Confidential Information

EU Risk Management Plan (Version 8.2)

Global Patient Safety
Signatory information is available on request.
Initial EU Risk Management Plan electronically approved by Lilly on date provided below.
Revised Risk Management Plan (Version 6) Approved by Lilly: 07 Jun 2013
Revised Risk Management Plan (Version 7) Approved by Lilly: 01 May 2015
Revised Risk Management Plan (Version 8) Approved by Lilly: 22 Jun 2016
Revised Risk Management Plan (Version 8.1) Approved by Lilly: 06 Oct 2016

Risk Management Plan (Version 8.2) electronically approved by Lilly on date provided below.

Approval Date: 07-Dec-2016 GMT

Active Substance(s) (INN or common name):	Tadalafil (pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-,(6R,12aR)-)
Pharmaco-therapeutic group (ATC Code):	Urologicals, drugs used in erectile dysfunction, ATC code: G04BE08
Name of Marketing Authorisation Holder or Applicant:	Eli Lilly and Company
Number of medicinal products to which this RMP refers:	2
Product(s) concerned (brand name[s]):	CIALIS®, ADCIRCA®, Tadalafil Lilly

Data lock point for this RMP	31 March 2016
Version number:	Version 8.2
Date of final sign off:	Approval date on page 1

Part I. Product Overview

Administrative Information on the RMP

Part	Module/Annex	Date last updated for submission (sign-off date)	Version number of RMP when last submitted
Part II Safety Specification	**SI** Epidemiology of the indication and target population(s)	01 May 2015	8.1
	SII Non-clinical part of the safety specification	22 June 2016	8.1
	SIII Clinical trial exposure	01 May 2015	8.1
	SIV Populations not studied in clinical trials	22 June 2016	8.1
	SV Post-authorisation experience	22 June 2016	8.1
	SVI Additional EU requirements for the safety specification	22 June 2016	8.1
	SVII Important identified and potential risks	See date on cover page	8.1
	SVIII Summary of the Safety Concerns	See date on cover page	8.1
Part III Pharmacovigilance Plan		See date on cover page	8.1
Part IV Plans for post-authorisation efficacy studies		22 June 2016	8.1
Part V EU Risk minimisation measures		See date on cover page	8.1
Part VI Summary of Activities in the RMP by Product		See date on cover page	8.1
Part VII Annexes		--	--
	Annex 1 EudraVigilance Interface	--	--
	Annex 2 SmPC and Package Leaflet	22 June 2016	8.1
	Annex 3 Worldwide Marketing Status by Country	22 June 2016	8.1
	Annex 4 Synopsis of Ongoing and Completed EU Clinical Trial Programme	22 June 2016	8.1
	Annex 5 Synopsis of Ongoing and Completed Pharmacoepidemiological Study Programme	22 June 2016	8.1
	Annex 6 Protocols for Proposed and Ongoing Studies in Categories 1-3 of the Section "Summary Table of Additional Pharmacovigilance Activities" in RMP Part III	22 June 2016	8.1
	Annex 7 Specific Adverse Event Follow-Up Forms	07 Jun 2013	8.1
	Annex 8 Protocols for Proposed and Ongoing Studies in RMP Part IV	07 Jun 2013	8.1
	Annex 9 Newly available study reports for RMP Parts III - IV	22 June 2016	8.1

Part	Module/Annex	Date last updated for submission (sign-off date)	Version number of RMP when last submitted
	Annex 10 Details of Proposed Additional Risk Minimisation Measures (if applicable)	07 Jun 2013	8.1
	Annex 11 Mock-up of Proposed Additional EU Risk Minimisation Measures (if applicable)	07 Jun 2013	8.1
	Annex 12 Other Supporting Data (including Referenced Material)	22 June 2016	8.1

Abbreviations: EU = European Union; SmPC = Summary of Medicinal Product Characteristics; RMP = risk management plan.

QPPV name:	**Name on file.**
QPPV signature:	**Signature on file.**
Contact person for this RMP:	**Please refer to the cover letter accompanying this RMP for Contact Information.**
Email address or telephone number of contact person:	

Overview of Versions

Version number of last agreed-upon RMP:	Tadalafil (CIALIS, ADCIRCA)-Version 8
Version number	Version 8.2
Agreed within	Centralised procedure

Current RMP Versions under Evaluation

Not applicable. There are no other versions currently submitted for evaluation.

Invented name(s) in the European Economic Area (EEA)	CIALIS®, ADCIRCA®, Tadalafil Lilly
Authorisation procedure	Centralised procedure
Brief description of the product • Chemical class	Phosphodiesterase type 5 (PDE5) inhibitor
• Summary of mode of action	PDE5 inhibitors block hydrolysis of cyclic guanosine monophosphate (cGMP) leading to relaxation of smooth muscle
• Important information about its composition (e.g., origin of active substance biological, relevant adjuvants or residues for vaccines)	Chemical origin of active substance tadalafil. Excipients included with a known effect: lactose (as monohydrate)
Indications in the EEA Current	**CIALIS (5 mg, 10 mg, and 20 mg):**

	On-demand treatment of erectile dysfunction in adult males. **CIALIS (2.5, 5 mg):** Once-a-day treatment of erectile dysfunction in adult males. **CIALIS (5 mg):** Treatment of the signs and symptoms of benign prostatic hyperplasia (BPH) in adult males. **ADCIRCA (40 mg** (two 20-mg tablets)): ADCIRCA is indicated in adults for the treatment of pulmonary arterial hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity.
Proposed	Not applicable
Posology and route of administration in the EEA Current	**CIALIS Posology:** *On-demand erectile dysfunction* In general, the recommended dose is 10 mg taken prior to anticipated sexual activity and with or without food. In those patients in whom tadalafil 10 mg does not produce an adequate effect, 20 mg might be tried. It may be taken at least 30 minutes prior to sexual activity. The maximum dose frequency is once per day. Tadalafil 10 and 20 mg is intended for use prior to anticipated sexual activity and it is not recommended for continuous daily use. *Once-a-day erectile dysfunction* In patients who anticipate a frequent use of CIALIS (i.e., at least twice weekly) a once-daily regimen with the lowest dose of CIALIS might be considered suitable, based on patient choice and the physician's judgement. In these patients, the recommended dose is 5 mg taken once a day at approximately the same time of day. The dose may be decreased to 2.5 mg once a day based on individual tolerability. The appropriateness of continued use of the daily regimen should be reassessed periodically. *BPH in adult men* The recommended dose is 5 mg, taken at approximately the same time every day with or without food. For adult men being treated for both BPH and erectile dysfunction, the recommended dose is also 5 mg taken at approximately the same time every day. Patients who are unable to tolerate tadalafil 5 mg for the treatment of BPH should consider an alternative therapy as the efficacy of tadalafil 2.5 mg for the treatment of BPH has not been demonstrated. **ADCIRCA Posology** The recommended dose is 40 mg (2 x 20 mg) taken once daily with or without food. **Route of administration**

	Tadalafil as CIALIS and ADCIRCA is for oral use.
Proposed	Not applicable
Pharmaceutical form(s) and strengths Current	**CIALIS** Film-coated tablets: 2.5 mg, 5 mg, 10 mg, and 20 mg **ADCIRCA** Film-coated tablets: 20 mg
Proposed	Not applicable

Country and date of first authorisation worldwide	Australia	15 October 2002
Country and date of first launch worldwide	Australia	03 February 2003
Country and date of first authorisation in the EEA	EU	12 November 2002
Is the product subject to additional monitoring in the EU?	Yes ☐	No X

Part II. Safety Specification

Module SI. Epidemiology of the Indication(s) and Target Population

SI.1. Erectile Dysfunction (Cialis,Tadalafil Lilly)

SI.1.1. Epidemiology of the Disease

SI.1.1.1. Incidence and Prevalence of Target Indication

The incidence of erectile dysfunction (ED) is not well reported in the European Union (EU). In the United States, the crude incidence of ED was reported to be 26/1000 patient years (PYs) in men 40 to 69 years of age. The incidence of ED increases with age: 12.4/1000 PY in men 40 to 49 years of age, 29.8/1000 PY in men 50 to 59 years of age, and 46.4/1000 PY in men 60 to 69 years of age (Johannes et al. 2000).

The rates of ED vary by country, as reported in a multinational European study that assessed the prevalence of ED from 2003 to 2005: Spain (23%), Sweden (24%), Italy (25%), Hungary (30%), Belgium (32%), United Kingdom (31%), Poland (36%), and Estonia (43%) (Corona et al. 2010a).

The prevalence of ED increases with age: 40-44 years: 9%, 45-49 years: 12%, 50-54 years: 18%, 55-59 years: 29%, 60-64 years: 38%, and 65-70 years: 54% (Nicolosi et al. 2003). In the United States, the overall prevalence of ED in 2011 was 37.7%, with younger men reporting higher rates of mild ED and older men reporting higher rates of severe ED (Shaeer and Shaeer 2012). Differences in the definitions of ED and in the methodology used in the studies, together with varying cultural perceptions of ED, may explain the variation in the reported prevalence rates (Lyseng-Williamson and Wagstaff 2002).

SI.1.1.2. Risk Factors for the Disease

Common risk factors associated with sexual dysfunction include the health status of the individual, the presence of diabetes mellitus and cardiovascular (CV) disease, concurrence of other genitourinary disease, psychiatric/psychological disorders, other chronic diseases, socio-demographic conditions, as well as smoking and hormonal factors (Lewis et al. 2010). Age is also a risk factor (Lyseng-Williams 2002), as the prevalence and severity of ED progressively increases with advancing age. In an international survey study, men aged 70-75 years have a 14-fold higher relative risk for ED compared to respondents in their twenties (Shabsigh et al. 2005). Diabetes mellitus and hypertension were reported to increase ED risk by 1.38 and 1.60, respectively (Sun and Swindle 2005; Sun et al. 2006). History of CV events have been widely studied as ED risk factors, including prior CV events (relative risk [RR] 1.35) (Vlachopoulos et al. 2013), heart failure (RR 8.00), atrioventricular and left bundle branch block (RR 6.62), peripheral atherosclerosis (RR 2.47), peripheral vascular disease (RR 1.92), acute myocardial infarction (RR 1.66), ischaemic heart disease (RR 1.60), and "other" cardiovascular disease (RR 1.26) (Banks et al. 2013).

SI.1.1.3. Mortality and Morbidity in Target Indication

A worldwide review and meta-analysis through 2012 found the pooled RR for all-cause mortality to be 1.25 for those with ED compared to those without ED (Vlachopoulos et al. 2013). Among men with no prior CV disease in an Australian 2006-2009 cohort >45 years of age (N=95,038), severe ED was associated with a RR of 1.93 for all-cause mortality (Banks et al. 2013). A United States study reported a higher incidence rate of any CV events among patients with ED compared to patients without ED, and the unadjusted incidence rate was 0.024 vs. 0.015 per person-year, respectively (Thompson et al. 2005).

SI.1.1.4. Demographic Profile of Target Population

Erectile dysfunction is the most frequently diagnosed sexual dysfunction in the older male population (Alberson et al. 2012), with 52% of males between the ages of 40 and 70 years having some degree of ED. The incidence, prevalence, and severity of ED increases progressively with age; the majority of men with ED in the United States were in age groups 45 to 55 years (34%-35.7%) and 55 to 65 years (34.4%-35.3%) (Feldman et al. 1994; Johannes et al. 2000; Sun and Swindle 2005; Cameron et al. 2006). In a multinational study, 73% of men with ED were ≥50 years of age (Shabsigh et al. 2008).

In a United States study that assessed ED by race, 41.5% of men with ED were white, 24.4% were black, and 19.9% were Hispanic (Laumann et al. 2007).

The incidence of self-reported ED is inversely related to baseline education and income (Johannes et al. 2000). In the United States, the incidence (per 1000 PYs) of ED was 32.9 for high school or less, 30.9 for some college or bachelor's degree, and 16.8 for some graduate school or a graduate degree (Johannes et al. 2000).

SI.1.1.5. Main Treatment Options

Pharmacologic Therapies

PDE 5 Inhibitors: Oral PDE5 inhibitors, such as sildenafil and vardenafil, are approved for on-demand treatment of ED. Two recent review articles noted that the PDE5 inhibitors are safe and effective, with reported efficacy rates of 60 to 70% (Costa et al. 2009; Hatzimouratidis and Hatzichristou 2005).

Intracavernosal Injections: Intracavernosal injections are considered second-line therapy in patients for whom oral therapy is ineffective. Drugs administered in this manner include papaverine, prostaglandin E1 (PGE1), and phentolamine, which may be used alone or in combination. These injection therapies are effective in treating ED, resulting in full erections in 70%-80% of patients as measured with various endpoints, including stiffness measured by Rigiscan® and successful sexual intercourse (Lea et al. 1996; Hatzimouratidis and Hatzichristou 2005).

Intraurethral Therapies: Intraurethral therapies, such as the medicated urethral system for erection (MUSE) that administers alprostadil, result in and maintain erections in up to 55% of patients (Hatzimouratidis and Hatzichristou 2005).

SI.1.2. Concomitant Medication(s) in the Target Population

Concomitant medications in patients with ED include oral anti-hyperglycaemic agents, insulin, antidepressants, anti-hypertensives and CV agents such as beta-blockers, angiotensin-converting-enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs), diuretics, calcium channel blockers, and statins (Aversa et al. 2004; Blumentals et al. 2004; Lewis et al. 2005; Corona et al. 2010b).

SI.1.3. Important Co-morbidities Found in the Target Population

Hypertension: Hypertension is present in 38% to 42% of men with ED, and approximately 35% of men with hypertension have some degree of ED (Nehra 2009). In a United Kingdom population of males >18 years of age with ED, the 3-month incidence of hypertension was 1.35% compared to 0.95% in age-matched controls (Kirby et al. 2011). By comparison, the 6-month incidence in a United States population >18 years of age was 6.68% in the ED population and 1.8% in age-matched controls (Cameron et al. 2006).

Other cross-national studies showed the prevalence ranging from 19.93% in the United Kingdom (Kirby et al. 2011) to 27.3% in Italy (Boddi et al. 2012). In a cross-national survey of males 20 to 75 years of age, the prevalence of hypertension also increased with ED severity, with 25% occurring in patients with mild ED and 39% to 42% in patients with moderate to severe ED (Shabsigh et al. 2005).

Hyperlipidaemia: The overall incidence of hypercholesterolaemia in a United Kingdom ED population ≥18 years of age was 1.04% (0.43% controls) for a 3-month period, compared with an incidence of 8.48% (1.81% controls) for a 6-month period in a United States ED population ≥18 years of age (Cameron et al. 2006; Kirby et al. 2011).

The prevalence of hyperlipidaemia increased with ED severity, with 25% to 27% occurring in the mild/moderate ED population and 35% to 38% in the moderate/severe population in a cross-national survey of patients 20-75 years of age (Shabsigh et al. 2005). Overall, the cross-national prevalence was 42.5% in 2004 (Shabsigh et al. 2008) and ranged from 19% to 20% in France, Spain, and the United Kingdom to 35% to 43% in Germany and the United States (Shabsigh et al. 2005).

Diabetes Mellitus (DM): The overall incidence of DM in a United Kingdom ED population ≥18 years of age was 0.69% for a 3-month follow-up period (Kirby et al. 2011). The overall incidence was 2.51% for a 6-month follow up period in United States men with ED ≥18 years of age (Cameron et al. 2006).

The worldwide prevalence of DM was 20.7% (Shabsigh et al. 2008). By region, the prevalence ranged from 6% for France and Spain to 11% for the United Kingdom and up to 17% to 20% for the United States and Italy (Shabsigh et al. 2005). The prevalence of DM increased with ED severity: 8%-11% occurring in the mild/moderate ED population and 16%-24% in the moderate/ severe population 20 to 75 years of age (Shabsigh et al. 2005). The prevalence of DM in men with ED in the United States increased with age: 2.6% in the age group 18-25 years, 28.7% among men 66 to 75 years of age, and 26.1% among men ≥86 years of age (Sun et al. 2006).

Cardiovascular Disease (CVD): The yearly incidence rate of CVD in Italy during 2000-2007 was 0.23% in an ED population 17 to 88 years of age (Corona et al. 2010b). In the United States, the incidence of ED was statistically significantly associated with subsequent angina, myocardial infarction, and stroke. The unadjusted risk of an incident CV event among men with ED was 0.024 per person-year compared to 0.015 per person-year in men without ED, and was comprised of angina, myocardial infarction, myocardial infarction or angina, stroke, congestive heart failure, transient ischemic attack, and arrhythmia (Thompson et al. 2005). The incidence of CV disease increased with age among individuals with ED, with 1.06% of men 18 to 25 years of age having CV disease, compared to 11.94% of men >85 years of age during a 6-month follow-up period (Cameron et al. 2006).

Prevalence of CV disease increased by ED severity, with 7% to 10% occurring with mild/ moderate ED, 16% with moderate ED, and 34% with severe ED in a cross-national survey of men 20-75 years of age (Shabsigh et al. 2005). Overall, cross-national prevalence of angina was 25.7% in 2004 and 11.6% for coronary heart disease (Shabsigh et al. 2008; Corona et al. 2010b). Heart disease ranged from 5% to 8% in Spain, France, and Italy, and rose to 14% in Germany and 18% in the United Kingdom and United States (Shabsigh et al. 2005). Boddi et al. (2012) found the prevalence of CV disease to be 12% in an Italian cohort 17 to 88 years of age (Boddi et al. 2012).

SI.2. Benign Prostatic Hyperplasia (Cialis, Tadalafil Lilly)

SI.2.1. Epidemiology of the Disease

SI.2.1.1. Incidence and Prevalence of Target Indication

Benign prostatic hyperplasia (BPH) is one of the most common diseases of aging men. In the United Kingdom, it is estimated to affect approximately 3.2 million middle-aged and older men (Kirby et al. 2010). Benign prostatic hyperplasia is present in nearly 3 out of 4 men in the United States who are 60 to 69 years of age (Wei et al. 2005). The initial development of BPH begins as early as 25 to 30 years of age (Oesterling 1996). Rates of BPH increase with age (Verhamme et al. 2002), with the risk of total BPH increasing 4% with each additional year of age (Kristal et al. 2007).

The overall incidence of BPH in the Netherlands was 15.46 per 1000 man-years in men ≥45 years of age and increased with age, with 2.96 per 1000 man-years for ages 45-49 years and 38.30 for ages 75-79 (Verhamme et al. 2002).

In a Dutch cohort (1995-2000), the overall prevalence of BPH/LUTS (lower urinary tract symptoms) was 10.3% with 2.7% in the 40-45 year group and increased with age until a maximum of 24% by age 80 (Verhamme et al. 2002).

SI.2.1.2. Risk Factors for the Disease

Age is the major risk factor for BPH. Over half of men develop BPH by age 60 and about 85% of men have BPH by age 85. It is uncommon for BPH to cause symptoms before age 40 (Roehrborn 2005).

SI.2.1.3. Mortality and Morbidity in Target Indication

Mortality from BPH is essentially due to complications of therapy. Using death certificate data and the World Health Organization (WHO) database for the period 1955–1998, the overall mortality from complications of BPH therapy in the EU fell from 5.9 per million in the early 1950s to 3.5 per million in the early 1990s. Deaths from complications of BPH therapy in men 45-65 years of age are rare. Declines in mortality from BPH treatment have also been observed in the United States and Japan, with 1990 rates of 1.8 per million in the United States and 1.4 per million in Japan (Levi et al. 2003). These trends are most likely due to improvements in understanding the disease and availability of more effective medical treatment (Levi et al. 2003).

SI.2.1.4. Demographic Profile of Target Population

The incidence of BPH increases with age, body mass index, and waist-to-hip ratio. By race, the risk of BPH is 41% higher for Black and Hispanic men compared to White men, and for severe BPH these increases were 68% and 59%, respectively (Kristal et al. 2007). The presence of histologically-identifiable BPH, which has been examined in several autopsy studies around the world, is approximately 10% for men in their 30s, 20% for men in their 40s, 50% to 60% for men in their 60s, and 80% to 90% for men in their 70s and 80s (Berry et al. 1984; Oesterling 1996; Roehrborn 2005).

SI.2.1.5. Main Treatment Options

Alpha Adrenergic Blockers: Men with bothersome moderate-to-severe LUTS may be treated with alpha 1-selective alpha blockers (including tamsulosin, alfuzosin, doxazosin, terazosin, and silodosin) and, broadly speaking, they all have similar efficacy. Studies of 3 to 9 months in duration showed a symptom score improvement of approximately 2 to 2.5 points over placebo (Oelke et al. 2013; AUA BPH Guidelines [WWW]).

5 Alpha-Reductase Inhibitors (5-ARIs): Men with demonstrable prostatic enlargement and bothersome LUTS may be treated with 5-ARIs (including finasteride and dutasteride). Dutasteride has been found to provide symptom improvement of approximately 2 points over placebo, and to reduce the risk of acute urinary retention and surgery by 57% and 48%, respectively (AUA BPH Guidelines [WWW]).

Alpha Blocker and 5-ARI Combination Therapy: In some patients, combination therapy with an alpha blocker and 5-ARI may be considered appropriate. The only approved fixed combination therapy for the treatment of BPH is dutasteride/tamsulosin. In the CombAT study, the International Prostate Symptom Score adjusted mean difference between combination therapy and tamsulosin at month 24 was -1.8, and the adjusted mean difference between combination therapy and dutasteride was -1.3. Combination therapy resulted in significantly greater improvements in symptoms versus dutasteride alone from month 3, and from month 9 for tamsulosin alone (Roehrborn et al. 2008).

Nonpharmacologic Therapies

Watchful Waiting: Watchful waiting is suitable for men with mild or non-bothersome LUTS, and includes education, reassurance, lifestyle advice, and periodic monitoring.

Surgical Treatment: Minimally invasive surgical treatments such as transurethral resection of the prostate (TURP) or transurethral incision of the prostate (TUIP) have been shown to reduce benign prostatic obstruction (BPO) and secondarily, LUTS.

Other Therapies

Transurethral microwave therapy (TUMT), transurethral needle ablation (TUNA), or holmium laser enucleation of the prostate are additional methods that are in current use for the removal of prostatic tissue and result in reduction of LUTS.

SI.2.2. Concomitant Medication(s) in the Target Population

Concomitant medications taken by patients with BPH include beta-blockers, thiazide or other diuretics, calcium-channel blockers, ACE-inhibitors, other antihypertensive drugs, nitrates, aspirin, non-aspirin non-steroidal anti-inflammatory drugs, angiotensin-receptor blockers, statins, insulin and oral diabetic agents (Broderick et al. 2010).

SI.2.3. Important Co-Morbidities Found in the Target Population

Hypertension: The incidence rates for hypertension in BPH patients are not well documented. In a cross national study in the EU, the prevalence of hypertension in patients with BPH/LUTS was 36.5% overall, ranging between 29.5% in Poland and 43.7% in France (Hutchison et al. 2006). In the United States MMAS (Massachusetts Male Aging Study) study, the prevalence of having both comorbid conditions of BPH and hypertension was 30.3% (Meigs et al. 2001). In 2 other United States studies, the prevalence ranged from 28.8% in the BPH population to 53% in the BPH/LUTS population (Roehrborn et al. 2007; Broderick et al. 2010).

Cardiovascular Disease (CVD): The incidence of CV disease in BPH patients is not well documented in the EU. One United States study found incident CV disease (including hypertension) in 24.6% of the total BPH population >35 years of age (Shah et al. 2007).

Two other studies have reported the prevalence of CV events in the EU. The Trans European Research study found the prevalence of coronary heart disease to be 12.5% (ranging from 7.7% in Italy to 20.7% in the United Kingdom); 3.8% for heart failure (2.2% in Poland to 6.2% in France); and 4.0% for cerebrovascular accident/transient ischaemic attack (1.8% in Poland to 7.0 in France) (Hutchison et al. 2006). Another EU study found overall cardiovascular comorbidity (including hypertension) to be 52.7%, ranging from 47.5% in France to 61.1% in Germany (Fourcade et al. 2008). The variations in estimating prevalence rate are mainly due to the different definition for CV disease (e.g., some studies included the diagnosis of hypertension).

Hyperlipidaemia: Incidence rates of hyperlipidaemia are not well defined. Prevalence rates in the EU are not well defined. In a United States study, 60% of men with both BPH and CV disease had hyperlipidaemia compared with 47% of men with CV disease only (Shah et al. 2007).
In 2 United States studies of BPH/LUTS patients, co-morbid hyperlipidaemia ranged from 19.4% to 45% (Roehrborn et al. 2007; Broderick et al. 2010).

Diabetes: Incidence rates for diabetes are not well defined. The Trans European Research study found the overall prevalence for diabetes in the BPH/LUTS population to be 10.3%, and ranged from 7.8% in Poland to 13.4% in Germany (Hutchison et al. 2006). By comparison, 2 United States studies with BPH/LUTS cohorts found the prevalence of diabetes to range from 4.7% to 17% (Roehrborn et al. 2007; Broderick et al. 2010). In a United States BPH cohort, diabetes was between 6.8% and 8.1% (Meigs et al. 2001; Sarma et al. 2008).

Prostate Cancer: In a nationwide population-based study in Sweden among men diagnosed with BPH and followed for up to 26 years, the overall incidence of prostate cancer was 7.59/1000 person years, with a standardised incidence ratio of 1.02 (Chokkalingam et al. 2003). In a United States study that followed a BPH cohort over an 11-year period, prostate cancer was diagnosed in 9% of the patients in this cohort, with approximately 7.3% of Caucasian men developing prostate cancer compared with 14.3% of African-American men. This translated into African-American men being approximately 2.2 times more likely to develop prostate cancer than Caucasian men (Pettaway et al. 2011).

In a cohort study of Danish male population (Orsted et al. 2011), the cumulative incidence of prostate cancer in the BPH population undergoing an operation for BPH was 24.1% while the cumulative incidence of prostate cancer among the hospitalised BPH population was 8.64% (1980-2006). Similarly, a study using data from the Prostate Cancer Prevention trial, reported that the incidence of prostate cancer in patients diagnosed with prevalent BPH was 25.4% (394/1549) (Schenk et al. 2011). The relative risk of prostate cancer was not greater in men with prevalent BPH compared to those without BPH in this trial. According to large historical autopsy studies, >80% of men with prostate carcinoma also have BPH (Bostwick et al. 1992). Rates are not well defined in the EU. A case-control study in the United States (700 cases, 604 controls) found the overall odds ratio for developing prostate cancer in patients with a history of BPH to be 2.4. The odds ratio was 2.7 for African-Americans and 2.3 for Caucasians (Patel et al. 2005).

Renal Dysfunction: The incidence rates of renal dysfunction in patients with BPH are not well defined. In the EU, data collected by the TRIUMPH Project, that included patients from 6 European countries, found an overall prevalence of renal failure of 1.8% in the BPH/LUTS population, with rates ranging from 0.5% in Poland to 3.9% in France and the United Kingdom (Hutchison et al. 2006). Prevalence rates are not well defined in the United States population.

SI.3. Pulmonary Arterial Hypertension (Adcirca)

SI.3.1. Epidemiology of the Disease

SI.3.1.1. Incidence and Prevalence of Target Indication

The incidence of pulmonary arterial hypertension (PAH) ranges from 1.1 per million per year in the United Kingdom and Ireland to 7.1 cases per million per year in Scotland (Humbert et al. 2006; Peacock et al. 2007; Ling et al. 2012). A study conducted in France using the French National Registry among adults ages 18 years or older yielded an annual incidence of 2.4 per million population from 2002-2003 (Humbert et al. 2006). The differences between the studies could be due to differences in the definitions of the disease.

The prevalence of PAH varies widely in the published literature. The overall population prevalence of PAH in Scotland over a period of 16 years was 52 cases per million population among adults ages 16 years to 65 years (Peacock et al. 2007). In France, the prevalence ranged from 5 to 25 cases per million population (Humbert et al. 2006). A more recent longitudinal observational study based in the United Kingdom and Ireland reported an estimated prevalence in 2009 of 6.6 PAH cases per million population (Ling et al. 2012).

SI.3.1.2. Risk Factors for the Disease

Using baseline characteristic data from the REVEAL cohort (the Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management) based in the United States, obesity may be a risk factor for PAH. Additionally, the same study showed that the prevalence of recreational drug use, especially cocaine and amphetamines, could be indicative of emerging risk factors for PAH (Badesch et al. 2010).

SI.3.1.3. Mortality and Morbidity in Target Indication

An Australian PAH registry reported an annual mortality of 13.6% overall, with 11% in patients with idiopathic PAH, and 16.6% in patients with connective tissue disease related PAH (Keogh et al. 2011). The 1-year survival among the incident cases (n=121) was 88.4% according to data from the French National Registry and 71.8% estimated using the National Institutes of Health (NIH) equation (Humbert et al. 2006). The 3-year survival was 68% for PAH patients in the United Kingdom from 2001 to 2010 (Hurdman et al. 2012).

The most common cause of death in PAH is progressive right heart failure (D'Alonzo et al. 1991; Hoeper et al. 2002), followed by respiratory failure and sudden death (Hoeper et al. 2002).

At the time of diagnosis, patients with PAH tend to already have severe clinical impairment (Humbert et al. 2006). For example, among those newly diagnosed in the French National Registry, more than 80% were New York Heart Association (NYHA) functional class III or IV (Humbert et al. 2006).

SI.3.1.4. Demographic Profile of Target Population

In general, PAH is more common in females than males (Humbert et al. 2006; Peacock et al. 2007; Frost et al. 2011). For example, in a Scottish study, the annual incidence of idiopathic pulmonary arterial hypertension (IPAH) was 2.5 and 4.0 cases per million population in males

and females, respectively (Peacock et al. 2007). Data from the French national registry support this finding, with a female to male ratio of 1.9 (Humbert et al. 2006). With respect to race/ethnicity, data from the REVEAL cohort show the following distribution of race/ethnicity adjusted for sex and age: White (72.8%), Black (12.2%), Hispanic (8.9%), Asian/Pacific Islander (3.3%), and other/unknown (2.8%) (Frost et al. 2011).

Data from the French national registry show that PAH can develop in a wide range of ages, with 25% of cases occurring after the age of 60 and an age range of 18 to 85 years among all cases (Humbert et al. 2006). Data from a recent study conducted in the United Kingdom and Ireland reported a median age of onset of 50 years (Ling et al. 2012).

The majority of PAH cases tend to be idiopathic in aetiology, followed by connective tissue diseases and congenital heart disease-associated. Familial PAH is a less frequent with only 3.9% to 5.4% of patients having this aetiology (Humbert et al. 2006; Ling et al. 2012). Studies have shown that genetics may play a role in the development of idiopathic PAH and familial PAH (Yu et al. 2009).

SI.3.1.5. Main Treatment Options

Prostanoids

Epoprostenol, delivered through a continuous portable infusion pump and indwelling central venous catheter, has led to improvements in exercise capacity, haemodynamics, and quality of life, and appears to improve survival in patients with the most advanced disease. Iloprost is an inhaled prostanoid which significantly improves the combined endpoint of New York Heart Association (NYHA) functional class and demonstrates a 10% improvement in 6-minute walk distance (p=0.007). Treprostinil, administered subcutaneously, improves placebo-adjusted 6-minute walk test distance by 16 meters in a dose-dependent manner.

Endothelin Receptor Antagonists (ERAs)

In the Bosentan Trial of ERA therapy (BREATHE-1), bosentan-treated patients showed a placebo-adjusted difference in the 6-minute walk test distance of 44 meters. Bosentan treatment also improved Borg dyspnoea scores and time to clinical worsening in as early as 16 weeks. Ambrisentan treatment improved the 6-minute walk test distance and time to clinical worsening in the Ambrisentan in Pulmonary Artery Hypertension, Randomised, Double-Blinded, Multicenter, Efficacy Study I and II (ARIES I and II).

Phosphodiesterase Type-5 Inhibitors

Patients taking sildenafil 3 times daily showed improvement compared with those taking placebo in the 6-minute walk test as early as 4 weeks and extending to 12 weeks.

Guanylate Cyclase Stimulators

Riociguat a molecule in the new class of guanylate cyclase stimulators was recently approved for the treatment of functional class II or III PAH alone or in combination with ERAs (Adempas SmPC 2014). The 2014 CHEST (chronic-thromboembolic-pulmonary-hypertension) guidelines for the treatment of PAH advise that treatment-naïve PAH patients with WHO functional class II

or III symptoms who are not candidates for, or who have failed calcium channel blocker therapy, should be initiated with a currently approved ERA, PDE5 inhibitor, or riociguat. The guidelines also state that based upon currently available evidence showing a risk of systemic hypotension when riociguat is coadministered with a PDE5 inhibitor, male patients treated with riociguat should be cautioned not to use PDE5 inhibitors for ED (Taichman et al. 2014). In the Adempas SmPC, the co-administration of riociguat with PDE 5 inhibitors is contraindicated. Riociguat is also approved in the EU for the treatment of adult patients with WHO Functional Class (FC) II to III with inoperable Chronic Thromboembolic Pulmonary Hypertension (CTEPH), or persistent or recurrent CTEPH after surgical treatment, to improve exercise capacity.

Balloon Atrial Septostomy (BAS)

The recommended technique of graded balloon dilation atrial septostomy produces equivalent improvements in haemodynamics and symptoms, but reduced risk compared with the original blade technique. Evidence suggests a benefit in patients who are in World Health Organization Functional Class (WHO-FC) IV with right heart failure refractory to medical therapy or with severe syncopal symptoms. Balloon Atrial Septostomy has shown to lead to improvements in cardiac index (CI), decreases in right atrial pressure with improvement in 6-minute walk test distance (Galie et al. 2009).

Transplantation

Transplantation should remain an option for patients who fail on medical therapies. Both heart and lung transplantation have been performed for PAH, although the threshold of unrecoverable right ventricle (RV) systolic function and/or left ventricle (LV) diastolic function is unknown. While RV afterload is immediately reduced after double lung transplantation, RV systolic and LV diastolic functions do not improve immediately and haemodynamic instability is a common problem in the early postoperative period. Both single and bilateral procedures have been performed with similar survival. Any complications occurring in the allograft following single lung transportation is associated with severe hypoxaemia. The overall 5-year survival rate following transplantation for PAH is 45% to 50% with evidence of a good quality of life (Galie et al. 2009).

SI.3.2. Concomitant Medication(s) in the Target Population

Concomitant medications that are used in the PAH population include warfarin, diuretics, calcium channel blockers, digoxin (Galie et al. 2002), oxygen, thyroid replacement, calcium channel blockers, SSRIs and other antidepressants, aspirin and other anti-inflammatory agents, statins, beta-blockers, psychotropic drugs, corticosteroids, ACE inhibitors, and clopidogrel (Badesch et al. 2010).

SI.3.3. Important Co-Morbidities Found in the Target Population

Heart Failure (includes congestive heart failure and right heart failure): There was no available information for incidence or prevalence of heart failure within the PAH population.

Myocardial Infarction: A study using medical records assessed the prevalence of coronary artery disease among 162 adult patients with PAH in Canada. At baseline, 2.5% of the PAH patients reported a previous myocardial infarction (Shimony et al. 2011). Other than these data,

there are no other available data of the incidence of myocardial infarction within the PAH population.

Ischaemic Stroke/TIA: There was no available information for incidence or mortality of ischaemic stroke or TIA in the PAH population.

Arrhythmia: No information was available in the literature regarding the incidence and prevalence of arrhythmia in the PAH population.

Chronic obstructive pulmonary disease: Obstructive airway disease (including obstructive lung disease, reactive airways disease, and COPD) was listed as a comorbid condition among idiopathic PAH patients (n=1114) in the REVEAL registry, resulting in a prevalence of 23.2%. Among all PAH patients in the registry, (n=2438) obstructive airway disease was diagnosed at enrolment in 21.9% of these patients (Badesch et al. 2010).

Pneumonia: There was no available information for incidence or prevalence of pneumonia.

Pulmonary embolism: There was no available information for incidence of pulmonary embolism. Among all PAH participants in the REVEAL registry, the prevalence of pulmonary embolism was 6.9% (Badesch et al. 2010). Among idiopathic PAH patients (n=1114) in the registry, the prevalence of pulmonary embolism was 8.6% (Badesch et al. 2010).

Module SII. Nonclinical Part

Table SII.1. Key Safety Findings from Nonclinical Studies and Relevance to Humans

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Target Organ Toxicity: • Testicular degeneration observed in repeat-dose studies in dogs • Regression of the seminiferous tubular epithelium was observed in dogs given tadalafil daily at doses of 25 mg/kg and above for 6 to 12 months, which resulted in decreased spermatogenesis in some dogs.	To address these nonclinical testicular findings in dogs, the Marketing Authorisation Holder (MAH) conducted 3 .clinical studies in men evaluating the potential effect of tadalafil 10 mg (one 6-month study) and tadalafil 20 mg (one 6-month and one 9-month study) administered daily on spermatogenesis. No adverse effects were noted on sperm morphology or sperm motility in any study. In the studies of tadalafil 10 mg for 6 months and tadalafil 20 mg for 9 months, mean sperm concentrations in men decreased compared with placebo. This effect was not seen with the 6-month study of tadalafil 20 mg. In the 9-month study, decreased sperm concentration was associated with higher ejaculation frequency. Ejaculation frequency was not assessed in the 6-month studies. No adverse effects were noted on mean concentrations of reproductive hormones, including testosterone, luteinising hormone, or follicle stimulating hormone, with either tadalafil 10 or 20 mg compared with placebo. These studies indicate that tadalafil does not affect male fertility in humans.
Cardiovascular Safety: • Decrease in blood pressure in dog and hypertensive rat studies. • In conscious dogs, orally administered doses up to 200 mg/kg had no effect on heart rate, electrocardiogram waveform rhythm, or PR and QT intervals. At doses of 20 and 200 mg/kg, a slight decrease in mean arterial blood pressure was observed. In anesthetised dogs, intravenous administration of tadalafil at a dose of 3 mg/kg produced a reduction in blood pressure by decreasing vascular resistance without affecting cardiac output. • When administered orally to spontaneously hypertensive rats, deoxycorticosterone acetate (DOCA-salt) treated rats, or renal vascular hypertensive rats, single oral tadalafil doses of 1 and 5 mg/kg lowered blood pressure for at least 7 hours, without affecting heart rate. This effect was long lasting and was not subject to the development of tolerance on repeated administration. A similar but less pronounced effect was also seen in normal rats.	Hypotension/increased hypotensive effect has been observed in tadalafil clinical trials. It is a class effect and an important identified risk for tadalafil.
Mechanisms for drug interactions • No relevant non-clinical data	Refer to Part II Module SVII (Section SVII.4) of this RMP.
Other toxicity-related information or data • No relevant non-clinical data	No key safety findings.

SII.1. Conclusions on Nonclinical Data

Tadalafil has been evaluated in a variety of toxicology studies in laboratory animals and in vitro test systems. Studies included single-dose toxicity in mice, rats, and dogs; repeat-dose toxicity in mice, rats, and dogs; safety pharmacology; in vitro and in vivo genotoxicity; carcinogenic potential in mice and rats; juvenile toxicity in rats and reproductive and developmental toxicity in mice and rats.

Nonclinical data reveal no significant risk from tadalafil for humans, as also borne out by extensive post-approval experience. There was no evidence of teratogenicity, embryotoxicity, or foetotoxicity in rats or mice receiving up to 1000 mg/kg/day. In a rat pre- and postnatal development study, the no-observed-effect dose was 30 mg/kg/day. There was no impairment of fertility in male and female rats. No adverse effects were observed in juvenile male rats administered doses up to 1000 mg/kg.

Nonclinical data did reveal a blood pressure lowering effect with tadalafil, which has been confirmed in clinical trials. This is an identified risk of PDE5 inhibitors, including tadalafil.

Table SII.2. Important Safety Concerns Based on Nonclinical Data

Safety Concerns
Important Identified Risks (Confirmed by Clinical Data)
• Hypotension/increased hypotensive effect
Important Potential Risks (Not Refuted by Clinical Data or which are of Unknown Significance)
• None
Important Missing Information
• None

Module SIII. Clinical Trial Exposure

SIII.1. Brief Overview of Development

Tadalafil is an orally administered phosphodiesterase type-5 (PDE5) inhibitor initially developed by Lilly for the on-demand treatment of men with erectile dysfunction (ED). Tadalafil 10- or 20-mg on-demand dosing was authorised in the European Union (EU) on 12 November 2002 for the treatment of ED.

Following EU marketing authorisation as an on-demand therapy, tadalafil was investigated for once-a-day treatment of men with ED, men with signs and symptoms of benign prostatic hyperplasia (BPH), as well as for the treatment of pulmonary arterial hypertension (PAH). Tadalafil 2.5- and 5-mg once-a-day were approved in the EU for the treatment of ED in the EU on 20 June 2007. Subsequently, tadalafil 40-mg once-a-day was approved in the EU on 30 November 2009 for the treatment of PAH, classified as World Health Organization (WHO) functional class II and III, to improve exercise capacity. Marketing authorisation in the EU was granted on 24 October 2012 for tadalafil 5-mg once-a-day for the treatment of signs and symptoms of BPH. Marketing authorisation for all indications has been granted in multiple countries worldwide.

The clinical development programme for the all approved indications included approximately 25,000 patients. The clinical trial exposures are presented below for all studies (for approved indications) combined (ED on-demand, ED once-a-day, BPH, and PAH), followed by exposures for each individual indication. Tables combining exposure from all ED (both on-demand and once-a-day) and BPH studies have also been included, as these conditions often coexist. This provides a larger population for determination of frequency of identified and potential risks. Some tables presented below also include studies of other non-approved indications.

SIII.2. Clinical Trial Exposure

Table SIII.1. Duration of Exposure (All Studies, Including Other Indications)

Total Patient Population		
Duration of Exposure (at least)	**Persons**	**Person-Time (Years)**
≥1 day	25336	11291.0
≥30 days (1 month)	23745	11207.9
≥90 days (3 months)	16494	9806.7
≥180 days (6 months)	4736	5967.9
≥270 days (9 months)	3101	5024.9
≥365 days (1 year)	2450	4473.3
≥547 days (1.5 years)	1364	3216.4
≥730 days (2 years)	837	2282.8

Studies included for the analysis: GPEC, LVAC, LVBD, LVBE, LVBF, LVBG, LVBI, LVBJ, LVBK, LVBL, LVBN, LVBO, LVBQ, LVBR, LVCD, LVCE, LVCF, LVCG, LVCI, LVCK, LVCO, LVCQ, LVCR, LVCU, LVCV, LVCY, LVCZ, LVDG, LVDI, LVDJ, LVDR, LVDU, LVDW, LVDX, LVDY, LVDZ, LVEB, LVEF, LVEG, LVEH, LVEI, LVEK, LVEL, LVEM, LVEQ, LVFD, LVFE, LVFH, LVFL, LVFN, LVFP, LVFR, LVFY, LVFZ, LVGC, LVGD, LVGH, LVGO, LVGU, LVGX, LVGXE, LVGY, LVHB, LVHG, LVHJ, LVHK, LVHR, LVHS, LVHT, LVHX, LVHZ, LVIA, LVID, LVIJ, LVIK, LVIP, LVIR, LVIW, LVIY, LVIZ, LVJF, S002, S024

Notes: Count a subject only once if he/she rolled over from one study to another.
Tadalafil exposure for the unique subject across studies will be added together.

Source: /lillyce/prd/ly450190/integrations/swiss_rmp_2013/programs_stat/tfl_output/smexph01_a1.rtf

Table SIII.2. Duration of Exposure (All Placebo-Controlled Studies, Including Other Indications)

Total Patient Population				
	Placebo		**Tadalafil**	
Duration of Exposure (at least)	**Persons**	**Person-Time (Years)**	**Persons**	**Person-Time (Years)**
≥1 day	5839	1508.1	11232	2786.6
≥30 days (1 month)	5271	1486.0	10077	2736.4
≥90 days (3 months)	2231	859.8	4753	1628.4
≥180 days (6 months)	696	408.4	896	537.5
≥270 days (9 months)	160	124.1	207	161.2

Studies included for the analysis: LVAC, LVBF, LVBG, LVBI, LVBJ, LVBK, LVBN, LVBO, LVBQ, LVBR, LVCD, LVCE, LVCI, LVCK, LVCO, LVCQ, LVCR, LVCV, LVCZ, LVDG, LVDI, LVDJ, LVDU, LVDW, LVDX, LVDY, LVDZ, LVEF, LVEG, LVEH, LVEl, LVEK, LVEL, LVEQ, LVFD, LVFE, LVFP, LVFY, LVFZ, LVGC, LVGH, LVGO, LVGU, LVGY, LVHB, LVHG, LVHJ, LVHK, LVHR, LVHS, LVHT, LVHX, LVHZ, LVIA, LVlD, LVIK, LVIP, LVIR, LVlW, LVJF

Source: /lillyce/prd/ly450190/integrations/swiss_rmp_2013/programs_stat/tfl_output/smexph01_c1.rtf

Table SIII.3. Duration of Exposure (All Erectile Dysfunction Studies - On Demand/Once a Day)

Duration of Exposure (at least)	Persons	Person-Time (Years)
Erectile Dysfunction (On demand and once a day)		
≥1 day	21035	8567.6
≥30 days (1 month)	19729	8494.3
≥90 days (3 months)	14299	7483.0
≥180 days (6 months)	3151	3842.9
≥270 days (9 months)	2013	3159.0
≥365 days (1 year)	1638	2832.0
≥547 days (1.5 years)	1083	2177.8
≥730 days (2 years)	565	1260.3
Erectile Dysfunction (On demand)		
≥1 day	17538	7082.7
≥30 days (1 month)	16871	7041.7
≥90 days (3 months)	12353	6210.9
≥180 days (6 months)	2498	2980.1
≥270 days (9 months)	1468	2355.7
≥365 days (1 year)	1179	2109.2
≥547 days (1.5 years)	914	1789.5
≥730 days (2 years)	416	912.2
Erectile Dysfunction (Once a day)		
≥1 day	3519	1404.0
≥30 days (1 month)	2700	1361.5
≥90 days (3 months)	1802	1184.7
≥180 days (6 months)	599	800.0
≥270 days (9 months)	493	741.6
≥365 days (1 year)	416	669.9
≥547 days (1.5 years)	164	373.3
≥730 days (2 years)	136	321.7

Abbreviations: BPH = benign prostatic hypertrophy; ED = erectile dysfunction.
Studies included for the analysis: GPEC, LVAC, LVBD, LVBE, LVBF, LVBG, LVBI, LVBJ, LVBK, LVBL, LVBN, LVBO, LVCE, LVCF, LVCG, LVCI, LVCK, LVCO, LVCQ, LVCR, LVCU, LVCV, LVCY, LVDG, LVDI, LVDJ, LVDR, LVDU, LVDW, LVDX, LVDY, LVDZ, LVEB, LVEF, LVEG, LVEH, LVEI, LVEK, LVEL, LVEM, LVEQ, LVFD, LVFH, LVFL, LVFN, LVFP, LVFR, LVFY, LVFZ, LVGD, LVGH, LVHR, LVHX, LVHZ, LVIJ, LVIK, LVIP, LVIZ, S002, S024
Notes: Count a subject only once if he/she rolled over from one study to another.
Tadalafil exposure for the unique subject across studies will be added together.
LVHR is an ED/BPH study, and is included in summaries for both populations.
Source: /lillyce/prd/ly450190/integrations/swiss_rmp_2013/programs_stat/tfl_output/smexph01_a2.rtf through smexph01_a4.rtf

Table SIII.4. Duration of Exposure (All Erectile Dysfunction Placebo-Controlled Studies - On Demand/Once a Day)

	Placebo		Tadalafil	
Duration of Exposure (at least)	**Persons**	**Person-Time (Years)**	**Persons**	**Person-Time (Years)**
Erectile Dysfunction (On demand and once a day)				
≥1 day	3186	726.3	7251	1697.2
≥30 days (1 month)	2772	709.4	6339	1655.5
≥90 days (3 months)	1263	419.0	3334	1054.3
≥180 days (6 months)	178	117.8	357	236.6
Erectile Dysfunction (On demand)				
≥1 day	2116	516.7	4716	1118.5
≥30 days (1 month)	2005	510.2	4445	1102.5
≥90 days (3 months)	947	318.7	2432	723.4
≥180 days (6 months)	147	102.1	180	119.2
Erectile Dysfunction (Once a day)				
≥1 day	1211	301.4	2535	578.7
≥30 days (1 month)	904	290.9	1894	553.0
≥90 days (3 months)	439	189.7	902	330.9
≥180 days (6 months)	150	103.3	177	117.5

Abbreviations: BPH = benign prostatic hypertrophy; ED = erectile dysfunction.
Studies included for the analysis: LVAC, LVBF, LVBG, LVBI, LVBJ, LVBK, LVBN, LVBO, LVCE, LVCI, LVCK, LVCO, LVCQ, LVCR, LVCV, LVDG, LVDI, LVDJ, LVDU, LVDW, LVDX, LVDY, LVDZ, LVEF, LVEG, LVEH, LVEI, LVEK, LVEL, LVEQ, LVFD, LVFP, LVFY, LVFZ, LVGH, LVHR, LVHX, LVHZ, LVIK, LVIP
Notes: LVHR is an ED/BPH study, and is included in summaries for both populations.
Source: /lillyce/prd/ly450190/integrations/swiss_rmp_2013/programs_stat/tfl_output/ smexph01_c2.rtf through smexph01_c4.rtf

Table SIII.5. Duration of Exposure (All Benign Prostatic Hyperplasia Studies)

Benign Prostatic Hyperplasia		
Duration of Exposure (at least)	**Persons**	**Person-Time (Years)**
≥1 day	3564	1447.5
≥30 days (1 month)	3366	1439.0
≥90 days (3 months)	1463	1019.1
≥180 days (6 months)	966	867.8
≥270 days (9 months)	678	717.5
≥365 days (1 year)	516	583.0

Studies included for the analysis: LVGC, LVHB, LVHG, LVHJ, LVHK, LVHR, LVHS, LVHT, LVIA, LVID, LVIR, LVIW, LVIY, LVJF
Notes: Count a subject only once if he/she rolled over from one study to another.
Tadalafil exposure for the unique subject across studies will be added together.
Source: /lillyce/prd/ly450190/integrations/swiss_rmp_2013/programs_stat/tfl_output/smexph01_a5.rtf

Table SIII.6. Duration of Exposure (Benign Prostatic Hyperplasia – Placebo-Controlled Studies)

Benign Prostatic Hyperplasia				
	Placebo		Tadalafil	
Duration of Exposure (at least)	Persons	Person-Time (Years)	Persons	Person-Time (Years)
≥1 day	2196	565.8	3317	817.9
≥30 days (1 month)	2113	561.9	3158	810.7
≥90 days (3 months)	536	210.6	764	275.4
≥180 days (6 months)	228	116.0	249	127.0
≥270 days (9 months)			1	0.8

Abbreviations: BPH = benign prostatic hypertrophy; ED = erectile dysfunction.
Studies included for the analysis: LVGC, LVHB, LVHG, LVHJ, LVHK, LVHR, LVHS, LVHT, LVIA, LVID, LVIR, LVIW, LVJF
Notes: LVHR is an ED/BPH study, and is included in summaries for both populations.
Source: /lillyce/prd/ly450190/integrations/swiss_rmp_2013/programs_stat/tfl_output/ smexph01_c5.rtf

Table SIII.7. Duration of Exposure (All Erectile Dysfunction [On Demand/Once a Day] and Benign Prostatic Hyperplasia Studies)

Duration of Exposure (at least)	Persons	Person-Time (Years)
Erectile Dysfunction (On demand and once a day) and Benign Prostatic Hyperplasia		
≥1 day	24194	9926.4
≥30 days (1 month)	22714	9845.7
≥90 days (3 months)	15688	8483.3
≥180 days (6 months)	4117	4710.6
≥270 days (9 months)	2691	3876.5
≥365 days (1 year)	2154	3415.0
≥547 days (1.5 years)	1083	2177.8
≥730 days (2 years)	565	1260.3
Erectile Dysfunction (Once a day) and Benign Prostatic Hyperplasia		
≥1 day	6678	2762.9
≥30 days (1 month)	5685	2713.0
≥90 days (3 months)	3191	2185.0
≥180 days (6 months)	1565	1667.8
≥270 days (9 months)	1171	1459.1
≥365 days (1 year)	932	1252.9
≥547 days (1.5 years)	164	373.3
≥730 days (2 years)	136	321.7

Abbreviations: BPH = benign prostatic hypertrophy; ED = erectile dysfunction.
Studies included for the analysis: GPEC, LVAC, LVBD, LVBE, LVBF, LVBG, LVBI, LVBJ, LVBK, LVBL, LVBN, LVBO, LVCE, LVCF, LVCG, LVCI, LVCK, LVCO, LVCQ, LVCR, LVCU, LVCV, LVCY, LVDG, LVDI, LVDJ, LVDR, LVDU, LVDW, LVDX, LVDY, LVDZ, LVEB, LVEF, LVEG, LVEH, LVEI, LVEK, LVEL, LVEM, LVEQ, LVFD, LVFH, LVFL, LVFN, LVFP, LVFR, LVFY, LVFZ, LVGC, LVGD, LVGH, LVHB, LVHG, LVHJ, LVHK, LVHR, LVHS, LVHT, LVHX, LVHZ, LVIA, LVID, LVIJ, LVIK, LVIP, LVIR, LVIW, LVIY, LVIZ, LVJF, S002, S024
Notes: Count a subject only once if he/she rolled over from one study to another.
Tadalafil exposure for the unique subject across studies will be added together.
LVHR is an ED/BPH study, and is included in summaries for both populations.
Source: /lillyce/prd/ly450190/integrations/swiss_rmp_2013/programs_stat/tfl_output/smexph01_a7.rtf
/lillyce/prd/ly450190/integrations/swiss_rmp_2013/programs_stat/tfl_output/smexph01_a8.rtf

Table SIII.8. Duration of Exposure (All Erectile Dysfunction and Benign Prostatic Hyperplasia – Placebo-Controlled Studies)

	Placebo		Tadalafil	
Duration of Exposure (at least)	**Persons**	**Person-Time (Years)**	**Persons**	**Person-Time (Years)**
Erectile Dysfunction (On demand and once a day) and Benign Prostatic Hyperplasia				
≥1 day	5183	1249.4	10163	2426.5
≥30 days (1 month)	4701	1229.2	9116	2378.7
≥90 days (3 months)	1766	621.1	4024	1310.8
≥180 days (6 months)	406	233.8	606	363.6
≥270 days (9 months)	62	48.1	111	86.9
Erectile Dysfunction (Once a day) and Benign Prostatic Hyperplasia				
≥1 day	3208	824.5	5447	1308.1
≥30 days (1 month)	2833	810.7	4671	1276.2
≥90 days (3 months)	942	391.8	1592	587.4
≥180 days (6 months)	378	219.3	426	244.4
≥270 days (9 months)	62	48.1	55	44.0

Studies included for the analysis: LVAC, LVBF, LVBG, LVBI, LVBJ, LVBK, LVBN, LVBO, LVCE, LVCI, LVCK, LVCO, LVCQ, LVCR, LVCV, LVDG, LVDI, LVDJ, LVDU, LVDW, LVDX, LVDY, LVDZ, LVEF, LVEG, LVEH, LVEI, LVEK, LVEL, LVEQ, LVFD, LVFP, LVFY, LVFZ, LVGC, LVGH, LVHB, LVHG, LVHJ, LVHK, LVHR, LVHS, LVHT, LVHX, LVHZ, LVIA, LVID, LVIK, LVIP, LVIR, LVIW, LVJF
Source: /lillyce/prd/ly450190/integrations/swiss_rmp_2013/programs_stat/tfl_output/ smexph01_c7.rtf
/lillyce/prd/ly450190/integrations/swiss_rmp_2013/programs_stat/tfl_output/ smexph01_c8.rtf

Table SIII.9. Duration of Exposure (All PAH Studies)

Pulmonary Arterial Hypertension		
Duration of Exposure (at least)	**Persons**	**Person-Time (Years)**
≥1 day	393	1097.1
≥30 days (1 month)	378	1096.5
≥90 days (3 months)	356	1093.0
≥180 days (6 months)	329	1083.5
≥270 days (9 months)	314	1074.1
≥365 days (1 year)	296	1058.4
≥547 days (1.5 years)	281	1038.6
≥730 days (2 years)	272	1022.6

Abbreviations: PAH = pulmonary arterial hypertension.
Studies included for the analysis: LVGX, LVGXE, LVGY
While a total of 399 PAH patients were exposed to tadalafil in all PAH studies, 6 patients in these PAH trials had missing exposure durations and are therefore not included above.
Notes: Count a subject only once if he/she rolled over from one study to another.
Tadalafil exposure for the unique subject across studies will be added together.
Source: /lillyce/prd/ly450190/integrations/swiss_rmp_2013/programs_stat/tfl_output/smexph01_a6.rtf

Table SIII.10. Duration of Exposure (PAH – Placebo-Controlled)

Pulmonary Arterial Hypertension				
	Placebo		Tadalafil	
Duration of Exposure (at least)	Persons	Person-Time (Years)	Persons	Person-Time (Years)
≥1 day	82	23.1	320	92.5
≥30 days (1 month)	77	22.7	308	92.1
≥90 days (3 months)	69	21.4	279	87.2

Abbreviations: PAH = pulmonary arterial hypertension.
Study included for the analysis: LVGY
Source: /lillyce/prd/ly450190/integrations/swiss_rmp_2013/programs_stat/tfl_output/ smexph01_c6.rtf

Table SIII.11. Tadalafil Exposure by Dose and Indication (All Studies, Approved Indications)

	All Studies		Placebo-Controlled Studies	
Dose of Exposure	Persons	Person-Time (Years)	Persons	Person-Time (Years)
Erectile Dysfunction (On demand and once a day)				
2 mg	77	8.6	77	8.6
2.5 mg	798	151.1	796	150.7
5 mg	3950	1454.2	2021	491.0
10 mg	3358	1031.6	1393	253.9
20 mg	15938	5733.4	3081	775.7
25 mg	303	116.4	136	12.3
40 mg	3	0.4	--	--
>40 mg	269	79.7	160	6.1
Erectile Dysfunction (On demand)				
2 mg	77	8.6	77	8.6
2.5 mg	74	18.2	74	18.2
5 mg	982	205.0	455	82.3
10 mg	2961	957.6	1167	225.3
20 mg	15820	5712.9	3081	775.7
25 mg	291	113.1	79	9.0
40 mg	3	0.4	--	--
>40 mg	131	73.6	--	--
Erectile Dysfunction (Once a day)				
2.5 mg	724	132.9	722	132.5
5 mg	2811	1170.7	1566	408.7
10 mg	409	73.4	226	28.7
20 mg	116	18.6	--	--
25 mg	57	3.3	57	3.3
>40 mg	160	6.1	160	6.1
Benign Prostatic Hyperplasia				
2.5 mg	704	158.1	704	158.1
5 mg	2727	1161.5	2092	531.0
10 mg	216	47.1	216	47.1
20 mg	433	81.7	433	81.7

Dose of Exposure	All Studies		Placebo-Controlled Studies	
	Persons	Person-Time (Years)	Persons	Person-Time (Years)
Erectile Dysfunction (On demand and once a day) and Benign Prostatic Hyperplasia				
2 mg	77	8.6	77	8.6
2.5 mg	1305	266.0	1303	265.6
5 mg	6469	2570.3	3905	976.6
10 mg	3574	1078.7	1609	301.1
20 mg	16371	5815.1	3514	857.4
25 mg	303	116.4	136	12.3
40 mg	3	0.4	--	--
>40 mg	269	79.7	160	6.1
Erectile Dysfunction (Once a day) and Benign Prostatic Hyperplasia				
2.5 mg	1231	247.7	1229	247.3
5 mg	5330	2286.8	3450	894.3
10 mg	625	120.6	442	75.8
20 mg	549	100.3	433	81.7
25 mg	57	3.3	57	3.3
>40 mg	160	6.1	160	6.1
Pulmonary Arterial Hypertension				
2.5 mg	81	22.9	81	22.9
10 mg	79	23.2	79	23.2
20 mg	82	78.9	82	23.4
40 mg	351	972.2	78	23.0

Abbreviations: BPH = benign prostatic hypertrophy; ED = erectile dysfunction.
Studies included for the analysis: GPEC, LVAC, LVBD, LVBE, LVBF, LVBG, LVBI, LVBJ, LVBK, LVBL, LVBN, LVBO, LVCE, LVCF, LVCG, LVCI, LVCK, LVCO, LVCQ, LVCR, LVCU, LVCV, LVCY, LVDG, LVDI, LVDJ, LVDR, LVDU, LVDW, LVDX, LVDY, LVDZ, LVEB, LVEF, LVEG, LVEH, LVEI, LVEK, LVEL, LVEM, LVEQ, LVFD, LVFH, LVFL, LVFN, LVFP, LVFR, LVFY, LVFZ, LVGC, LVGD, LVGH, LVHB, LVHG, LVHJ, LVHK, LVHR, LVHS, LVHT, LVHX, LVHZ, LVIA, LVID, LVIJ, LVIK, LVIP, LVIR, LVIW, LVIY, LVIZ, LVJF, S002, S024, LVGX, LVGXE, LVGY
Notes: Count a subject only once if he/she rolled over from one study to another.
Tadalafil exposure for the unique subject across studies will be added together.
LVHR is an ED/BPH study, and is included in summaries for both populations.
Source: /lillyce/prd/ly450190/integrations/swiss_rmp_2013/programs_stat/tfl_output/smexph02_a2.rtf through smexph02_a8.rtf and
/lillyce/prd/ly450190/integrations/swiss_rmp_2013/programs_stat/tfl_output/smexph02_c2.rtf through smexph02_c8.rtf

Table SIII.12. Exposure by Dose (All Studies, Including Other Indications)

Total Population				
	All Studies		Placebo-Controlled Studies	
Dose of Exposure	Persons	Person-Time (Years)	Persons	Person-Time (Years)
2 mg	77	8.6	77	8.6
2.5 mg	1386	288.9	1384	288.5
5 mg	6667	2632.4	4103	1038.7
10 mg	3861	1160.7	1896	383.1
20 mg	16794	6040.5	3937	1027.4
25 mg	303	116.4	136	12.3
40 mg	354	972.6	78	23.0
>40 mg	269	79.7	160	6.1

Abbreviations: BPH = benign prostatic hypertrophy; ED = erectile dysfunction.
Studies included for the analysis: GPEC, LVAC, LVBD, LVBE, LVBF, LVBG, LVBI, LVBJ, LVBK, LVBL, LVBN, LVBO, LVBQ, LVBR, LVCD, LVCE, LVCF, LVCG, LVCI, LVCK, LVCO, LVCQ, LVCR, LVCU, LVCV, LVCY, LVCZ, LVDG, LVDI, LVDJ, LVDR, LVDU, LVDW, LVDX, LVDY, LVDZ, LVEB, LVEF, LVEG, LVEH, LVEI, LVEK, LVEL, LVEM, LVEQ, LVFD, LVFE, LVFH, LVFL, LVFN, LVFP, LVFR, LVFY, LVFZ, LVGC, LVGD, LVGH, LVGO, LVGU, LVGX, LVGXE, LVGY, LVHB, LVHG, LVHJ, LVHK, LVHR, LVHS, LVHT, LVHX, LVHZ, LVIA, LVID, LVIJ, LVIK, LVIP, LVIR, LVIW, LVIY, LVIZ, LVJF, S002, S024
Notes: Count a subject only once if he/she rolled over from one study to another.
Tadalafil exposure for the unique subject across studies will be added together.
LVHR is an ED/BPH study, and is included in summaries for both populations.
Source: /lillyce/prd/ly450190/integrations/swiss_rmp_2013/programs_stat/tfl_output/smexph02_a1.rtf
/lillyce/prd/ly450190/integrations/swiss_rmp_2013/programs_stat/tfl_output/smexph02_c1.rtf

Table SIII.13. Exposure by Age Group, Gender, and Indication (All Studies, Approved Indications)

Indication	Persons		Person-Time (Years)	
Age Group	Male	Female	Male	Female
Erectile Dysfunction (On demand and once a day)				
<18 years	1	N/A	0.1	N/A
≥18 to <65 years	17166	N/A	7003.6	N/A
≥65 years	3848	N/A	1556.5	N/A
Missing	20	N/A	7.3	N/A
Total	21035	N/A	8567.6	N/A
Erectile Dysfunction (On demand)				
<18 years	1	N/A	0.1	N/A
≥18 to <65 years	14468	N/A	5865.9	N/A
≥65 years	3049	N/A	1209.4	N/A
Missing	20	N/A	7.2	N/A
Total	17538	N/A	7082.7	N/A
Erectile Dysfunction (Once a day)				
≥18 to <65 years	2729	N/A	1077.7	N/A
≥65 years	790	N/A	326.3	N/A
Total	3519	N/A	1404.0	N/A
Benign Prostatic Hyperplasia				
≥18 to <65 years	2056	N/A	799.9	N/A
≥65 years	1508	N/A	647.6	N/A
Total	3564	N/A	1447.5	N/A

Indication	Persons		Person-Time (Years)	
Age Group	Male	Female	Male	Female
Erectile Dysfunction (On demand and once a day) and Benign Prostatic Hyperplasia				
<18 years	1	N/A	0.1	N/A
≥18 to <65 years	18966	N/A	7747.8	N/A
≥65 years	5207	N/A	2171.2	N/A
Missing	20	N/A	7.3	N/A
Total	24194	N/A	9926.4	N/A
Erectile Dysfunction (Once a day) and Benign Prostatic Hyperplasia				
≥18 to <65 years	4529	N/A	1821.9	N/A
≥65 years	2149	N/A	941.0	N/A
Total	6678	N/A	2762.9	N/A
Pulmonary Arterial Hypertension				
<18 years	0	1		3.4
≥18 to <65 years	54	230	142.8	654.3
≥65 years	32	76	87.3	209.2
Total	86	307	230.1	866.9

Abbreviations: BPH = benign prostatic hypertrophy; ED = erectile dysfunction.
Studies included for the analysis: GPEC, LVAC, LVBD, LVBE, LVBF, LVBG, LVBI, LVBJ, LVBK, LVBL, LVBN, LVBO, LVCE, LVCF, LVCG, LVCI, LVCK, LVCO, LVCQ, LVCR, LVCU, LVCV, LVCY, LVDG, LVDI, LVDJ, LVDR, LVDU, LVDW, LVDX, LVDY, LVDZ, LVEB, LVEF, LVEG, LVEH, LVEI, LVEK, LVEL, LVEM, LVEQ, LVFD, LVFH, LVFL, LVFN, LVFP, LVFR, LVFY, LVFZ, LVGC, LVGD, LVGH, LVHB, LVHG, LVHJ, LVHK, LVHR, LVHS, LVHT, LVHX, LVHZ, LVIA, LVID, LVIJ, LVIK, LVIP, LVIR, LVIW, LVIY, LVIZ, LVJF, S002, S024, LVGX, LVGXE, LVGY
Notes: Count a subject only once if he/she rolled over from one study to another.
Tadalafil exposure for the unique subject across studies will be added together.
LVHR is an ED/BPH study, and is included in summaries for both populations.
Source: /lillyce/prd/ly450190/integrations/swiss_rmp_2013/programs_stat/tfl_output/smexph03_a2.rtf through smexph03_a8.rtf

Table SIII.14. Tadalafil Exposure by Age Group, Gender, and Indication (Placebo-Controlled Studies, Approved Indications)

Indication	Persons		Person-Time (years)	
Age Group	Male	Female	Male	Female
Erectile Dysfunction (On demand and once a day)				
≥18 to <65 years	5770	N/A	1363.7	N/A
≥65 years	1480	N/A	333.2	N/A
Missing	1	N/A	0.3	N/A
Total	7251	N/A	1697.2	N/A
Erectile Dysfunction (On demand)				
≥18 to <65 years	3803	N/A	918.6	N/A
≥65 years	912	N/A	199.6	N/A
Missing	1	N/A	0.3	N/A
Total	4716	N/A	1118.5	N/A
Erectile Dysfunction (Once a day)				
≥18 to <65 years	1967	N/A	445.1	N/A
≥65 years	568	N/A	133.6	N/A
Total	2535	N/A	578.7	N/A
Benign Prostatic Hyperplasia				
≥18 to <65 years	1940	N/A	474.8	N/A
≥65 years	1377	N/A	343.2	N/A
Total	3317	N/A	817.9	N/A
Erectile Dysfunction (On demand and once a day) and Benign Prostatic Hyperplasia				
≥18 to <65 years	7454	N/A	1782.7	N/A
≥65 years	2708	N/A	643.5	N/A
Missing	1	N/A	0.3	N/A
Total	10163	N/A	2426.5	N/A
Erectile Dysfunction (Once a day) and Benign Prostatic Hyperplasia				
≥18 to < 65 years	3651	N/A	864.2	N/A
≥65 years	1796	N/A	443.9	N/A
Total	5447	N/A	1308.1	N/A
Pulmonary Arterial Hypertension				
<18 years	0	1	-	0.3
≥18 to <65 years	46	186	13.6	54.3
≥65 years	25	62	7.1	17.2
Total	71	249	20.7	71.8

Abbreviations: BPH = benign prostatic hypertrophy; ED = erectile dysfunction.
Studies included for the analysis: GPEC, LVAC, LVBD, LVBE, LVBF, LVBG, LVBI, LVBJ, LVBK, LVBL, LVBN, LVBO, LVCE, LVCF, LVCG, LVCI, LVCK, LVCO, LVCQ, LVCR, LVCU, LVCV, LVCY, LVDG, LVDI, LVDJ, LVDR, LVDU, LVDW, LVDX, LVDY, LVDZ, LVEB, LVEF, LVEG, LVEH, LVEI, LVEK, LVEL, LVEM, LVEQ, LVFD, LVFH, LVFL, LVFN, LVFP, LVFR, LVFY, LVFZ, LVGC, LVGD, LVGH, LVHB, LVHG, LVHJ, LVHK, LVHR, LVHS, LVHT, LVHX, LVHZ, LVIA, LVID, LVIJ, LVIK, LVIP, LVIR, LVIW, LVIY, LVIZ, LVJF, S002, S024, LVGX, LVGXE, LVGY
Notes: Count a subject only once if he/she rolled over from one study to another.
Tadalafil exposure for the unique subject across studies will be added together.
LVHR is an ED/BPH study, and is included in summaries for both populations.
Source: /lillyce/prd/ly450190/integrations/swiss_rmp_2013/programs_stat/tfl_output/smexph03_c2.rtf through smexph03_c8.rtf

Table SIII.15. Tadalafil Exposure by Age Group and Gender (All Studies, Including Other Indications)

Total Population				
	Persons		Person-Time (years)	
Age Group	Male	Female	Male	Female
<18 years	1	1	0.1	3.4
≥18 to < 65 years	19502	478	8111.1	697.0
≥65 years	5255	79	2262.4	209.6
Missing	20	0	7.3	-
Total	24778	558	10381.0	910.0

Abbreviations: BPH = benign prostatic hypertrophy; ED = erectile dysfunction.
Studies included for the analysis: GPEC, LVAC, LVBD, LVBE, LVBF, LVBG, LVBI, LVBJ, LVBK, LVBL, LVBN, LVBO, LVBQ, LVBR, LVCD, LVCE, LVCF, LVCG, LVCI, LVCK, LVCO, LVCQ, LVCR, LVCU, LVCV, LVCY, LVCZ, LVDG, LVDI, LVDJ, LVDR, LVDU, LVDW, LVDX, LVDY, LVDZ, LVEB, LVEF, LVEG, LVEH, LVEI, LVEK, LVEL, LVEM, LVEQ, LVFD, LVFE, LVFH, LVFL, LVFN, LVFP, LVFR, LVFY, LVFZ, LVGC, LVGD, LVGH, LVGO, LVGU, LVGX, LVGXE, LVGY, LVHB, LVHG, LVHJ, LVHK, LVHR, LVHS, LVHT, LVHX, LVHZ, LVIA, LVID, LVIJ, LVIK, LVIP, LVIR, LVIW, LVIY, LVIZ, LVJF, S002, S024
Notes: Count a subject only once if he/she rolled over from one study to another.
Tadalafil exposure for the unique subject across studies will be added together.
LVHR is an ED/BPH study, and is included in summaries for both populations.
Source: /lillyce/prd/ly450190/integrations/swiss_rmp_2013/programs_stat/tfl_output/smexph03_a1.rtf

Table SIII.16. Tadalafil Exposure by Age Group and Gender (All Placebo-Controlled Studies, Including Other Indications)

Total Population				
	Persons		Person-Time (years)	
Age Group	Male	Female	Male	Female
<18 years	0	1	-	0.3
≥18 to < 65 years	7982	434	2016.9	97.0
≥65 years	2749	65	654.5	17.6
Missing	1	0	0.3	-
Total	10732	500	2671.7	114.9

Studies included for the analysis: LVAC, LVBF, LVBG, LVBI, LVBJ, LVBK, LVBN, LVBO, LVBQ, LVBR, LVCD, LVCE, LVCI, LVCK, LVCO, LVCQ, LVCR, LVCV, LVCZ, LVDG, LVDI, LVDJ, LVDU, LVDW, LVDX, LVDY, LVDZ, LVEF, LVEG, LVEH, LVEI, LVEK, LVEL, LVEQ, LVFD, LVFE, LVFP, LVFY, LVFZ, LVGC, LVGH, LVGO, LVGU, LVGY, LVHB, LVHG, LVHJ, LVHK, LVHR, LVHS, LVHT, LVHX, LVHZ, LVIA, LVID, LVIK, LVIP, LVIR, LVIW, LVJF
Source: /lillyce/prd/ly450190/integrations/swiss_rmp_2013/programs_stat/tfl_output/smexph03_c1.rtf

Table SIII.17. Exposure by Ethnic or Racial Origin and Indication (All Studies, Approved Indications)

	All Studies		Placebo-Controlled Studies	
	Persons	Person-Time (Years)	Persons	Person-Time (Years)
Erectile Dysfunction (On demand and once a day))				
White	16391	7117.3	5542	1307.1
Black or African American	941	291.8	292	56.3
Asian	2047	567.7	1010	243.2
Native Hawaiian or Other Pacific Islander	1	0.0	--	--
American Indian or Alaska Native	13	3.6	9	1.8
Other	1611	579.2	383	87.0
Multiple	20	2.9	14	1.6
Missing	11	5.0	1	0.2
Total	21035	8567.6	7251	1697.2
Erectile Dysfunction (On demand)				
White	13376	5803.0	3347	797.3
Black or African American	714	217.0	145	28.3
Asian	2005	553.9	976	236.8
American Indian or Alaska Native	3	1.6	1	0.7
Other	1431	503.1	247	55.3
Multiple	1	0.4	--	--
Missing	8	3.6	--	--
Total	17538	7082.7	4716	1118.5
Erectile Dysfunction (Once a day)				
White	3035	1234.0	2195	509.8
Black or African American	228	74.3	147	28.0
Asian	43	13.7	34	6.3
Native Hawaiian or Other Pacific Islander	1	0.0	--	--
American Indian or Alaska Native	10	2.1	8	1.1
Other	180	76.1	136	31.6
Multiple	19	2.5	14	1.6
Missing	3	1.3	1	0.2
Total	3519	1404.0	2535	578.7
Benign Prostatic Hyperplasia				
White	2129	838.1	2034	522.7
Black or African American	93	33.4	90	21.0
Asian	1130	508.2	987	222.0
Native Hawaiian or Other Pacific Islander	1	0.2	1	0.2
American Indian or Alaska Native	85	27.0	85	27.0
Other	117	37.7	111	22.3
Multiple	9	2.8	9	2.8
Total	3564	1447.5	3317	817.9

	All Studies		Placebo-Controlled Studies	
	Persons	Person-Time (Years)	Persons	Person-Time (Years)
Erectile Dysfunction (On demand and once a day) and Benign Prostatic Hyperplasia				
White	18146	7873.6	7202	1747.9
Black or African American	1019	322.1	367	74.1
Asian	3165	1073.1	1985	462.4
Native Hawaiian or Other Pacific Islander	2	0.3	1	0.2
American Indian or Alaska Native	97	30.3	93	28.5
Other	1728	616.9	494	109.3
Multiple	26	5.1	20	3.8
Missing	11	5.0	1	0.2
Total	24194	9926.4	10163	2426.5
Erectile Dysfunction (once a day) and Benign Prostatic Hyperplasia				
White	4790	1990.3	3855	950.6
Black or African American	306	104.6	222	45.8
Asian	1161	519.2	1009	225.5
Native Hawaiian or Other Pacific Islander	2	0.3	1	0.2
American Indian or Alaska Native	94	28.8	92	27.8
Other	297	113.8	247	53.9
Multiple	25	4.7	20	3.8
Missing	3	1.3	1	0.2
Total	6678	2762.9	5447	1308.1
Pulmonary Arterial Hypertension				
White	315	915.5	252	73.2
Black or African American	34	79.8	27	7.8
Asian	33	77.8	30	8.6
Native Hawaiian or Other Pacific Islander	2	5.1	2	0.5
American Indian or Alaska Native	5	14.2	5	1.6
Multiple	4	4.5	4	0.8
Total	393	1097.1	320	92.5

Abbreviations: BPH = benign prostatic hypertrophy; ED = erectile dysfunction.
Studies included for the analysis: GPEC, LVAC, LVBD, LVBE, LVBF, LVBG, LVBI, LVBJ, LVBK, LVBL, LVBN, LVBO, LVCE, LVCF, LVCG, LVCI, LVCK, LVCO, LVCQ, LVCR, LVCU, LVCV, LVCY, LVDG, LVDI, LVDJ, LVDR, LVDU, LVDW, LVDX, LVDY, LVDZ, LVEB, LVEF, LVEG, LVEH, LVEI, LVEK, LVEL, LVEM, LVEQ, LVFD, LVFH, LVFL, LVFN, LVFP, LVFR, LVFY, LVFZ, LVGC, LVGD, LVGH, LVHB, LVHG, LVHJ, LVHK, LVHR, LVHS, LVHT, LVHX, LVHZ, LVIA, LVID, LVIJ, LVIK, LVIP, LVIR, LVIW, LVIY, LVIZ, LVJF, S002, S024, LVGX, LVGXE, LVGY
Notes: Count a subject only once if he/she rolled over from one study to another.
Tadalafil exposure for the unique subject across studies will be added together.
LVHR is an ED/BPH study, and is included in summaries for both populations.
Source: /lillyce/prd/ly450190/integrations/swiss_rmp_2013/programs_stat/tfl_output/smexph04_a2.rtf through smexph04_a8.rtf and /lillyce/prd/ly450190/integrations/eu_rmp_2013/programs_stat/tfl_output/smexph04_c2.rtf through smexph04_c8.rtf

Table SIII.18. Exposure by Ethnic or Racial Origin (All Studies, Including Other Indications)

Total Population				
	All Studies		Placebo-Controlled Studies	
	Persons	Person-Time (Years)	Persons	Person-Time (Years)
White	19066	9008.8	8059	2040.7
Black or African American	1140	429.3	481	109.3
Asian	3216	1154.7	2033	474.8
Native Hawaiian or Other Pacific Islander	4	5.4	3	0.8
American Indian or Alaska Native	103	44.8	99	30.3
Other	1766	633.5	532	125.9
Multiple	30	9.6	24	4.7
Missing	11	5.0	1	0.2
Total	25336	11291.0	11232	2786.6

Abbreviations: BPH = benign prostatic hypertrophy; ED = erectile dysfunction.
Studies included for the analysis: GPEC, LVAC, LVBD, LVBE, LVBF, LVBG, LVBI, LVBJ, LVBK, LVBL, LVBN, LVBO, LVBQ, LVBR, LVCD, LVCE, LVCF, LVCG, LVCI, LVCK, LVCO, LVCQ, LVCR, LVCU, LVCV, LVCY, LVCZ, LVDG, LVDI, LVDJ, LVDR, LVDU, LVDW, LVDX, LVDY, LVDZ, LVEB, LVEF, LVEG, LVEH, LVEI, LVEK, LVEL, LVEM, LVEQ, LVFD, LVFE, LVFH, LVFL, LVFN, LVFP, LVFR, LVFY, LVFZ, LVGC, LVGD, LVGH, LVGO, LVGU, LVGX, LVGXE, LVGY, LVHB, LVHG, LVHJ, LVHK, LVHR, LVHS, LVHT, LVHX, LVHZ, LVIA, LVID, LVIJ, LVIK, LVIP, LVIR, LVIW, LVIY, LVIZ, LVJF, S002, S024
Notes: Count a subject only once if he/she rolled over from one study to another.
Tadalafil exposure for the unique subject across studies will be added together.
LVHR is an ED/BPH study, and is included in summaries for both populations.
Source: /lillyce/prd/ly450190/integrations/swiss_rmp_2013/programs_stat/tfl_output/smexph04_a1.rtf
/lillyce/prd/ly450190/integrations/swiss_rmp_2013/programs_stat/tfl_output/smexph04_c1.rtf

Table SIII.19. Clinical Pharmacology Study Exposure by Special Population

Clinical Pharmacology Studies		
	Persons	Person-Time
Pregnant women	NS	NA
Lactating women	NS	NA
Renal impairment[a]	32	NA
Hepatic impairment[a]	25	NA
Cardiac impairment	NS	NA
Subpopulations with genetic polymorphisms	NS	NA
Immuno-compromised	NS	NA

Abbreviations: NS = not studied; NA = not applicable.
[a] Subjects in the renal and hepatic impairment studies only received 1 or 2 doses of tadalafil.

Module SIV. Populations Not Studied in Clinical Trials

SIV.1. Limitations of Adverse Drug Reaction Detection Common to Clinical Trial Development Programmes

Table SIV.1. Ability to Detect Adverse Reactions (Limitation of Trial Programme) – Erectile Dysfunction

Ability to Detect Adverse Reactions	Limitation of Trial Programme	Discussion of Implications for Target Population
Which are rare	21,035 patients have been exposed to tadalafil on-demand or once-a-day during the entire clinical trial programme of the ED indication.	The 95% CI for the rate of any undetected ADR for tadalafil for all patients exposed to any dose is 0.01% or less.
Due to prolonged exposure	In long-term ED studies, a total of 1,638 patients were exposed for ≥365 days.	At this time, there are no known effects due to prolonged exposure from clinical trial data. However, the postmarketing experience with >57 million patients exposed to tadalafil does not suggest any adverse effects following long-term exposure.
Due to cumulative effects	There is no evidence of cumulative effects with tadalafil, such as specific organ toxicity.	The cumulative effects, if any, are unknown at this point from clinical trial data. However, the postmarketing experience with >57 million patients exposed to tadalafil does not suggest that there is specific organ toxicity due to cumulative effects.
Which have a long latency	There is no long-term follow-up information following exposure in ED clinical trials.	It is unknown, from clinical trial data, if ADRs occurring with long latency could occur after exposure to tadalafil. However, the postmarketing experience with >57 million patients exposed to tadalafil does not suggest adverse effects due to long latency.

Abbreviations: ADR = adverse drug reaction; CI = confidence interval; ED = erectile dysfunction.

Table SIV.2. Ability to Detect Adverse Reactions (Limitation of Trial Programme) – Benign Prostatic Hyperplasia

Ability to Detect Adverse Reactions	Limitation of Trial Programme	Discussion of Implications for Target Population
Which are rare	3,564 patients have been exposed to tadalafil during the entire clinical trial programme of the BPH indication.	The 95% CI for the rate of any undetected ADR for tadalafil for all patients exposed to any dose is 0.08% or less.
Due to prolonged exposure	In long-term BPH studies, a total of 516 patients were exposed for approximately 1 year.	At this time, there are no known effects due to prolonged exposure from clinical trial data. However, the postmarketing experience with >57 million patients exposed to tadalafil does not suggest any adverse effects following long term exposure. Although experience in the BPH population is limited to date, the potential for ADRs from prolonged tadalafil exposure would not be expected to differ between the ED and BPH populations.
Due to cumulative effects	There is no evidence of cumulative effects with tadalafil, such as specific organ toxicity.	The cumulative effects, if any, are unknown at this point from clinical trial data. However, the postmarketing experience with >57 million patients exposed to tadalafil does not suggest that there is specific organ toxicity due to cumulative effects. Although experience in the BPH population is limited to date, the potential for ADRs from cumulative effects of tadalafil would not be expected to differ between the ED and BPH populations.
Which have a long latency	There is no long-term follow-up information following exposure in BPH clinical trials.	It is unknown, from clinical trial data, if ADRs occurring with long latency could occur after exposure to tadalafil. However, the postmarketing experience with >57 million patients exposed to tadalafil does not suggest adverse effects due to long latency. Although experience in the BPH population is limited to date, the potential for ADRs due to this effect would not be expected to differ between the ED and BPH populations.

Abbreviations: ADR = adverse drug reaction; BPH = benign prostatic hyperplasia; CI = confidence interval; ED = erectile dysfunction.

Table SIV.3. Ability to Detect Adverse Reactions (Limitation of Trial Programme) -- Pulmonary Arterial Hypertension

Ability to Detect Adverse Reactions	Limitation of Trial Programme	Discussion of Implications for Target Population
Which are rare	399 patients were exposed to tadalafil over the PAH clinical trial programme.	The 95% CI for the rate of any undetected ADR for tadalafil for all patients exposed to any dose is 0.8% or less, which would allow detection of uncommon, but not rare ADRs that are specific to the PAH population.
Due to prolonged exposure	296 patients were exposed to tadalafil for ≥365 days and 272 patients for ≥730 days over the entire clinical trial PAH programme	At this time, there are no known effects due to prolonged exposure. A large proportion of the PAH clinical trial population was exposed for greater than 2 years and no effects of prolonged exposure were identified. Additionally, the postmarketing experience with >57 million patients exposed to tadalafil does not suggest effects due to prolonged exposure.
Due to cumulative effects	There is no evidence of cumulative effects with tadalafil, such as specific organ toxicity.	The cumulative effects, if any, are unknown at this point. A large proportion of the PAH clinical trial population was exposed for greater than 2 years and no evidence of cumulative effects were identified. Additionally, the postmarketing experience with >57 million patients exposed to tadalafil does not suggest effects of specific organ toxicity due to cumulative effects.
Which have a long latency	There is no long-term follow-up information following exposure in PAH clinical trials.	It is unknown from clinical trial data, if ADRs occurring with long latency could occur after exposure to tadalafil. However, the postmarketing experience with >57 million patients exposed to tadalafil does not suggest adverse effects due to long latency.

Abbreviations: ADR = adverse drug reaction; CI = confidence interval; PAH = pulmonary arterial hypertension.

SIV.2. Effect of Exclusion Criteria in the Clinical Trial Development Plan

In the tadalafil clinical development programmes for ED, BPH, and PAH, a core set of exclusion criteria was used, most of which were intended to ensure safety and minimise risk in a research setting, and in some cases, to minimise confounding of the efficacy results. For the purpose of this section, the focus is solely on those exclusion criteria intended to ensure safety and minimise risk. In clinical trials of tadalafil for all indications, patients using any form of organic nitrate, those with a known hypersensitivity to tadalafil, and patients with hypotension (<90/50 mm Hg) or uncontrolled hypertension have been excluded. While patients with severe renal impairment

or hepatic insufficiency have generally been excluded from clinical trials, these special populations have been studied in clinical pharmacology studies.

In the clinical trials of ED and BPH, additional exclusions were significant cardiovascular disease such as myocardial infarction within 90 days before screening, unstable angina or angina occurring during sexual intercourse, uncontrolled arrhythmias, and stroke within the 6 months prior to screening. In ED studies, additional exclusions were New York Heart Association Class 2 or greater heart failure in the 6 months prior to screening or conditions which may predispose patients to priapism. Additional exclusions in the BPH programme included New York Heart Association Class 3 or greater heart failure in the 6 months prior to screening or clinical evidence of prostate cancer.

In the PAH development programme, the following populations were excluded: women who were nursing or pregnant, paediatric patients <12 years of age, patients with cardiovascular disease such as significant aortic or mitral valve disease, pericardial constriction, restrictive or congestive cardiomyopathy, significant left ventricle dysfunction, life-threatening arrhythmias, and symptomatic coronary artery disease.

In light of the extensive post-authorisation experience, with >57 million estimated postmarketing patient exposures worldwide, the pre-authorisation phase population limitations have either been adequately addressed in the labelling or have not given rise to any safety concerns in clinical practice. Exclusion criteria resulting in contraindications have allowed for appropriate patient selection in clinical practice to minimise risk. The safety of tadalafil in populations such as patients with hepatic or renal impairment, are regularly assessed and have been presented in the periodic safety update reports since the first tadalafil marketing authorisation. No new risks or specific issues relating to these populations have been observed.

Table SIV.4. Exclusion Criteria Which Will Remain as Contraindications for Erectile Dysfunction

Erectile Dysfunction Indication	
Criteria	**Implications for target population**
Co-administration of tadalafil with any form of organic nitrate	The concomitant use of tadalafil with nitrates is contraindicated due to the augmentation of hypotensive effects of nitrates. Drug utilisation studies suggest that there is very limited coadministration of tadalafil with nitrates.
Use in patients with a known hypersensitivity to tadalafil or any component of the tablet	In patients known to be hypersensitive to tadalafil or other constituents of the product, severe allergic reactions may occur.
Use in patients with hypotension (<90/50 mm Hg)	Tadalafil is a mild vasodilator, so in this population tadalafil may induce a further blood pressure decrease resulting in symptomatic hypotension.
Use in patients with myocardial infarction within last 90 days	Sexual activity carries a potential cardiac risk for patients with cardiovascular disease. Therefore, tadalafil should not be used in patients with cardiac disease for whom sexual activity is inadvisable. Patients with significant cardiovascular disease have a high risk of serious complications. Additionally, patients with myocardial infarction are likely to require treatment with nitrates.
Use in patients with significant cardiovascular disease (Unstable angina/angina during intercourse, Significant cardiac disease making intercourse inadvisable, Clinically significant heart failure, Uncontrolled arrhythmias or hypertension, Stroke)	Sexual activity carries a potential cardiac risk for patients with cardiovascular disease. Therefore, tadalafil should not be used in patients with cardiac disease for whom sexual activity is inadvisable. Patients with significant cardiovascular disease have a high risk of serious complications. Additionally, patients with unstable angina are likely to require treatment with nitrates.

Table SIV.5. Exclusion Criteria Which Will Remain as Contraindications for Benign Prostatic Hyperplasia

Benign Prostatic Hyperplasia Indication	
Criteria	**Implications for target population**
Co-administration of tadalafil with any form of organic nitrate	The concomitant use of tadalafil with nitrates is contraindicated due to the augmentation of hypotensive effects of nitrates.
Use in patients with a known hypersensitivity to tadalafil or any component of the tablet	In patients known to be hypersensitive to tadalafil or other constituents of the product, severe allergic reactions may occur.
Use in patients with hypotension (<90/50 mm Hg)	Tadalafil is a mild vasodilator, so in this population tadalafil may induce a further blood pressure decrease resulting in symptomatic hypotension.
Use in patients with myocardial infarction within last 90 days	Patients with significant cardiovascular disease have a high risk of serious complications. Additionally, patients with myocardial infarction are likely to require treatment with nitrates.
Use in patients with significant cardiovascular disease (Unstable angina/angina during intercourse, Significant cardiac disease making intercourse inadvisable, Clinically significant heart failure, Uncontrolled arrhythmias or hypertension, Stroke)	Sexual activity carries a potential cardiac risk for patients with cardiovascular disease. Therefore, tadalafil should not be used in patients with cardiac disease for whom sexual activity is inadvisable. Patients with significant cardiovascular disease have a high risk of serious complications. Additionally, patients with unstable angina are likely to require treatment with nitrates.

Table SIV.6. Exclusion Criteria Which Will Remain as Contraindications for Pulmonary Arterial Hypertension

Pulmonary Arterial Hypertension Indication	
Criteria	**Implications for target population**
Co-administration of tadalafil with any form of organic nitrate	The concomitant use of tadalafil with nitrates is contraindicated due to the augmentation of hypotensive effects of nitrates.
Use in patients with a known hypersensitivity to tadalafil or any component of the tablet	In patients known to be hypersensitive to tadalafil or other constituents of the product, severe allergic reactions may occur.
Use in patients with hypotension (<90/50 mm Hg)	Tadalafil is a mild vasodilator, so in this population tadalafil may induce a further blood pressure decrease resulting in symptomatic hypotension.
Use in patients with myocardial infarction within last 90 days	Patients with significant cardiovascular disease have a high risk of serious complications. Additionally, patients with myocardial infarction are likely to require treatment with nitrates.

Table SIV.7. Exclusion Criteria which are NOT Proposed to Remain as Contraindications for Erectile Dysfunction and Benign Prostatic Hyperplasia Indications

Erectile Dysfunction and Benign Prostatic Hyperplasia Indication		
Criteria	**Reason for being an Exclusion Criterion**	**Justification for Not being a Contraindication**
Once-a-day dosing in patients with severe renal impairment.	Due to increased tadalafil exposure (AUC), limited clinical experience and the lack of ability to influence clearance by dialysis	Although tadalafil exposure in patients with severe renal impairment would be expected to be increased, the low daily doses administered are within the range of doses that have been safely administered in clinical trials, as the 5 mg daily dose results in tadalafil exposure that is no greater than doses of 20 mg taken 2 – 3 times weekly. The postmarketing experience in patients with renal impairment has not identified any new safety concerns for tadalafil use in this population. The SmPC includes a warning that the use of tadalafil once-daily is not recommended in patients with severe renal failure.
Patients with conditions which may predispose them to priapism	These conditions may predispose patients to the risk of priapism and may confound efficacy results.	Although priapism is a class warning for PDE5 inhibitors, the event has been very rarely reported with tadalafil in the postmarketing setting. The overall risk of this event is considered low and it is monitorable and treatable. The SmPC includes a warning that tadalafil should be used with caution in patients with conditions that may predispose to priapism.
Patients with hepatic insufficiency, including Child-Pugh Class C	There is limited clinical data on the safety of single-dose administration of tadalafil in patients with severe hepatic insufficiency (Child-Pugh Class C). Once-a-day dosing has not been evaluated in patients with hepatic insufficiency.	The exposure of tadalafil in patients with hepatic insufficiency appears to be reduced. Patients with severe hepatic insufficiency were not studied, so the impact is unknown. In patients with mild and moderate hepatic impairment (Child-Pugh Class A and B) tadalafil exposure (AUC) is comparable to exposure in healthy subjects when a dose of 10 mg is administered. The postmarketing experience in patients with hepatic impairment has not identified any new safety concerns for tadalafil use in this population. The SmPC includes a warning that if tadalafil is prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician.

Table SIV.8. Exclusion Criteria which are NOT Proposed to Remain as Contraindications for Pulmonary Arterial Hypertension Indication

Pulmonary Arterial Hypertension Indication		
Criteria	**Reason for being an Exclusion Criterion**	**Justification for Not being a Contraindication**
Patients with severe hepatic impairment, Child-Pugh Grade C	There is limited clinical data on the safety of single-dose administration of tadalafil in patients with severe hepatic insufficiency (Child-Pugh Class C). There are no available data about the administration of doses higher than 10 mg of tadalafil to patients with hepatic impairment.	A careful individual benefit/risk evaluation should be undertaken by the prescribing physician; in some patients the benefit may exceed the risk. However, tadalafil exposure (AUC) in patients 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. The postmarketing experience in patients with hepatic impairment has not identified any new safety concerns for tadalafil use in this population. The SmPC includes a warning that patients with severe hepatic cirrhosis (Child-Pugh Class C) have not been studied and therefore tadalafil use is not recommended.
Patients with severe renal insufficiency	Due to increased tadalafil exposure (AUC), limited clinical experience and the lack of ability to influence clearance by dialysis	A careful individual benefit/risk evaluation should be undertaken by the prescribing physician; in some patients the benefit may exceed the risk. The postmarketing experience in patients with renal impairment has not identified any new safety concerns for tadalafil use in this population. The SmPC includes language that indicates in patients with severe renal impairment the use of tadalafil is not recommended.
Patients with the following cardiovascular disease: • clinically significant aortic and mitral valve disease • pericardial constriction • restrictive or congestive cardiomyopathy • significant left ventricular dysfunction • life-threatening arrhythmias • symptomatic coronary artery disease • uncontrolled hypertension	This purpose of this criterion was to prohibit patients who have physical existing conditions that would confound the trial results and minimise risk in patients in a clinical trial setting.	A careful individual benefit/risk evaluation should be undertaken by the prescribing physician; in some patients the benefit may exceed the risk. The SmPC includes a warning that since there are no clinical data on the safety of tadalafil in these patients, the use of tadalafil is not recommended.

SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

SIV.3.1. Children

ED and BPH

Erectile dysfunction and BPH disease states are not relevant in children and teenagers.

PAH

Clinical studies of tadalafil for the treatment of PAH did not exclude patients who were less than 18 years of age and greater than 12 years of age, although only 1 patient in this age group was enrolled. Currently tadalafil is under investigation for the treatment of PAH in paediatric patients.

There are postmarketing reports of off-label use in PAH patients under 18 years of age. Reviews of these cases have not raised any new safety concerns.

SIV.3.2. Elderly

ED and BPH

The CHMP indicated that the safety profile of the use of once-a-day tadalafil in elderly patients (≥65 years) for the ED and BPH indications is not well characterised and may potentially present additional risks in the elderly population (≥65 years). As a result, it has been requested that the safety profile in elderly patients (≥65 years) be included in the RMP as important missing information.

The elderly population in the once-a-day ED and BPH clinical trials was representative of the age distribution of patients anticipated to be treated for either ED or BPH in clinical practice. In the pivotal ED studies, approximately 25% of patients were >65 years of age; in the pivotal BPH studies approximately 41% of patients were ≥65 years of age. A further analysis was performed that included the integrated BPH database, additional Asian studies of men with BPH, and the integrated once-a-day ED studies. This analysis revealed that 1272 patients (38% of the total population) in the combined ED and BPH databases were ≥65 years of age. In this dataset, there were generally no meaningful differences in the safety profile of the elderly (≥65 years) compared with the non-elderly (<65 years).

Based upon annual reviews of postmarketing and clinical trial data, the MAH has found that there were no clinically meaningful differences in the safety profile in the elderly population (≥65 years) compared with the non-elderly (<65 years) in a combined analysis of ED and BPH patients. Given the fact that elderly patients often have multiple comorbidities and may be taking many concomitant medications, they may be at a higher risk for certain adverse drug reactions (ADRs) for tadalafil (for example, hypotensive events). Thus, the MAH will continue to monitor adverse events in the elderly through routine pharmacovigilance activities.

PAH

Approximately 28% of the patients enrolled in the PAH trial LVGY were elderly (≥65). The clinical trial data do not suggest that there are clinically important differences in the safety profile of tadalafil in elderly PAH patients compared with those that are nonelderly. In addition, the postmarketing experience has not revealed any safety concerns for the use of tadalafil in elderly PAH patients.

SIV.3.3. Pregnant or Breast-feeding Women

ED and BPH

Erectile dysfunction and BPH disease states are not relevant in women.

PAH

PAH is a disease that affects predominantly women, including those of childbearing age. Women who were nursing or pregnant were excluded from participation in PAH trials. Females of childbearing potential were enrolled only if they agreed to use 2 medically reliable methods of contraception (for example, barrier with spermicidal or hormonal contraception) until study completion.

A cumulative review of pregnancy and lactation cases from tadalafil clinical trials, postmarketing reports, and spontaneous reports through 15 January 2016 did not reveal any new important safety concerns.

SIV.3.4. Patients with Hepatic Impairment

ED and BPH

In clinical practice, ED and BPH patients with severe hepatic impairment would not commonly be treated with tadalafil.

Tadalafil data in patients with mild-to-moderate hepatic impairment is limited, but exposure is comparable in these patients to healthy subjects when a single dose of 10 mg is administered. Clinical data are also limited in patients with severe hepatic impairment (Child-Pugh Class C). Thus, in ED patients administered tadalafil on-demand with any severity of hepatic impairment, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician. Once-a-day dosing of tadalafil for ED or BPH has not been evaluated in men with hepatic impairment. In these patients, daily dosing is not recommended.

The postmarketing experience has not revealed any new safety concerns for tadalafil use in ED or BPH patients with hepatic impairment.

PAH

Patients with PAH may have comorbid hepatic impairment as part of their underlying disease.

Due to limited clinical experience in patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A and B), following single doses of 10 mg, a starting dose of 20 mg once per day may be considered. If tadalafil is prescribed, a careful individual benefit/risk evaluation should

be undertaken by the prescribing physician. Patients with severe hepatic cirrhosis (Child-Pugh Class C) have not been studied and therefore dosing of tadalafil is not recommended.
The postmarketing experience has not revealed any new safety concerns for tadalafil use in PAH patients with hepatic impairment.

SIV.3.5. Patients with Renal Impairment

All Indications

As diabetes commonly co-exists with ED and BPH, and renal dysfunction may co-exist with BPH, the presence of some level of renal impairment in these patient populations is not unexpected.

Pulmonary arterial hypertension patients may have some renal impairment as a sequella of their disease.

Patients with severe renal impairment have generally been excluded from clinical trials across all indications. 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, once-a-day dosing of tadalafil is not recommended in patients with severe renal impairment in either the CIALIS or ADCIRCA SPC.

The postmarketing experience has not revealed any new safety concerns for the use of tadalafil in patients with renal impairment.

SIV.3.6. Patients with Other Relevant Co-morbidities

ED and BPH

The ED and ED/BPH clinical development programmes included patients with common co-morbidities, such as hypertension, diabetes, and cardiovascular disease. The postmarketing experience has not revealed any new safety concerns for tadalafil use in ED and BPH patients with comorbid conditions.

PAH

The PAH clinical development programme included patients with co-morbid connective tissue disease. The postmarketing experience has not revealed any new safety concerns for tadalafil use in PAH patients with comorbid conditions.

SIV.3.7. Patients with a Disease Severity Different from the Inclusion Criteria in the Clinical Trial Population

ED and BPH

CIALIS is indicated for the treatment of ED on-demand or once-a-day, as well as for the treatment of signs and symptoms of BPH, regardless of disease severity. The clinical

development programmes included patients with a broad range of disease severities. The postmarketing experience does not suggest any important differences in the safety of tadalafil based upon disease severity.

PAH

ADCIRCA is indicated in adults for the treatment of PAH classified as WHO functional class II and III, to improve exercise capacity. It is unknown whether ADCIRCA is less effective in patients with WHO functional class I and class IV, because of the limited clinical trial data in these patients. Postmarketing data does not suggest significant use of the ADCIRCA in patients with WHO functional class I and IV; however, information on WHO functional class is generally not provided in postmarketing reports.

SIV.3.8. Sub-populations Carrying Known and Relevant Polymorphisms

Not applicable.

SIV.3.9. Patients of Different Racial and/or Ethnic Origin

At this time, there are no known clinically important racial or ethnic differences in the pharmacokinetics, efficacy, or frequency of adverse reactions. The postmarketing experience with >57 million patients exposed to tadalafil, does not suggest any adverse effects attributable to differences in racial or ethnic origin.

ED and BPH

Multiple studies of tadalafil on-demand for the treatment of Asian men with ED were conducted; results were similar to those in non-Asian men. In addition, results from 3 BPH studies to support registration in Japan are generally consistent with results of the 4 pivotal studies that supported tadalafil authorisation for the treatment of signs and symptoms of BPH in the EU.

PAH

Although there were a limited number of patients enrolled in PAH clinical trials that were non-Caucasian, there are no known differences in efficacy or safety of tadalafil in these populations.

SIV.4. Conclusions on the Populations Not Studied and other Limitations of the Clinical Trial Development Programme

During the clinical trial development programme of tadalafil, there have been populations not studied and other limitations, as described in previous sections. These pre-authorisation phase population limitations are considered minimal in light of the extensive post-authorisation safety experience with more than 57 million patient exposures.

The CHMP has determined that the safety profile for the use of once-a-day tadalafil in elderly patients (≥65 years) for the ED and BPH indications is not well characterised and may potentially present additional risks. As a result, it has been included in the RMP as important

missing information. At this time, there is no evidence of this concern. The necessity to continue to consider the elderly as missing information will be re-evaluated in the next update of the RMP in the light of existing and new information.

Table SIV.9. Safety Concerns due to Limitations of the Clinical Trial Programme

		Outstanding Concern?
Safety Concern	**Comment**	**Yes/No**
1	Characterisation of adverse events in elderly patients (≥65 years of age)	Yes

Module SV. Post-authorisation Experience

SV.1. Action Taken by Regulatory Authorities and/or Marketing Authorisation Holders for Safety Reasons

There were no new company initiated significant actions taken for safety reasons in the last RMP update (version 7). In August 2014 the tadalafil Core Data Sheet (CDS), Special Warnings and Special Precautions for Use, was updated to add a warning regarding the use of the combination of tadalafil and guanylate cyclase stimulators, such as riociguat, since it may lead to symptomatic hypotension. This update was initiated based on the review of the riociguat label in which the concomitant administration of riociguat with PDE5 inhibitors (such as sildenafil, tadalafil, and vardenafil) is contraindicated because of a potential increased risk of hypotension. As a result of the CDS update, requests were made to regulatory authorities to update local labels accordingly. In the EU, this submission resulted in a Contraindication for the concomitant use of riociguat and tadalafil in the EU Summary of Product Characteristics (SmPC) for tadalafil. Lilly did not agree with the proposed location of the new safety label language, because there is insufficient evidence to support a Contraindication in the tadalafil label as described in the previous PSUR/PBRER; however, Lilly accepted the proposed label language change to be consistent with the class statement for PDE5 inhibitor products.

Significant actions taken for safety reasons since the last RMP update are detailed in Table SV.1 and the cumulative list of actions is provided in Table SV.2.

Table SV.1. Detailed Description of Actions Taken since Last Update to this Module

Safety Issue 1: Sudden Hearing Loss	
Background to Issue	A cumulative review was performed to evaluate the association between sudden hearing loss and tadalafil because since the previous review in 2007, the increase in the number of patients in the tadalafil clinical trial database for the ED as needed (PRN) indication and the accumulation of postmarketing reports and scientific literature warranted an updated comprehensive review.
Evidence Source	Nonclinical studies, clinical trials, postmarketing safety studies, pharmacoepidemiological studies, published scientific literature, and spontaneously reported adverse events (AEs) from postmarketing experience cumulatively through 14 February 2015.
Action Taken	Based upon the cumulative review, Lilly determined that SHL remains an important potential risk for PDE5 inhibitors, including tadalafil. Given that SHL is an otologic emergency, and prompt treatment is crucial, a new Warning and Precaution was added to the tadalafil CDS. A proposed change to Section 4.4 of the EU SmPC for both Cialis and Adcirca was submitted for review: following comments from Member States, Lilly was requested to supply a cumulative review as a follow-up measure.
Countries Affected	Global; EU regulatory procedure planned
Date of Action	01 Jul 2015

Safety Issue 2: Non-Arteritic Anterior Ischaemic Optic Neuropathy (NAION)	
Background to Issue	The results of the Pfizer observational study on NAION were published.
Evidence Source	Campbell et al. 2015
Action Taken	Based upon the review of this publication, Lilly determined that the data from this observational study should be added to the NAION language in the Warning and Precautions Section of the tadalafil CDS. Lilly proposed EU label updates related to the risk of NAION as part of the PSUR (16 October 2014 – 15 October 2015) for tadalafil in December 2015; following the subsequent PRAC recommendation, the results of the Lilly observational study LVHQ, examining the association between PDE5 inhibitors and NAION, are now being provided before a decision is made on whether or not to include the proposed updates in the SmPC.
Countries Affected	Global; EU regulatory procedure ongoing
Date of Action	01 Jul 2015

Abbreviations: EU=European Union; PSUSA= Periodic Safety Update Report EU single assessment.

Table SV.2. Cumulative List of Actions Taken

Coadministration with Guanylate Cyclase Stimulators			
Countries	**Action Taken**	**Comment**	**Date(s)**
United States and the EU	USPIs, PPIs and EU SmPCs.	A Contraindication for the concomitant use of guanylate cyclase stimulators, such as riociguat, and tadalafil was approved for the Adcirca and Cialis USPIs, PPIs and EU SmPC.	Adcirca and Cialis – Aug 2015 (EU) Adcirca – April 2015 and Cialis – Sept 2015 (US)
Hearing Loss and Sudden Deafness			
Countries	**Action Taken**	**Comment**	**Date(s)**
United States (FDA)	USPI labelling change	Following FDA cumulative review of hearing loss/hearing impairment in patients treated with PDE5 inhibitors including tadalafil, sudden hearing loss (otologic) language was provided under PRECAUTIONS, ADVERSE REACTIONS, and Postmarketing surveillance sections of USPI.	October 2007

Combination with other PDE5 Inhibitors			
Countries	**Action Taken**	**Comment**	**Date(s)**
EU, Norway and Iceland	CIALIS SPC updated	Type II variation approved to add wording to Section 4.4 (Special warnings and precautions for use) regarding the safety and efficacy of combinations of ADCIRCA and other PDE5 inhibitors or other treatments for erectile dysfunction.	November 2010
EU, Norway and Iceland	ADCIRCA SPC updated	Type II variation approved to add wording to Section 4.4 (Special warnings and precautions for use) regarding the safety and efficacy of combinations of CIALIS and other PDE5 inhibitors.	September 2010
United States	USPI labelling change	Description of change: Section 5.11 Combination With Other Erectile Dysfunction Therapies Added the wording "PDE5 inhibitors" to Section 5.11 subheading and to the statement in Section 5.11 that discusses concomitant use of tadalafil with other treatments for ED.	July 2009

Nonarteritic Anterior Ischaemic Optic Neuropathy (NAION)			
Countries	**Action Taken**	**Comment**	**Date(s)**
Australia and New Zealand (TGA)	Label update	The labels for Australia and New Zealand contain a contraindication requested by the Australian regulatory authority (TGA) as follows: **Contraindications** Tadalafil is contraindicated in patients who have loss of vision in one eye because of nonarteritic anterior ischaemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous PDE5-inhibitor exposure (see PRECAUTIONS).	July 2006

EU (EMEA)	CIALIS SPC update	**Update to Summary of Product Characteristics (SPC)** Following the review of the MAH response to supplementary information on NAION and PDE5 inhibitors, CHMP requested a submission of a Type II variation to update Section *4.3, Contraindications*, *4.4 Special warnings and special precautions for use* and *4.8 Undesirable effects* of the SPC. In response to this request, the MAH submitted a Type II variation on 07 February 2006. A positive CHMP opinion was adopted on 27 April 2006 and the European Commission Decision was received on 12 June 2006. Following the review of the 6 monthly Periodic Safety Update Reports (PSUR) 05 and 06, CHMP requested a submission of a Type II variation to update Section *4.8 Undesirable effects* of the SPC to add the term epistaxis. In response to this request, the MAH submitted a Type II variation on 20 April 2006.	June 2006
Canada (Health Canada)	Dear Healthcare Professional Letter issued	A 'Dear Healthcare Professional Letter' and "Public Communication" was released in Canada for PDE5-inhibitor class medications regarding reports of vision loss including NAION.	June 2006

US (FDA)	USPI labelling change	Due to a FDA request, the MAH on 17 May 2006 updated the USPI to include the following wording to the Special Warnings and Precautions for Use section: "Nonarteritic anterior ischemic optic neuropathy (NAION) is a cause of decreased vision including permanent loss of vision. There are rare postmarketing reports of NAION in temporal association with the use of all PDE5 inhibitors. Currently it is not possible to determine whether NAION is related directly to the use of PDE5 inhibitors or other factors. Physicians should advise patients to stop use of tadalafil and seek medical attention in the event of a sudden loss of vision. Physicians should also discuss with patients that individuals who have already experienced NAION are at increased risk of NAION."	May 2006

EU (EMEA)	CIALIS SPC update	Following the review of information on certain visual adverse events, the CHMP requested (13 October 2005) updates to Section 4.8 *Undesirable effects* and Section 5.1 *Pharmacodynamic properties* (if relevant) of the SPC for tadalafil. In response to this request, the MAH submitted a Type II variation on 07 July 2005. Subsequently, the CHMP also requested that Section 4.4 *Special warnings and special precautions for use* be updated. Therefore, the summary of changes included in the proposed SPC is as follows: Section 4.4: The use of PDE5 inhibitors is not recommended in patients with a previous episode of NAION. Section 4.8: Non-arteritic anterior ischemic optic neuropathy (NAION), blurred vision, retinal vascular occlusion, and visual field defect.	October 2005

EU (EMEA)	CIALIS SPC update	As mentioned in PSUR 06 (16 April 2005 – 15 October 2005), following a review of selected visual adverse events, the CHMP requested the submission of a Type II variation to update Section *4.8 Undesirable effects* and *5.1 Pharmacodynamic properties* (if relevant) of the SPC for tadalafil. In addition, the CHMP also requested the update of *Section 4.4 Special warnings and special precautions for use.* A positive CHMP opinion for this variation was adopted on 13 October 2005 and the European Commission Decision was received on 15 November 2005. In addition to the above mentioned Type II variation, the CHMP also requested that the MAH submit supplementary information on NAION and PDE5 inhibitors. Following the review of our response, CHMP requested a submission of a Type II variation to update Section *4.3 Contraindications*, *4.4 Special warnings and special precautions for use* and *4.8 Undesirable effects* of the SPC. In response to this request, the MAH submitted a Type II variation on 07 February 2006. A positive CHMP opinion was adopted on 27 April 2006 and the European Commission Decision was received on 12 June 2006.	November 2005

Hepatotoxicity			
Countries	**Action Taken**	**Comment**	**Date**
EU (EMEA)	CIALIS SPC update	A type II variation to the SPC was submitted on 13 May 2003 with regard to the use of tadalafil in patients with impaired renal function. In addition, information on the use of tadalafil in patients with impaired hepatic function, already included in Section 4.4 of the SPC, was introduced in Sections 4.2 and 5.2: • caution is advised in severe hepatically impaired patients due to limited clinical data • 10 mg is the maximum recommended dose in severe renally impaired patients • haemodialysis contributes negligibly to tadalafil elimination A positive CPMP opinion was adopted on 25 September 2003 and the European Commission decision was received January 2004.	January 2004

Priapism			
Countries	**Action Taken**	**Comment**	**Date**
EU (EMEA)	CIALIS SPC update	Following the review of the first PSUR covering the reporting period of 15 October 2002 to 15 April 2003, the CPMP requested the MAH to include information on *priapism* and *erection increased* as adverse reactions possibly related to tadalafil. Company has included further information on priapism and erection increased as possible adverse reactions in Section 4.9 of the SPC. A positive CPMP opinion was adopted on 26 February 2004 and the European Commission decision was received 26 February 2004.	July 2004

SV.2. Non-study Post-authorisation Exposure

SV.2.1. Method used to Calculate Exposure

The methodology uses internal bulk sales data, samples distributed, IMS Midas days of therapy and standard units, IMS National Disease and Therapeutic Index data, IMS National Prescription Audit, and IMS age and gender data. A weighted average of the total possible days of therapy from the internal bulk sales data and the IMS Midas data was determined. The possible days of therapy were then factored by an average length of therapy and average courses of treatment, assumptions to determine the patient exposure estimate for each country or region. Other common assumptions, such as the amount of drug not ingested and the amount of product in inventory, were not included; thus, the resulting patient exposure estimates do not account for product that may not have reached patients.

Please note that Lilly does not currently have sufficient data available to calculate an average length of therapy per patient or distribution patients by age and gender for the ADCIRCA brand of tadalafil. As such, the ADCIRCA patient exposure estimate is provided in terms of patient years and no age and gender distribution is included in this report.

SV.2.2. Exposure

Table SV.3. Postmarketing Exposure by Age Group and Gender

	Gender			
Age Group	**Male**	**Female**	**Not Reported**	**Totals[a]**
Cialis PRN				
0 to 17 years	30,000	4,000	0	35,000
18 to 65 years	34,479,000	161,000	24,000	34,665,000
>65 years	12,053,000	39,000	7,000	12,100,000
Not Reported	770,000	0	25,000	796,000
Total[a]	**47,334,000**	**205,000**	**57,000**	**47,597,000**
Cialis QD				
0 to 17 years	6,000	900	0	7,000
18 to 65 years	7,530,000	35,000	5,000	7,571,000
> 65 years	2,632,000	8,000	1,000	2,642,000
Not Reported	168,000	0	5,000	173,000
Total[a]	**10,338,000**	**44,000**	**12,000**	**10,395,000**
Adcirca				
0 to 17 years	1,600	2,500	--	4,100
18 to 65 years	26,000	50,100	--	76,200
> 65 years	12,000	22,300	--	34,400
Total[a]	**39,700**	**75,100**	**--**	**114,800**

Abbreviations: PRN = as needed; QD=once daily.

[a] Totals may not sum due to independent rounding.

Table SV.4. Postmarketing Exposure by Indication

Data not available.

Indication	Persons	Exposure
N/A	N/A	N/A

Abbreviation: N/A = not available.

Table SV.5. Postmarketing Exposure by Route of Administration

Route of Administration	Persons	Exposure
N/A	N/A	N/A

Abbreviation: N/A = not available.

Table SV.6. Postmarketing Exposure by Country/Region

Country/Region	Cumulative Patients	Cumulative Patient Years
Cialis PRN		
Europe	14,755,000	1,393,000
Japan	720,000	67,000
United States	15,462,000	1,587,000
Other Countries	16,659,000	1,550,000
Worldwide[a]	**47,597,000**	**4,599,000**
Cialis QD		
Europe	2,326,000	668,000
Japan[b]	402,000	115,000
United States	5,204,000	1,496,000
Other Countries	2,461,000	707,000
Worldwide[a]	**10,395,000**	**2,988,000**
Adcirca		
Europe	17,000	15,000
Japan	14,000	13,000
United States	79,000	72,000
Other Countries	3,000	3,000
Worldwide[a]	**114,800**	**105,000**

Abbreviations: PRN = as needed; QD=once daily.

[a] Worldwide totals may not sum due to independent rounding;

[b] Trade name in Japan is Zalutia.

SV.3. Post-authorisation Use in Populations not Studied in Clinical Trials

No market research or drug utilisation data are available in the following populations: paediatrics, elderly, pregnant or lactating women, hepatic impairment, renal impairment, or other use.

SV.4. Post-authorisation Off-label Use

There is limited information in the published literature documenting the off-label use of tadalafil in clinical practice. There have been a few reports received by the MAH regarding the use of tadalafil for sexual enhancement in women. There have also been reports in the literature of the use of tadalafil in patients with Raynaud's disease (Roustit et al. 2013), paediatric PAH (Baquero et al. 2006; Takatsuki et al. 2012), and cystic fibrosis (Poschet et al. 2006). Tadalafil is approved for the treatment of ED and BPH, disease states not typically afflicting children and teenagers; therefore, a limited potential for paediatric off-label use for these indications exists. Tadalafil also is approved (in some regions) for the treatment of PAH in patients ≥18 years of age. However, PAH is a disease state that also afflicts children and teenagers; therefore, a potential for paediatric off-label use for this indication exists. Tadalafil has been used in paediatric patients with PAH (Takatsuki et al. 2012; Kohno et al. 2014; Sabri and Beheshtian 2014) and in exercise-induced skeletal muscle ischaemia in boys with Duchenne muscular dystrophy (DMD) (Nelson et al. 2014). To date, the MAH has only received a small number of postmarketing

reports from the EU of tadalafil use in paediatric patients. A review of these reports did not identify any new safety concerns.

No market research/drug utilisation data are available that describe off-label use in the EU.

SV.5. Epidaemiological Study Exposure

Tadalafil epidaemiological studies are listed in Table SV.7.

Table SV.7. Epidaemiological Studies

Study Title and Study Type	Objective(s)	Population Studied	Duration	Number of Persons and Person Time	Comment
PEM Study - An observational cohort study investigating the cardiovascular safety of tadalafil when prescribed in primary care in England: mortality due to ischaemic heart disease	To examine the safety of tadalafil and to compare the mortality rate due to IHD in tadalafil users with that in the male population in England.	Patients prescribed tadalafil in England identified using data from dispensed NHS prescriptions, written by general practitioners	At least 6 months after the issue of first prescription The median duration of observation is 282 days	6266 patients Total patient months (60,130) of observation during whole study period	Study Published (Hazell et al. 2007)
PEM Study - The safety profile of tadalafil as prescribed in general practice in England: results from a prescription-event monitoring study involving 16,129 patients	To examine the safety of tadalafil as used in general practice in England, and to compare the mortality rate due to IHD) in tadalafil users with that in the male population in England.	Patients prescribed tadalafil in England identified using data from dispensed NHS prescriptions, written by general practitioners	At least 12 months after the issue of first prescription Median duration of observation is 490 days	16,129 patients Total patient months (277,195) of observation during whole study period	Study Published (Hazell et al. 2009)
H6D-MC-LVHQ: A Prospective Case-Crossover Study to Evaluate the Possible Association Between the Use of PDE5 Inhibitors and the Risk of Acute Nonarteritic Anterior Ischemic Optic Neuropathy (NAION)	To evaluate the possible association between the use of PDE5 inhibitors and the acute risk of NAION	Male patients in the United States aged ≥18 who experienced abrupt visual loss in 1 eye and had a diagnosis of NAION within 45 days of onset of NAION symptoms to initial visit to an ophthalmologist	Single visit study; subjects were enrolled within 45 days of the NAION onset	Of 279 subjects with adjudication-confirmed NAION 26 reported PDE5 inhibitor use in the 12 months prior to NAION onset and enrolment in study.	Study report completed May 2016

Study Title and Study Type	Objective(s)	Population Studied	Duration	Number of Persons and Person Time	Comment
B009 study (i3 study)	The primary objective of this study was to estimate the rate of codispensing of organic nitrates and tadalafil in a cohort of tadalafil recipients.	Male patients in the United States aged 18+ filling PDE5 inhibitors	54.1% patients were followed up within one year, 45.9% patients were followed up more than one year.	Tadalafil patients: 35,436; Sildenafil patients: 35,436; Vardenafil: patients: 24,400	Study report completed May 2007
B009 study (IMS Study)	To compare the proportion of patients who are dispensed nitrates among those on tadalafil compared to a control group of patients. In addition, determine the proportions of patients dispensed the PDE5 inhibitors sildenafil or vardenafil who also are codispensed nitrates.	Male patients in the United States aged 18+ filling PDE5 inhibitors	Over a period of 28 months was assessed.	2,391,030 patients with at least 1 Rx of PDE5 inhibitors, includes 601,063 (25.2%) tadalafil patients	Study report completed September 2007
H6D-JE-B012	To confirm the efficacy and safety of CILAIS for ED patients in the clinical practice	Japanese patients with ED prescribed CIALIS during study period	3 months after starting CIALIS. Additional 6 months for patients if dose is increased up to 20 mg	Completed	Study completed January 2012
H6D-KL-B019	To estimate the frequency of treatment-emergent adverse events and serious adverse events among Korean patients with BPH under CIALIS 5 mg once a day therapy in a normal clinical practice setting.	Korean patients with BPH prescribed CIALIS during study period	12 to 24 months after starting CIALIS	At least 600 patients included in safety analysis (Korea regulatory requirements)	Study ongoing
H6D-JE-TD01	To investigate the long-term safety and effectiveness of ADCIRCA in PAH patients in the clinical practice	Japanese patients with PAH prescribed ADCIRCA during study period	up to two years after initiation of ADCIRCA	During the enrolment period (until February 2014), a total of 1809 patients were enrolled in the study. A total of 1676 cases were analysed for safety	Study completed 22 March 2016

Study Title and Study Type	Objective(s)	Population Studied	Duration	Number of Persons and Person Time	Comment
H6D-JE-B020	Post-Marketing Observational Study of Tadalafil in Japanese Patients with Benign Prostatic Hyperplasia-Lower Urinary Tract Symptom (BPH-LUTS)	Japanese men with BPH-LUTS	September 2014 to March 2017	Number of patients enrolled: 1507	Data collection: started Expected study completion date: April 2018
H6D-GH-B022	To investigate the long term safety profile (frequency/severity of all AEs) of tadalafil in ED patients, including the characterisation of AEs in patients aged 22 to 69 years under daily clinical practice	Adult, Chinese men with ED	24 months (3 months in Study Period 1 and 21 months in Study Period 2)	Number of randomised patients: 635	Study ongoing (Data collection started)

Abbreviations: PEM = Prescription Event Monitoring; Rx = prescription; ED = erectile dysfunction; BPH = benign prostate hyperplasia; PAH = pulmonary arterial hypertension; PDE5 = phosphodiesterase type 5; NAION = nonarteritic anterior ischemic optic neuropathy; IHD = ischaemic heart disease; NHS = National Health Service.

Module SVI. Additional EU Requirements

SVI.1. Potential for Harm from Overdose

Tadalafil has a low potential for serious consequences from accidental or intentional overdose. Single doses of tadalafil of up to 500 mg have been given to healthy subjects, and multiple-daily doses up to 100 mg have been given to patients; adverse events (AEs) were similar to those seen at lower doses. Tadalafil displayed less than dose-proportional increase in exposure with doses greater than 20 mg, with both rate and extent of absorption decreasing as doses increased (Study LVCS). Occasional cases of prescribed, accidental, and intentional overdose have been reported in the postmarketing database. These cases have not resulted in any new safety concerns regarding overdose of tadalafil.

SVI.2. Potential for Transmission of Infectious Agents

Ingestion of tadalafil is unlikely to result in transmission of an infectious agent. Tadalafil is a small molecule given in tablet form. It is highly unlikely that the CIALIS/Tadalafil Lilly tablet contains infectious agents, as described by the "Guideline on Reporting of Suspected Transmission of Any Infectious Agent Via a Medicinal Product" (EMA [WWW]). With the exception of the lactose excipient (a milk product unlikely to present risk of contamination [EMA/410/01]), the reagents and starting materials used in the manufacturing of tadalafil and the excipients in CIALIS/Tadalafil Lilly tablets are from non-animal sources. Microbiological testing of the primary stability lots at product release demonstrated the absence of *E. coli* and *Salmonella* and minimal microbial, mould, and yeast counts and showed that routine testing is not required. Microbiological quality is tested on a non-routine basis (at least 1 lot per year, if manufactured during the year) to the specifications given within the European Pharmacopeia (Ph Eur; Section 5.1.4, Category 3A).

The use of tadalafil offers no protection against sexually transmitted diseases.

SVI.3. Potential for Misuse for Illegal Purposes

Tadalafil has no overt toxic effects in overdose. Further, it does not result in euphoria, central nervous system stimulation, or addictive behaviour, which could make it suitable for illegal use.

SVI.4. Potential for Medication Errors

SVI.4.1. Description of Medication Errors during the Clinical Trial Programme

In the light of the extensive post-authorisation experience, with >57 million estimated post-marketing patient exposures worldwide, medication errors in clinical practice are considered more relevant than medication errors during clinical trials. See SVI.4.4 for description of medication errors with the marketed product.

SVI.4.2. Preventive Measures for the Final Product(s) being Marketed

The prevention of medication errors for marketed products has been addressed by having distinct packaging, tablet colour, and tablet printing for CIALIS on demand, CIALIS once a day, and ADCIRCA.

Additional measures have been taken to assure the appropriate and safe use of tadalafil. Patients are provided with a Package Leaflet for tadalafil which provides information about how the product should be stored, how the product should be administered (for example, oral, with or without food), what to do in case of side effects or overdose, and describes the shape and colour of the tablets. Additionally, in the Package Leaflet, patients are informed to let the doctor know of any other medications they may be taking, not to take more than the total daily dose in a 24-hour period, to take the medication as instructed by the doctor, to take the tablets whole, and not to use tadalafil after the expiry date.

SVI.4.3. Effect of Device Failure

Not applicable.

SVI.4.4. Reports of Medication Errors with the Marketed Product(s)

Table SVI.1. Reports of Medication Errors with the Marketed Product(s)

Tadalafil				
Description of Error	**Number of Occurrences**	**Analysis of Cause**	**Steps taken to Prevent**	**Comment**
Wrong dose (strength, form, concentration, amount)	1018	Patients taking incorrect dose, frequency, splitting tablets, prescribing and dispensing errors	SmPC clearly describes the proper dosing and frequency. Package leaflet states to swallow the tablet whole.	Based upon the postmarketing exposure of >57 million patients, medication errors are very rarely reported. Reviews of these spontaneous reports have not revealed any new safety concerns or any significant new information indicative of systemic errors involving the prescribing, dispensing, or administration of tadalafil.
Wrong patient	69	There have been a limited number of exposures to children and adults	Labelling clearly states that the product must be stored out of the sight and reach of children. To prevent confusion in patients taking multiple medications, tadalafil tablets have a unique shape, colour, and printing.	
Wrong technique	1042	Splitting tablets	Package leaflet states to swallow the tablet whole. To discourage patients from splitting tablets, the tablets are not scored.	
Poor quality drug administered	103	Expired drug taken	Package leaflet states that the product should not be used after expiry date.	
Suspected counterfeit drug	136	N/A	The package leaflet describes the unique shape, colour, and printing on the tablets.	

Abbreviations: N/A = not applicable, SmPC = summary of product characteristics.

SVI.5. Potential for Off-label Use

Limited information is available on the off-label use of tadalafil in adults. There have been reports in the literature of the use of tadalafil in adult patients with Raynaud's disease (Roustit et al. 2013) and a few reports received by the MAH regarding the use of tadalafil for sexual enhancement in women. Based on the data to date, reviews of off-label use have not identified new safety concerns.

SVI.6. Specific Paediatric Issues

SVI.6.1. Issues Identified in Paediatric Investigation Plans

The current Paediatric Investigation Plan (PIP) agreed to with the Paediatric Committee (PDCO) includes the following:

- an ongoing pharmacokinetic study of paediatric patients with PAH (Study LVIG),
- an ongoing placebo-controlled study (Study LVHV), of tadalafil for the treatment of paediatric PAH, and

- two studies (Study LVJD and Study LVJC) of tadalafil for persistent pulmonary hypertension of the newborn (PPHN).

For the LVIG and LVHV studies, the 2-year open-label treatment periods of the studies include safety assessments for growth, neurocognitive development, sexual maturation, and reproductive endocrine function.

For the neonates participating in the PPHN studies, appropriate long-term follow-up safety measures of vision and hearing, neurocognitive development, language and motor development, and respiratory function will be performed according to physical examinations and/or age-appropriate current validated scales.

Table SVI.2. Issues Identified in Paediatric Investigation Plans

Tadalafil PIP (EMA decision P/0118/2012)		
Issue (Safety or Efficacy)	**Background**	**Relevance to Indications covered in this RMP and how, if appropriate, it will be addressed.**
Safety: Visual and hearing acuity	Sudden hearing loss and NAION have been designated as important potential risks for PDE5 inhibitors, including tadalafil, as a result of postmarketing reports in males with ED. Routine pharmacovigilance activities for these events include targeted follow-up investigations. However, the effects of tadalafil in neonates have not previously been studied, thus the potential impact on changes in vision or hearing are unknown.	The events of NAION and sudden hearing loss reported in the post-marketing setting with tadalafil would not be anticipated to affect this young patient population, as both events are most commonly reported in an older, adult population. Treatment of neonates with tadalafil has not previously been studied; therefore, any potential safety issues identified to date with tadalafil will be appropriately monitored. Prior to initiation of the PPHN trials, Study LVIG (PK and safety) will be completed, which includes paediatric patients ≥6 months of age. For the neonates who participate in the PPHN studies, long-term safety follow-up will be conducted to determine any potential impact of tadalafil therapy on this neonatal patient population.
Safety: • Early childhood development (neurocognitive development, language, motor) • Respiratory function	As the effects of tadalafil in neonates have not previously been studied, these developmental issues are of particular interest.	Tadalafil is currently indicated only for the treatment of adult patients, thus these factors are not relevant for the approved indications. For neonates participating in the PPHN studies, assessments of early childhood development and respiratory function will be conducted to determine any potential impact of tadalafil therapy on this patient population.

SVI.6.2. Potential for Paediatric Off-label Use

Tadalafil is approved for the treatment of ED and BPH. Both of these disease states do not typically afflict children and teenagers; therefore, a limited potential for paediatric off-label use for these indications exists.

Tadalafil is approved (in some regions) for the treatment of PAH in patients ≥18 years of age. However, PAH is a disease state that also afflicts children and teenagers; therefore, a potential for paediatric off-label use for this indication exists. There have been publications in the medical literature about the use of PDE5 inhibitors to treat paediatric disorders, including PAH (Baquero et al. 2006; Takatsuki et al. 2012) and cystic fibrosis (Poschet et al. 2006). In addition, the MAH has received postmarketing reports of paediatric off label use.

Although there have been postmarketing reports of off-label tadalafil use in the paediatric population, a review of these cases did not raise any new safety concerns.

SVI.7. Conclusions

In adults, there are post-marketing reports of the off-label use of tadalafil for the treatment of Raynaud's disease and for sexual enhancement in women. Reviews of these cases have not raised any new safety concerns.

Although there is evidence of off-label use of tadalafil in paediatric patients, a cumulative review of these spontaneous cases did not raise any new safety concerns.

The MAH is currently conducting a paediatric development programme for PAH and Duchenne muscular dystrophy (DMD). Completion of the Phase 3 studies will provide important safety and efficacy data for tadalafil in these patient populations.

Module SVII. Important Identified and Potential Risks

SVII.1. Newly Identified Important Safety Concerns (Since this Module was Last Submitted)

There have been no new safety concerns since the last RMP (Version 7 for CIALIS and ADCIRCA).

SVII.2. Recent Study Reports with Implications for Important Safety Concerns

One study, H6D-MC-LVHQ, with implications for the safety concern of NAION has recently been completed.

The primary objective of this study was to evaluate the rate ratio (RR) for NAION occurring in association with exposure to PDE5 inhibitors, defined using the number of days of exposure to PDE5 inhibitors within 30 days before the onset of NAION. The Mantel-Haenszel RR for the risk of NAION associated with PDE5 inhibitor exposure (N=22) within 1 to 5 half-lives of NAION onset was 2.27 (95% confidence interval [CI]: 0.99, 5.20). The sensitivity analyses modifying the exposure definition and imputing missing exposure information were statistically significant. A secondary analysis using the person-time method was conducted to evaluate the association between the risk of NAION and PDE5 inhibitor use in the 12 months before IDO. The RR for PDE5 inhibitor exposure within 1 to 5 half-lives of NAION onset was 3.52 (95% CI: 1.59, 7.79).

The primary analysis was not statistically significant; however, the results of both the main (primary and secondary) and sensitivity person-time analyses are suggestive of an increased risk of NAION occurring in association with PDE5 inhibitor exposure. The matched-interval analyses were also not statistically significant, although the statistical power of the matched-interval analyses was limited. Campbell et al. (2015) used a similar case-crossover study design, although with different assumptions, and reported an increased risk of NAION occurring within 5 half-lives of PDE5 inhibitor dosing (OR=2.15; 95% CI: 1.06, 4.34). The overall conclusions from this study are consistent with those of Campbell et al. (2015), although the assumptions and study design were different, and Study LVHQ took a more conservative approach to classifying an exposed case. The case crossover design in both the Lilly and Pfizer-sponsored studies evaluating the rarely occurring AE of NAION, addresses the concerns regarding the potential for bias and confounding in the ED population by selecting a suitable comparator population, i.e., in a cohort or case-control study.

NAION occurs rarely in males aged 50 years and over (annual incidence rate of 2.5-11.8 per 100,000 [Johnson and Arnold 1994; Hattenhauer et al. 1997]); and is very rarely reported in association with tadalafil in post marketing reports. The impact on public health is therefore low and the benefit-risk balance has not changed. This potential risk is managed entirely by routine pharmacovigilance and existing label language in relation to dose and monitoring and additional pharmacovigilance or risk minimisation activities are not warranted. Routine pharmacovigilance and targeted follow-up of reported NAION cases will continue.

Additional details are provided in Table SVII.1 and in Annex 5.

SVII.3. Details of Important Identified and Potential Risks from Clinical Development and Post-authorisation Experience (including Newly Determined)

Table SVII.1 details the important identified and important potential risks of tadalafil. The data in the tables are presented by the ED and BPH indications combined and the PAH indication separately. Although no new clinical trials have been completed since the last RMP update, the clinical trial risk tables have been updated to MedDRA version 18.1.

Since version 8.1 of this RMP, there has been a cumulative review of the data on increased uterine bleeding in female PAH patients. Based upon the conclusions of the review, this risk is no longer considered to have a significant impact on the benefit-risk profile for tadalafil, and has been removed from the RMP as an important potential risk. See Section III.2 for additional information.

Table SVII.1. Important Identified and Potential Risks from Clinical Development and Postmarketing Experience

Identified Risk: Hypotension/Increased Hypotensive Effect

Frequency with 95% CI

Clinical Trial Programme (Placebo-Controlled Studies):

	Placebo (%)	Tadalafil (%)	Risk Difference (95% Confidence Interval)
ED and BPH			
Number of Patients	5209	10205	
Subjects with ≥1 TEAE	55 (1.06)	132 (1.29)	0.24 (-0.12, 0.59)
PAH			
Number of Patients	82	324	
Subjects with ≥1 TEAE	9 (10.98)	40 (12.35)	1.37 (-6.29, 9.03)

Abbreviations: ED=erectile dysfunction; BPH=Benign Prostatic Hyperplasia; PAH= Pulmonary Arterial Hypertension; TEAE=treatment-emergent adverse event.

Source: home/lillyce/prd/ly450190/integrations_reg2016/2016_05_002_ct_rmp/programs_stat/tfl_output/smaesa3_11.rtf
home/lillyce/prd/ly450190/integrations_reg2016/2016_05_002_ct_rmp/programs_stat/tfl_output/smaesa3_12.rtf

Clinical Trial Programme (All ED, BPH and PAH Studies):

	Tadalafil (%)	95% Confidence Interval[a]
ED and BPH		
Number of Patients	24148	
Subjects with ≥1 TEAE	335 (1.39)	1.24 - 1.54
PAH		
Number of Patients	399	
Subjects with ≥1 TEAE	125 (31.33)	26.81 - 36.13

[a] Clopper-Pearson method was used for the confidence interval calculation.

Abbreviations: ED=erectile dysfunction; BPH=Benign Prostatic Hyperplasia; PAH= Pulmonary Arterial Hypertension; TEAE=treatment-emergent adverse event.

Source: home/lillyce/prd/ly450190 _reg2016/2016_05_002_ct_rmp/programs_stat/tfl_output/smaesa2_11.rtf
home/lillyce/prd/ly450190/ _reg2016/2016_05_002_ct_rmp/programs_stat/tfl_output/smaesa2_12.rtf

Post-marketing Data:

ED and BPH: There were 1613 events of hypotension/increased hypotensive effect. These events are considered very rarely reported (0.003%) based on an estimated patient exposure to Cialis of more than 57 million patients.

PAH: There were 0.31 events of hypotension/increased hypotensive effect per 100 patient years, based on an estimated patient exposure to Adcirca of 105,000 patient years.

Table SVII.1. Important Identified and Potential Risks from Clinical Development and Postmarketing Experience (continued)

Identified Risk: Hypotension/Increased Hypotensive Effect (*continued*)

Seriousness/outcomes

Clinical Trial Programme (All ED, BPH and PAH Studies):

	Fatal	Recovered/ Resolved	Not Recovered/ Not Resolved	Recovered/ Resolved with Sequelae	Recovering/ Resolving	Unknown	Total
ED and BPH							
Number of Serious TEAE	0 (0.00)	6 (0.02)	1 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	7 (0.03)
Number of Non-Serious TEAE	0 (0.00)	278 (1.15)	58 (0.24)	0 (0.00)	0 (0.00)	0 (0.00)	336 (1.39)
Total	0 (0.00)	284 (1.18)	59 (0.24)	0 (0.00)	0 (0.00)	0 (0.00)	343 (1.42)
PAH							
Number of Serious TEAE	0 (0.00)	16 (4.01)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	16 (4.01)
Number of Non-Serious TEAE	0 (0.00)	93 (23.31)	33 (8.27)	0 (0.00)	0 (0.00)	1 (0.25)	127 (31.83)
Total	0 (0.00)	109 (27.32)	33 (8.27)	0 (0.00)	0 (0.00)	1 (0.25)	143 (35.84)

Abbreviations: ED=erectile dysfunction; BPH=Benign Prostatic Hyperplasia; PAH=Pulmonary Arterial Hypertension; TEAE=treatment-emergent adverse event.

Source: home/lillyce/prd/ly450190_reg2016/2016_05_002_ct_rmp/programs_stat/tfl_output/smaesa1_11.rtf
home/lillyce/prd/ly450190/_reg2016/2016_05_002_ct_rmp/programs_stat/tfl_output/smaesa1_12.rtf

Post-marketing Data:

sequellae

ED and BPH: Of the 1613 reported events, 14.1% of the post-marketing events were serious while 85.9% were non-serious. Outcomes reported in post-marketing events included fatal (0.1%), recovered/recovered with sequellae/recovering (45.5%), not recovered (8.7%), unknown (45.4%), and worsened (0.2%).*

PAH: Of the 322 reported events, 28% of the post-marketing events were serious while 72% were non-serious. Outcomes reported in post-marketing events included fatal (0.3%), recovered/recovering (23.9%), not recovered (8.4%), unknown (67.1%), and worsened (0.3%).

*Due to rounding, numbers may not equal 100% sequellae.

Table SVII.1. Important Identified and Potential Risks from Clinical Development and Postmarketing Experience (continued)

Identified Risk: Hypotension/Increased Hypotensive Effect (*continued*)

Severity and nature of risk

Clinical Trial Programme (Placebo-Controlled studies):

Subjects with ≥1 TEAE by Maximum Severity	Placebo (%)	Tadalafil (%)	Mantel-Haenszel Odds Ratio[a]
ED and BPH			
Mild	41 (0.79)	96 (0.94)	
Moderate	11 (0.21)	28 (0.27)	
Severe	3 (0.06)	8 (0.08)	1.1589
Total	55 (1.06)	132 (1.29)	1.3169
PAH			
Mild	5 (6.10)	26 (8.02)	
Moderate	4 (4.88)	9 (2.78)	
Severe	0 (0.00)	5 (1.54)	
Total	9 (10.98)	40 (12.35)	1.1424

Abbreviations: ED=erectile dysfunction; BPH=Benign Prostatic Hyperplasia; PAH= Pulmonary Arterial Hypertension; OR=odds ratio; TEAE=treatment-emergent adverse event.

[a] Mantel-Haenszel Odds Ratio stratified by study. Tadalafil is numerator and Placebo is denominator. For 'Severe', the OR compares incidence of any Severe TEAE to no Severe TEAE. For 'Total', the OR compares any TEAE to no TEAE.

Source: home/lillyce/prd/ly450190/integrations_reg2016/2016_05_002_ct_rmp/programs_stat/tfl_output/smaesa6_11.rtf
home/lillyce/prd/ly450190 _reg2016/2016_05_002_ct_rmp/programs_stat/tfl_output/smaesa6_12.rtf

Post-marketing Data: Not applicable

Table SVII.1. Important Identified and Potential Risks from Clinical Development and Postmarketing Experience (continued)

Identified Risk: Hypotension/Increased Hypotensive Effect (*continued*)	
Background incidence/prevalence	**Tadalafil ED and BPH Trials:** In tadalafil placebo controlled studies (51 integrated tadalafil studies), there were 5209 subjects randomised to placebo; of those subjects, 55 (1.06%) reported TEAEs of hypotension/increased hypotensive effect. **Tadalafil PAH Trials:** In the tadalafil placebo-controlled study, there were 82 subjects randomised to placebo; of those subjects, 9 (10.98%) reported TEAEs of hypotension/increased hypotensive effect. **PAH patient population:** Incidence and prevalence data in the PAH population is limited. Three clinical trials with varying results were conducted in the EU and the United States comparing the effects of epoprostenol and conventional therapy in PAH populations. When epoprostenol plus conventional therapy was compared to conventional therapy alone, no hypotension was reported (Barst et al. 1996). When epoprostenol was combined with sildenafil or placebo, hypotension was reported in 9% of the sildenafil arm and 6% in the placebo arm (Galie et al. 2002). When epoprostenol was administered during dose escalation, 16% reported hypotension and during chronic drug administration 13% reported hypotension compared to 0% in the conventional therapy arm (Fuentes et al. 2012; Veletri package insert, 2012). One clinical trial conducted in the EU compared beraprost to placebo and found no hypotension in the treatment or placebo groups (Galie et al. 2002). Two clinical trials were conducted in the EU and the United States comparing the effects of bosentan to placebo in PAH populations. After 12 weeks of treatment, there were no reports of hypotension in either arm (Channick et al. 2001; Rubin et al. 2002). **BPH Patient Population:** Two United States phase 3 clinical trials were conducted comparing the effects of silodosin to placebo. The pooled results showed incidence of orthostatic hypotension to be 2.6% in the silodosin arm and 1.5% in the placebo arm (Marks et al. 2013). No prevalence data are available for ED, BPH, or PAH.
Risk groups or risk factors	The concomitant use of PDE5 inhibitors with nitrates is contraindicated because of the increased risk of hypotension, which may be sudden and severe. Tadalafil was shown to augment the hypotensive response to short-acting nitrates. Caution should be exercised when prescribing tadalafil to patients who are taking alpha[1] blockers, such as doxazosin, as simultaneous administration may lead to symptomatic hypotension in some patients. Tadalafil may augment the blood pressure lowering effects of antihypertensive agents [calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, beta-adrenergic receptor blockers, thiazide diuretics, and angiotensin II receptor blockers alone or in combination]. Additionally, in patients taking multiple antihypertensive agents whose hypertension was not well controlled, greater reductions in blood pressure were observed. These reductions were not associated with hypotensive symptoms in the vast majority of patients. The combination of PDE5 inhibitors and guanylate cyclase stimulators, such as riociguat, is not recommended because it may lead to symptomatic hypotension. 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.

Table SVII.1. Important Identified and Potential Risks from Clinical Development and Postmarketing Experience (continued)

Identified Risk: Hypotension/Increased Hypotensive Effect (*continued*)	
Potential mechanisms	The risk of hypotension/increased hypotensive effect is considered a pharmacological class effect of PDE5 inhibitors. PDE5 inhibitors are known to have mild systematic vasodilatory properties that may result in transient decreases in blood pressure. Vascular smooth muscle cells in the arterial and venous system contain high activity of PDE5. Therefore, inhibition of PDE5 results in smooth muscle relaxation and lowering of arterial blood pressure (Reffelmann et al. 2008). The increased hypotensive effect from the coadministration of nitrates is considered a pharmacological class effect of PDE5 inhibitors. Organic nitrates increase cyclic GMP production whereas PDE5 inhibitors decrease cyclic GMP breakdown. Therefore, there is a synergistic drop in BP when PDE5 inhibitors are given with organic nitrates that may result in symptomatic hypotension in some patients (Kloner 2007).
Preventability	Adherence with the approved label will mitigate the risk of hypotension/increased hypotensive effect in patients treated with tadalafil. Tadalafil labelling provides guidance regarding hypotension/increased hypotensive effect monitoring and contraindications. Tadalafil is contraindicated in patients with hypotension (<90/50 mm Hg) and in patients who are using any form of organic nitrates. The concomitant use of tadalafil with alpha-blockers, antihypertensive medications, or substantial quantities of alcohol (≥5 units) may lead to hypotension. In some patients, concomitant use of these drugs with tadalafil can lower blood pressure significantly, which may lead to symptomatic hypotension (including increased heart rate, dizziness, headache, and/or syncope). When initiating daily treatment with tadalafil, appropriate clinical considerations should be given to a possible dose adjustment of the antihypertensive therapy. The combination of tadalafil and doxazosin is not recommended.
Impact on individual patient	Hypotension can lead to dizziness and/or syncope, which may in turn lead to injury from falls. Fall-related injuries, such as a broken hip, can impact a person's quality of life. Hypotensive events may be more evident in very elderly patients (75 years and older) who have multiple comorbidities and concomitant medications.
Potential public health impact of safety concern	Not Applicable
Evidence source	**Clinical Trial Programme:** Integrated tadalafil clinical trial database **Post-marketing Data:** Lilly Safety System
MedDRA terms	**Clinical Trial Program and Post-marketing Data:** Search terms for hypotension/increased hypotensive effect include the following MedDRA (Version 18.1 for clinical trial data and postmarketing data) preferred terms: hypotension, orthostatic hypotension, blood pressure ambulatory decreased, blood pressure decreased, blood pressure diastolic decreased, blood pressure systolic decreased, blood pressure orthostatic decreased, blood pressure orthostatic, dizziness, dizziness exertional, dizziness postural, presyncope, syncope.

Table SVII.1. Important Identified and Potential Risks from Clinical Development and Postmarketing Experience (continued)

Identified Risk: Priapism

Frequency with 95% CI

Clinical Trial Programme (Placebo-Controlled Studies):

	Placebo (%)	Tadalafil (%)	Risk Difference 95% Confidence Interval
ED and BPH			
Number of Patients	5209	10205	
Subjects with ≥1 TEAE	0 (0.00)	1 (0.01)	0.01 (-0.01, 0.03)
PAH			
Number of Patients	17	71	
Subjects with ≥1 TEAE	0 (0.00)	1 (1.41)	1.41 (-1.33, 4.15)

Abbreviations: ED=erectile dysfunction; BPH=Benign Prostatic Hyperplasia; PAH= Pulmonary Arterial Hypertension; TEAE=treatment-emergent adverse event.

Source: home/lillyce/prd/ly450190 _reg2016/2016_05_002_ct_rmp/programs_stat/tfl_output/smaesa3_21.rtf
home/lillyce/prd/ly450190/ _reg2016/2016_05_002_ct_rmp/programs_stat/tfl_output/smaesa3_22.rtf

Clinical Trial Programme (All ED, BPH and PAH Studies):

	Tadalafil (%)	95% Confidence Interval[a]
ED and BPH		
Number of Patients	24147	
Subjects with ≥1 TEAE	1 (0.00)	0.00 - 0.02
PAH		
Number of Patients	86	
Subjects with ≥1 TEAE	1 (1.16)	0.03 - 6.31

[a] Clopper-Pearson method was used for the confidence interval calculation

Abbreviations: ED=erectile dysfunction; BPH=Benign Prostatic Hyperplasia; PAH= Pulmonary Arterial Hypertension; TEAE=treatment-emergent adverse event.

Source: home/lillyce/prd/ly450190 _reg2016/2016_05_002_ct_rmp/programs_stat/tfl_output/smaesa2_21.rtf
home/lillyce/prd/ly450190/ _reg2016/2016_05_002_ct_rmp/programs_stat/tfl_output/smaesa2_22.rtf

Post-marketing Data:

ED and BPH: There were 588 events of priapism. These events are considered very rarely reported (0.001%) based on an estimated patient exposure to Cialis of more than 57 million patients.

PAH: There were 0.004 events of priapism per 100 patient years, based on an estimated patient exposure to Adcirca of 105,000 patient years.

Table SVII.1. Important Identified and Potential Risks from Clinical Development and Postmarketing Experience (continued)

Identified Risk: Priapism (*continued*)

Seriousness/outcomes

Clinical Trial Programme (All ED, BPH and PAH Studies):

	Fatal	Recovered/ Resolved	Not Recovered/ Not Resolved	Recovered/ Resolved with Sequelae	Recovering/ Resolving	Unknown	Total
ED and BPH							
Number of Serious TEAE	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Number of Non-Serious TEAE	0 (0.00)	1 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.00)
Total	0 (0.00)	1 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.00)
PAH							
Number of Serious TEAE	0 (0.00)	1 (1.16)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (1.16)
Number of Non-Serious TEAE	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Total	0 (0.00)	1 (1.16)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (1.16)

Abbreviations: ED=erectile dysfunction; BPH=Benign Prostatic Hyperplasia; PAH=Pulmonary Arterial Hypertension; TEAE=treatment-emergent adverse event.

Source: home/lillyce/prd/ly450190 _reg2016/2016_05_002_ct_rmp/programs_stat/tfl_output/smaesa1_21.rtf
home/lillyce/prd/ly450190 _reg2016/2016_05_002_ct_rmp/programs_stat/tfl_output/smaesa1_22.rtf

Post-marketing Data:

ED and BPH: Of the 588 reported events, 41.5% of the post-marketing events were serious while 58.5% were non-serious. Outcomes reported in post-marketing events included recovered/recovered with sequellae/ recovering (39.8%), not recovered (10.7%), unknown (49.3%), and disability/incapacitated (0.2%).

PAH: All 4 events of priapism were non-serious. Outcomes reported in post-marketing events included recovered (25%) and unknown (75%).

Table SVII.1. Important Identified and Potential Risks from Clinical Development and Postmarketing Experience (continued)

Identified Risk: Priapism (*continued*)

Severity and nature of risk

Clinical Trial Programme (Placebo-Controlled Studies):

Subjects with ≥1 TEAE by Maximum Severity	Placebo (%)	Tadalafil (%)	Mantel-Haenszel Odds Ratio[a]
ED and BPH			
Mild	0 (0.00)	1 (0.01)	
Total	0 (0.00)	1 (0.01)	--
PAH			
Severe	0 (0.00)	1 (1.41)	
Total	0 (0.00)	1 (1.41)	--

Abbreviations: ED=erectile dysfunction; BPH=Benign Prostatic Hyperplasia; PAH= Pulmonary Arterial Hypertension; OR=odds ratio; TEAE=treatment-emergent adverse event.

[a] Mantel-Haenszel Odds Ratio stratified by study. Tadalafil is numerator and Placebo is denominator. For 'Severe', the OR compares incidence of any Severe TEAE to no Severe TEAE. For 'Total', the OR compares any TEAE to no TEAE.

Source: home/lillyce/prd/ly450190/integrations _reg2016/2016_05_002_ct_rmp/programs_stat/tfl_output/smaesa6_21.rtf
home/lillyce/prd/ly450190/integrations _reg2016/2016_05_002_ct_rmp/programs_stat/tfl_output/smaesa6_22.rtf

Post-marketing Data: Not applicable

Background incidence/prevalence

Tadalafil ED and BPH Trials:

In tadalafil placebo controlled studies (51 integrated tadalafil studies), there were 5068 subjects randomised to placebo; of those subjects, none reported a TEAE of priapism.

Prevalence Rates are unavailable for ED, BPH, or PAH.

Risk groups or risk factors

Tadalafil should be used with caution in patients who have conditions which may predispose them to priapism. These conditions may include haematological disorders, vasoactive erectile agents, malignancy, perineal or penile trauma, neurological disorders, and use of medications (alpha blockers, anti-anxiety agents, anticoagulants, antidepressants, antipsychotics and recreational drugs (Broderick et al. 2010; Burnett and Sharlip 2013).

Potential mechanisms

PDE5 inhibitors block hydrolysis of cyclic guanosine monophosphate (cGMP) leading to relaxation of smooth muscle, thus enhancing and prolonging the activity of cGMP that is already present in penile arterial and smooth muscle tissue.

Table SVII.1. Important Identified and Potential Risks from Clinical Development and Postmarketing Experience (continued)

Identified Risk: Priapism (*continued*)	
Preventability	Adherence with the approved label will mitigate the risk of priapism in patients treated with tadalafil. Labelling provides guidance that tadalafil should be used with caution in patients who have conditions that might predispose them to priapism (such as sickle cell anaemia, multiple myeloma, or leukaemia), or in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis, or Peyronie's disease).
Impact on individual patient	If priapism is not treated immediately, penile tissue damage and permanent loss of potency may result.
Potential public health impact of safety concern	Not applicable.
Evidence source	**Clinical Trial Programme:** Integrated clinical trial database **Post-marketing Data:** Lilly Safety System
MedDRA terms	**Clinical Trial Program:** The search terms for priapism have been modified since the last RMP (version 7) because of changes to MedDRA since Version 15.0. The search terms now only include the following MedDRA (Version 18.1) preferred term: Priapism. **Post-marketing Data:** Search terms for priapism include the following MedDRA (Version 18.1) preferred terms: priapism, erection increased.

Table SVII.1. Important Identified and Potential Risks from Clinical Development and Postmarketing Experience (continued)

Potential Risk: Nonarteritic Anterior Ischaemic Optic Neuropathy (NAION)

Frequency with 95% CI

Clinical Trial Programme (Placebo-controlled studies): No events match the criteria.

Clinical Trial Programme (All ED, BPH and PAH Studies): One subject (95% Confidence interval: 0.00 - 0.02) on an open-label ED study reported an event of optic neuritis. At the time of the event, he was receiving tadalafil 20-mg on demand.

Post-marketing Data:

ED and BPH: There were 81 events of NAION. These events are considered very rarely reported (0.0001%) based on an estimated patient exposure to Cialis of more than 57 million patients.

PAH: There have been no spontaneous cases reported based on an estimated patient exposure to Adcirca of 114 800.

Seriousness/outcomes

Clinical Trial Programme (All ED, BPH and PAH studies):

	Fatal	Recovered/ Resolved	Not Recovered/ Not Resolved	Recovered/ Resolved with Sequelae	Recovering/ Resolving	Unknown	Total
ED and BPH or PAH							
Number of Serious TEAE	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Number of Non-Serious TEAE	0 (0.00)	0 (0.00)	1 (0.00)[a]	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.00)
Total	0 (0.00)	0 (0.00)	1 (0.00)[a]	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.00)

Abbreviations: ED=erectile dysfunction; BPH=Benign Prostatic Hyperplasia; PAH= Pulmonary Arterial Hypertension; TEAE=treatment-emergent adverse event.

[a] Optic neuritis.

Source: home/lillyce/prd/ly450190/integrations_reg2016/2016_05_002_ct_rmp/programs_stat/tfl_output/smaesa1_31.rtf

Post-marketing Data:

sequellae

ED and BPH: Of the 81 reported events, 95.1% of the post-marketing events were serious while 4.9% were non-serious. Outcomes reported in post-marketing events included recovered/recovered with sequellae/ recovering (24.7%), not recovered (38.3), unknown (35.8%), and disability/incapacitated (1.2%).

PAH: Not applicable.

Table SVII.1. Important Identified and Potential Risks from Clinical Development and Postmarketing Experience (continued)

Potential Risk: Nonarteritic Anterior Ischaemic Optic Neuropathy (NAION) *(continued)*	
Severity and nature of risk	**Clinical Trial Programme:** There were no patients with this event in placebo controlled clinical trials of tadalafil. The 1 event of optic neuritis from an ED trial was considered mild in severity, and was non-serious. **Post-marketing Data:** Not applicable.
Background incidence/prevalence	Tadalafil ED and BPH Trials: • In tadalafil placebo controlled studies (51 integrated tadalafil studies), there were 5150 subjects randomised to placebo; of those subjects, none reported NAION. Prevalence rates of NAION are unavailable for ED, BPH or PAH populations. Based on published literature, the annual incidence of NAION is 2.5-11.8 cases per 100,000 in males aged ≥50 (Johnson and Arnold 1994; Hattenhauer et al. 1997).
Risk groups or risk factors	Risk factors for developing NAION following use of PDE5 inhibitors have not been identified. An observational case-crossover study of men with recent intermittent use of PDE5 inhibitors (sildenafil, tadalafil or vardenafil) reported an increased risk of NAION within 5 half-lives of PDE5 inhibitor use (Campbell et al. 2015). More recently, data from the Lilly-sponsored LVHQ study became available and are similarly suggestive of an increased risk (RR=2.27 [95% CI 0.99-5.20]) of NAION occurring in association with episodic PDE5 inhibitor exposure. Risk factors associated with NAION include small cup to disk ratio (crowded disk), age over 50, hypertension, atherosclerosis, hyperlipidaemia, nocturnal hypotension, diabetes mellitus, ischaemic heart disease, smoking, and sleep apnoea among others (Behbehani et al. 2005; Pomeranz 2006). Because patients who have already experienced NAION are at increased risk of recurrent NAION, tadalafil is contraindicated in patients who have loss of vision in 1 eye.
Potential mechanisms	NAION refers to nonarteritic anterior ischaemic optic neuropathy not due to inflammation of the arteries. It results from transient poor circulation in the capillaries of the optic nerve head resulting in infarction of the anterior optic nerve (Johnson and Arnold 1994). The effects of sildenafil on ocular blood flow have been reported to increase ocular blood flow (Pache et al. 2002; Polak et al. 2003; Koksal et al. 2005) or have no effects (Grunwald et al. 2002). No studies have shown a decrease in ocular blood flow with sildenafil or other PDE5 inhibitors. There is no currently established definitive mechanism for a role of PDE5 inhibitors and the occurrence of NAION. Men with ED prescribed PDE5 inhibitors share many of the cardiovascular risk factors associated with increased risk of NAION.
Preventability	Since a plausible mechanism for the role of PDE5 inhibitors in the occurrence of NAION has not been identified, preventative strategies cannot be formulated at this time. Tadalafil labelling provides guidance regarding NAION. Tadalafil is contraindicated in patients who have loss of vision in 1 eye, regardless of whether this episode was in connection or not with previous PDE5 inhibitor exposure.
Impact on individual patient	Patients should be advised that in case of sudden visual defect, they should stop taking tadalafil and consult a physician immediately. NAION may have an impact on quality of life because of impaired vision and disability during the course of the condition.

Table SVII.1. Important Identified and Potential Risks from Clinical Development and Postmarketing Experience (continued)

Potential Risk: Nonarteritic Anterior Ischaemic Optic Neuropathy (NAION) ***(continued)***	
Potential public health impact of safety concern	Not applicable.
Evidence source	**Clinical Trial Programme:** Integrated clinical trial database **Post-marketing Data:** Lilly Safety System
MedDRA terms	**Clinical Trial Program and Post-marketing Data:** Search terms for NAION include the following MedDRA (Version 18.1) preferred terms: optic ischaemic neuropathy, optic neuropathy, optic neuritis.

Table SVII.1. Important Identified and Potential Risks from Clinical Development and Postmarketing Experience (continued)

Potential Risk: Sudden Hearing Loss

Frequency with 95% CI

Clinical Trial Programme (Placebo-Controlled Studies):

	Placebo (%)	Tadalafil (%)	Risk Difference 95% Confidence Interval
ED and BPH			
Number of Patients	5209	10205	
Subjects with >= 1 TEAE	1 (0.02)	8 (0.08)	0.06 (-0.01, 0.13)
PAH			
Number of Patients	82	324	
Subjects with ≥1 TEAE	1 (1.22)	0 (0.00)	-1.22 (-3.60, 1.16)

Abbreviations: ED=erectile dysfunction; BPH=Benign Prostatic Hyperplasia; PAH= Pulmonary Arterial Hypertension; TEAE=treatment-emergent adverse event.

Source: home/lillyce/prd/ly450190/integrations _reg2016/2016_05_002_ct_rmp/programs_stat/tfl_output/smaesa3_41.rtf
home/lillyce/prd/ly450190/integrations _reg2016/2016_05_002_ct_rmp/programs_stat/tfl_output/smaesa3_42.rtf

Clinical Trial Programme (All ED, BPH and PAH Studies):

	Tadalafil (%)	95% Confidence Interval[a]
ED and BPH		
Number of Patients	24148	
Subjects with ≥1 TEAE	21 (0.09)	0.05 - 0.13
PAH		
Number of Patients	399	
Subjects with ≥1 TEAE	8 (2.01)	0.87 - 3.91

Abbreviations: ED=erectile dysfunction; BPH=Benign Prostatic Hyperplasia; PAH= Pulmonary Arterial Hypertension; TEAE=treatment-emergent adverse event.

[a] Clopper-Pearson method was used for the confidence interval calculation

Source: home/lillyce/prd/ly450190/integrations _reg2016/2016_05_002_ct_rmp/programs_stat/tfl_output/smaesa2_41.rtf
home/lillyce/prd/ly450190/integrations _reg2016/2016_05_002_ct_rmp/programs_stat/tfl_output/smaesa2_42.rtf

Post-marketing Data:

ED and BPH: There were 359 events of sudden hearing loss. These events are considered very rarely reported (0.0006%) based on an estimated patient exposure to Cialis of more than 57 million patients.

PAH: There were 0.04 events per 100 patient years, based on an estimated patient exposure to Adcirca of 105,000 patient years.

Table SVII.1. Important Identified and Potential Risks from Clinical Development and Postmarketing Experience (continued)

Potential Risk: Sudden Hearing Loss (*continued*)

Seriousness/outcomes

Clinical Trial Programme (All ED, BPH and PAH Studies):

	Fatal	Recovered/ Resolved	Not Recovered/ Not Resolved	Recovered/ Resolved with Sequelae	Recovering/ Resolving	Unknown	Total
ED and BPH							
Number of Serious TEAE	0 (0.00)	1 (0.00)	2 (0.01)	0 (0.00)	0 (0.00)	0 (0.00)	3 (0.01)
Number of Non-Serious TEAE	0 (0.00)	8 (0.03)	10 (0.04)	0 (0.00)	0 (0.00)	0 (0.00)	18 (0.07)
Total	0 (0.00)	9 (0.04)	12 (0.05)	0 (0.00)	0 (0.00)	0 (0.00)	21 (0.09)
PAH							
Number of Serious TEAE	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Number of Non-Serious TEAE	0 (0.00)	2 (0.50)	7 (1.75)	0 (0.00)	0 (0.00)	0 (0.00)	9 (2.26)
Total	0 (0.00)	2 (0.50)	7 (1.75)	0 (0.00)	0 (0.00)	0 (0.00)	9 (2.26)

Abbreviations: ED=erectile dysfunction; BPH=Benign Prostatic Hyperplasia; PAH=Pulmonary Arterial Hypertension; TEAE=treatment-emergent adverse event.

Source: home/lillyce/prd/ly450190/integrations _reg2016/2016_05_002_ct_rmp/programs_stat/tfl_output/smaesa1_41.rtf
home/lillyce/prd/ly450190/integrations _reg2016/2016_05_002_ct_rmp/programs_stat/tfl_output/smaesa1_42.rtf

Post-marketing Data:

ED and BPH: Of the 359 reported events, 70.8% of the post-marketing events were serious while 29.2% were non-serious. Outcomes reported in post-marketing events included recovered/recovered with sequellae/recovering (27.6%), not recovered (34%), unknown (37.3%), worsened (0.3%), and disability/incapacitated (0.8%).

PAH: Of the 42 reported events, 66.7% of the post-marketing events were serious while 33.3% were non-serious. Outcomes reported in post-marketing events included recovered / recovered with sequellae/recovering (26.2%), not recovered (23.8%), and unknown (50.0%).

Table SVII.1. Important Identified and Potential Risks from Clinical Development and Postmarketing Experience (continued)

Potential Risk: Sudden Hearing Loss (*continued*)

Severity and nature of risk

Clinical Trial Programme (Placebo-Controlled Studies):

Subjects with ≥1 TEAE by Maximum Severity	Placebo (%)	Tadalafil (%)	Mantel-Haenszel Odds Ratio[a]
ED and BPH			
Mild	0 (0.00)	5 (0.05)	
Moderate	1 (0.02)	3 (0.03)	
Total	1 (0.02)	8 (0.08)	4.4322
PAH			
Mild	1 (1.22)	0 (0.00)	
Total	1 (1.22)	0 (0.00)	0.0000

Abbreviations: ED=erectile dysfunction; BPH=Benign Prostatic Hyperplasia; PAH= Pulmonary Arterial Hypertension; OR=odds ratio; TEAE=treatment-emergent adverse event.

[a] Mantel-Haenszel Odds Ratio stratified by study. Tadalafil is numerator and Placebo is denominator. For 'Severe', the OR compares incidence of any Severe TEAE to no Severe TEAE. For 'Total', the OR compares any TEAE to no TEAE.

Source: home/lillyce/prd/ly450190/integrations _reg2016/2016_05_002_ct_rmp/programs_stat/tfl_output/smaesa6_41.rtf
home/lillyce/prd/ly450190/integrations _reg2016/2016_05_002_ct_rmp/programs_stat/tfl_output/smaesa6_42.rtf

Post-marketing Data: Not applicable.

Background incidence/prevalence

Tadalafil ED and BPH Trials:

- In the tadalafil placebo controlled studies (51 integrated tadalafil studies), there were 5209 subjects randomised to placebo; of those subjects, 1 (0.02%) reported TEAEs of sudden hearing loss.

Prevalence rate in ED patient Population:

In Taiwan, a population-based dataset using a case-control study design (cases=4,504, controls=22,520) found the prevalence of sudden sensorineural hearing loss (SSNHL) in 0.49% of the ED population aged ≥40 years at baseline. In the controls, SSNHL was only 0.08%. This study revealed an association between ED and prior SSNHL with an adjusted odds ratio of 6.06 when compared to controls (Keller et al. 2012).

Prevalence rates are unavailable for BPH or PAH.

Table SVII.1. Important Identified and Potential Risks from Clinical Development and Postmarketing Experience (continued)

Potential Risk: Sudden Hearing Loss (*continued*)	
Risk groups or risk factors	Risk factors for developing sudden hearing loss following use of PDE5 inhibitors have not been established. In the majority of cases of sudden hearing loss (an estimated 75 to 90%), the obvious cause is not identified (Mattox and Lyles 1989; NIH 2000). The epidaemiology literature suggests that patients who have SHL share similar risk factors with ED and BPH patients i.e., diabetes and cardiovascular comorbidities (Sun and Swindle 2005; Banks et al. 2013), which have been associated with SHL (Aimoni et al. 2010; Keller et al. 2013; Chang et al. 2014). PAH patients may have additional confounding comorbidities such as systemic sclerosis, SLE, and other connective tissue diseases (Lin et al. 2013, Sara et al. 2014). Literature suggests that males are equally affected by sudden hearing loss as females (Shaia and Sheehy 1976; Russolo and Poli 1980; Feldmann 1981; Megighian et al. 1986; Sara et al. 2014). The average age at onset was reported to be 46 to 49 years of age, and the incidence was found to increase with age (Byl 1984). The incidence rate was 12/100 000 in those aged 18 to 34 years, rising to 19/100 000 in 35 to 44 year-olds and 30/100 000 in 45 to 54 year-olds. In those aged 55 to 64 years, the incidence rate was 47/100 000, and rising significantly to 70/100 000 in those aged 65 and older (Alexander and Harris 2013). Also, compared to white (non-Hispanic) people, black, and Mexican-American people have significantly lower odds of hearing loss (Agrawal et al. 2008).
Potential mechanisms	Sudden hearing loss has been identified as a potential class effect associated with PDE5 inhibitor use. Hearing assessments have been performed in toxicology studies with tadalafil in rats and dogs, and there were no compound-related effects on hearing in any of these studies at doses higher than clinically efficacious doses. In addition, a potential mechanism for PDE5 inhibition-mediated ototoxicity was considered because an increased production of nitric oxide (NO) in the ear has been implicated in the ototoxicity of cisplatin (Watanabe et al. 2000) and gentamicin (Takumida et al. 1999). However, there are no known reports of PDE enzyme expression in the mammalian inner ear. Moreover, diffusion of NO from blood or other organs is not expected because NO exists intracellularly as a free radical species with a short half-life. Taken together, these data indicate that ototoxicity is likely not associated with PDE inhibition in the ear. Although the literature suggests a possible biological mechanism for a relationship between PDE5 inhibitor-induced hypotension contributing to SHL, there is a lack of confirmatory evidence supporting this potential biological mechanism. Impaired or altered blood circulation (including rapid drops in blood pressure and hypotension) and vascular occlusion are potential risk factors for SHL. The cochlea may be sensitive to even a brief reduction in oxygen perfusion. In fact there are a few small observational studies (Pirodda et al. 1997, 2001; Ballesteros et al. 2012) and a case report that attribute hypotension as a causal factor in the development of SHL (Chao 2004). However, a review of the literature and individual postmarketing reports does not reveal a consistent pattern of hypotension occurring with SHL.
Preventability	Since a probable plausible mechanism for the role of PDE5 inhibitors in the occurrence of sudden hearing loss has not been identified, preventative strategies cannot be formulated at this time.
Impact on individual patient	Sudden hearing loss may have an impact on quality of life, which is further impaired if there is significant associated tinnitus and/or dizziness. For patients with unilateral hearing loss, difficulty in localising sound may increase the risk of accidents.
Potential public health impact of safety concern	Not applicable.
Evidence source	**Clinical Trial Programme:** integrated clinical trial database **Post-marketing Data:** Lilly Safety System

Table SVII.1. Important Identified and Potential Risks from Clinical Development and Postmarketing Experience (continued)

Potential Risk: Sudden Hearing Loss (*continued*)	
MedDRA terms	**Clinical Trial Program and Post-marketing Data:** Search terms for sudden hearing loss include the following MedDRA (Version 18.1) preferred terms: sudden hearing loss, deafness, deafness neurosensory, hearing impaired, deafness permanent, deafness transitory, deafness bilateral, conductive deafness, deafness unilateral, deafness traumatic, mixed deafness, hypoacusis. Since the last RMP, the term deafness traumatic has been removed as a search term because it implies an aetiology other than drug-induced hearing loss. **Post-marketing Data:** Search terms for sudden hearing loss include the following MedDRA (Version 18.1) preferred terms: sudden hearing loss, deafness, deafness neurosensory, hearing impaired, deafness permanent, deafness transitory, deafness bilateral, conductive deafness, deafness unilateral, mixed deafness, hypoacusis.

SVII.4. Identified and Potential Interactions

SVII.4.1. Overview of Potential for Interactions

Tadalafil is predominantly metabolised by the cytochrome P450 (CYP) 3A4 isoform. For the treatment of PAH, concomitant use of tadalafil with potent CYP3A4 inhibitors or inducers is not recommended. For the treatment of ED and BPH, concomitant use of tadalafil with potent CYP3A4 inhibitors should be done with caution (See Table SVII.2).

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.

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).

SVII.4.2. Important Identified and Potential Interactions

Table SVII.2. Important Identified and Potential Interactions

Co-administration of Tadalafil with Nitrates	
Effect of interaction	Tadalafil was shown to augment the hypotensive response to short-acting nitrates
Evidence source	Clinical pharmacology studies
Possible mechanisms	The risk of hypotension/increased hypotensive effect is considered a pharmacological class effect of PDE5 inhibitors and nitrates. Organic nitrates increase cyclic GMP production whereas PDE5 inhibitors decrease cyclic GMP breakdown. Therefore, there is a synergistic drop in BP when PDE5 inhibitors are given with organic nitrates that result in symptomatic hypotension in some patients (Kloner 2007).
Potential health risk	Hypotension can lead to dizziness and/or syncope, which may in turn lead to injury from falls. Severe drops in blood pressure (<30mm Hg) can lead to hypoperfusion, hypoxia, and shock.
Discussion	Based upon the two drug utilisation studies that evaluated the coadministration of tadalafil with nitrates, risk minimisation activities have been effective. There is very limited coadministration of tadalafil with nitrates.

continued

Table SVII.2. Important Identified and Potential Interactions (continued)

Potent Inhibitors of CYP3A4	
Effect of interaction	Potent CYP3A4 inhibitors may cause a clinically significant increase in tadalafil exposure.
Evidence source	Clinical pharmacology studies
Possible mechanisms	Tadalafil is principally metabolised by CYP3A4. A selective inhibitor of CYP3A4, ketoconazole (400 mg daily), increased tadalafil single-dose exposure (area under the curve [AUC]) by 312% and maximum concentration (C_{max}) by 22%; ketoconazole (200 mg daily) increased tadalafil single-dose exposure (AUC) by 107% and C_{max} by 15% relative to the AUC and C_{max} values for tadalafil alone. Ritonavir (200 mg twice daily), an inhibitor of CYP3A4, CYP2C9, CYP2C19, and CYP2D6, increased single-dose exposure (AUC) by 124% with no change in C_{max}. Ritonavir (500 mg or 600 mg twice daily) increased tadalafil (20 mg) single-dose exposure (AUC) by 32% with a 30% reduction in C_{max}. Although specific interactions have not been studied, human immunodeficiency virus type 1 (HIV-1) protease inhibitors (such as saquinavir) and other CYP3A4 inhibitors (such as erythromycin and itraconazole) would likely increase tadalafil exposure. For PAH patients taking concomitant potent inhibitors of CYP3A4 such as ketoconazole or ritonavir, the use of tadalafil is not recommended. In patients with ED and/or BPH, co-administration of tadalafil with potent inhibitors of CYP3A4 should be done with caution.
Potential health risk	Increases in tadalafil exposure may result in an increase in the frequency and severity of the adverse effects.
Discussion	This risk is adequately described in the SmPc.
Potent inducers of CYP3A4	
Effect of interaction	Potent inducers of CYP3A4 may cause a clinically significant reduction in tadalafil exposure.
Evidence source	Clinical pharmacology studies
Possible mechanisms	A selective CYP3A4 inducer, rifampin (600 mg daily), reduced tadalafil (10 mg) single-dose exposure (AUC) by 88% and Cmax by 46%, relative to the AUC and C_{max} values for tadalafil alone. It can be expected that concomitant administration of other CYP3A4 inducers will also decrease plasma concentrations of tadalafil. The reduced exposure of tadalafil with the coadministration of rifampin can be anticipated to decrease the efficacy of tadalafil dosed once a day; the magnitude of decreased efficacy is unknown. For PAH patients taking concomitant potent inducers of CYP3A4 such as rifampin, the use of tadalafil is not recommended.
Potential health risk	Decreases in tadalafil exposure may result in reduced efficacy of tadalafil for the treatment of PAH.
Discussion	This risk is adequately described in the SmPC.
Co-administration of Tadalafil with Antihypertensive Medications	
Effect of interaction	Augmentation of blood pressure lowering effect of antihypertensive medications.
Evidence source	Clinical pharmacology studies
Possible mechanisms	Tadalafil has systemic vasodilatory properties, and may augment the blood pressure lowering effects of antihypertensive agents.
Potential health risk	Hypotension can lead to dizziness and/or syncope, which may in turn lead to injury from falls.
Discussion	This risk is adequately described in the SmPC.

continued

Table SVII.2. Important Identified and Potential Interactions (continued)

Co-administration of Tadalafil with Alpha[1]-Adrenergic Blockers	
Effect of interaction	Co-administration may cause symptomatic hypotension in some patients.
Evidence source	Clinical pharmacology studies
Possible mechanisms	PDE5 inhibitors, including tadalafil, and alpha–adrenergic blocking agents are both vasodilators with blood-pressure-lowering effects.
Potential health risk	Hypotension can lead to dizziness and/or syncope, which may in turn lead to injury from falls.
Discussion	This risk is adequately described in the SmPC.
Coadministration of Tadalafil with Guanylate Cyclase Stimulators	
Effect of interaction	Coadministration may cause symptomatic hypotension in some patients
Evidence source	Preclinical and clinical pharmacology studies of riociguat in combination with either sildenafil or vardenafil, PATENT-PLUS study.
Possible mechanisms	Guanylate cyclase stimulators and PDE5 inhibitors both act on the NO-sGC-cGMP pathway. Therefore, there is a theoretical risk of an additive hypotensive effect with concomitant use of these medications.
Potential health risk	Hypotension can lead to dizziness and/or syncope, which may in turn lead to injury from falls.
Discussion	This risk is adequately described in the SmPC.

SVII.5. Pharmacological Class Effects

SVII.5.1. Pharmacological Class Risks already included as Important Identified or Potential Risks

Table SVII.3. Pharmacological Class Risks included as Important Identified or Potential Risks

Risk	Frequency in Clinical Trials of Medicinal Product	Frequency seen with Other Products in same Pharmacological Class (Source of Data/Journal Reference) Sildenafil and Vardenafil	Comment
Hypotension/ Increased Hypotensive Effect	**i3 study** **Nitrate Co-dispensing Proportion** Tadalafil: • 1.2% patients received tadalafil ▪ 0.3% for chronic nitrates ▪ 1.1% for intermittent nitrates **Incidence Rate:** 12-53.2 per 1000 PYs	**i3 study** **Nitrate Co-dispensing Proportion** Sildenafil: • 1.8% patients received sildenafil ▪ 0.4% for chronic nitrates ▪ 1.6% for intermittent nitrates **Incidence Rate:** 17.7 – 75.4 per 1000 PYs Vardenafil: • 1.9% in patients received vardenafil ▪ 0.5% for chronic nitrates ▪ 1.6% for intermittent nitrates Matched control cohort: • 1.6% in patients received sildenafil ▪ 0.5% for chronic nitrates ▪ 1.3% for intermittent nitrates **Incidence Rate** 16.2 – 65.8 per 1000 PYs	
	Tadalafil Placebo-Controlled Clinical Studies: ED and BPH: 1.32% (131/9932) of patients reported this TEAE. PAH: 12.35% (40/324) of patients reported this TEAE.	**Sildenafil** (SmPC)**:** ED: hypotension (≥1/1000 to <1/100) PAH: hypotension incidence listed as not known **Vardenafil** (SmPC)**:** hypotension ≥1/10,000 to <1/1,000	

Table SVII.3. Pharmacological Class Risks included as Important Identified or Potential Risks (continued)

Risk	Frequency in Clinical Trials of Medicinal Product	Frequency seen with Other Products in same Pharmacological Class (Source of Data/Journal Reference) Sildenafil and Vardenafil	Comment
Priapism	**Tadalafil Placebo-Controlled Clinical Studies**: ED and BPH: 0.01% (1/9932) of patients reported this TEAE. PAH: 1.41% (1/71) of patients reported this TEAE.	**Sildenafil** (SmPC)**:** ED: Priapism ≥ 1/10,000 to <1/1000 reported during post-marketing surveillance only Increased erection: ≥ 1/10,000 to <1/1000 PAH: Priapism incidence listed as not known. Prolonged erection incidence listed as not known. **Vardenafil** (SmPC)**:** Increase in Erection-≥1/1,000 to <1/100; priapism ≥1/10,000 to <1/1,000	
Sudden Hearing Loss	**Tadalafil Placebo-Controlled Clinical Studies**: ED and BPH: 0.08% (8/9932) of patients reported this TEAE. PAH: 0% (0/324) of patients reported this TEAE.	**Sildenafil** (SmPC)**:** ED: deafness ≥1/10,000 to <1/1,000 PAH: sudden deafness incidence listed as unknown **Vardenafil** (SmPC)**:** Sudden deafness incidence listed as not known.	
NAION	**Tadalafil Placebo-Controlled Clinical Studies**: There were no placebo cases of NAION in ED, BPH or PAH.	**Sildenafil** (SmPC)**:** ED: NAION to ≥1/10,000 to <1/1,000 reported during post-marketing surveillance only PAH: NAION incidence listed as not known. **Vardenafil** (SmPC)**:** NAION incidence listed as not known.	

Abbreviations: BPH = Benign Prostatic Hyperplasia; ED = erectile dysfunction; NAION = Nonarteritic Anterior Ischaemic Optic Neuropathy; PAH = Pulmonary Arterial Hypertension; PYs = patient years; SmPC = Summary of Product Characteristics; TEAE = treatment-emergent adverse event.

SVII.5.2. Important Pharmacological Class Effects not Discussed Above

As a result of a CHMP discussion on signals of penile haemorrhage and haematospermia following the use of sildenafil, the CHMP requested MAHs of phosphodiesterase type 5 (PDE5) inhibitors to submit a cumulative overview of the adverse event terms penile haemorrhage, haematospermia, haematuria, and penile haematoma (with the indications of erectile dysfunction and pulmonary arterial hypertension discussed separately). Lilly performed and submitted to the EMA a review of all available data sources, and did not find a causal association between tadalafil and these urological adverse events. However, based upon their review of data from all PDE5 inhibitors, the CHMP determined these events to be a class effect and requested that the tadalafil SmPCs be updated to include events of penile haemorrhage, haematospermia and haematuria. The SmPC for CIALIS and ADCIRCA have been updated accordingly. It was subsequently requested by the CHMP that the RMP be updated to include genitourinary bleeding events as a potential class effect. The MAH does not consider these events to be important identified risks as they do not have a significant impact on benefit risk or public health. (See Table SVII.4).

Table SVII.4. Important Pharmacological Class Effects (Not Important Identified or Potential Risks)

Genitourinary Bleeding (haematospermia, haematuria, penile haemorrhage)

Frequency with 95% CI

Clinical Trial Programme (Placebo-Controlled Studies):

	Placebo	Tadalafil	Exact Risk Difference 95% Confidence Interval
ED and BPH			
Number of Patients	5209	10205	
Subjects with >= 1 TEAE	4 (0.08)	14 (0.14)	0.06 (-0.04, 0.16)
PAH (Males Only)			
Number of Patients	17	71	
Subjects with >= 1 TEAE	0 (0.00)	0 (0.00)	--
PAH (Females Only)[a]			
Number of Patients	65	253	
Subjects with >= 1 TEAE	0 (0.00)	2 (0.79)	0.79 (-0.30, 1.88)

Abbreviations: ED=erectile dysfunction; BPH=Benign Prostatic Hyperplasia; PAH= Pulmonary Arterial Hypertension; TEAE=treatment-emergent adverse event.

[a] Haematuria events only.

Source: home/lillyce/prd/ly450190/integrations_reg2016/2016_05_002_ct_rmp/programs_stat/tfl_output/smaesa3_71.rtf
home/lillyce/prd/ly450190/integrations_reg2016/2016_05_002_ct_rmp/programs_stat/tfl_output/smaesa3_72.rtf
home/lillyce/prd/ly450190/integrations_reg2016/2016_05_002_ct_rmp/programs_stat/tfl_output/smaesa3_81.rtf

Clinical Trial Programme (All Studies):

	Tadalafil (%)	95% Confidence Interval[a]
ED and BPH		
Number of Patients	24147	
Subjects with ≥1 TEAE	53 (0.22)	0.16 - 0.29
PAH (Males Only)		
Number of Patients	86	
Subjects with ≥1 TEAE	0 (0.00)	--
PAH (Females Only)[b]		
Number of Patients	313	
Subjects with ≥1 TEAE	4 (1.28)	0.35 - 3.24

Abbreviations: ED=erectile dysfunction; BPH=Benign Prostatic Hyperplasia; PAH= Pulmonary Arterial Hypertension; TEAE=treatment-emergent adverse event.

[a] Clopper-Pearson method was used for the confidence interval calculation

[b] Haematuria events only.

Source: home/lillyce/prd/ly450190/integrations_reg2016/2016_05_002_ct_rmp/programs_stat/tfl_output/smaesa2_71.rtf
home/lillyce/prd/ly450190/integrations_reg2016/2016_05_002_ct_rmp/programs_stat/tfl_output/smaesa2_72.rtf
home/lillyce/prd/ly450190/integrations_reg2016/2016_05_002_ct_rmp/programs_stat/tfl_output/smaesa2_81.rtf

Table SVII.4. Important Pharmacological Class Effects (Not Important Identified or Potential Risks) (continued)

Genitourinary Bleeding (haematospermia, haematuria, penile haemorrhage) (*continued*)

Seriousness/outcomes

Clinical Trial Programme (All ED, BPH and PAH Studies):

	Fatal	Recovered/ Resolved	Not Recovered/ Not Resolved	Recovered/ Resolved with Sequellae	Recovering/ Resolving	Unknown	Total
ED and BPH							
Number of Serious TEAE	0 (0.00)	1 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.00)
Number of Non-Serious TEAE	0 (0.00)	43 (0.18)	9 (0.04)	0 (0.00)	2 (0.01)	0 (0.00)	54 (0.23)
Total	0 (0.00)	44 (0.19)	9 (0.04)	0 (0.00)	2 (0.01)	0 (0.00)	55 (0.23)
PAH (Males only)							
Number of Serious TEAE	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Number of Non-Serious TEAE	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Total	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
PAH (Females only) [a]							
Number of Serious TEAE	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Number of Non-Serious TEAE	0 (0.00)	2 (0.64)	1 (0.32)	0 (0.00)	0 (0.00)	1 (0.32)	4 (1.28)
Total	0 (0.00)	2 (0.64)	1 (0.32)	0 (0.00)	0 (0.00)	1 (0.32)	4 (1.28)

Abbreviations: ED=erectile dysfunction; BPH=Benign Prostatic Hyperplasia; PAH=Pulmonary Arterial Hypertension; TEAE=treatment-emergent adverse event.

[a] Haematuria events only.

Source: home/lillyce/prd/ly450190/integrations_reg2016/2016_05_002_ct_rmp/programs_stat/tfl_output/smaesa1_71.rtf
home/lillyce/prd/ly450190/integrations_reg2016/2016_05_002_ct_rmp/programs_stat/tfl_output/smaesa1_72.rtf
home/lillyce/prd/ly450190/integrations_reg2016/2016_05_002_ct_rmp/programs_stat/tfl_output/smaesa1_81.rtf

Table SVII.4. Important Pharmacological Class Effects (Not Important Identified or Potential Risks) (continued)

Genitourinary Bleeding (haematospermia, haematuria, penile haemorrhage) (*continued*)

Severity and nature of risk

Clinical Trial Programme (All ED, BPH and PAH Studies):

Subjects with ≥1 TEAE by Maximum Severity	Placebo (%)	Tadalafil (%)	Mantel-Haenszel Odds Ratio[a]
ED and BPH			
Mild	3 (0.06)	9 (0.09)	
Moderate	1 (0.02)	5 (0.05)	
Total	4 (0.08)	14 (0.14)	1.8133
PAH (Males Only)			
Mild	0 (0.00)	0 (0.00)	
Moderate	0 (0.00)	0 (0.00)	
Total	0 (0.00)	0 (0.00)	--
PAH (Females Only)[b]			
Mild	0 (0.00)	1 (0.40)	
Moderate	0 (0.00)	1 (0.40)	
Total	0 (0.00)	2 (0.79)	--

Abbreviations: ED=erectile dysfunction; BPH=Benign Prostatic Hyperplasia; PAH= pulmonary arterial Hypertension; TEAE=treatment-emergent adverse event.

[a] Mantel-Haenszel Odds Ratio stratified by study. Tadalafil is numerator and Placebo is denominator. For 'Severe', the OR compares incidence of any Severe TEAE to no Severe TEAE. For 'Total', the OR compares any TEAE to no TEAE.

[b] Haematuria events only.

Source: home/lillyce/prd/ly450190/integrations_reg2016/2016_05_002_ct_rmp/programs_stat/tfl_output/smaesa6_71.rtf
home/lillyce/prd/ly450190/integrations_reg2016/2016_05_002_ct_rmp/programs_stat/tfl_output/smaesa6_72.rtf
home/lillyce/prd/ly450190/integrations_reg2016/2016_05_002_ct_rmp/programs_stat/tfl_output/smaesa6_81.rtf

Frequency with other members of the same or similar pharmacological class with 95%CI

Sildenafil SmPC:

ED: Haematospermia ≥1/1,000 to <1/100; haematuria ≥1/1,000 to <1/100; penile haemorrhage ≥1/1,000 to <1/100

PAH: Haematospermia ≥1/1,000 to <1/100; haematuria ≥1/1,000 to <1/100; penile haemorrhage ≥1/1,000 to <1/100

Vardenafil SmPC: haematospermia incidence listed as not known, haematuria incidence listed as not known, penile haemorrhage incidence listed as not known

Table SVII.4. Important Pharmacological Class Effects (Not Important Identified or Potential Risks) (continued)

Genitourinary Bleeding (haematospermia, haematuria, penile haemorrhage) (*continued*)	
Risk groups or risk factors	There are no known patient characteristics relevant to the risk of genitourinary bleeding events with tadalafil treatment. Penile haematoma and penile haemorrhage commonly result from penetrating injuries or non-penetrating injuries (Savoca 2008). Haematuria in the general population has many possible causes: glomerular (including glomerulonephritis caused by systemic disease, thrombotic thrombocytic purpura (TTP) or subacute bacterial endocarditis), nonglomerular (including renal infection or tumour, nephritis, bladder infection, prostate infection, drug/radiation induced inflammation [cystitis], kidney stones, urological tumours, or benign prostatic hyperplasia), coagulopathy related (including warfarin/heparin induced bleeding), and trauma related (Sokolovsky 2001).
Potential mechanisms	PDE5 is expressed in platelets, and inhibition of PDE5 with consequent increases in platelet cGMP could theoretically inhibit platelet aggregation under certain conditions and affect bleeding time (Gresele et al. 2011). Although no clinical pharmacological study has monitored tadalafil and platelet function in man, there have been clinical pharmacology studies in healthy patients evaluating the effect of tadalafil on bleeding and prothrombin time which have demonstrated that there were no clinically-relevant pharmacokinetic or pharmacodynamic interactions between tadalafil and either warfarin or aspirin.
Comment	A recent 2012 analysis and review of clinical trial and spontaneous cases of haematospermia, haematuria, and penile haemorrhage did not provide evidence of a causal relationship between tadalafil and these events. In the clinical trials, the patient-year incidence of these events was low regardless of indication, there was no clear relationship to dose or duration of treatment with tadalafil, and the majority of the cases had alternative aetiologies for these events suggesting that it was result of underlying disease and/or concomitant medications which are prevalent in the populations being studied. Many of the spontaneous cases from the ED indication had confounders or insufficient information to make an assessment of causality. Of the cases in which indication was provided, all were from ED; there were no spontaneous cases reported in the PAH indication. At the request of the CHMP, these genitourinary bleeding events were added to the SmPC. Since these events were generally nonserious, no new warning or precaution for use, or additional risk minimisation activities were warranted. Therefore, these events do not meet the definition of an important risk as they do not significantly impact benefit risk or public health.
Evidence source	**Clinical Trial Programme:** integrated clinical trial database **Post-marketing Data:** Lilly Safety System

Module SVIII. Summary of the Safety Concerns

Table SVIII.1. Summary of Safety Concerns (Important Identified Risks, Important Potential Risks, and Missing Information)

Summary of Safety Concerns	
Important Identified Risks	All Indications: • Hypotension/Increased Hypotensive Effect • Priapism
Important Potential Risks*	All Indications: • Nonarteritic anterior ischaemic optic neuropathy (NAION) • Sudden hearing loss
Important Missing Information	Tadalafil Once-a-Day ED and BPH Indications: • Characterisation of adverse events in elderly patients (≥65 years of age)

Abbreviations: BPH = benign prostatic hyperplasia; ED = erectile dysfunction; NAION = nonarteritic anterior ischaemic optic neuropathy; PAH = pulmonary arterial hypertension.

*Increased Uterine Bleeding is no longer considered an important potential risk.

Part III. Pharmacovigilance Plan

III.1. Safety Concerns and Overview of Planned Pharmacovigilance Actions

Table III.1. Hypotension/Increased Hypotensive Effects and Planned Pharmacovigilance Activities

Hypotension/Increased Hypotensive Effects		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional Pharmacovigilance Activities**	**Objectives**
The occurrence of hypotension in the very elderly for the ED once-a-day and BPH indications	Annual review of hypotension cases in the very elderly (≥75) years for a total of 3 years. The need to continue this review will be assessed at the end of this period in the light of the results of successive analyses and current experience. Routine pharmacovigilance including targeted follow-up forms for cardiac events (including arrhythmia, chest pain/angina, myocardial infarction, hypotension/syncope/dizziness).	To better understand the effect of tadalafil on the frequency and severity of hypotension in the very elderly (≥75 years). Signal and risk management.

Table III.2. Priapism and Planned Pharmacovigilance Activities

Priapism		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional Pharmacovigilance Activities**	**Objectives**
None	Routine pharmacovigilance including targeted follow-up forms.	Targeted follow-up investigations will facilitate the collection of clinically relevant data/information as applicable or as possessed by the HCP. Signal and risk management.

Abbreviation: HCP = healthcare professional.

Important Potential Risks (All Indications):

Table III.3. NAION and Planned Pharmacovigilance Activities

NAION		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional Pharmacovigilance Activities**	**Objectives**
None.	. Routine pharmacovigilance including targeted follow-up investigations, as *visual abnormalities* have been designated a surveillance term for tadalafil.	Targeted follow-up investigations will facilitate the collection of clinically relevant data/information as applicable or as possessed by the HCP. Signal and risk management.

Abbreviations: HCP = healthcare professional; NAION = nonarteritic anterior ischaemic optic neuropathy.

Table III.4. Sudden Hearing Loss and Planned Pharmacovigilance Activities

Sudden Hearing Loss		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional Pharmacovigilance Activities**	**Objectives**
None	Annual review of hearing abnormality cases. The need to continue this review will be assessed at the end of this period in the light of the results of successive analyses and current experience. Routine pharmacovigilance including targeted follow-up investigations, as *hearing abnormalities (i.e., sudden hearing loss, hearing impairment, deafness, vertigo, tinnitus)* have been designated as a surveillance term for tadalafil.	Targeted follow-up investigations will facilitate the collection of clinically relevant data/information as applicable or as possessed by the HCP . Signal and risk management.

Abbreviation: HCP = healthcare professional.

Important Missing Information (Erectile Dysfunction [Once a day] and BPH Indications):

Table III.5. Characterisation of Adverse Events in Elderly Patients (≥65 Years of Age) and Planned Pharmacovigilance Activities

Characterisation of adverse events in elderly patients (≥65 years of age) (Erectile Dysfunction [Once a day] and BPH Indications)		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional Pharmacovigilance Activities**	**Objectives**
There is considered to be insufficient safety data in the elderly (≥65 years) for the ED once-a-day and BPH indications.	For ED and BPH indications only: • Annual comparative analysis of spontaneous ADR reports by SOC with once a day dosing data according to patient age: elderly (≥65 years) and patients <65 years for a total of 3 years. • Clinical trials: Annual cumulative comparison of adverse events reported in the elderly (≥65 years) and patients <65 years from completed placebo-controlled tadalafil studies using once-a-day dosing for a total of 3 years. • Annual review cases of hypotension in the very elderly (≥75 years) for a total of 3 years. Routine pharmacovigilance including targeted follow-up forms.	Better characterise the safety profile of tadalafil in elderly patients. Signal and risk management.

Abbreviations: ADR = adverse drug reaction; BPH = benign prostatic hyperplasia; ED = erectile dysfunction; SOC = system organ class.

III.2. Studies and Other Activities Completed Since Last Update of Pharmacovigilance Plan

H6D-MC-LVHQ

Study H6D-MC-LVHQ (LVHQ) used an observational multicentre, case-crossover study design to evaluate the possible association between PDE5 inhibitor use and the risk of acute NAION in adult males using a person-time analysis. Adult males visiting one of 41 participating ophthalmology and neuro-ophthalmology centres in the US between 05 May 2010 and 15 December 2015 with physician-diagnosed NAION within 45 days of onset, were considered. There were 344 adult males with suspected NAION who met the inclusion and exclusion criteria. Of these, 279 subjects were confirmed as having NAION based on adjudication committee decision. The primary analysis for this study evaluated the risk of NAION associated with PDE5 inhibitor use in the 30 days prior to index date of onset (IDO); examining exposure period immediately prior to IDO (hazard period) compared with the remainder of the 30 days prior to IDO (control period). There were 22 subjects who were reported as intermittent users of PDE5 inhibitors with nonchronic exposure within the 30 days prior to the IDO. The Mantel-Haenszel

risk ratio (RR) for exposure to PDE5 inhibitors during the hazard period (within 5 half-lives preceding NAION onset) relative to the control period was 2.27 (95% CI: 0.99, 5.20). Sensitivity analyses were conducted modifying the exposure definition and imputing missing exposure information. The RRs for these analyses ranged from 2.55 to 2.84 and were statistically significant. In summary, the primary analysis was not statistically significant; however, considering both the main (primary and secondary) and sensitivity person-time analyses, the results are suggestive of an increased risk of NAION occurring in association with PDE5 inhibitor exposure.

Based upon the cumulative data, there is sufficient evidence to support the existing classification of NAION as an ADR for tadalafil. NAION occurs rarely in males aged 50 years and over (annual incidence rate of 2.5-11.8 per 100,000 [Johnson and Arnold 1994; Hattenhauer et. al. 1997]); and is very rarely reported in association with tadalafil in post marketing reports. The impact on public health is therefore low and the benefit-risk balance has not changed. This rare ADR is managed entirely by routine pharmacovigilance and existing label language in relation to dose, and monitoring and additional pharmacovigilance or risk minimisation activities are not warranted.

H6D-JE-TD01

Study H6D-JE-TD01 (TD01) was a postmarketing study conducted as a condition for approval in Japan that enrolled all patients in the contracted sites from the start of marketing of tadalafil (ADCIRCA®) 20-mg tablet from December 2009 until August 2014. Patients with pulmonary arterial hypertension (PAH) who received tadalafil were analysed. All sites that purchased tadalafil were invited to participate in this postmarketing study, and a written contract was provided only after the sites agreed to cooperate in this study. The information about all of the cases receiving tadalafil at the contracted sites was collected, irrespective of the patients' age. The maximum duration of the observational period was 2 years. The incidence of adverse events (AEs) in patients with long-term tadalafil use and, in particular, the incidence of AEs of low blood pressure, bleeding (such as uterine bleeding), abnormal vision, and sudden hearing loss were evaluated. Information about the safety and effectiveness in paediatric patients, safety and effectiveness in patients with concomitant medication use for PAH, and dosage, safety, and effectiveness in patients with renal/hepatic impairments were analysed.

During the enrolment period (until February 2014), a total of 1809 patients were enrolled in the study, and 1704 case reports were collected. A total of 105 case report forms (CRFs) could not be collected due to lack of investigator's cooperation (103) or loss of CRF (2). A total of 1676 cases were analysed for safety; the number of patients excluded from the safety analysis was 28, due to duplicate registration (11), contract violation (8), no visit after enrolment (6), unknown whether AEs exist or not (3). A total of 1556 cases were analysed for efficacy; the number of patients excluded from the efficacy analysis was 120, all due to the primary disease other than PAH.

Among the 1676 patients analysed for safety, the overall incidence of ADRs (adverse drug reaction [ADR] is defined as a TEAE that is determined to be treatment-related by the investigator) was 31.21%. Commonly reported ADRs (in $\geq$1% patients) were: headache,

diarrhoea, platelet count decreased, anaemia, epistaxis, nausea, flushing, hepatic function abnormal, hot flush, and myalgia.

Among the 1556 patients analysed for effectiveness, the point estimate for survival at 1 year and 2 years (95% CI) was 93.0% (91.5%-94.3%) and 86.3% (84.1%-88.3%), respectively. Changes in WHO classification and QoL (representing symptoms), six-minute walk test (representing exercise tolerance), and pulmonary haemodynamics (representing signs) have shown a tendency toward improvement.

Important investigated items included long-term administration, safety, and effectiveness in patients with concomitant medication specific to PAH, safety and effectiveness in paediatric and elderly patients, and administration, safety, and effectiveness in patients with renal/hepatic impairment. No significant findings were reported.

Consequently, there are no significant findings in the safety and effectiveness of tadalafil for the treatment of PAH. No additional risk minimisation measures are needed.

Tadalafil Increased Uterine Bleeding Safety Topic Report

Increased or abnormal uterine bleeding is a symptom of various underlying conditions, including polyps, malignancies, coagulopathies, and ovulatory disorders. Increased uterine bleeding associated with menses (i.e., menorrhagia) is reported in up to 54% of women, and thus is an expected event in females of child-bearing potential. Increased uterine bleeding can have a substantial impact on women's quality of life, productivity, and health care costs. Although infrequent episodes of menorrhagia are common and often self-limiting, severe cases can result in anaemia requiring transfusion, and uncontrolled uterine bleeding can rarely be fatal. Treatment for increased uterine bleeding includes both medical therapies and surgical procedures.

There is biological plausibility for tadalafil to increase bleeding by inhibiting platelet aggregation. Inhibition of PDE5 may also have direct effects on the myometrium where PDE5 is expressed. In addition, uterine artery blood flow and endometrial thickness were increased after treatment with sildenafil. However, a role of PDE5 inhibitors in the occurrence of increased uterine bleeding (including menorrhagia) in patients with PAH has not been established.

Over 16 weeks of treatment in the placebo controlled Study LVGY, significantly more tadalafil-treated female patients (3.2% [8/253]) compared with placebo-treated female patients (0/65) reported ≥1 TEAE related to increased uterine bleeding (risk difference = 3.16 [95% CI 1.01, 5.32]). In Study LVGY and Study LVGX combined (placebo-controlled plus open-label with up to approximately 72 months of tadalafil treatment), 6.4% (20/313) of tadalafil-treated female patients reported ≥1 TEAE related to increased uterine bleeding. Most of the events were mild or moderate in severity, 1 led to discontinuation, and 2 were SAEs. The 2 patients reporting SAEs of menorrhagia had significant confounding factors, including concomitant use of anticoagulants, previous history of dilation and curettage (1 patient) and concurrent leiomyoma (1 patient).

In the postmarketing setting through 31 July 2016, 17 events related to increased uterine bleeding were reported in 16 cases. Thus, approximately 0.02% (16/75 100) of women prescribed tadalafil reported adverse events related to increased uterine bleeding with an estimated incidence of 0.15 cases per 1000 PY. The majority of cases originated in the US

(62.5%) and were reported by consumers (62.5%). Based on the 6 cases with information on time to onset, there was no apparent relationship between the occurrence of increased uterine bleeding and the time of initiation of tadalafil therapy. Most of the postmarketing cases contained limited or no information on medical history, dose or start date of tadalafil therapy, concomitant medications, or event outcome. However, confounding factors that could impact uterine bleeding were reported in a majority of cases. For example, 8 (50%) cases reported use of ≥1 concomitant medication that is known to increase the risk of bleeding (e.g., anticoagulants, prostacyclin analogues) and 1 patient reported medical history of bleeding problems. There were 2 SAEs of vaginal haemorrhage in the postmarketing setting; these 2 cases were reported by consumers with very limited information provided, including no information on outcome or status of tadalafil therapy.

Compared with reports in the general population (cumulative 12-month incidence of 25%), the frequency of increased uterine bleeding reported by females taking tadalafil was very low in both PAH clinical trials (6.4%) and in the postmarketing setting (0.02%). In addition, many of the cases reported confounding factors including concomitant use of medications known to increase bleeding. The estimated incidence (0.15 cases per 1000 PY) in the postmarketing setting was also low, and likely reflects the underreporting limitation of spontaneous reporting.

Based on this cumulative review, and on the fact that it is generally a nonserious event in a population being treated for a life-threatening disease, increased uterine bleeding in patients with PAH is no longer considered an important potential risk for tadalafil. In addition, anaemia that may result from the increased uterine bleeding can be monitored and treated, and is generally reversible. Thus, this risk is not considered to have a significant impact to the benefit-risk profile for tadalafil and will be removed from the RMP as an important potential risk. Increased uterine bleeding will be retained in the tadalafil CDS as an ADR in patients with PAH and in the Undesirable Events section of the SmPC. No additional risk minimisation activities are warranted. Information on increased uterine bleeding and the use of tadalafil from available data sources will continue to be monitored via standard pharmacovigilance activities, including targeted follow-up on reports related to increased uterine bleeding.

III.3. Details of Outstanding Additional Pharmacovigilance Activities

Not applicable.

III.4.1. Imposed Mandatory Additional Pharmacovigilance Activity (Key to Benefit Risk)

Not applicable.

III.4.2. Mandatory Additional PhV Activity (being a Specific Obligation)

Not applicable.

III.4.3. Required Additional Pharmacovigilance Activities to Address Specific Safety Concerns or to Measure Effectiveness of Risk Minimisation Measures

Per a request from the FDA to all manufacturers of PDE5 inhibitors, the MAH has completed an observational prospective case-crossover study to evaluate the possible causal association between the use of PDE5 inhibitors and the acute risk of NAION. The results of the study are described in Section III.2.

III.4.4 Stated Additional Pharmacovigilance Activities

Table III.6. Stated Additional Pharmacovigilance Activities

	Description of Activity	Expected Date of Report
1	H6D-KL-B019: Post-Marketing Surveillance Study on Cialis® 5mg (Tadalafil) Use Among BPH Patients in Korea	03-Apr-2017
2	H6D-JE-B020: Post-Marketing Observational Study of Tadalafil in Japanese Patients with Benign Prostatic Hyperplasia-Lower Urinary Tract Symptom (BPH-LUTS)	30-APR-2018
3	H6D-GH-B022: Post-marketing Surveillance Study: A Randomized, Open-Label, 3-Month Interventional Study of Tadalafil Effectiveness (2.5 mg and 5 mg) and Long -Term Safety Administered Once Daily in Chinese Men with Erectile Dysfunction	31-AUG-2017

Abbreviations: BPH = benign prostatic hyperplasia; LUTS = lower urinary tract symptom.

III.5. Summary of the Pharmacovigilance Plan

III.5.1. Table of Ongoing and Planned Additional Pharmacovigilance Studies/Activities in the Pharmacovigilance Plan

Not applicable.

III.5.2. Table of Completed Studies/Activities from the Pharmacovigilance Plan

Table III.7. Completed Studies from the Postmarketing Pharmacovigilance Development Plan

Study/Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Completed)	Date of Submission of Final Report
H6D-MC-LVHQ: A Prospective Case-Crossover Study to Evaluate the Possible Association Between the Use of PDE5 Inhibitors and the Risk of Acute Nonarteritic Anterior Ischemic Optic Neuropathy (NAION) Category 3	Study H6D-MC-LVHQ was an observational, prospective, case crossover study examining the possible association between the use of PDE5 inhibitors and the risk of acute NAION in adult male subjects (279 NAION cases were included).	The possible association between the use of PDE5 inhibitors and the risk of acute NAION in adult male subjects	Study completed	Report approval May 2016 Submitted June 2016

Abbreviations: NAION = nonarteritic anterior ischemic optic neuropathy; PDE5 = phosphodiesterase type 5.

Part IV. Plans for Post-authorisation Efficacy Studies

IV.1. Applicability to Efficacy to All Patients in the Target Population

Tadalafil has been studied in 5 pivotal ED on-demand registration trials as well as 3 pivotal erectile dysfunction (ED) once-a-day trials. Consistent results were observed across 17 randomised, placebo-controlled, double-blind clinical trials for on-demand tadalafil administration (Rosen et al. 2011). For the once-a-day treatment of ED, results from 2 additional randomised, placebo-controlled studies were consistent with those of the pivotal registration studies.

A total of 21,035 patients have been exposed to tadalafil across all ED trials (On demand and once a day) in the entire clinical development programme. The ED clinical development programme for both on-demand and once-a-day dosing encompassed patients in the age group known to be representative of the general population of men with ED, as well as patients with various ethnic/racial backgrounds, disease severities (mild-to-severe ED), and patients with common co-morbidities (for example, hypertension, diabetes, and cardiovascular disease).

Four pivotal registration trials were conducted in men with signs and symptoms of BPH. Subsequently, 3 placebo-controlled studies in Asian men and a single study in men with BPH and prostatic enlargement co-administered finasteride have been completed; consistent efficacy results were observed across all efficacy studies in men with BPH. A total of 3564 patients have been exposed to tadalafil across the BPH clinical development programme. The BPH clinical development programme recruited patients with moderate-to-severe symptoms of BPH, although some patients had mild symptoms upon completion of the placebo lead-in period (at the time of randomisation) and therefore were included in the study. Consistent with clinical practice guidelines (Oelke et al. 2013; AUA Guidelines [WWW]), men with mild BPH symptoms are suitable for watchful waiting, thus the moderate-to-severe patient population anticipated to be treated with tadalafil in clinical practice would be consistent with the majority of patients assessed in the clinical development programme. Additionally, the ethnic/racial backgrounds, age, and co-morbidities of patients studied are representative of patients anticipated to be treated in clinical practice.

The efficacy of tadalafil for the treatment of PAH was established in a pivotal Phase 3 placebo controlled trial. The efficacy observed in the pivotal Phase 3 placebo-controlled trial was maintained for up to 52 weeks (in the double-blind, open-label extension study), demonstrating durability and consistency in efficacy. A total of 399 PAH patients have been exposed to tadalafil in controlled clinical trials. The clinical development programme allowed patients with PAH classified as WHO Functional Class I, II, III, or IV to be enrolled. The majority (97%) of patients were classified as WHO Functional Class II or III at baseline. The SmPC states that ADCIRCA is approved for the treatment of PAH classified as WHO Functional Class II or III, consistent with the population studied. Other baseline characteristics (for example, age, gender, ethnicity/race, concomitant bosentan use) of patients in the clinical programme were consistent

with the adult patient population anticipated to receive tadalafil for the treatment of PAH in clinical practice.

Based on all the available data, no major gaps in knowledge about efficacy remain at this time, and the populations studies in the clinical development programmes are consistent with those anticipated to be treated with tadalafil in clinical practice.

IV.2. Tables of Post-authorisation Efficacy Studies

No post-authorisation efficacy studies are considered necessary by the MAH or have been imposed by CHMP or National Competent Authority.

IV.3. Summary of Post-authorisation Efficacy Development Plan

The post-authorisation development plan does not include any studies to address efficacy uncertainties.

IV.4. Summary of Completed Post-authorisation Efficacy Studies for Authorised Indications

No post-authorisation efficacy studies have been considered necessary to address any efficacy uncertainties.

Part V. EU Risk Minimisation Measures

V.1. Risk Minimisation Measures

V.1.1. All Indications

Table V.1. Risk Minimisation Measures by Safety Concern – All Indications

Important Identified Risk: Hypotension/Increased Hypotensive Effect	
Objective(s) of the risk minimisation measures	To ensure that prescribers are appropriately informed about this risk through labelling.
Routine risk minimisation measures	**Labelling:** • Specific label text in the SmPC under Section 4.3 (Contraindications) indicates that CIALIS/ADCIRCA is contraindicated in patients using any form of organic nitrate, have, hypotension (<90/50mmHg), or uncontrolled hypertension. • Specific label text in the SmPC under Section 4.4 (Special warnings and precautions) describing the risk of hypotension with tadalafil. • Specific label text in Section 4.3 of the SmPC contraindicating the use of tadalafil and guanylate cyclase stimulators, such as riociguat, because it may potentially lead to symptomatic hypotension. • Specific label text in the SmPC Section 4.5 (Interaction with other medicinal products and other forms of interaction) for nitrates, anti-hypertensives, and alcohol. • Hypotension has been listed as an adverse reaction under SmPC Section 4.8 (Undesirable effects). • The package leaflet, instructs patient not to take CIALIS/ADCIRCA if they are taking any form of organic nitrate or nitric oxide donors such as amyl nitrite or if they have low blood pressure • The package leaflet instructs patients to tell the doctor if they are taking alpha-blockers. • The package leaflet under Possible Side Effects (Section 4) includes low blood pressure
	Comment: None
	Other routine risk minimisation measures: None
Additional risk minimisation measure(s)	None proposed.
	Not applicable.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	No further studies are planned.
Criteria for judging the success of the proposed risk minimisation measures	Not applicable.
Planned dates for assessments	Not applicable.

Table V.1. Risk Minimisation Measures by Safety Concern – All Indications (continued)

Important Identified Risk: Hypotension/Increased Hypotensive Effect (*continued*)	
Effectiveness of risk minimisation measures (*continued*)	

Results of effectiveness measurement (studies completed in 2007)	The effectiveness of labelling (that is, USPI) in preventing the coadministration of nitrates with tadalafil was evaluated in two studies that assessed the frequency of tadalafil/nitrate co-prescribing among men aged 18 years and older.
	
	i3Study:
	
	The first study (i3) was conducted using automated medical and pharmacy claims' data from the Ingenix Research Data Mart, a large database of commercial insurance claims for patients enrolled in a variety of health plans across the United States between 01 December 2003 and 31 January 2006.
	
	Nitrate Co-dispensing Proportion:
	
	• 1.2% in patients who received tadalafil
	  o 0.3% for chronic nitrates;
	  o 1.1% for intermittent nitrates
	
	Incidence Rate of Co-dispensing Nitrates and Tadalafil
	
	• 12-53.2 per 1000 PYs
	
	The study found a lower rate of co-dispensing of tadalafil and nitrates compared to the rates of co-dispensing of other PDE5 inhibitors with nitrates. There was a lower rate of nitrate dispensing in the matched tadalafil cohort than in the matched general population comparator cohort and a lower rate of nitrate dispensing in the tadalafil cohort than in other PDE5 inhibitor cohorts. During the course of the study, the average monthly number of co-dispensing of tadalafil and nitrates per 1,000 tadalafil dispensings decreased from the first half of the study to the second half. The majority of co-dispensing of tadalafil and nitrates was by family practitioners, internists, cardiologists, and urologists.
	
	IMS Study:
	
	The IMS study compared the proportion of patients who were dispensed nitrates among those taking tadalafil compared to a control group of patients and determined the proportions of patients co-dispensed the PDE5 inhibitors of sildenafil or vardenafil with nitrates. The study was conducted using a United States longitudinal prescription database sourced from retail pharmacies in male patients aged 18 years and older between 01 December 2003 and 31 March 2006.
	
	Nitrate Co-dispensing Proportion:
	
	• 1.02% - 3.31% in patients who received tadalafil
	  o 0.23% - 0.79% for chronic nitrates;
	  o 0.86% - 2.95% for intermittent nitrates
	
	The final study cohort included 2,391,030 unique PDE5 inhibitor patients, including 601,063 (25.2%) tadalafil patients. This study also concluded that patients on tadalafil had the lowest co-dispensing proportion among the 3 PDE5 inhibitor cohorts for both chronic and intermittent nitrates across all exposure windows. When compared to the matched cohort, tadalafil patients also had lower rates of co-dispensing for both chronic and intermittent nitrates.

Impact of risk minimisation	Risk minimisation appears to be effective.
Comment	Not applicable.

continued

Table V.1. Risk Minimisation Measures by Safety Concern – All Indications (continued)

Important Identified Risk: Priapism	
Objective(s) of the risk minimisation measures	To ensure that prescribers are appropriately informed about this risk through labelling.
Routine risk minimisation measures	**Labelling** • Specific label text in the SmPC under Special Warnings and Precautions (Section 4.4) states that patients who experience erections lasting 4 hours or more should be instructed to seek immediate medical assistance. • Priapism and Prolonged erections are listed in the SmPC as undesirable effects under Section 4.8. • The package leaflet instructs patients to inform the doctor immediately if the erection lasts continuously for more than 4 hours and instructs patients to inform their doctor before taking CIALIS/ADCIRCA if they have any deformation of the penis.
	Comment : None
	Other routine risk minimisation measures: None
Additional risk minimisation measure(s)	None proposed
	Not applicable
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Not applicable
Criteria for judging the success of the proposed risk minimisation measures	Not applicable
Planned dates for assessments	Not applicable
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	No additional risk minimisation activities are needed at this time.

continued

Table V.1. Risk Minimisation Measures by Safety Concern – All Indications (continued)

Important Potential Risk: Nonarteritic Anterior Ischaemic Optic Neuropathy (NAION)	
Objective(s) of the risk minimisation measures	To ensure that prescribers are appropriately informed about this risk through labelling.
Routine risk minimisation measures	**Labelling** • Specific label text in the SmPCs under Section 4.3 (Contraindications) indicates that CIALIS/ADCIRCA is contraindicated in patients who have loss of vision in one eye because of NAION. • Specific label text in the SmPC under Special Warnings and Precautions (Section 4.4) states that visual defects and cases of NAION have been reported in connection with the intake of CIALIS/ADCIRCA and other PDE5 inhibitors. The patient should be advised that in case of sudden visual defect he should consult a physician immediately. • NAION has been listed in the SmPC as an adverse reaction under Section 4.8 (Undesirable effects). • The package leaflet, instructs patient not to take CIALIS/ADCIRCA if they have ever had loss of vision because of NAION • The package leaflet under Possible Side Effects (Section 4) includes partial, temporary or permanent decrease or loss of vision in one or both eyes.
	Comment: None
	Other routine risk minimisation measures: None
Additional risk minimisation measure(s)	None proposed
	Not applicable
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Not applicable
Criteria for judging the success of the proposed risk minimisation measures	Not applicable
Planned dates for assessments	Not applicable
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	No additional risk minimisation activities are needed at this time.

continued

Table V.1. Risk Minimisation Measures by Safety Concern – All Indications (continued)

Important Potential Risk: Sudden Hearing Loss	
Objective(s) of the risk minimisation measures	To ensure that prescribers are appropriately informed about this risk through labelling.
Routine risk minimisation measures	**Labelling** ▪ Following assessment of a cumulative review of sudden hearing loss, the PRAC has recommended the inclusion of specific label text to the SmPC under Special Warnings and Precautions (Section 4.4) describing that sudden hearing loss has been reported with use of tadalafil and that patients should be advised to seek prompt medical attention in the event of a sudden decrease or loss of hearing. A procedure is planned to include appropriate labelling in the SmPC. ▪ Sudden hearing loss has been listed in the SmPC as an adverse reaction under Section 4.8 (Undesirable effects). ▪ The package leaflet includes this risk of sudden hearing loss.
	Comment: None
	Other routine risk minimisation measures: None
Additional risk minimisation measure(s)	None proposed
	Not applicable
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Not applicable
Criteria for judging the success of the proposed risk minimisation measures	Not applicable
Planned dates for assessments	Not applicable
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	No additional risk minimisation activities are needed at this time.

V.1.2 Erectile Dysfunction (Once a day) and Benign Prostatic Hyperplasia Indications

Table V.2. Risk Minimisation Measures by Safety Concern – Erectile Dysfunction (Once a day) and Benign Prostatic Hyperplasia Indications

Important Missing Information: Characterisation of adverse events in elderly patients (≥65 years of age)	
Objective(s) of the risk minimisation measures	To ensure that prescribers are appropriately informed that the data, including safety, in elderly (≥65 years) patients receiving tadalafil for once-a-day dosing in ED and BPH are limited.
Routine risk minimisation measures	**Labelling** Section 4.8 of the CIALIS SmPC informs that data in patients over 65 years of age receiving tadalafil in clinical trials, either for the treatment of erectile dysfunction or the treatment of benign prostatic hyperplasia, are limited.
	Comment : None
	Other routine risk minimisation measures: None
Additional risk minimisation measure(s)	None proposed
	Not applicable
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	At this time no specific measure of effectiveness is planned. However, adverse events in the elderly are being monitored by the pharmacovigilance activities described in Table III.1.7 of the PV plan and Table V.5. If new risks are identified in this population, they will be addressed through labelling or additional risk minimisation activities, as appropriate.
Criteria for judging the success of the proposed risk minimisation measures	Not applicable
Planned dates for assessments	Not applicable
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	No additional risk minimisation activities are needed at this time.

V.2. Risk Minimisation Measure Failure

Not applicable.

V.2.1. Analysis of Risk Minimisation Measure Failure

Not applicable.

V.2.2. Revised Proposal for Risk Minimisation

No new or revised risk minimisation measures are proposed.

V.3. Summary Table of EU Risk Minimisation Measures

Table V.3. Summary of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Identified Risks – All Indications		
Hypotension/Increased Hypotensive Effect	**Labelling** • Specific label text in the SmPC under Section 4.3 (Contraindications) indicates that CIALIS/ADCIRCA is contraindicated in patients who using any form of organic nitrate, or who have hypotension (<90/50mmHg), or uncontrolled hypertension. Package leaflet states that CIALIS should not be taken if already taking nitrates. • Specific label text in the SmPC under Section 4.4 (Special warnings and precautions) describing the risk of hypotension with tadalafil. • Specific label text in Section 4.3 of the SmPC contraindicating the use of tadalafil and guanylate cyclase stimulators, such as riociguat, because it may potentially lead to symptomatic hypotension. • Specific label text in the SmPC Section 4.5 (Interaction with other medicinal products and other forms of interaction) for nitrates, anti-hypertensives, and alcohol. • Hypotension has been listed as an adverse reaction in the SmPC under Section 4.8 (Undesirable effects). • The package leaflet instructs patients to tell the doctor if they are taking alpha-blockers. • The package leaflet under Possible Side Effects (Section 4) includes low blood pressure	None.
Priapism	**Labelling** • Specific label text in the SmPC under Special Warnings and Precautions (Section 4.4) states that patients who experience erections lasting 4 hours or more should be instructed to seek immediate medical assistance. • Priapism and Prolonged erections are listed in the SmPC as undesirable effects under Section 4.8. • The package leaflet instructs patients to inform the doctor immediately if the erection lasts continuously for more than 4 hours and instructs patients to inform their doctor before taking CIALIS/ADCIRCA if they have any deformation of the penis.	None.

continued

Table V.3. Summary of Risk Minimisation Measures (continued)

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Potential Risks – All Indications		
Nonarteritic Anterior Ischaemic Optic Neuropathy (NAION)	**Labelling** • Specific label text in the SmPCs under Section 4.3 (Contraindications) indicates that CIALIS/ADCIRCA is contraindicated in patients who have loss of vision in one eye because of NAION. • Specific label text in the SmPC under Special Warnings and Precautions (Section 4.4) states that visual defects and cases of NAION have been reported in connection with the intake of CIALIS/ADCIRCA and other PDE5 inhibitors. The patient should be advised that in case of sudden visual defect he should consult a physician immediately. • NAION has been listed in the SmPC as an adverse reaction under Section 4.8 (Undesirable effects). • The package leaflet instructs patient not to take CIALIS/ADCIRCA if they have ever had loss of vision because of NAION. The package leaflet, under Possible Side Effects (Section 4) includes partial, temporary, or permanent decrease or loss of vision in one or both eyes.	None.
Sudden Hearing Loss	**Labelling** • Following assessment of a cumulative review of sudden hearing loss, the PRAC has recommended the inclusion of specific label text to the SmPC under Special Warnings and Precautions (Section 4.4) describing that sudden hearing loss has been reported with use of tadalafil and that patients should be advised to seek prompt medical attention in the event of a sudden decrease or loss of hearing. A procedure is planned to include appropriate labelling in the SmPC. • Sudden hearing loss has been listed in the SmPC as an adverse reaction under Section 4.8 (Undesirable effects). • The package leaflet includes this risk of sudden hearing loss.	None.
Important Missing Information – Erectile Dysfunction (Once a day) and Benign Prostatic Hyperplasia Indications		
Characterisation of adverse events in elderly patients (≥65 years)	**Labelling** • Section 4.8 of the CIALIS SmPC informs that data in patients over 65 years of age receiving tadalafil in clinical trials, either for the treatment of erectile dysfunction or the treatment of benign prostatic hyperplasia, are limited.	None.

Abbreviations: NA = not applicable; SmPC = summary of product characteristics.

Part VI. Summary of Activities in the Risk Management Plan by Product

CIALIS/TADALAFIL LILLY

VI.1. Elements for Summary Tables in the European Public Assessment Report (EPAR)

VI.1.1. Summary Table of Safety Concerns

Table VI.1. Summary of Safety Concerns

Summary of Safety Concerns	
Important Identified Risks	• Hypotension/Increased Hypotensive Effect • Priapism
Important Potential Risks	• Nonarteritic anterior ischaemic optic neuropathy (NAION) • Sudden hearing loss
Important Missing Information	Tadalafil Once-a-Day ED and BPH Indications: • Characterisation of adverse events in elderly patients (≥65 years of age)

VI.1.2. Table of Ongoing and Planned PhV Studies/Activities in the Pharmacovigilance Development Plan

There are no ongoing or planned Pharmacovigilance studies/activities in the Pharmacovigilance Plan.

Table VI.2. EU Ongoing and Planned Additional Pharmacovigilance Studies/Activities in the Pharmacovigilance Plan

Study/Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
N/A	N/A	N/A	N/A	N/A

Abbreviation: N/A = not applicable.

VI.1.3. Summary of Post-authorisation Efficacy Development Plan

Not applicable.

Table VI.3. Summary of Post-authorisation Efficacy Development Plan

Study (Type and Study Number)	Objectives	Efficacy Uncertainties Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports
N/A	N/A	N/A	N/A	N/A

Abbreviation: N/A = not applicable.

VI.1.4. Summary Table of Risk Minimisation Measures

Table VI.4. Summary of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Identified Risks		
Hypotension/Increased Hypotensive Effect	• Specific label text in the SmPC under Section 4.3 (Contraindications) indicates that CIALIS is contraindicated in patients using any form of organic nitrate, or who have hypotension (<90/50mmHg) or uncontrolled hypertension. Package leaflet states that CIALIS should not be taken if already taking nitrates or if they have low blood pressure. • Specific label text in Section 4.3 of the SmPC contraindicating the use of tadalafil and guanylate cyclase stimulators, such as riociguat, because it may potentially lead to symptomatic hypotension. • Specific label text in the SmPC under Section 4.4 (Special warnings and precautions) describing the risk of hypotension with tadalafil. • Specific label text in the SmPC Section 4.5 (Interaction with other medicinal products and other forms of interaction) for nitrates, anti-hypertensives, and alcohol. • Hypotension has been listed as an adverse reaction under Section 4.8 (Undesirable effects). • The package leaflet instructs patients to tell the doctor if they are taking alpha-blockers. • The package leaflet under Possible Side Effects (Section 4) includes low blood pressure	None

continued

Table VI.4. Summary of Risk Minimisation Measures (continued)

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Identified Risks (*continued*)		
Priapism	• Specific label text in the SmPC under Special Warnings and Precautions (Section 4.4) states that patients who experience erections lasting 4 hours or more should be instructed to seek immediate medical assistance. • Priapism and Prolonged erections are listed in the SmPC as undesirable effects under Section 4.8. • The package leaflet instructs patients to inform the doctor immediately if the erection lasts continuously for more than 4 hours and instructs patients to inform their doctor before taking CIALIS if they have any deformation of the penis.	None
Important Potential Risks		
Nonarteritic Anterior Ischaemic Optic Neuropathy (NAION)	**Labelling** • Specific label text in the SmPC under Section 4.3 (Contraindications) indicates that CIALIS/ADCIRCA is contraindicated in patients who have loss of vision in one eye because of NAION. • Specific label text in the SmPC under Special Warnings and Precautions (Section 4.4) states that visual defects and cases of NAION have been reported in connection with the intake of CIALIS/ADCIRCA and other PDE5 inhibitors. The patient should be advised that in case of sudden visual defect, to consult a physician immediately. • NAION has been listed in the SmPC as an adverse reaction under Section 4.8 (Undesirable effects). • The package leaflet instructs patient not to take CIALIS/ADCIRCA if they have ever had loss of vision because of NAION. • The package leaflet, under Possible Side Effects (Section 4) includes partial, temporary, or permanent decrease or loss of vision in one or both eyes.	None.

continued

Table VI.4. Summary of Risk Minimisation Measures (continued)

Important Potential Risks *(continued)*		
Sudden Hearing Loss	• Following assessment of a cumulative review of sudden hearing loss, the PRAC has recommended the inclusion of specific label text to the SmPC under Special Warnings and Precautions (Section 4.4) describing that sudden hearing loss has been reported with use of tadalafil and that patients should be advised to seek prompt medical attention in the event of a sudden decrease or loss of hearing. A procedure is planned to include appropriate labelling in the SmPC. • Sudden hearing loss has been listed in the SmPC as an adverse reaction under Section 4.8 (Undesirable effects). • The package leaflet includes this risk of sudden hearing loss.	None
Important Missing Information		
Characterisation of adverse events in elderly patients (≥65 years)	Section 4.8 of the CIALIS SmPC informs that data in patients over 65 years of age receiving tadalafil in clinical trials, either for the treatment of erectile dysfunction or the treatment of benign prostatic hyperplasia, are limited.	None

Abbreviations: SmPC = summary of product characteristics.

VI.2. Elements for a Public Summary (CIALIS/TADALAFIL LILLY)

VI.2.1. Overview of Disease Epidaemiology

Erectile dysfunction (ED):

Erectile dysfunction (ED) is a condition in which a man cannot get or keep a hard, erect penis suitable for sexual activity. Erectile dysfunction is the most common sexual problem in older men, with around half of men between the ages of 40 and 70 having some ED.

Benign prostatic hyperplasia (BPH):

Benign prostatic hyperplasia (BPH) is an increase in the size of the prostate. The prostate is a walnut-sized gland in the male, located below the bladder. This increase in size of the prostate can cause urinary symptoms (e.g., difficulty in starting to pass urine, a feeling of not completely emptying the bladder, and a more frequent need to pass urine even at night), and is one of the most common diseases of aging men. Over half of men get BPH by age 60 and about 9 of 10 men have BPH by age 85.

VI.2.2. Summary of Treatment Benefits

Erectile dysfunction (ED):

The active substance in CIALIS/Tadalafil Lilly is tadalafil, which is in a class of drugs called phosphodiesterase type-5 (PDE5) inhibitors. Following sexual stimulation, PDE5 inhibitors

work by helping the blood vessels in the penis to relax, allowing the flow of blood into the penis, and allowing the patient to keep a hard, erect penis suitable for sexual activity.

CIALIS, when taken 'on demand' before sexual activity, has been studied in six main studies including 1,328 patients with erectile dysfunction. One of these studies contained only diabetic men. Once-a-day dosing of CIALIS was studied in three further studies involving a total of 853 patients. In all studies, the effects of CIALIS were compared with those of placebo (a dummy treatment), and the main measure of effectiveness was based on answers to questionnaires. The questions asked the patient about his ability to get and maintain an erection to successfully complete intercourse.

CIALIS was significantly more effective than placebo in all studies in erectile dysfunction.

Benign prostatic hyperplasia (BPH):

CIALIS/Tadalafil Lilly improves the blood flow to, and relaxes the muscles of, the prostate and bladder. This may reduce the problems with the flow of urine, which are symptoms of BPH. CIALIS has been studied in patients with BPH. Four main studies comparing CIALIS with placebo were carried out in 1,500 patients with the condition, including some who also had erectile dysfunction. The main measure of effectiveness was the improvement in symptoms after 12 weeks.

CIALIS given at a dose of 5 mg was also more effective than placebo in all the studies in patients with benign prostatic hyperplasia, with the results showing a significant improvement in symptoms after 12 weeks compared with placebo.

VI.2.3. Unknowns Relating to Treatment Benefits

Some things are not known about tadalafil for the treatment of ED and BPH. Although daily tadalafil was studied in men 65 years of age and older with ED or BPH, less information is available regarding its use in this population than in younger patients (less than 65 years of age).

VI.2.4. Summary of Safety Concerns

Table VI.5. Important Identified Risks

Risk	What is Known	Preventability
Decrease in blood pressure [Hypotension/Increased Hypotensive Effect]	As with other PDE5 inhibitors, tadalafil can cause decreases in blood pressure (hypotension) that last for a short time. Patients with other medical problems, such as those that affect the left side of the heart and low blood pressure, could be affected by this medicine. Tadalafil may further decrease blood pressure when given with nitrates (drugs that treat chest pain) and guanylate cyclase stimulators such as riociguat (drugs used for pulmonary arterial hypertension [high blood pressure in the arteries of the lungs] and chronic pulmonary hypertension [high blood pressure in the lungs due to blood clots]). Also, patients who are taking blood pressure medications or whose blood pressure is not well controlled may have greater decreases in their blood pressure with tadalafil. In patients taking tadalafil for ED or BPH, reports of hypotension were uncommon (seen in 1 to 10 in every 1,000 patients).	• You must not take tadalafil with nitrates (medication used to treat chest pain), riociguat, or if you have low blood pressure (< 90/50 mm Hg). • Before taking tadalafil, you should tell your doctor if you are taking nitrates (or are unsure if you are taking them), are on blood pressure medications, have high blood pressure that is not controlled by medicine, or have low blood pressure. • Before taking tadalafil, you should tell your doctor if you are taking an alpha blocker such as doxazosin, a drug used to treat high blood pressure and BPH. • Drinking alcohol may temporarily lower your blood pressure. If you have taken or are planning to take tadalafil, avoid excessive drinking (blood alcohol level of 0.08 % or greater), since this may increase the risk of dizziness when standing up.
Long-lasting erection which many be painful [Priapism]	Priapism (a long-lasting erection which may be painful) has been reported with PDE5 inhibitors, like tadalafil. Priapism can result in long-lasting problems that can be avoided by treating it early. In patients taking tadalafil for ED or BPH, reports of priapism were rare (seen in 1 to 10 in every 10,000 people).	• Before taking tadalafil, tell your doctor if you have any of the following conditions: sickle cell anaemia (an abnormality of red blood cells), multiple myeloma (cancer of the bone marrow), leukaemia (cancer of the blood cells), or an abnormal shape of your penis. These conditions can increase your risk of developing priapism. • In order to prevent long-lasting problems, contact your doctor immediately if you have an erection that lasts continuously for more than 4 hours.

Abbreviations: BPH = Benign prostatic hyperplasia; ED = erectile dysfunction; PDE5 = phosphodiesterase type 5.

Table VI.6. Important Potential Risks

Risk	What is known (including Reason Why it is Considered a Potential Risk)
Loss of blood supply ("stroke") to the optic nerve (the nerve that connects the eye to the brain). [Nonarteritic Anterior Ischaemic Optic Neuropathy (NAION)]	NAION is a loss of blood supply ("stroke") to the optic nerve (the nerve that connects the eye to the brain). This can cause sudden vision loss in the affected eye, without any pain, and is a possible risk with the use of PDE5 inhibitors, including tadalafil. It is not known if NAION is caused by PDE5 inhibitors rather than other disorders, as these disorders are common in men with ED who are also taking this type of drug. This event may result in permanent blindness in the affected eye. There have been no reported cases of NAION from tadalafil clinical trials of ED or BPH. The results of two studies have shown an increased risk of NAION in patients taking PDE5 inhibitors (including tadalafil) on an as needed basis for the treatment of erectile dysfunction. Tadalafil should not to be given to patients who have loss of vision in 1 eye as a result of NAION.
Sudden Hearing Loss	Sudden hearing loss is a potential risk based on reports of this event after the drug was on the market. This hearing loss might be permanent. There were few cases of sudden hearing loss in tadalafil clinical studies for ED. In patients taking tadalafil for ED or BPH, reports of sudden hearing loss were rare (seen in 1 to 10 in every 10,000 people).

Abbreviations: BPH = benign prostatic hyperplasia; ED = erectile dysfunction; PDE5 = phosphodiesterase type 5.

Table VI.7. Missing Information about

Risk	What is Known
There is insufficient information about the safety of tadalafil in patients greater than 65 years of age who are taking tadalafil every day for ED or BPH	Although daily tadalafil was studied in men 65 years of age and older with ED or BPH, less information is available regarding its use in this population than in younger patients (less than 65 years of age). If new risks are discovered in patients over 65 years of age, they will be added to the labelling (drug information and the patients' information).

Abbreviations: BPH = Benign prostatic hyperplasia; ED = erectile dysfunction.

VI.2.5. Summary of Risk Minimisation Measures by Safety Concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks, and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for CIALIS can be found in the CIALIS'S EPAR page.

There are no additional risk minimisation measures or activities beyond the labelling.

VI.2.6. Planned Post-authorisation Development Plan

Not applicable.

VI.2.6.1. Studies that are a Condition of the Marketing Authorisation

None.

VI.2.7. Summary of Changes to the Risk Management Plan over Time

Table VI.8. Major Changes to the Risk Management Plan over Time

Version	Date	Safety Concerns	Comments
4.0	16 December 2009	The important identified risks of priapism (a long-lasting erection which may be painful) and decreases in blood pressure (hypotension/ increased hypotensive effects) were added. Sudden hearing loss was added as a potential risk. Characterisation of adverse events in elderly patients using once-daily tadalafil for erectile dysfunction was added as a potential risk.	This version was created using an updated Lilly RMP template, which was based on new regulatory and industry guidelines. As a result, this has substantial structural changes and provides more detailed information than the previous revision.
5.0	26 August 2011	Characterisation of adverse events in elderly patients using once-a-day tadalafil for ED was removed as a potential risk. Information about the studies from the BPH indication were added to the RMP	A comparable safety profile was found between elderly and non-elderly subjects in the integrated database for BPH submission where more than 40% of patients were over 65 years.
5.1	20 March 2012	Revisions made to the document to indicate that safety data in very elderly patients (≥75 years) is important missing information	
5.2	19 July 2012	The characterisation of adverse events in very elderly patients (≥75 years) as important missing information was replaced with the characterisation of adverse events in elderly patients (≥65 years) as important missing information for the ED once-a-day and BPH indications.	These changes were made at the request of the regulators.
6.0	07 Jun 2013	No new safety concerns.	As requested by the PRAC to implement the format details in Module V.
7.0	30 April 2015	No new safety concerns.	Timeline for study LVHQ updated.
8.0/8.1	08 October 2016	Inclusion of the results of the LVHQ and TD01 studies.	The cumulative data for NAION, including the LVHQ and Campbell et al. (2015) studies, support the existing classification of NAION as an adverse reaction for tadalafil.

Table VI.8. Major Changes to the Risk Management Plan over Time (continued)

Version	Date	Safety Concerns	Comments
8.2		Removal of increased risk of uterine bleeding in patients with PAH as an important potential risk for tadalafil.	The cumulative data for increased risk of uterine bleeding in patients with PAH support the existing classification of increased risk of uterine bleeding in patients with PAH as an adverse reaction for tadalafil; however, the MAH does not consider this event to be 'important' in the context of the risk management plan, as the impact of this event on public health is low and. in the context of the PAH indication, this risk does not change the benefit-risk balance.

ADCIRCA

VI.3. Elements for Summary Tables in the European Public Assessment Report (EPAR)

VI.3.1. Summary Table of Safety Concerns

Table VI.9. Summary of Safety Concerns

Summary of Safety Concerns	
Important Identified Risks	• Hypotension/Increased Hypotensive Effect • Priapism
Important Potential Risks	• Nonarteritic anterior ischaemic optic neuropathy (NAION) • Sudden hearing loss

VI.3.2. Table of Ongoing and Planned Studies in the Post-authorisation Pharmacovigilance Development Plan

Not applicable. There are no ongoing or planned Pharmacovigilance studies/activities in the Pharmacovigilance Plan.

VI.3.3. Summary of Post-authorisation Efficacy Development Plan

Not applicable.

VI.3.4. Summary Table of Risk Minimisation Measures

Table VI.10. Summary of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Identified Risks		
Hypotension/Increased Hypotensive Effect	• Specific label text in the SmPC under Section 4.3 (Contraindications) indicates that ADCIRCA is contraindicated in patients using any form of organic nitrate, or who have hypotension (<90/50mmHg) or uncontrolled hypertension. Package leaflet states that ADCIRCA should not be taken if already taking nitrates or if they have low blood pressure. • Specific label text in Section 4.3 of the SmPC contraindicating the use of tadalafil and guanylate cyclase stimulators, such as riociguat, because it may potentially lead to symptomatic hypotension. • Specific label text in the SmPC under Section 4.4 (Special warnings and precautions) describing the risk of hypotension with tadalafil. • Specific label text in the SmPC Section 4.5 (Interaction with other medicinal products and other forms of interaction) for nitrates, anti-hypertensives, and alcohol. • Hypotension has been listed as an adverse reaction under Section 4.8 (Undesirable effects). • The package leaflet instructs patients to tell the doctor if they are taking alpha-blockers. • The package leaflet under Possible Side Effects (Section 4) includes low blood pressure	None
Priapism	• Specific label text in the SmPC under Special Warnings and Precautions (Section 4.4) states that patients who experience erections lasting 4 hours or more should be instructed to seek immediate medical assistance. • Priapism and Prolonged erections are listed in the SmPC as undesirable effects under Section 4.8. • The package leaflet instructs patients to inform the doctor immediately if the erection lasts continuously for more than 4 hours and instructs patients to inform their doctor before taking ADCIRCA if they have any deformation of the penis.	None

Table VI.10. Summary of Risk Minimisation Measures (continued)

Important Potential Risks		
Nonarteritic Anterior Ischaemic Optic Neuropathy (NAION)	• Specific label text in the SmPC under Section 4.3 (Contraindications) indicates that ADCIRCA is contraindicated in patients who have loss of vision in one eye because of NAION. • Specific label text in the SmPC under Special Warnings and Precautions (Section 4.4) states that visual defects and cases of NAION have been reported in connection with the intake of ADCIRCA and other PDE5 inhibitors. The patient should be advised that in case of sudden visual defect, to consult a physician immediately. • NAION has been listed in the SmPC as an adverse reaction under Section 4.8 (Undesirable effects). • The package leaflet, instructs patients not to take ADCIRCA if they have ever had loss of vision because of NAION • The package leaflet under Possible Side Effects (Section 4) includes partial, temporary or permanent decrease or loss of vision in one or both eyes	None
Sudden Hearing Loss	• Following assessment of a cumulative review of sudden hearing loss, the PRAC has recommended the inclusion of specific label text to the SmPC under Special Warnings and Precautions (Section 4.4) describing that sudden hearing loss has been reported with use of tadalafil and that patients should be advised to seek prompt medical attention in the event of a sudden decrease or loss of hearing. A procedure is planned to include appropriate labelling in the SmPC. • Sudden hearing loss has been listed in the SmPC as an adverse reaction under Section 4.8 (Undesirable effects). • The package leaflet includes this risk of sudden hearing loss.	None

Abbreviation: SmPC = summary of product characteristics.

VI.4. Elements for a Public Summary (ADCIRCA)

VI.4.1. Overview of Disease Epidaemiology

Pulmonary arterial hypertension (PAH) is serious, rare condition that affects mostly females; it causes high blood pressure in the blood vessels that carry blood from the heart to the lungs, which makes the heart have to work harder. PAH is serious condition with decreased life expectancy. Most PAH cases have no known cause.

Adcirca is used in patients with class-II or -III disease. The 'class' reflects the seriousness of the disease: 'class II' involves slight limitation of physical activity and 'class III' involves marked limitation of physical activity.

VI.4.2. Summary of Treatment Benefits

The active substance in ADCIRCA is tadalafil, which belongs to a group of medicines called PDE5 inhibitors. These drugs help the blood vessels in the lungs relax, and improve the blood flow into the lungs, resulting in an improved ability to exercise.

Four doses of ADCIRCA (2.5, 10, 20 and 40 mg once a day) were compared with placebo (a dummy treatment) in one main study involving 406 patients with PAH, most of whom had mild to moderate disease that was of unknown cause or caused by collagen vascular disease. The main measure of effectiveness was the change in exercise capacity (the ability to do physical activity) measured by the distance the patients could walk in six minutes after 16 weeks of treatment.

ADCIRCA was more effective than placebo at improving exercise capacity. Before treatment, the patients could walk an average of 343 metres in six minutes. After 16 weeks, this distance had increased by 26 metres more in the patients taking 40 mg ADCIRCA than in the patients taking placebo.

VI.4.3. Unknowns Relating to Treatment Benefits

There are some things that are not known about tadalafil for the treatment of PAH. Because PAH is a rare disease, tadalafil was studied in small number of PAH patients (393). Also, there is limited information from women who are pregnant or breastfeeding.

VI.4.4. Summary of Safety Concerns

Table VI.11. Important Identified Risks

Risk	What is Known	Preventability
Decrease in blood pressure [Hypotension/Increased Hypotensive Effect]	As with other PDE5 inhibitors, tadalafil can cause decreases in blood pressure (hypotension) that last for a short time. Patients with other medical problems, such as those that affect the left side of the heart and low blood pressure, could be affected by this medicine. Tadalafil may further decrease blood pressure when given with nitrates (drugs that treat chest pain) and guanylate cyclase stimulators such as riociguat (drugs used for pulmonary arterial hypertension [high blood pressure in the arteries of the lungs] and chronic pulmonary hypertension (high blood pressure in the lungs due to blood clots]). Also, patients who are taking blood pressure medications or whose blood pressure is not well controlled may have greater decreases in their blood pressure with tadalafil. In patients taking tadalafil for PAH, reports of hypotension were common (seen in 1 to 10 in every 100 patients).	• You must not take tadalafil with nitrates (medication used to treat chest pain), riociguat or if you have low blood pressure (< 90/50 mm Hg). • Before taking tadalafil, you should tell your doctor if you are taking nitrates, are on blood pressure medications, have high blood pressure that is not controlled by medicine, or have low blood pressure. • Before taking tadalafil, you should tell your doctor if you are taking an alpha blocker such as doxazosin, a drug used to treat high blood pressure and benign prostatic hyperplasia • Drinking alcohol may temporarily lower your blood pressure. If you have taken or are planning to take tadalafil, avoid excessive drinking (blood alcohol level of 0.08 % or greater), since this may increase the risk of dizziness when standing up.
Long-lasting erection which may be painful [Priapism]	Priapism, (a condition that only affects men), is a long-lasting erection which may be painful, and has been reported with PDE5 inhibitors, like tadalafil. Priapism can result in long-lasting problems that can be avoided by treating it early. In patients taking tadalafil for PAH, reports of priapism were uncommon (seen in 1 to 10 in every 1,000 patients).	• Before taking tadalafil, tell your doctor if you have any of the following conditions: sickle cell anaemia (an abnormality of red blood cells), multiple myeloma (cancer of the bone marrow), leukaemia (cancer of the blood cells), or an abnormal shape of your penis. These conditions can increase your risk of developing priapism. • In order to prevent long-lasting problems, contact your doctor immediately if you have an erection that lasts continuously for more than 4 hours.

Abbreviations: PDE5 = phosphodiesterase type 5; PAH = pulmonary arterial hypertension.

Table VI.12. Important Potential Risks

Risk	What is known (including Reason Why it is Considered a Potential Risk)
Loss of blood supply ("stroke") to the optic nerve (the nerve that connects the eye to the brain) Nonarteritic Anterior Ischaemic Optic Neuropathy (NAION)]	NAION is a loss of blood supply ("stroke") to the optic nerve (the nerve that connects the eye to the brain). This can cause sudden vision loss in the affected eye, without any pain, and is a possible risk with the use of PDE5 inhibitors, including tadalafil. It is not known if NAION is caused by PDE5 inhibitors rather than other disorders, as these disorders are common in men with erectile dysfunction who are also taking this type of drug. This event may result in permanent blindness in the affected eye. There have been no reported cases of NAION from tadalafil clinical trials of ED or BPH. The results of two studies have shown an increased risk of NAION in patients taking PDE5 inhibitors (including tadalafil) on an as needed basis for the treatment of erectile dysfunction. Tadalafil should not to be given to patients who have loss of vision in 1 eye as a result of NAION. There have been no reported cases of NAION from tadalafil studies of PAH.
[Sudden Hearing Loss]	Sudden hearing loss is a potential risk based on reports of this event after the drug was on the market. This hearing loss might be permanent. In patients taking tadalafil for PAH, there were no reports of sudden hearing loss, so the risk of sudden hearing loss in this population is unknown.

Abbreviation: PDE5 = phosphodiesterase type 5.

VI.4.5. Summary of Additional Risk Minimisation Measures by Safety Concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for ADCIRCA can be found in the ADCIRCA'S EPAR page

There are no additional risk minimisation measures or activities beyond the labelling.

VI.4.6. Planned Post-authorisation Development Plan

Not applicable.

Table VI.13. List of Studies in Post-authorisation Development Plan

Study/Activity (including Study Number)	Objectives	Safety Concerns /Efficacy Issue Addressed	Status	Planned Date for Submission of Final Results
N/A	N/A	N/A	N/A	N/A

Abbreviation: N/A = not applicable.

VI.4.6.1. Studies which are a Condition of the Marketing Authorisation

None.

VI.4.7. Summary of Changes to the Risk Management Plan over Time

Table VI.14. Major Changes to the Risk Management Plan over Time

Version	Date	Safety Concerns	Comments
1.1	20 April 2009	Decreases in blood pressure (hypotension/increased hypotensive effects) became an identified risk. It was previously a potential risk. Review of the safety data for subjects with PAH revealed that the safety profile of tadalafil in the PAH population is similar to that seen in the ED population.	
6.0	07 June 2013	No new safety concerns	As requested by the PRAC to implement the format details in Module V.
7.0	30 April 2015	No new safety concerns	Timeline for Study LVHQ updated.
8.0/8.1	08October 2016	Inclusion of the results of the LVHQ and TD01 studies.	The cumulative data for NAION, including the LVHQ and Campbell et al. (2015) studies, support the existing classification of NAION as an adverse reaction for tadalafil..
8.2		Removal of increased risk of uterine bleeding in patients with PAH as an important potential risk for tadalafil.	The cumulative data for increased risk of uterine bleeding in patients with PAH support the existing classification of increased risk of uterine bleeding in patients with PAH as an adverse reaction for tadalafil; however, the MAH does not consider this event to be 'important' in the context of the risk management plan, as the impact of this event on public health is low and, in the context of the PAH indication, this risk does not change the benefit-risk balance for tadalafil.

Abbreviations: ED = erectile dysfunction; NAION = Nonarteritic Anterior Ischemic Optic Neuropathy; PAH = pulmonary arterial hypertension; PRAC = Pharmacovigilance Risk Assessment Committee.

Part VII. Annexes

Table of Annexes

Annex 7. Specific Adverse Event Follow-up Forms

Spontaneous Adverse Event Follow-up Forms*

Specific Adverse Event Follow-up Form	Event(s) Associated with the form
Spontaneous Follow-up Form – Cardiac Disorders	Cardiac events (including chest pain/angina and myocardial infarction)
Spontaneous Follow-up Form – Arrhythmia	Arrhythmia
Spontaneous Follow-up Form – Syncope	Syncope
Spontaneous Follow-up Form – Cerebrovascular Accident	Cerebrovascular accident/ stroke
Spontaneous Follow-up Form – Hearing Loss	Hearing abnormalities (e.g. sudden hearing loss, deafness, vertigo, tinnitus, hearing impaired)
Spontaneous Follow-up Form – Priapism	Priapism
Spontaneous Follow-up Form – Visual Impairment	Visual abnormalities (all events including NAION, cataracts, macular degeneration/maculopathy)
Spontaneous Follow-up Form – Mortality	Death for any reason
Spontaneous Follow-up Form – General Form	All cases where patient age is ≥65 years old or unknown (*Surveillance term does not have a specific form. This form may be also utilised for reports of hypotension*)
Spontaneous Follow-up Form – Pancreatitis	Pancreatitis
Spontaneous Follow-up Form – General Bleeding (PAH Indication Only)	General bleeding events
Spontaneous Follow-up Form – Epistaxis (PAH Indication Only)	Epistaxis
Spontaneous Follow-up Form – Vaginal Bleeding (PAH Indication Only)	Increased uterine bleeding (including menorrhagia, menometrorrhagia, metrorrhagia, vaginal bleeding, vaginal haemorrhage)

* *These forms represent standard questions that may be requested as routine follow up of the designated surveillance terms. Each follow up form is individualised by case, based upon an assessment of the most pertinent outstanding data needed to complete the case.*

Clinical Trial Follow-up Forms

Specific Adverse Event Follow-up Form	Event(s) Associated with the form
Clinical Trial AESI eCRF – Dizziness/Fall/ Hypotension/Syncope/Loss of Consciousness	Hypotensive events and other related events
Clinical Trial AESI eCRF – Hearing Abnormality	Hearing abnormalities including sudden hearing loss, deafness, tinnitus, and hearing impaired
Clinical Trial AESI eCRF – Hepatobiliary Events	Hepatic adverse events or laboratory abnormalities, including drug-induced liver injury, hepatic failure, hepatotoxicity, increased transaminases, and increased bilirubin
Clinical Trial AESI eCRF – Prolonged Erection	Events including prolonged (increased) erection or priapism
Clinical Trial AESI eCRF – Abnormal Uterine Bleeding	Events including menorrhagia, menometrorrhagia, metrorrhagia, and increased vaginal bleeding
Clinical Trial AESI eCRF – Visual Abnormality	Visual abnormalities such as NAION, blurred vision, visual impairment, blindness

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: _____ **Lilly Case #:** _____

Information Provided By:
(Enter Name and Title) _____ **Signature/Initials:** _____

Patient Name or Initials: _____ **Patient Birth Date or Age:** _____

Gender: ○ F ○ M ○ Unknown	**Race:** ○ Caucasian ○ Asian ○ Black ○ Other	**Weight:** _____ ○ lb ○ kg	**Height:** _____ ○ in ○ cm

Reported Drug: Cialis® (tadalafil)

Lot/Control Number (if available): _____ **Indication:** _____

Dose: _____ **Frequency:** _____ **Formulation:** _____

Start Date: _____ **Dose when event occurred:** _____ **Route:** _____

Drug D/C? ○ No ○ Yes **Date D/C:** _____ **If Discontinued, did the event resolve?** ○ Yes ○ No

Drug Restarted? ○ No ○ Yes **Date Restarted:** _____ **If Restarted, did the event reoccur?** ○ Yes ○ No

Cialis® (tadalafil)
Indication: ○ Erectile dysfunction ○ Other: _____
Dose: ○ 2.5 mg ○ 5 mg ○ 10 mg ○ 20 mg ○ Other: _____
Current Dosing Frequency: ○ As Needed ○ Daily

Cardiac Disorders

Primary Diagnosis for the Reported Event(s)

☐ Chest Pain/Angina ☐ Myocardial Infarction ☐ Arrhythmia ☐ Other - please describe:

Hospitalization for this event? ○ Yes ○ No

Presenting Signs/Symptoms

☐ Heart rate: _____ ☐ Blood pressure: _____
☐ Palpitations ☐ Shortness of breath
☐ Syncope ☐ Chest pain (please specify): _____
☐ Cardiac exam: _____
☐ Pulmonary exam: _____
☐ Other (please specify): _____

Relevant Medical History (please specify if needed)

☐ Atrial Arrhythmia ☐ Ventricular Arrhythmia
☐ Conduction Disorders ☐ Congenital Heart Abnormalities
☐ Cardiovascular Disease ☐ Hypertension
☐ Cardiovascular Infection ☐ Cardiac Surgeries
☐ Pulmonary Disease ☐ Pulmonary Embolism
☐ Metabolic Disorders ☐ Psychiatric/Emotional Disorders
☐ Pericarditis ☐ Syncope

Eli Lilly and Company - Global Patient Safety **Case Number:**

☐ Poor Compliance with BP/Cardiac Meds ☐ Dizziness
☐ Substance Abuse
☐ Family history of cardiac disease, congenital QT prolongation, premature cardiac death
☐ Other (please specify):_____

Historic Drugs (please specify)
☐ Antiarrhythmics: ☐ Antihypertensives:
_____ _____
☐ Psychiatric medications: ☐ Antibiotics:
_____ _____
☐ Others:_____

Concomitant Meds (include prescription, substance, OTC and herbal)
☐ Nitrates/Nitrites ☐ Alpha blocker
☐ ED medication (please specify):_____ ☐ Others:_____

Relevant Laboratory Tests	Normal Range for Your Institution	Baseline Value for Patient	Abnormal Value	Improvement Value
		Date:	Date:	Date:
Cardiac Enzyme (please specify): _____				
Serum Potassium				
Serum Calcium				
pO2				
O2 Saturation				

Other Diagnostic Tests	Results
EKG (Q waves)/EKG (QTC Interval)	
Myocardial Scan	
Echocardiogram (ECHO)	
Coronary angiography	
Exercise Stress Test	
QT Interval (milliseconds)	
QTc (Corrected Value)	
How was QT interval measured?	○ Machine ○ Manually ○ Other
QT correction formula	○ Bazett ○ Frederica ○ Other
Other (please specify):	

Treatment
☐ Cardioversion/defibrillation ☐ Treatment not required
☐ Medication (please specify):_____ ☐ Ablation
☐ Other (please specify):

Was this event related to a Lilly drug? If yes, please provide name of drug:

Eli Lilly and Company - Global Patient Safety **Case Number:**

	☐ Yes	☐ Likely	☐ Unlikely	☐ No	☐ Unknown
Were any events related to the Lilly Drug? If yes, please name the drug and list event(s) and relatedness:					

Event Outcome

○ Recovered ○ Worsened ○ Recovering

○ Not Recovered ○ Unknown

○ Recovered with Sequellae (Please provide details): _____

○ Other outcome, please describe:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: _____ **Lilly Case #:** _____

Information Provided By:
(Enter Name and Title) _____ **Signature/Initials:** _____

Patient Name or Initials: _____ **Patient Birth Date or Age:** _____

Gender: ○ F ○ M ○ Unknown	**Race:** ○ Caucasian ○ Asian ○ Black ○ Other	**Weight:** _____ ○ lb ○ kg	**Height:** _____ ○ in ○ cm

Reported Drug: Cialis® (tadalafil)

Lot/Control Number (if available): _____ **Indication:** _____

Dose: _____ **Frequency:** _____ **Formulation:** _____

Start Date: _____ **Dose when event occurred:** _____ **Route:** _____

Drug D/C? ○ No ○ Yes **Date D/C:** _____ **If Discontinued, did the event resolve?** ○ Yes ○ No

Drug Restarted? ○ No ○ Yes **Date Restarted:** _____ **If Restarted, did the event reoccur?** ○ Yes ○ No

Cialis® (tadalafil)
Indication: ○ Erectile dysfunction ○ Other: _____
Dose: ○ 2.5 mg ○ 5 mg ○ 10 mg ○ 20 mg ○ Other: _____
Current Dosing Frequency: ○ As Needed ○ Daily

Cerebrovascular Accident

Primary Diagnosis for the reported event(s):

Hospitalization for this event? ○ Yes ○ No

Concomitant Medications/Substances(please include prescription, OTC and herbal)

Presenting Signs/Symptoms

Onset Date: End Date:

Impairments:

☐ Paralysis (specify): _____ ☐ Dysarthria ☐ Impaired consciousness
☐ Weakness (specify): _____ ☐ Visual field defect ☐ Seizure
☐ Dysphagia ☐ Aphasia ☐ Other findings:

Severity

☐ No/Mild ☐ Moderate ☐ Severe

Relevant Medical History

Eli Lilly and Company - Global Patient Safety **Case Number:**

☐ Diabetes ☐ Artrial fibrillation ☐ Head trauma
☐ Smoking ☐ Hypertension ☐ Prior stroke
☐ Myocardial infarction ☐ Hyperlipidemia ☐ Other (please specify):

Relevant Laboratory Tests	Normal range for your institution	Baseline value for patient	Abnormal value	Improvement value
		Date:	Date:	Date:
Hemoglobin				
WBC				
Platelet Count				
Glucose				
INR				
aPTT				
Thrombin Time				
Fibrinogen				
Other:_____				
Other:_____				

Other Tests	Results
CT	
MRI	
Angiography	
EEG	
Other:	

Treatment

☐ Support and organization ☐ Thrombolytic agent ☐ Ablation
☐ Antiplatelet agent ☐ Anticoagulant ☐ Other:

Was this event related to a Lilly drug? If yes, please provide name of drug:

	☐ Yes	☐ Likely	☐ Unlikely	☐ No	☐ Unknown

Were any events related to the Lilly Drug? If yes, please name the drug and list event(s) and relatedness:

Event Outcome

○ Recovered ○ Worsened ○ Recovering
○ Not Recovered ○ Unknown
○ Recovered with Sequellae (Please provide details): _____
○ Other outcome, please describe:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: _____ **Lilly Case #:** _____

Information Provided By:
(Enter Name and Title) _____ **Signature/Initials:** _____

Patient Name or Initials: _____ **Patient Birth Date or Age:** _____

Gender: ○ F ○ M ○ Unknown	**Race:** ○ Caucasian ○ Asian ○ Black ○ Other	**Weight:** _____ ○ lb ○ kg	**Height:** _____ ○ in ○ cm

Reported Drug: Adcirca® (tadalafil)

Lot/Control Number (if available): _____ **Indication:** _____

Dose: _____ **Frequency:** _____ **Formulation:** _____

Start Date: _____ **Dose when event occurred:** _____ **Route:** _____

Drug D/C? ○ No ○ Yes **Date D/C:** _____ **If Discontinued, did the event resolve?** ○ Yes ○ No

Drug Restarted? ○ No ○ Yes **Date Restarted:** _____ **If Restarted, did the event reoccur?** ○ Yes ○ No

Epistaxis

Primary Diagnosis for the reported event(s):

Hospitalization for this event? ○ Yes ○ No

General Questions

1. What was the anatomic site of bleeding: _____
2. What was the cause of bleeding: _____
3. Grade of bleeding: _____

Was there a procedure performed? ○ No ○ Yes (please specify):

Presenting Signs/Symptoms

☐ Nasal Obstruction ☐ Hypertension ☐ Nasal Deformity

☐ Other symptoms/signs:

_____

Concurrent/Recent Events

☐ Upper respiratory infection ☐ Sinus infection

☐ Trauma to face/nose ☐ Nasogastric/nasotracheal intubation

☐ Other:

_____

Medical History

☐ Prior episodes of epistaxis ☐ Hepatic disease

☐ Deviated nasal septum ☐ Nasal trauma

☐ Hypertension ☐ Bleeding disorder: _____

Eli Lilly and Company - Global Patient Safety **Case Number:**

☐ Other:

_____

Concomitant Meds/Substances (include OTC, herbal, recently discontinued drugs)

☐ NSAIDS:_____ ☐ Antiplatelet agents:_____

☐ Oral anticoagulant ☐ Thrombolytic agents:_____

☐ Other:

_____

Laboratory Test	Normal range for your institution	Baseline value for patient	Abnormal value	Improvement value
Hemoglobin				
WBC				
Platelets				
INR/Prothrombin Time				
aPTT				
Creatinine				
Other:				
Other:				

Treatment

☐ Intravenous fluids ☐ RBC transfusion (units):_____

☐ Platelet transfusion (units):_____ ☐ Fresh frozen plasma (units):_____

☐ Nasal packing ☐ Cautery

☐ Other:

_____

Was this event related to a Lilly drug? If yes, please provide name of drug:

	☐ Yes	☐ Likely	☐ Unlikely	☐ No	☐ Unknown
Were any events related to the Lilly Drug? If yes, please name the drug and list event(s) and relatedness:					

Event Outcome

○ Recovered ○ Worsened ○ Recovering

○ Not Recovered ○ Unknown

○ Recovered with Sequellae (Please provide details): _____

○ Other outcome, please describe:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: _____ **Lilly Case #:** _____

Information Provided By:
(Enter Name and Title) _____ **Signature/Initials:** _____

Patient Name or Initials: _____ **Patient Birth Date or Age:** _____

Gender: ○ F ○ M ○ Unknown	**Race:** ○ Caucasian ○ Asian ○ Black ○ Other	**Weight:** _____ ○ lb ○ kg	**Height:** _____ ○ in ○ cm

Reported Drug: Adcirca® (tadalafil)

Lot/Control Number (if available): _____ **Indication:** _____

Dose: _____ **Frequency:** _____ **Formulation:** _____

Start Date: _____ **Dose when event occurred:** _____ **Route:** _____

Drug D/C? ○ No ○ Yes **Date D/C:** _____ **If Discontinued, did the event resolve?** ○ Yes ○ No

Drug Restarted? ○ No ○ Yes **Date Restarted:** _____ **If Restarted, did the event reoccur?** ○ Yes ○ No

General Bleeding

Primary Diagnosis for the reported event(s):

Hospitalization for this event? ○ Yes ○ No

General Questions

1. What was the anatomic site of bleeding: _____
2. What was the cause of bleeding: _____
3. Grade of bleeding: _____

Was there a procedure performed? ○ No ○ Yes (please specify):

Medical History/Risk Factors:

☐ Hematological Disorder ☐ Liver Disease ☐ Esophageal Varices
☐ Prior Bleeding Episodes ☐ Alcohol use/abuse ☐ Gastric Ulcer
☐ Other _____

Medications at the time of event: ***please include prescription, OTC and herbal preparations***

☐ Heparin ☐ Aspirin
☐ Clopidogrel ☐ NSAID
☐ Glycoprotein IIb/IIIa Inhibitor ☐ Oral anticoagulant
☐ Anti-thrombin therapy ☐ Fibrinolytic/Thrombolytic therapy
☐ Acetaminophen or Paracetamol ☐ Other, please specify: _____

Laboratory Tests/Investigations ***(please fill in the appropriate lab values with units, dates and lab values for your institution where applicable)***

Lab Data	Normal Range	Baseline Value	Most Abnormal Value	Improvement Value

Eli Lilly and Company - Global Patient Safety **Case Number:**

		Date:	Date:	Date:
INR/Prothrombin Time (PT)				
Platelet Count				
APTT				
Serum Creatinine				
Hemoglobin				
Hematocrit				
Other:_____				

Relevant Diagnostic Testing

☐ Ultrasound

Other testing performed:

Special Treatment Provided

☐ Prolonged Arterial Compression
☐ Fluid administration #of units:_____
☐ Blood transfusion #of units:_____
☐ Platelet transfusion #of units:_____
☐ Surgical intervention
☐ Inotropic support
☐ Other, please specify:

Was this event related to a Lilly drug? If yes, please provide name of drug:

	☐ Yes	☐ Likely	☐ Unlikely	☐ No	☐ Unknown

Were any events related to the Lilly Drug? If yes, please name the drug and list event(s) and relatedness:

Event Outcome

○ Recovered ○ Worsened ○ Recovering
○ Not Recovered ○ Unknown
○ Recovered with Sequellae (Please provide details): _____
○ Other outcome, please describe:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: _____ **Lilly Case #:** _____

Information Provided By:
(Enter Name and Title) _____ **Signature/Initials:** _____

Patient Name or Initials: _____ **Patient Birth Date or Age:** _____

Gender: ○ F ○ M ○ Unknown	**Race:** ○ Caucasian ○ Asian ○ Black ○ Other	**Weight:** _____ ○ lb ○ kg	**Height:** _____ ○ in ○ cm

Reported Drug: Cialis® (tadalafil)

Lot/Control Number (if available): _____ **Indication:** _____

Dose: _____ **Frequency:** _____ **Formulation:** _____

Start Date: _____ **Dose when event occurred:** _____ **Route:** _____

Drug D/C? ○ No ○ Yes **Date D/C:** _____ **If Discontinued, did the event resolve?** ○ Yes ○ No

Drug Restarted? ○ No ○ Yes **Date Restarted:** _____ **If Restarted, did the event reoccur?** ○ Yes ○ No

Cialis® (tadalafil)
Indication: ○ Erectile dysfunction ○ Other: _____
Dose: ○ 2.5 mg ○ 5 mg ○ 10 mg ○ 20 mg ○ Other: _____
Current Dosing Frequency: ○ As Needed ○ Daily

Primary diagnosis for the reported event(s):

Hospitalization for this event? ○ Yes ○ No

Relevant Medical History:

Concomitant Medications/Substances (please include prescription, OTC and herbal)

Treatment provided (please describe)

Was this event related to a Lilly drug? If yes, please provide name of drug:

	☐ Yes	☐ Likely	☐ Unlikely	☐ No	☐ Unknown

Were any events related to the Lilly Drug? If yes, please name the drug and list event(s) and relatedness:

Event Outcome
○ Recovered ○ Worsened ○ Recovering

Eli Lilly and Company - Global Patient Safety **Case Number:**

○ Not Recovered ○ Unknown
○ Recovered with Sequellae (Please provide details): _____
○ Other outcome, please describe:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: _____ **Lilly Case #:** _____

Information Provided By:
(Enter Name and Title) _____ **Signature/Initials:** _____

Patient Name or Initials: _____ **Patient Birth Date or Age:** _____

Gender: ○ F ○ M ○ Unknown	**Race:** ○ Caucasian ○ Asian ○ Black ○ Other	**Weight:** _____ ○ lb ○ kg	**Height:** _____ ○ in ○ cm

Reported Drug: Cialis® (tadalafil)

Lot/Control Number (if available): _____ **Indication:** _____

Dose: _____ **Frequency:** _____ **Formulation:** _____

Start Date: _____ **Dose when event occurred:** _____ **Route:** _____

Drug D/C? ○ No ○ Yes **Date D/C:** _____ **If Discontinued, did the event resolve?** ○ Yes ○ No

Drug Restarted? ○ No ○ Yes **Date Restarted:** _____ **If Restarted, did the event reoccur?** ○ Yes ○ No

Cialis® (tadalafil)
Indication: ○ Erectile dysfunction ○ Other: _____
Dose: ○ 2.5 mg ○ 5 mg ○ 10 mg ○ 20 mg ○ Other: _____
Current Dosing Frequency: ○ As Needed ○ Daily

Hearing Loss

Primary diagnosis for the reported event(s):

Hospitalization for this event? ○ Yes ○ No

Concomitant Medications/Substances(please include prescription, OTC and herbal)

Medical History

☐ Otitis ☐ Loud noise exposure ☐ Cerebrovascular disease
☐ Otosclerosis ☐ Meniere's disease ☐ Autoimmune disorder
☐ Barotrauma ☐ Labyrinthitis
☐ Other: _____

Prior Exposures

☐ Cisplatin/carboplatin ☐ Vancomycin ☐ Furosemide
☐ Vincristine ☐ Aminoglycosides ☐ Sildenafil/vardenifil
☐ Carboplatin ☐ Macrolide Antibiotics ☐ Quinine/quinadine
☐ Other: _____

Eli Lilly and Company - Global Patient Safety **Case Number:**

	Normal Range for your institution	Baseline Value for patient	Abnormal Value	Improvement Value
		Date:	Date:	Date:
Hemoglobin				
WBC				
Platelet				
ANA				
RA				
INR				
Glucose				
FTA-abs				
Other:_____				
Other:_____				

Other Relevant Studies	Results
Otoscopic examination	
Weber/Rinne test	
Audiogram	
CT/MRI	
Vestibular studies	
Other:_____	

Treatment provided (please describe)

Was this event related to a Lilly drug? If yes, please provide name of drug:

	☐ Yes	☐ Likely	☐ Unlikely	☐ No	☐ Unknown
Were any events related to the Lilly Drug? If yes, please name the drug and list event(s) and relatedness:					

Event Outcome

○ Recovered ○ Worsened ○ Recovering

○ Not Recovered ○ Unknown

○ Recovered with Sequellae (Please provide details): _____

○ Other outcome, please describe:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: _____ **Lilly Case #:** _____

Information Provided By:
(Enter Name and Title) _____ **Signature/Initials:** _____

Patient Name or Initials: _____ **Patient Birth Date or Age:** _____

Gender: ○ F ○ M ○ Unknown	**Race:** ○ Caucasian ○ Asian ○ Black ○ Other	**Weight:** _____ ○ lb ○ kg	**Height:** _____ ○ in ○ cm

Reported Drug: Cialis® (tadalafil)

Lot/Control Number (if available): _____ **Indication:** _____

Dose: _____ **Frequency:** _____ **Formulation:** _____

Start Date: _____ **Dose when event occurred:** _____ **Route:** _____

Drug D/C? ○ No ○ Yes **Date D/C:** _____ **If Discontinued, did the event resolve?** ○ Yes ○ No

Drug Restarted? ○ No ○ Yes **Date Restarted:** _____ **If Restarted, did the event reoccur?** ○ Yes ○ No

Cialis® (tadalafil)

Indication: ○ Erectile dysfunction ○ Other: _____

Dose: ○ 2.5 mg ○ 5 mg ○ 10 mg ○ 20 mg ○ Other: _____

Current Dosing Frequency: ○ As Needed ○ Daily

Mortality

Primary Diagnosis for the reported event(s):

Hospitalization for this event? ○ Yes ○ No

Concomitant Medications/Substances(please include prescription, OTC and herbal)

Date of Death: _____	Underlying Cause of Death: _____
Was an autopsy performed? ○ Yes ○ No *Please provide a copy of the death certificate or autopsy report, if available.*	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source of (e.g. family member), please specify: _____ ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ○ No ○ Unlikely ○ Likely ○ Yes ○ Unknown	
Please provide a brief explanation:	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: _____ **Lilly Case #:** _____

Information Provided By:
(Enter Name and Title) _____ **Signature/Initials:** _____

Patient Name or Initials: _____ **Patient Birth Date or Age:** _____

Gender: ○ F ○ M ○ Unknown	**Race:** ○ Caucasian ○ Asian ○ Black ○ Other	**Weight:** _____ ○ lb ○ kg	**Height:** _____ ○ in ○ cm

Reported Drug: Cialis® (tadalafil)

Lot/Control Number (if available): _____ **Indication:** _____

Dose: _____ **Frequency:** _____ **Formulation:** _____

Start Date: _____ **Dose when event occurred:** _____ **Route:** _____

Drug D/C? ○ No ○ Yes **Date D/C:** _____ **If Discontinued, did the event resolve?** ○ Yes ○ No

Drug Restarted? ○ No ○ Yes **Date Restarted:** _____ **If Restarted, did the event reoccur?** ○ Yes ○ No

Cialis® (tadalafil)

Indication: ○ Erectile dysfunction ○ Other: _____

Dose: ○ 2.5 mg ○ 5 mg ○ 10 mg ○ 20 mg ○ Other: _____

Current Dosing Frequency: ○ As Needed ○ Daily

Pancreatitis

Primary Diagnosis for the reported event(s):

Hospitalization for this event? ○ Yes ○ No

Clinical Findings	Yes	No	Unknown	Please provide brief description
Recent heavy alcohol use	○	○	○	
Recent abdominal trauma/surgery	○	○	○	
Recent ERCP	○	○	○	
Abdominal pain	○	○	○	
Nausea	○	○	○	
Vomiting	○	○	○	
Recent weight loss	○	○	○	
Jaundice	○	○	○	
Other:				

Relevant Medical History

Eli Lilly and Company - Global Patient Safety **Case Number:**

☐ Biliary Tract Disease ☐ Hypercalcemia ☐ Hyperbilirubinemia/Jaundice
☐ Alcoholism ☐ Hypertriglyceridemia ☐ Abdominal Trauma
☐ Peptic Ulcer Disease ☐ Pancreatitis ☐ Renal insufficiency
☐ HIV Infection ☐ Gallstones ☐ ERCP
Other (please specify):

Concomitant Medications/Substances

☐ Diuretics (thiazides, furosemide) ☐ Corticosteroids
☐ Anticonvulsants (valproic acid, carbamazepine) ☐ ACE inhibitors
☐ Chemotherapeutic agents (e.g., azathioprine) ☐ NSAIDS
☐ Antibiotics (sulfa, tetracycline, erythromycin) ☐ Estrogens
Other:

Relevant Laboratory Tests	Normal Range for Your Institution	Baseline Value for Patient	Abnormal Value	Improvement Value
		Date:	Date:	Date:
Amylase				
Lipase				
ALT				
Bilirubin				
Alkaline Phosphatase				
Triglycerides				
Calcium				
Other:_____				
Other:_____				

Other Studies	Results
Ultrasound	
MRI	
CT Scan	
ERCP	
Other:_____	

Treatment Provided

☐ NPO ☐ Intravenous fluids
☐ ERCP (e.g., sphincterotomy) ☐ Cholecystectomy
☐ Other:

Was this event related to a Lilly drug? If yes, please provide name of drug:

	☐ Yes	☐ Likely	☐ Unlikely	☐ No	☐ Unknown

Were any events related to the Lilly Drug? If yes, please name the drug and list event(s) and relatedness:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Event Outcome

○ Recovered ○ Worsened ○ Recovering
○ Not Recovered ○ Unknown
○ Recovered with Sequellae (Please provide details): _____
○ Other outcome, please describe:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: _____ **Lilly Case #:** _____

Information Provided By:
(Enter Name and Title) _____ **Signature/Initials:** _____

Patient Name or Initials: _____ **Patient Birth Date or Age:** _____

Gender: ○ F ○ M ○ Unknown	**Race:** ○ Caucasian ○ Asian ○ Black ○ Other	**Weight:** _____ ○ lb ○ kg	**Height:** _____ ○ in ○ cm

Reported Drug: Cialis® (tadalafil)

Lot/Control Number (if available): _____ **Indication:** _____

Dose: _____ **Frequency:** _____ **Formulation:** _____

Start Date: _____ **Dose when event occurred:** _____ **Route:** _____

Drug D/C? ○ No ○ Yes **Date D/C:** _____ **If Discontinued, did the event resolve?** ○ Yes ○ No

Drug Restarted? ○ No ○ Yes **Date Restarted:** _____ **If Restarted, did the event reoccur?** ○ Yes ○ No

Cialis® (tadalafil)
Indication: ○ Erectile dysfunction ○ Other: _____
Dose: ○ 2.5 mg ○ 5 mg ○ 10 mg ○ 20 mg ○ Other: _____
Current Dosing Frequency: ○ As Needed ○ Daily

Priapism

Primary diagnosis for the reported event(s):

Hospitalization for this event? ○ Yes ○ No

Concomitant Medications/Substances (include prescription, OTC, herbal, and substances of abuse)

☐ Nitrates/nitrites: _____ ☐ Alpha blockers
☐ Trazodone ☐ Other antidepressants
☐ Antipsychotics ☐ Antihypertensives
☐ Anticoagulants ☐ Other (specify): _____

Event Description:

Time from last dose to event onset:			
What was the patient's activity at the time of the event?			
Duration of Erection:	☐ <4 Hours	☐ 4-6 Hours	☐ >6 Hours
Was erection associated with pain?	☐ Yes	☐ No	
Did patient experience difficulty urinating as a result of prolonged erection?	☐ Yes	☐ No	

 Please fax to: Lilly (US) Global Patient Safety - (866) 644-1697 DC 4027

Eli Lilly and Company - Global Patient Safety **Case Number:**

Was the patient receiving testosterone replacement therapy?	☐ Yes	☐ No	
What medical interventions were required?	☐ None	☐ Analgesics	☐ Transfusion
☐ Other _____	☐ Alpha or Beta adrenergic agonist	☐ Intracavernosal Injection	☐ Surgical Intervention

Signs and Symptoms:

☐ Testicular pain ☐ Persistent penile erection unrelated to sexual arousal (if yes, how long):_____

☐ Swelling of the Glans Penis ☐ Other (please describe):_____

Medical History:

☐ Prolonged penile erection (if yes, provide date(s) and intervention(s) if applicable):_____

☐ Erectile Dysfunction/Impotence	☐ Prostatitis/Urethritis/Cystitis	☐ Sickle Cell Disease
☐ Hemochromatosis	☐ Mump Orchitis or prior infection of the genitalia esp. testes/scrotum (please describe):	
☐ Hypopituitarism	☐ Spinal Cord Injury/Disease (please describe):	
☐ Cirrhosis	☐ Carcinoma and/or tumors of pelvis, bladder or testes	
☐ Leukemia	☐ Other (please list/describe):	
Has the patient ever received any treatment for ED?	☐ No ☐ Unknown ☐ Yes (please describe):	

Was this event related to a Lilly drug? If yes, please provide name of drug:

	☐ Yes	☐ Likely	☐ Unlikely	☐ No	☐ Unknown

Were any events related to the Lilly Drug? If yes, please name the drug and list event(s) and relatedness:

Event Outcome

○ Recovered ○ Worsened ○ Recovering

○ Not Recovered ○ Unknown

○ Recovered with Sequellae (Please provide details): _____

○ Other outcome, please describe:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: _____ **Lilly Case #:** _____

Information Provided By:
(Enter Name and Title) _____ **Signature/Initials:** _____

Patient Name or Initials: _____ **Patient Birth Date or Age:** _____

Gender: ○ F ○ M ○ Unknown	**Race:** ○ Caucasian ○ Asian ○ Black ○ Other	**Weight:** _____ ○ lb ○ kg	**Height:** _____ ○ in ○ cm

Reported Drug: Cialis® (tadalafil)

Lot/Control Number (if available): _____ **Indication:** _____

Dose: _____ **Frequency:** _____ **Formulation:** _____

Start Date: _____ **Dose when event occurred:** _____ **Route:** _____

Drug D/C? ○ No ○ Yes **Date D/C:** _____ **If Discontinued, did the event resolve?** ○ Yes ○ No

Drug Restarted? ○ No ○ Yes **Date Restarted:** _____ **If Restarted, did the event reoccur?** ○ Yes ○ No

Cialis® (tadalafil)

Indication: ○ Erectile dysfunction ○ Other: _____

Dose: ○ 2.5 mg ○ 5 mg ○ 10 mg ○ 20 mg ○ Other: _____

Current Dosing Frequency: ○ As Needed ○ Daily

Syncope

Primary diagnosis for the reported event(s):

Hospitalization for this event? ○ Yes ○ No

Presenting Signs/Symptoms

Circumstances Prior to Event	
☐ Emotional reaction (e.g., anxiety, fear)	☐ While arising from recumbent/sitting position
☐ Pain	☐ While recumbent
☐ During exertion	☐ Hunger
☐ After exertion	☐ Warm ambient environment
☐ During cough	☐ Alcohol consumption
☐ Unknown circumstances	☐ Other: _____
Prodromal Symptoms	
☐ Nausea	☐ Palpitations
☐ Diaphoresis	☐ Chest pain
☐ Lightheadedness	☐ Neurologic impairment (e.g., diplopia, ataxia)
☐ Dizziness/vertigo	☐ Severe headache
☐ No prodromal symptoms	☐ Other: _____

Eli Lilly and Company - Global Patient Safety **Case Number:**

Description of Event

- ☐ Loss of bowel or bladder control
- ☐ Tongue biting
- ☐ Confusion/combativeness upon awakening
- ☐ Other:_____
- ☐ Tonic/clonic activity
- ☐ Patient recalls hitting ground during fall
- ☐ Injury during fall:_____

Physical Examination

- ☐ Normal examination
- ☐ Blood pressure standing:_____
- ☐ Blood pressure lying:_____
- ☐ Heart rate:_____
- ☐ Glucose:_____
- ☐ Orthostatic hypotension
- ☐ Neurologic findings (please specify):_____
- ☐ Other (please specify):_____

Medical History

- ☐ Diabetes
- ☐ Myocardial infarction
- ☐ Valvular heart disease
- ☐ Arrhythmia (please specify):_____
- ☐ Other (please specify):_____
- ☐ Congestive heart failure
- ☐ Syncope
- ☐ Stroke
- ☐ Hypotension

Concomitant Medicines/substance (include prescription, substance, OTC and herbal)

- ☐ Diuretics:_____
- ☐ Beta blockers:_____
- ☐ Alpha blockers:_____
- ☐ Calcium channel blockers:_____
- ☐ Neuroleptic agents:_____
- ☐ Other (please specify):_____
- ☐ Antihypertensives:_____
- ☐ Nitrates:_____
- ☐ Antidepressants:_____
- ☐ Antiparkinson agents:_____

Relevant Laboratory Tests	Normal Range for Your Institution	Baseline Value for Patient	Abnormal Value	Improvement Value
		Date:	Date:	Date:
Glucose				
Hemoglobin				
Sodium				
Creatinine				
Other:_____				
Other:_____				

Other Study	Results
Electrocardiogram	
CT/MRI	
Holter monitor	
Tilt table	
Other:_____	

Treatment

Eli Lilly and Company - Global Patient Safety **Case Number:**

☐ Support and observation ☐ Hydration

☐ Other:_____

Was this event related to a Lilly drug? If yes, please provide name of drug:

	☐ Yes	☐ Likely	☐ Unlikely	☐ No	☐ Unknown
Were any events related to the Lilly Drug? If yes, please name the drug and list event(s) and relatedness:					

Event Outcome

○ Recovered ○ Worsened ○ Recovering

○ Not Recovered ○ Unknown

○ Recovered with Sequellae (Please provide details): _____

○ Other outcome, please describe:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: _____ **Lilly Case #:** _____

Information Provided By:
(Enter Name and Title) _____ **Signature/Initials:** _____

Patient Name or Initials: _____ **Patient Birth Date or Age:** _____

Gender: ○ F ○ M ○ Unknown	**Race:** ○ Caucasian ○ Asian ○ Black ○ Other	**Weight:** _____ ○ lb ○ kg	**Height:** _____ ○ in ○ cm

Reported Drug: Adcirca® (tadalafil)

Lot/Control Number (if available): _____ **Indication:** _____

Dose: _____ **Frequency:** _____ **Formulation:** _____

Start Date: _____ **Dose when event occurred:** _____ **Route:** _____

Drug D/C? ○ No ○ Yes **Date D/C:** _____ **If Discontinued, did the event resolve?** ○ Yes ○ No

Drug Restarted? ○ No ○ Yes **Date Restarted:** _____ **If Restarted, did the event reoccur?** ○ Yes ○ No

Vaginal Bleeding

Primary Diagnosis for the reported event(s):

Hospitalization for this event? ○ Yes ○ No

General Questions

1. What was the anatomic site of bleeding: _____
2. What was the cause of bleeding: _____
3. Grade of bleeding: _____

Was there a procedure performed? ○ No ○ Yes (please specify):

Presenting Signs/Symptoms

- ☐ Estimated blood loss (cc): _____
- ☐ Abdominal pain
- ☐ Other: _____
- ☐ Passing Clots
- ☐ Hypotension

Past Medical History (Vaginal Bleeding)

- ☐ Obesity
- ☐ Diabetes
- ☐ Nulliparity
- ☐ Hypothyroidism
- ☐ Cervical cancer
- ☐ Post-menopausal (years): _____
- ☐ Chronic liver disease
- ☐ Family history of bleeding
- ☐ Estrogen use
- ☐ Uterine cancer
- ☐ Uterine myomata
- ☐ Bleeding disorder: _____
- ☐ Menorrhagia
- ☐ Other (specify): _____

Eli Lilly and Company - Global Patient Safety **Case Number:**

Laboratory Tests	Normal range for your institution	Baseline value for patient	Abnormal value	Improvement value
		Date:	Date:	Date:
Hemoglobin				
WBC				
Platelets				
INR/Prothrombin time				
aPTT				
d-Dimer				
Beta-HCG				
Other:				
Other:				

Other Relevant Study (GYN Bleed)	Results
Pelvic examination	
Pelvic ultrasound	
Renal CT/MRI	
Biopsy (cervix, endometrium)	
Other:	

Treatment

☐ Intravenous fluids
☐ Platelet transfusion (units):_____
☐ Other:_____
☐ RBC transfusion (units):_____
☐ Fresh frozen plasma (units):_____

Was this event related to a Lilly drug? If yes, please provide name of drug:

	☐ Yes	☐ Likely	☐ Unlikely	☐ No	☐ Unknown

Were any events related to the Lilly Drug? If yes, please name the drug and list event(s) and relatedness:

Event Outcome

○ Recovered ○ Worsened ○ Recovering
○ Not Recovered ○ Unknown
○ Recovered with Sequellae (Please provide details): _____
○ Other outcome, please describe:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: _____ **Lilly Case #:** _____

Information Provided By:
(Enter Name and Title) _____ **Signature/Initials:** _____

Patient Name or Initials: _____ **Patient Birth Date or Age:** _____

Gender: ○ F ○ M ○ Unknown	**Race:** ○ Caucasian ○ Asian ○ Black ○ Other	**Weight:** _____ ○ lb ○ kg	**Height:** _____ ○ in ○ cm

Reported Drug: Cialis® (tadalafil)

Lot/Control Number (if available): _____ **Indication:** _____

Dose: _____ **Frequency:** _____ **Formulation:** _____

Start Date: _____ **Dose when event occurred:** _____ **Route:** _____

Drug D/C? ○ No ○ Yes **Date D/C:** _____ **If Discontinued, did the event resolve?** ○ Yes ○ No

Drug Restarted? ○ No ○ Yes **Date Restarted:** _____ **If Restarted, did the event reoccur?** ○ Yes ○ No

Cialis® (tadalafil)

Indication: ○ Erectile dysfunction ○ Other: _____

Dose: ○ 2.5 mg ○ 5 mg ○ 10 mg ○ 20 mg ○ Other: _____

Current Dosing Frequency: ○ As Needed ○ Daily

Vision Impairment

Primary diagnosis for the reported event(s):

Hospitalization for this event? ○ Yes ○ No

Diagnostic Test/Study	Result (include unit of measurement)
FM - 100 (Colour test)	
Visual acuity testing	
Slit lamp microscope/Fundoscopic exam	
Fluorescein angiography or indocyanine angiography	
Perimetry	
Relative afferent pupillary defect	
ESR	
Cup to disc ratio	
Retinal detachment or tears	
Visual field defect	
Other (specify): _____	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Medical History/Risk Factors

- ☐ Glaucoma
- ☐ Retinal disorders/optic nerve disorders
- ☐ Eye trauma
- ☐ Cardiovascular event
- ☐ Cerebrovascular event
- ☐ Causes of papilloedema
- ☐ Arteritis
- ☐ Eye infection
- ☐ Disc infiltration
- ☐ Alcoholism
- ☐ Macular degeneration
- ☐ Cataracts
- ☐ Hypertension
- ☐ Transient ischemic attacks
- ☐ Retinal vessel occlusion or obstruction (arterial/vein)
- ☐ Sudden vision loss
- ☐ Diabetes
- ☐ Severe anaemia
- ☐ Metabolic disorder
- ☐ Tobacco use
- ☐ Other (specify):

_____

☐ Relevant drug history:

_____

☐ Relevant family history (please specify):

_____

Concomitant Medications/Substance (please include prescription, OTC and herbal)

- ☐ Nitrates/Nitrites
- ☐ Alpha Blocker
- ☐ Other (please specify):

Hospitalization for this event? ○ Yes ○ No

Treatment provided (please describe)

Was this event related to a Lilly drug? If yes, please provide name of drug:

	☐ Yes	☐ Likely	☐ Unlikely	☐ No	☐ Unknown
Were any events related to the Lilly Drug? If yes, please name the drug and list event(s) and relatedness:					

Event Outcome

- ○ Recovered
- ○ Worsened
- ○ Recovering
- ○ Not Recovered
- ○ Unknown
- ○ Recovered with Sequellae (Please provide details): _____
- ○ Other outcome, please describe:

Annex 10. Details of Proposed Additional Risk Minimisation Measures

No additional risk minimisation measures are proposed at this time.