADCIRCA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and bottle after 'EXP'. The expiry date refers to the last day of that month.

Do not use the medicine if the bottle has been open for more than 110 days. This medicine does not require any special storage conditions.

Store in the original package. Store the bottle upright.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What ADCIRCA contains

The active substance is tadalafil. Each mL contains 2 mg of tadalafil.

The other ingredients are xanthan gum, microcrystalline cellulose, carmellose sodium, citric acid, sodium citrate, sodium benzoate (E211), silica (colloidal anhydrous), sorbitol (E420) (liquid crystallising), polysorbate 80, sucralose, simethicone emulsion (simethicone, methylcellulose, sorbic acid, purified water), artificial cherry flavour (contains propylene glycol (E1520) and water. See section 2 “ADCIRCA contains” for more information about sorbitol, sodium benzoate, propylene glycol and sodium.

What ADCIRCA looks like and contents of the pack

ADCIRCA 2 mg/mL is a white to practically white oral suspension.

ADCIRCA is packaged in a bottle containing 220 mL of oral suspension with a peelable seal and child-resistant closure, inside a carton. Each carton contains one bottle, a 10 mL graduated syringe with 1 mL graduations and a press-in-bottle adaptor.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: Eli Lilly Nederland B.V., Papendorpseweg 83, 3528 BJ Utrecht, The Netherlands

Manufacturer: Lilly S.A., Avda. de la Industria 30, 28108 Alcobendas, Madrid, Spain

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

Belgique/België/Belgien

Eli Lilly Benelux S.A./N.V.
Tél/Tel: + 32-(0)2 548 84 84

Lietuva

Eli Lilly Lietuva
Tel. +370 (5) 2649600

България

ТП "Ели Лили Недерланд" Б.В. - България
тел. + 359 2 491 41 40

Luxembourg/Luxemburg

Eli Lilly Benelux S.A./N.V.
Tél/Tel: + 32-(0)2 548 84 84

Česká republika

ELI LILLY ČR, s.r.o.
Tel: + 420 234 664 111

Magyarország

Lilly Hungária Kft.
Tel: + 36 1 328 5100

Danmark

Eli Lilly Danmark A/S
Tlf: +45 45 26 60 00

Malta

Charles de Giorgio Ltd.
Tel: + 356 25600 500

Deutschland

Lilly Deutschland GmbH
Tel. + 49-(0) 6172 273 2222

Eesti

Eli Lilly Nederland B.V.
Tel: +372 6 817 280

Ελλάδα

ΦΑΡΜΑΣΕΡΒ-ΛΙΛΛΥ Α.Ε.Β.Ε.
Τηλ: +30 210 629 4600

España

Lilly S.A.
Tel: + 34-91 663 50 00

France

Lilly France
Tél: +33-(0) 1 55 49 34 34

Hrvatska

Eli Lilly Hrvatska d.o.o.
Tel: +385 1 2350 999

Ireland

Eli Lilly and Company (Ireland) Limited
Tel: + 353-(0) 1 661 4377

Ísland

Icepharma hf.
Sími: + 354 540 8000

Italia

Eli Lilly Italia S.p.A.
Tel: + 39- 055 42571

Κύπρος

Phadisco Ltd
Τηλ: +357 22 715000

Latvija

Eli Lilly (Suisse) S.A Pārstāvniecība Latvijā
Tel: +371 67364000

Nederland

Eli Lilly Nederland B.V.
Tel: + 31-(0) 30 60 25 800

Norge

Eli Lilly Norge A.S.
Tlf: + 47 22 88 18 00

Österreich

Eli Lilly Ges.m.b.H.
Tel: + 43-(0) 1 711 780

Polska

Eli Lilly Polska Sp. z o.o.
Tel: +48 22 440 33 00

Portugal

Lilly Portugal Produtos Farmacêuticos, Lda
Tel: + 351-21-4126600

România

Eli Lilly România S.R.L.
Tel: + 40 21 4023000

Slovenija

Eli Lilly farmacevtska družba, d.o.o.
Tel: +386 (0)1 580 00 10

Slovenská republika

Eli Lilly Slovakia s.r.o.
Tel: + 421 220 663 111

Suomi/Finland

Oy Eli Lilly Finland Ab
Puh/Tel: + 358-(0) 9 85 45 250

Sverige

Eli Lilly Sweden AB
Tel: + 46-(0) 8 7378800

United Kingdom (Northern Ireland)

Eli Lilly and Company (Ireland) Limited
Tel: + 353-(0) 1 661 4377

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>

INSTRUCTIONS FOR USE
ADCIRCA 2mg/mL oral suspension
tadalafil

Before you use ADCIRCA oral suspension, read and carefully follow all the step-by-step instructions.

This “Instructions for Use” contains information on how to use ADCIRCA oral suspension.



IMPORTANT INFORMATION YOU NEED TO KNOW BEFORE USING ADCIRCA ORAL SUSPENSION



The adaptor represents a CHOKING HAZARD – small parts. Do not attach the oral syringe to the adaptor until the adaptor is fully inserted into the bottle. It must be inserted completely into the bottle for safe use. To be used only under adult supervision.

Do not let your child take the medicine without your help.

Do not use if bottle, seal, adaptor, or oral syringe is damaged.

Do not use the medicine if the bottle has been open for more than **110 days**. See the **Disposal** section to find out what to do with the medicine you don't use.

Record date of first opening of bottle here: _____

Do not wash the oral syringe with soap or detergent. Please see steps 4b - 4c for cleaning instructions.

Do not put the oral syringe in the dishwasher. The syringe may not work as well as it should.

Use a new oral syringe after **30 days**.

It is not recommended to mix the medicine with food or water. It may affect the taste or prevent the receiving full dose.

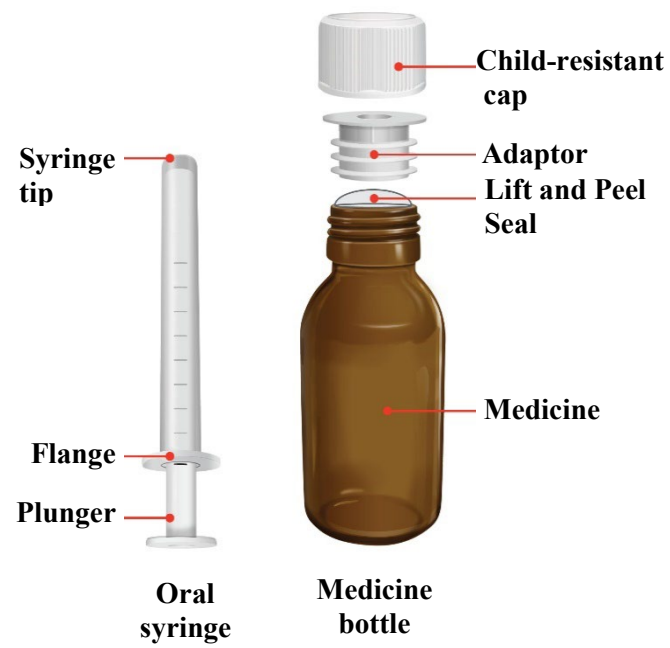
Give **ADCIRCA** oral suspension only using the oral syringe supplied with the medicine.

The medicine is white. Air gaps may be difficult to see in the oral syringe when preparing the dose and may result in an incorrect dose.



In case of overdose, contact your doctor, pharmacist or nurse immediately. Quick medical attention is important for adults and children even if you do not notice any signs or symptoms.

Parts of the ADCIRCA oral suspension administration system



STEP 1: PREPARE THE BOTTLE

1a



Gather the medicine bottle and adaptor.
Wash your hands with soap and water.

1b



Remove the cap from the bottle.

Firmly push the cap down while twisting it counter clockwise.
Remove the cap from the bottle.

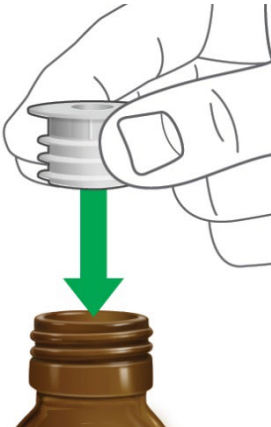
1c



Prior to first use only, remove the lift and peel seal.

Make sure the seal is completely removed.

1d



Prior to the first use only, push the adaptor all the way down into the opening of the bottle.



The adaptor represents a CHOKING HAZARD – small parts. It must be inserted completely into the bottle for safe use.

Do not attach the oral syringe to the adaptor until the adaptor is fully inserted into the bottle.

Do not twist the adaptor.

1e



Screw the cap back on the bottle tightly.

The cap will fit over the adaptor.

STEP 2: PREPARE THE DOSE

2a



Gather the medicine bottle with the adaptor inserted and oral syringe.

Make sure the cap is on tightly.

Wash your hands with soap and water.

2b



Shake the bottle.

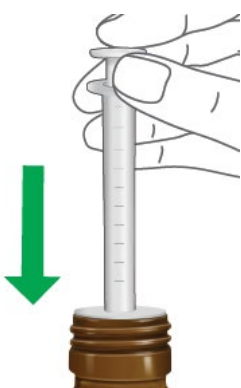
Shake the medicine bottle well for at least 10 seconds **before each use** to fully mix the suspension.

Shake again if the bottle sits longer than 15 minutes.

2c

Remove the cap from the bottle.

2d



Firmly insert the oral syringe into the opening of the adaptor.

Make sure that the syringe tip is fully inside the adaptor and the plunger is pushed all the way to the syringe tip.

2e

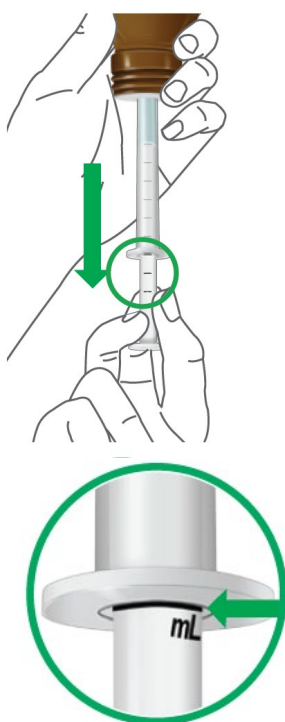


Turn the bottle with the oral syringe upside down while holding the syringe in place.

Make sure that the bottle is upside down.

Make sure the oral syringe stays completely inserted in the adaptor.

2f



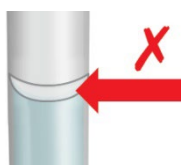
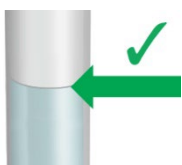
Draw the dose.

Slowly pull the plunger down until the mL graduation mark is visible below the bottom of the flange for the dose prescribed for your child.

The graduation mark is located on the plunger of the oral syringe.

Make sure the top edge of the graduation mark is aligned to the bottom of the flange.

2g



Turn the bottle upright and check closely for air gaps in the oral syringe.



An air gap may result in an incorrect dose.

The medicine is white, the same colour as the oral syringe. Air gaps may be difficult to see.

If there is an air gap, empty the medicine back into the bottle and repeat steps 2e through 2g.

2h



Remove the oral syringe from the bottle.

Do not touch the plunger.

STEP 3: GIVE THE DOSE



Put the oral syringe into a corner of your child's mouth. Tell your child not to bite the syringe.

Do not squirt the medicine into the back of the throat. Slowly and gently push down the plunger to the end of the syringe so that all of the medicine is in your child's mouth. Make sure your child swallows all of the medicine.

STEP 4: CLEAN UP

4a



Screw the cap back on the bottle tightly.
Do not remove the adaptor. The cap will fit over it.

4b



Fill the oral syringe with clean water.



Do not wash the oral syringe with soap or detergent.



Do not remove the plunger from the oral syringe.

Fill a cup with clean water, insert the oral syringe, and pull the plunger up to **fill the syringe with water**.

4c



Push the plunger down and squirt the water into the cup or into the sink.

Make sure to remove the water from the oral syringe. Shake excess water from the syringe and dry it with a paper towel.

Store the oral syringe and bottle in the original carton.

Wash your hands with soap and water.

DISPOSAL OF MEDICINE

Do not throw away any medicines via wastewater or household water. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

DISPOSAL OF SYRINGE

Ask your doctor, pharmacist or nurse how to dispose of your syringe.

HOW TO STORE YOUR MEDICINE

This medicine does not require any special storage conditions

Store the bottle standing upright.

Keep the bottle and oral syringe out of sight and reach of children.

COMMONLY ASKED QUESTIONS

Q. What if I see air gaps in my oral syringe?

A. Do not give the medicine. Air gaps may result in an incorrect dose. Empty the medicine back into the bottle and repeat steps 2c through 2g.

Q. What if there is too much medicine in the oral syringe?

A. Keep the syringe tip in the bottle. Hold the bottle upright. Push the plunger down until the correct dose is in the oral syringe.

Q. What if there is not enough medicine in the oral syringe?

A. Keep the syringe tip in the bottle. Hold the bottle upside down. Pull the plunger down until the correct dose is in the oral syringe.

Q. What if I get some medicine in my eye or in my child's eye?

A. Flush the eye immediately with water and call your doctor, pharmacist or nurse. As soon as possible, wash hands and surfaces that may have come in contact with the medicine.

Q. How do I travel with this medicine?

A. Make sure you have enough medicine for the entire trip. Take the oral syringe and medicine in its original container. Store the medicine in a safe place upright.

Q. Can I mix this medicine with food or water before I give it to my child?

A. It is not recommended to mix this medicine with food or water. This can affect the way the medicine tastes or prevent a full dose. You can give your child a glass of water to drink after he or she takes the entire dose of medicine.

Q. What if my child spits up the medicine?

A. **Do not** give additional medicine to your child. Contact your doctor, pharmacist or nurse.

Q. What if my child does not swallow all of the medicine?

A. Contact your doctor, pharmacist or nurse.

Q. What if my child swallows too much medicine?

A. Immediately contact your doctor, pharmacist or nurse.

FOR QUESTIONS OR MORE INFORMATION ABOUT ADCIRCA ORAL SUSPENSION

For questions or more information about ADCIRCA

- Call your doctor, pharmacist or nurse
- Call **Lilly**

Read the full package leaflet for ADCIRCA inside this box to learn more about your medicine.

For questions or more information about ADCIRCA oral suspension

If you have any questions or problems with your oral suspension syringe, contact **Lilly** or your doctor, pharmacist or nurse for assistance. Report all MEDICAL DEVICE COMPLAINTS or UNDESIRABLE SIDE EFFECTS, including SUSPECTED SERIOUS INCIDENTS, to **Lilly**.

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for tadalafil, the scientific conclusions of the CHMP are as follows:

In view of available data on serous central chorioretinopathy from the literature and spontaneous reports including in some cases a close temporal relationship, a positive de-challenge and/or re-challenge and in view of a plausible mechanism of action, the PRAC considers a causal relationship between tadalafil and central serous chorioretinopathy is at least a reasonable possibility. The PRAC concluded that the product information of products containing tadalafil should be amended accordingly.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the Marketing Authorisation(s)

On the basis of the scientific conclusions for tadalafil the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing tadalafil is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the Marketing Authorisation(s) should be varied.