EU Risk Management Plan (Version 9.2)

Global Patient Safety
Signatory information is available on request.
EU Risk Management Plan electronically approved by Lilly on date provided below.

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EU Risk Management Plan for tadalafil

RMP version to be assessed as part of the application: 9.2

Data lock point for this RMP: 29 July 2021

Date of final sign off: See cover page of this document.

Rationale for submitting an updated RMP:

Responses to the pharmacovigilance risk assessment committee D120 questions for Adcirca® (tadalafil) paediatric line extension application

Summary of significant changes in this RMP:

Part III and Annex 4: Removal of the information about specific adverse reaction follow-up questionnaires

Other RMP versions under evaluation

RMP version number: Not applicable

Submitted on: Not applicable

Procedure number: Not applicable

Details of the currently approved RMP

Version number: 8.2

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Date of approval (opinion date): 06 September 2017

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's Qualified Person for Pharmacovigilance (QPPV). The electronic signature is available on file.

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List of Abbreviations

Term	Definition
5-ARI	5-alpha-reductase inhibitor
6MWD	6-minute walk distance
ACE	angiotensin-converting enzyme
ADR	adverse drug reaction
ARB	angiotensin receptor blocker
BP	blood pressure
BPH	benign prostatic hyperplasia
CDS	Core Data Sheet
CHD	coronary heart disease
CTEPH	chronic thromboembolic pulmonary hypertension
CI	confidence interval
CV	cardiovascular
DDI	drug-drug interaction
DM	diabetes mellitus
ED	erectile dysfunction
EPAR	European Public Assessment Report
ERA	endothelin receptor antagonist
GVP	Good Pharmacovigilance Practice
IMS	Intercontinental Medical Statistics
IPAH	idiopathic pulmonary arterial hypertension
LUTS	lower urinary tract symptoms
LV	left ventricle
LVAB	H6D-LC-LVAB
LVBY	H6D-LC-LVBY
LVCM	H6D-EW-LVCM

LVDN	H6D-EW-LVDN
LVCP	H6D-EW-LVCP
MAH	Marketing Authorisation Holder
NYHA	New York Heart Association
NAION	non-arteritic anterior ischaemic optic neuropathy
OR	odds ratio
OS	oral suspension
PAH	pulmonary arterial hypertension
PBRER	Periodic Benefit–Risk Evaluation Report
PDE5	phosphodiesterase type 5
pPAH	paediatric pulmonary arterial hypertension
PSUR	Periodic Safety Update Report
PV	pharmacovigilance
PY	patient-years
RMP	risk management plan
RR	relative risk
RV	right ventricle
SAE	serious adverse event
SHL	sudden hearing loss
SmPC	summary of product characteristics
TIA	transient ischaemic attack
WHO	World Health Organization

Part I: Product(s) Overview

Table Part I.1. Product Overview

Active substance(s) (INN or common name)	Tadalafil
Pharmacotherapeutic group(s) (ATC Code)	Urological, drugs used in erectile dysfunction G04BE08
Marketing authorisation holder	Eli Lilly Nederland B.V.
Medicinal products to which this RMP refers	3 Cialis® Adcirca® Tadalafil Lilly®
Invented name(s) in the European Economic Area (EEA)	Cialis Adcirca Tadalafil Lilly
Marketing authorisation procedure	Centralised
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: Chemical origin of active substance tadalafil. Excipients included with a known effect: lactose (as monohydrate) and sodium (less than 1 mmol)
Hyperlink to the product information	See 1.13.1
Indication(s) in the EEA	**Current:** Erectile dysfunction (ED) Benign prostatic hyperplasia (BPH) ED and BPH (ED/BPH) Pulmonary arterial hypertension (PAH)
	Proposed: Paediatric pulmonary arterial hypertension (pPAH) Tadalafil is indicated for the treatment of paediatric patients aged 6 months to 17 years old with PAH classified as WHO Functional Classes II and III. Efficacy in patients ≥6 years in terms of improvement of exercise capacity has been shown in idiopathic pulmonary arterial hypertension (IPAH) and PAH associated with surgical repair of at least 6-month duration of simple congenital systemic to pulmonary shunt.
Dosage in the EEA	**Current:** Tadalafil can be taken regardless of food intake.

Indication	Recommended Dose
On-demand ED	10 mg taken prior to anticipated sexual activity. The maximum dose is 20 mg. The maximum dose frequency is once per day. Tadalafil has been proven effective up to

<table>
<tr><td></td><td>
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<tr><td></td><td>36 hours after dosing and as early as 16 minutes after dosing.</td></tr>
<tr><td>Once-daily dosing for ED, BPH, and ED/BPH</td><td>5 mg taken at approximately same time daily. Dose may be decreased to 2.5 mg based on individual tolerability.</td></tr>
<tr><td>Once-daily dosing for PAH</td><td>40 mg (2×20 mg) once daily. Dividing the dose over the course of the day is not recommended.</td></tr>
</table>
Proposed: Paediatric pulmonary arterial hypertension
<table>
<tr><th>Age and/or Weight</th><th>Recommended Dose</th></tr>
<tr><td>Age ≥2 years old</td><td></td></tr>
<tr><td>Body weight ≥40 kg</td><td>40 mg (two 20 mg tablets)</td></tr>
<tr><td>Body weight <40 kg</td><td>20 mg (one 20 mg tablet or 10 mL of oral suspension (OS), 2 mg/mL tadalafil)</td></tr>
<tr><td>Aged 1 year to <2 years old</td><td>6 mg (3 mL of OS, 2 mg/mL tadalafil)</td></tr>
<tr><td>Aged 6 months to <1 year old</td><td>4 mg (2 mL of OS, 2 mg/mL tadalafil)</td></tr>
</table>
</td></tr>
<tr><td>Pharmaceutical form(s) and strengths</td><td>Current: Tadalafil is available as film-coated tablets for oral administration. Each tablet contains 2.5, 5, 10, or 20 mg of tadalafil.</td></tr>
<tr><td></td><td>Proposed: Tadalafil OS, 2 mg/mL, for oral administration.</td></tr>
<tr><td>Is/will the product be subject to additional monitoring in the EU?</td><td>No</td></tr>
</table>

Abbreviations: ATC = Anatomical Therapeutic Chemical; BPH = benign prostatic hyperplasia; cGMP = cyclic guanosine monophosphate; ED = erectile dysfunction; EU = European Union; INN = International Nonproprietary Names; IPAH = idiopathic PAH; OS = oral suspension; PAH = pulmonary arterial hypertension; PDE5 = phosphodiesterase type 5; pPAH = paediatric PAH; RMP = risk management plan; WHO = World Health Organization.

Part II: Safety Specification

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

SI.1 Erectile Dysfunction

SI.1.1 Incidence

The incidence of ED varies by country. In Europe, incidence rates of ED have been reported in the Netherlands and Finland. In the Netherlands, the crude incidence rate of any ED among men 50 to 75 years of age was 98.6/1000 PY, significant ED = 32.8/1000 PY and clinically significant ED = 28.1/1000 PY (Schouten et al. 2005). In Finland, the incidence rates of minimal, moderate, and complete ED among men 50 to 70 years of age were 127/1000 PY, 41/1000 PY, and 18/1000 PY, respectively (Shiri et al. 2003). In both the countries, incidence rates of ED increased with increasing age.

In the US, the crude incidence of ED was reported to be 26/1000 PY in men 40 to 69 years of age and increased with increasing age from 12.4/1000 PY in men aged 40 to 49 years to 46.4/1000 PY in men aged 60 to 69 years.

SI.1.2 Prevalence

The prevalence rates of ED vary by country. In a multinational European study (Corona et al. 2010 a), the prevalence rates of ED from 2003 to 2005 were

- 23% (Spain)
- 24% (Sweden)
- 25% (Italy)
- 30% (Hungary)
- 31% (UK)
- 32% (Belgium)
- 36% (Poland), and
- 43% (Estonia).

In Australia, the overall prevalence of ED was even higher at 52.9% for community-dwelling men 35 to 80 years of age (Martin et al. 2012).

Similar to the incidence, the prevalence of ED increases with age globally (Nicolosi et al. 2003) as follows:

- 40 to 44 years: 9%
- 45 to 49 years: 12%
- 50 to 54 years: 18%
- 55 to 59 years: 29%
- 60 to 64 years: 38%, and
- 65 to 70 years: 54%.

In the US, the overall prevalence rate 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). Similar trends were observed in an Australian population of community-dwelling men. Prevalence rose from 45% for men 35 to 44 years of age to 91% for men 65 to 80 years of age (Martin et al. 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.1.3 Demographics of the Population in the Authorised Indication – and Risk Factors for the Disease

Demographic profile

Erectile dysfunction (ED) is the most frequently diagnosed sexual dysfunction in the older male population (Albersen 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 US were in age groups 45 to 55 years (34% to 35.7%) and 55 to 65 years (34.4% to 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 US 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 US, the incidence (per 1000 PY) 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).

Risk factors

As noted by Lewis et al. (2010), common risk factors associated with sexual dysfunction include

- the health status of the individual
- the presence of DM and CV disease
- concurrence of
    - other genitourinary disease
    - psychiatric/psychological disorders
    - other chronic diseases, and
    - socio-demographic conditions, and
- smoking and hormonal factors.

Age is also a risk factor (Lyseng-Williamson and Wagstaff 2002), as the prevalence and severity of ED progressively increases with advancing age. In an international survey study, men 70 to 75 years of age have a 14-fold higher RR for ED compared with respondents in their 20 s (Shabsigh et al. 2005). DM 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 has been widely studied as ED risk factors, including that of

- prior CV events (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" CV disease (RR 1.26) (Banks et al. 2013).

Concomitant medications

Concomitant medications in patients with ED (Aversa et al. 2004; Blumentals et al. 2004; Lewis et al. 2005; Corona et al. 2010b) include the following:

- oral antihyperglycaemic agents
- insulin
- antidepressants
- antihypertensives, and
- CV agents such as
    - beta-blockers
    - ACE inhibitors/ARBs
    - diuretics
    - calcium channel blockers, and
    - statins.

SI.1.4 Main Existing Treatment Options

Pharmacologic therapies

PDE5 inhibitors

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

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, and phentolamine, which may be used alone or in combination. These injection therapies are effective in treating ED, resulting in full erections in 70% to 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 that administers alprostadil, result in and maintain erections in up to 55% of patients (Hatzimouratidis and Hatzichristou 2005).

SI.1.5 Natural History of the Indicated Condition in the Population, Including Mortality and Morbidity

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

SI.1.6 Important Co-morbidities

Hypertension

Incidence

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 UK population of males >18 years of age with ED, the 3-month incidence of hypertension was 1.35% compared with 0.95% in age-matched controls (Kirby et al. 2011). By comparison, the 6-month incidence in a US 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 UK (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). In Taiwan, prevalence was 34.5% in the ED population ≥18 years of age (compared with 26.2% in patients without ED) (Keller et al. 2012).

Hyperlipidaemia

Incidence

The overall incidence of hypercholesterolaemia in a UK 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 US ED population ≥18 years of age (Cameron et al. 2006; Kirby et al. 2011).

Prevalence

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 to 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 UK to 35% to 43% in Germany and the US (Shabsigh et al. 2005). In Taiwan, prevalence was 30.8% in the ED population ≥18 years of age (compared with 17.5% in patients without ED) (Keller et al. 2012).

Diabetes mellitus

Incidence

The overall incidence of DM in a UK 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 US men ≥18 years of age with ED (Cameron et al. 2006).

Prevalence

The worldwide prevalence rate of DM was 20.7% (Shabsigh et al. 2008). By region, the prevalence ranged from 6% for France and Spain to 11% for the UK and up to 17% to 20% for the US and Italy (Shabsigh et al. 2005). In Taiwan, prevalence was 21.7% in the ED population ≥18 years of age (compared with 12.8% in patients without ED) (Keller et al. 2012). The prevalence of DM increased with ED severity: 8% to 11% occurring in the mild/moderate ED population and 16% to 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 US increased with age: 2.6% in the age group 18 to 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

Incidence

The yearly incidence rate of CV disease in Italy during the period from 2000 to 2007 was 0.23% in an ED population 17 to 88 years of age (Corona et al. 2010b). In the US, 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 with 0.015 per person-year in men without ED (Thompson et al. 2005) and comprised

- angina
- myocardial infarction
- myocardial infarction or angina
- stroke
- congestive heart failure
- TIA, and
- arrhythmia.

The incidence of CV disease increased with age among individuals with ED (Cameron et al. 2006), with 1.06% of men 18 to 25 years of age having CV disease, compared with 11.94% of men >85 years of age during a 6-month follow-up period (Cameron et al. 2006).

Prevalence

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 to 75 years of age (Shabsigh et al. 2005). Overall cross-national prevalence rate of angina was 25.7% in 2004 and 11.6% for CHD (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 UK and US (Shabsigh et al. 2005). Boddi et al. (2012) found the prevalence rate of CV disease to be 12% in an Italian cohort with men 17 to 88 years of age. In Taiwan, the prevalence rate of CHD was 15.7% in the ED population ≥18 years of age (compared with 10.3% in patients without ED) (Keller et al. 2012).

SI.2 Benign Prostatic Hyperplasia

SI.2.1 Incidence

Benign prostatic hyperplasia (BPH) is one of the most common diseases in aging men. In the UK, 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 US 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). BPH becomes a clinical entity when LUTS associated with it are bothersome enough for a patient to seek medical care (Egan 2016).

The overall incidence rate of LUTS suggestive of BPH in men over 45 years of age in the Netherlands (Verhamme et al. 2002) was 15 per 1000 man-years (95% CI: 14.8, 16.1). The incidence rate increased linearly ($r^2 = 0.99$) with age from 3 cases per 1000 man-years at the age of 45 to 49 years (95% CI: 2.4, 3.6) to a maximum of 38 cases per 1000 man-years at the age of 75 to 79 years (95% CI: 34.1, 42.9). After the age of 80 years, the incidence rate remained constant.

In the US, the overall incidence of clinically significant BPH per 1000 PY by age was 18.6 (Parsons et al. 2012; Schenk et al. 2012), ranging from

- 11.9 for ages 54 to 59 years
- 18.8 for ages 60 to 64 years, and
- 26.3 for ages >65 years.

By race, the incidence per 1000 PY (Parsons et al. 2012; Schenk et al. 2012) was as follows:

- 18.1 for Whites
- 24.5 for African Americans, and
- 23.0 for Hispanics.

SI.2.2 Prevalence

In a Dutch cohort (1995 to 2000), the overall prevalence rate of BPH with LUTS was 10.3%, with 2.7% in the 40- to 45-year age group and increased with age until a maximum of 24% by the age 80 of years (Verhamme et al. 2002). In the US, prevalence was 6.2% for men 50 to 79 years of age (Pettaway et al. 2011).

SI.2.3 Demographics of the Population in the Authorised Indication and Risk Factors for the Disease

Demographic profile

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 with 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 (Berry et al. 1984; Oesterling 1996; Roehrborn 2005), is approximately

- 10% for men in their 30 s
- 20% for men in their 40 s
- 50% to 60% for men in their 60 s, and
- 80% to 90% for men in their 70 s and 80 s.

Risk factors

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

Concomitant medications

Concomitant medications taken by patients with BPH (Broderick et al. 2010) include

- beta-blockers
- thiazide or other diuretics
- calcium channel blockers
- ACE inhibitors
- other antihypertensive drugs
- nitrates
- aspirin
- non-aspirin non-steroidal anti-inflammatory drugs
- ARBs
- statins
- insulin, and
- oral diabetic agents.

SI.2.4 Main Existing Treatment Options

Pharmacologic therapies

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 (AUA 2010; Oelke et al. 2013).

5-alpha-reductase inhibitors

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 2010).

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 or transurethral incision of the prostate, have been shown to reduce benign prostatic obstruction and, secondarily, LUTS.

Other therapies

Transurethral microwave therapy, transurethral needle ablation, and 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.2.5 Natural History of the Indicated Condition in the Population, Including Mortality and Morbidity

Mortality from BPH is essentially due to complications of therapy. Using death certificate data and the WHO database for the period 1955 to 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 to 65 years of age are rare. Declines in mortality from BPH treatment have also been observed in the US and Japan, with 1990 rates of 1.8 per million in the US 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.2.6 Important Co-morbidities

Hypertension

Incidence

The incidence rates for hypertension in patients with BPH are not well documented.

Prevalence

In a cross-national study in the EU, the prevalence rate 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 US Massachusetts Male Aging Study, the prevalence rate of having both comorbid conditions of BPH and hypertension was 30.3% (Meigs et al. 2001). In 2 other US 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). In studies conducted in Japan and Taiwan, prevalence was found to be 34.4% and 36.9%, respectively (Yamasaki et al. 2011; Chen et al. 2012).

Cardiovascular disease

Incidence

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

Prevalence

Two other studies have reported the prevalence of CV events in the EU. The Trans European Research Study reported a prevalence rate of 12.5% for CHD (ranging from 7.7% in Italy to 20.7% in the UK), 3.8% for heart failure (2.2% in Poland to 6.2% in France), and 4.0% for cerebrovascular accident/TIA (1.8% in Poland to 7.0% in France) (Hutchison et al. 2006). Another EU study found overall CV comorbidity (including hypertension) to be 52.7%, ranging from 47.5% in France to 61.1% in Germany (Fourcade et al. 2008). Previous studies have reported a prevalence rate of 29% for coronary artery disease, 10% for stroke/TIA, and 28% for myocardial infarction in the US (Weisman et al. 2000); the prevalence rate of CV disease was 18.8% in Japan (Yamasaki et al. 2011) and 15.4% in Taiwan (Chen et al. 2012). 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

Incidence rates of hyperlipidaemia are not well defined.

Prevalence

Prevalence rates in the EU are not well defined. In a US 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 US studies of patients with BPH/LUTS, comorbid hyperlipidaemia ranged from 19.4% to 45% (Roehrborn et al. 2007; Broderick et al. 2010). The prevalence rate of dyslipidaemia was 26.9% in Japan (Yamasaki et al. 2011) and 35.4% in Taiwan (Chen et al. 2012).

Diabetes mellitus

Incidence

Incidence rates for DM are not well defined.

Prevalence

The Trans European Research Study reported the overall prevalence rate for DM in the BPH/LUTS population to be 10.3%, ranging from 7.8% in Poland to 13.4% in Germany (Hutchison et al. 2006). By comparison, 2 US studies with BPH/LUTS cohorts found the prevalence rate of DM to range from 4.7% to 17% (Roehrborn et al. 2007; Broderick et al. 2010). In a US BPH cohort, DM was between 6.8% and 8.1% (Meigs et al. 2001; Sarma et al. 2008). The prevalence rate of BPH and DM was 21.3% in Japan and 16.1% in Taiwan (Yamasaki et al. 2011; Chen et al. 2012).

Prostate cancer

Incidence

In a nationwide population-based study in Sweden among men diagnosed with BPH and followed up 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 US study that followed a BPH cohort over an 11-year period, prostate cancer was diagnosed in 9.0% 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 the Danish male population (Ørsted et al. 2011), the cumulative incidence of prostate cancer in the BPH population undergoing an operation for BPH was 24.1%, whereas the cumulative incidence of prostate cancer among the hospitalised BPH population was 8.64%

(1980 to 2006). Similarly, a study using data from the Prostate Cancer Prevention Trial reported that the incidence rate of prostate cancer in patients diagnosed with prevalent BPH was 25.4% (394/1549); however, the RR of prostate cancer was not greater in men with prevalent BPH compared with those without BPH (Schenk et al. 2011).

Prevalence

According to large historical autopsy studies, most (>80%) prostate carcinomas develop in prostates with concomitant BPH (Bostwick et al. 1992). A case-control study in the US (700 cases, 604 controls) reported an overall OR for developing prostate cancer in patients with a history of BPH as 2.4. The OR was 2.7 for African Americans and 2.3 for Caucasians (Patel et al. 2005).

Renal dysfunction

Incidence

The incidence rates of renal dysfunction in patients with BPH are not well defined.

Prevalence

In the EU, data collected by the TRIUMPH Project that included patients from 6 European countries noted an overall prevalence rate 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 UK (Hutchison et al. 2006). Prevalence rates are not well defined in the US population. In Japan, the prevalence rate of chronic kidney disease in the BPH population was 36.88% (Yamasaki et al. 2011).

SI.3 Pulmonary Arterial Hypertension

SI.3.1 Incidence

The incidence of PAH ranges from 1.1 per million per year in the UK 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 18 years of age or older yielded an annual incidence of 2.4 per million population from 2002 to 2003 (Humbert et al. 2006). The differences between the studies could be due to differences in the definitions of the disease.

SI.3.2 Prevalence

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 16 to 65 years of age (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 UK and Ireland reported an estimated prevalence in 2009 of 6.6 PAH cases per million population (Ling et al. 2012). In a US study using administrative insurance claims data, the rates were reported to be higher: prevalence rates for those <65 years of age were 109 per million individuals (71 to 146 per million) and for those ≥65 years of age, they were 451 per million individuals (384 to 519 per million) (Kirson et al. 2011).

SI.3.3 Demographics of the Population in the Authorised Indication and Risk Factors for the Disease

Demographic profile

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 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 regard to race/ethnicity, data from the REVEAL cohort (Frost et al. 2011) 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%).

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 years and an age range of 18 to 85 years among all cases (Humbert et al. 2006). Data from a recent study conducted in the UK and Ireland reported a median age of onset of 50 years (Ling et al. 2012).

Risk factors

The majority of PAH cases tend to be idiopathic in aetiology, followed by connective tissue diseases and CHD associated. Familial PAH is 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 IPAH and familial PAH (Yu et al. 2009).

Using baseline characteristic data from the REVEAL cohort (the Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management) based in the US, 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).

Concomitant medications

Concomitant medications that are used in the PAH population (Badesch et al. 2010) include

- warfarin
- diuretics
- calcium channel blockers
- digoxin (Galiè et al. 2002)
- oxygen
- thyroid replacement
- selective serotonin reuptake inhibitors and other antidepressants
- aspirin and other anti-inflammatory agents

- statins
- beta-blockers
- psychotropic drugs
- corticosteroids
- ACE inhibitors, and
- clopidogrel.

Other treatment options for PAH are described in the following section and some of them (such as ERAs, e.g. Bosentan) may be concomitantly prescribed to PDE5 inhibitors.

SI.3.4 Main Existing Treatment Options

Pharmacologic therapies

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 that significantly improves the combined endpoint of NYHA functional class and demonstrates a 10% improvement in 6MWD ($p = 0.007$). Treprostinil, administered subcutaneously, improves placebo-adjusted 6-minute walk test distance by 16 m in a dose-dependent manner.

Endothelin receptor antagonists

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 m. 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, Multicentre, Efficacy Studies I and II (ARIES I and II). In the SERAPHIN trial, treatment with macitentan 10 mg resulted in a placebo-corrected mean increase in 6MWD of 22 m at 6 months ($p = 0.0078$), with significant improvement in 6MWD by 3 months. Macitentan 10 mg also led to an improvement of at least 1 WHO functional class at 6 months in 22% of patients compared with 13% of patients treated with placebo.

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 on its own or in combination with ERAs (Adempas summary of product characteristics). The CHEST guidelines for the treatment of PAH advise that treatment-naive patients with PAH having 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).

Riociguat is also approved for the treatment of adults with persistent/recurrent CTEPH after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class.

PDE5 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.

Selective prostacyclin receptor agonist

In the GRIPHON study, at Week 26, selexipag increased the 6MWD by 4 m from baseline in comparison with a decrease observed in the placebo group by a median of 9 m from baseline ($p = 0.003$). There was no significant difference between the placebo group and the selexipag group in the proportion of patients with no worsening in WHO functional class (74.9% and 77.8%, respectively; $p = 0.28$).

Nonpharmacologic therapies

Balloon atrial septostomy

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 WHO Functional Class 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 and decreases in right atrial pressure, with improvement in 6-minute walk test distance (Galiè 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 RV systolic function and/or LV diastolic function is unknown. Although 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 post-operative period. Both single and bilateral procedures have been performed with similar survival. Any complications occurring in the allograft following single lung transportation are 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 (Galiè et al. 2009).

SI.3.5 Natural History of the Indicated Condition in the Population, Including Mortality and Morbidity

An Australian PAH registry reported an annual mortality of 13.6% overall, with 11% in patients with IPAH 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 equation (Humbert et al. 2006). The 3-year survival was 68% for patients with PAH in the UK 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 NYHA Functional Class III or IV (Humbert et al. 2006).

SI.3.6 Important Co-morbidities

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 patients with PAH 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 chronic obstructive pulmonary disease) was listed as a comorbid condition among patients with IPAH (n = 1114) in the REVEAL registry, resulting in a prevalence rate of 23.2%. Among all patients with PAH in the registry (n = 2438), obstructive airway disease was diagnosed in 21.9% of these patients at enrolment (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 participants with PAH in the REVEAL registry, the prevalence rate of pulmonary embolism was 6.9% (Badesch et al. 2010). Among patients with IPAH (n = 1114) in the registry, the prevalence rate of pulmonary embolism was 8.6% (Badesch et al. 2010).

SI.4 Paediatric Pulmonary Arterial Hypertension

SI.4.1 Incidence

The overall incidence of pPAH has not been well characterised. However, the overall incidence rate for paediatric pulmonary PAH including both transient and persistent PAH in the Netherlands was estimated at 63.7 cases per million per year (van Loon et al. 2011). Incidence rates of pPAH after excluding transient PAH vary by country. Among countries in Europe, the annual incidence rate of persistent or progressive pPAH was 3.0 cases per million in the Netherlands (van Loon et al. 2011) and 4.03 per million in Spain (del Cerro Marín et al. 2014). In the US, the annual incidence rates of persistent pPAH between 2010 and 2013 ranged from 4.8 per million in 2013 to 8.1 per million in 2011 (Li et al. 2017). Majority of persistent pPAH have been attributed to IPAH and CHD-associated PAH (CHD-PAH) combined.

The incidence of paediatric IPAH varies by country. Among countries in Europe, the incidence of paediatric IPAH was estimated at 0.48 cases per million children per year in the UK (Moledina et al. 2010), 0.7 cases per million children per year among children aged 0 to 17 years in the Netherlands (van Loon et al. 2011), and 0.49 cases per million children per year in Spain (del Cerro Marín et al. 2014). In the US, the annual incidence of paediatric IPAH between 2010 and 2013 varied annually from 0.5 per million children-years in 2010 and 2013 to 0.8 and 0.9 per million children-years in 2011 and 2012, respectively (Li et al. 2017).

Among countries in Europe the annual incidence rate of CHD-PAH was 2.2 per million children per year in the Netherlands (van Loon et al. 2011) and 1.87 per million children in Spain (del Cerro Marín et al. 2014).

SI.4.2 Prevalence

The overall prevalence of pPAH is not well characterised in the existing literature. The point prevalence of persistent or progressive pPAH on January 1, 2006 was 20 cases per million in the Dutch paediatric population (van Loon et al. 2011) while the annual prevalence of persistent or progressive pPAH was 20.2 per million in Spain (del Cerro Marín et al. 2014). In the US, between 2010 and 2013 the annual prevalence of persistent pPAH ranged from 25.7 per million in 2010 to 32.6 per million in 2011 (Li et al. 2017). Similar to the incidence, majority of persistent pPAH has been attributed to IPAH and CHD-PAH combined. In Europe CHD-PAH accounts for a higher proportion than IPAH. For example, in the Netherlands national registry, 72% of progressive PAH was associated with CHD and 23% with IPAH (van Loon et al.2011). However, in the US, data from the REVEAL registry showed approximately half of the patients had IPAH and 35% had PAH associated with CHD (Li et al. 2017).

The prevalence of paediatric IPAH varies by country. The prevalence of paediatric IPAH was estimated at 2.07 cases per million children in the UK (Moledina et al. 2010), 2.2 cases per million children in the Netherlands (van Loon et al. 2011), 2.9 cases per million children in Spain (del Cerro Marín et al. 2014), and 3.6 per million children in Poland (Kwiatkowska et al. 2020). In the US, estimates of the annual prevalence of paediatric IPAH between 2010 and 2013 ranged from 4.4 to 6.0 per million children (Li et al. 2017). The prevalence of CHD-PAH was estimated at 15.6

per million in the Netherlands (van Loon et al. 2011), 7.8 per million in Poland (Kwiatkowska et al. 2020), and 10.1 per million in Spain (del Cerro Marín et al. 2014).

SI.4.3 Demographics of the Population in the Proposed Indication and Risk Factors for the Disease

Demographic profile

In the UK and Netherlands, the mean age of diagnosis of paediatric IPAH was 4.3 years (Moledina et al. 2010; van Loon et al. 2011) while in Poland the mean age at diagnosis was 5.9 years (Kwiatkowska et al. 2020). Overall, for paediatric patients with PAH, the median age at diagnosis was about 7 years (Barst et al. 2012 a).

There is no clear evidence of an association between paediatric IPAH and gender. While Moledina et al. (2010) found a higher female-to-male ratio (1.7:1) for paediatric IPAH among children in the UK, van Loon et al. (2011) found a slightly higher male to female ratio (1.1:1) for paediatric IPAH among children in the Netherlands.

In terms of race, among children with IPAH in the UK, majority (83.9%) were White, 12.5% were Asian, 3.6% were mixed race, and 0 were from Black and other ethnic groups (Moledina et al. 2010).

Risk factors

Pulmonary arterial hypertension (PAH) aetiologies in children are with a predominance of IPAH or associated with CHD (Abman et al. 2015). Pulmonary arterial hypertension is a rare, chronic, and progressive disease characterised by elevated pulmonary artery pressure and pulmonary vascular resistance leading to right heart failure and death (Rich 1998; Barst et al. 2011). Paediatric PAH often is associated with co-morbidities and developmental or genetic disorders.

SI.4.4 Main Existing Treatment Options

Therapies that are currently approved for the treatment of PAH in adults, in various geographies around the world include prostacyclin and its analogues (epoprostenol, treprostinil, iloprost, and beraprost), the ERAs (bosentan, macitentan, and ambrisentan), PDE5 inhibitors (sildenafil and tadalafil), soluble guanylate cyclase stimulator (riociguat), and selective prostacyclin receptor agonist (selexipag). Due to limited clinical data in children, treatment decisions are extrapolated from adult studies. However, various therapies have been used to treat PAH in children (Rosenzweig et al. 2019). Most of these are based upon prior studies in adults and evidence-based trials in adults (Galiè et al. 2009; Bai et al. 2011; Galiè et al. 2015). In the Tracking Outcomes and Practice in Paediatric Pulmonary Hypertension (TOPP) Registry, the most common initial therapy in PAH was a PDE5 inhibitor (Humpl et al. 2017). Similar studies have suggested that this class of therapy is commonly used initially or in combination with an ERA (Cohen et al. 2019). There is a growing body of evidence supporting the use of therapies approved in adults that has led to widespread off-label use (Beghetti 2009; Abman et al. 2015).

The use of PDE5 inhibitors, including sildenafil and tadalafil, has become very common in the treatment of paediatric patients with PAH. Barst et al. (2012 a) reported that in the REVEAL

registry, 57% of paediatric patients with PAH were taking a PDE5 inhibitor at the time they entered the registry. Vorhies and Ivy (2014) noted that PDE5 inhibitors have been used in pPAH treatment for over a decade and that tadalafil use has increased recently.

Supporting the observation that PDE5 inhibitors have become standard of care in pPAH is the World Symposium on Pulmonary Hypertension 2013 Consensus Paediatric idiopathic PAH (IPAH)/familial PAH Treatment Algorithm (Ivy et al. 2013), which includes PDE5 inhibitors as treatment options for both low- and high-risk patients with IPAH or familial PAH.

In the EU, bosentan, sildenafil, and ambrisentan are approved for paediatric patients with PAH. In the US, bosentan is the only approved drug for the treatment of paediatric patients with PAH.

SI.4.5 Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity

Progression of the disease may lead to right cardiac failure, cardiac failure, oedema, haemoptysis, cerebrovascular accidents from paradoxical emboli, cardiac arrhythmias, Eisenmenger syndrome, and thrombocytopenia (Rich 1998; Barst et al. 2011; Barst et al. 2012 a; Remková et al. 2016).

Without appropriate treatments, median survival rate after diagnosis of IPAH in children was about 10 months in the National Institutes of Health Registry of patients with IPAH (D'Alonzo et al. 1991; Rosenzweig and Barst 2009). The prognosis of children with PAH has improved over time due to new therapies and off-label use of adult PAH specific therapies being administered to paediatric patients (Vorhies and Ivy 2014). For example, the estimated survival rates at 1, 3, and 5 years from diagnosis in Registry to Evaluate Early And Long-Term PAH Disease Management (REVEAL registry) were estimated as 96 ± 4%, 84 ± 5%, and 74 ± 6%, respectively (Barst et al. 2012 a). It has been suggested that the clinical course of PAH is less predictable in children than in adults. If untreated, the condition may progress more rapidly in children leading to reduced survival in children compared with adults over time.

SI.4.6 Important Co-morbidities

Paediatric PAH, particularly among older children, shares common features or co-morbidities with adult PAH (Rosenzweig et al. 2019). Cardiac failure, cerebrovascular accidents from paradoxical emboli, arrhythmias, Eisenmenger syndrome, and respiratory infections including pneumonia are known important co-morbidities among adults as noted in Section SI.3 (Rich 1998; Barst et al. 2011; Barst et al. 2012 a; Remková et al. 2016). Important co-morbidities specific to childhood PAH include

Congenital heart disease

Congenital heart diseases have been frequently associated with pPAH. For example, in a large US claims database-based study, 75.1% of children with PAH were found to have at least 1 congenital heart defect (Li et al. 2017).

Chromosomal abnormalities

Paediatric PAH is frequently associated with chromosome, genetic, and syndromic anomalies (11%-52%). For example, in a study based on the Spanish Registry for Pediatric Pulmonary Hypertension (REHIPED), 38% of children with PAH were found to have chromosomopathy or multiple congenital abnormality syndromes (del Cerro Marín et al. 2014).

The most frequently reported chromosomal abnormality among children with PAH is Down's syndrome. In a PAH registry-based study in Poland, 30% of children with PAH had Down's syndrome (Kwiatkowska et al. 2020) while in a REHIPED-based study, 17% had Down's syndrome (del Cerro Marín et al. 2014). In the US, 12.5% of children with PAH were found to have Down's syndrome (Li et al. 2017).

Hypothyroidism

Paediatric PAH is also frequently associated with hypothyroidism. For example, in a PAH registry-based study in Poland, approximately 24% of children with PAH had hypothyroidism (Kwiatkowska et al. 2020) while in Spain, 14.3% of children with PAH were found to have concomitant hypothyroidism (del Cerro Marín et al. 2014).

Growth and mental retardation

Childhood PAH has also been associated with growth and mental retardation as well as neurological impairments. In a PAH registry-based study in Poland, approximately 40% of children with PAH were found to have mental retardation (Kwiatkowska et al. 2020), while in a PAH registry-based study in Spain, 28% of children with PAH had neurological impairments (del Cerro Marín et al. 2014).

Module SII - Nonclinical Part of the Safety Specification

SII.1 Toxicity

Target organ toxicity

Key safety findings

- 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.

Relevance to human usage

To address these non-clinical testicular findings in dogs, the 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 studies) 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 observed 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 mg or 20 mg compared with placebo. These studies indicate that tadalafil does not affect male fertility in humans.

SII.2 Safety Pharmacology

Cardiovascular safety

Key safety findings

- Decrease in BP 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 mg/kg and 200 mg/kg, a slight decrease in mean arterial BP was observed. In anaesthetised dogs, intravenous administration of tadalafil at a dose of 3 mg/kg produced a reduction in BP 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 mg/kg and 5 mg/kg lowered BP 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 observed in normal rats.

Relevance to human usage

Hypotension/increased hypotensive effect has been observed in tadalafil clinical trials. It is a class effect, and an important identified risk for tadalafil.

SII.3 Other Toxicity-Related Information or Data

Key safety findings

No relevant non-clinical data.

Relevance to human usage

No key safety findings.

Module SIII - Clinical Trial Exposure

The combined clinical development programmes across all approved indications included approximately 26,500 patients. The clinical trial exposures are presented in Table SIII.1 for all studies (for approved indications) combined (ED on-demand, ED once-a-day, BPH, PAH, and other disease states including essential hypertension and female sexual arousal disorder), followed by exposures for each individual indication. Clinical trial exposure for the non-approved indication of pPAH is shown in Table SIII.11. This provides a larger population for determination of frequency of identified and potential risks. Some tables presented in this module also include studies of other non-approved indications.

Table SIII.1. Duration of Exposure

Cumulative for All Indications (All Studies, Including Other Indications)		
Duration of Exposure (At Least)	**Patients**	**Person-Time (Years)**
≥1 day	26,490	12,548.9
≥30 days (1 month)	24,879	12,464.7
≥90 days (3 months)	17,429	11,032.1
≥180 days (6 months)	5323	7038.8
≥270 days (9 months)	3654	6078.1
≥365 days (1 year)	2984	5509.9
≥547 days (1.5 years)	1875	4225.3
≥730 days (2 years)	1034	2679.4

Studies included for the analysis: B022, 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, LVJE, LVJF, LVJK, S002, S024.

Note: Count a subject only once if the subject rolled over from 1 study to another.

Tadalafil exposure for the unique subject across studies will be added together.

Source: /lillyce/prd/ly450190/regulatory_Jun2021/output/smexph01_a1.rtf

Table SIII.2. Duration of Exposure

Cumulative for All Indications (All Placebo-Controlled Studies, Including Other Indications)				
Duration of Exposure (At Least)	**Placebo**		**Tadalafil**	
	Patients	**Person-Time (Years)**	**Patients**	**Person-Time (Years)**
≥1 day	6350	1692.9	11,756	2973.4
≥30 days (1 month)	5775	1670.4	10,588	2922.7
≥90 days (3 months)	2573	1019.5	5102	1790.2
≥180 days (6 months)	730	426.3	926	552.7
≥270 days (9 months)	161	124.9	207	161.2
≥365 days (1 year)	–	–	3	3.7
≥547 days (1.5 years)	–	–	1	1.6

Abbreviation: – = not applicable.

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, LVJE, LVJF, LVJK.

Source: /lillyce/prd/ly450190/regulatory_Jun2021/output/smexph01_c1.rtf

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

Duration of Exposure (At Least)	Patients	Person-Time (Years)
Erectile Dysfunction (On-Demand and Once-a-Day)		
≥1 day	22,022	9800.8
≥30 days (1 month)	20,703	9726.8
≥90 days (3 months)	15,234	8708.5
≥180 days (6 months)	3738	4913.8
≥270 days (9 months)	2566	4212.2
≥365 days (1 year)	2172	3868.5
≥547 days (1.5 years)	1594	3186.7
≥730 days (2 years)	762	1656.9
Erectile Dysfunction (On-Demand)		
≥1 day	17,538	7082.7
≥30 days (1 month)	16,871	7041.7
≥90 days (3 months)	12,353	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	4507	2637.3
≥30 days (1 month)	3674	2594.0
≥90 days (3 months)	2737	2410.1
≥180 days (6 months)	1186	1870.9
≥270 days (9 months)	1046	1794.8
≥365 days (1 year)	950	1706.4
≥547 days (1.5 years)	675	1382.2
≥730 days (2 years)	333	718.3

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

Studies included for the analysis: B022, 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, LVJE, S002, S024.

Note: Count a subject only once if the subject rolled over from 1 study to another.

Tadalafil exposure for the unique subject across studies will be added together.

Note: LVHR and LVJE are ED/BPH studies and are included in summaries for both populations.

Source: /lillyce/prd/ly450190/regulatory_Jun2021/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)

Duration of Exposure (At Least)	Placebo		Tadalafil	
	Patients	Person-Time (Years)	Patients	Person-Time (Years)
Erectile Dysfunction (On-Demand and Once-a-Day)				
≥1 day	3536	886.9	7608	1859.5
≥30 days (1 month)	3118	869.8	6690	1817.5
≥90 days (3 months)	1605	578.8	3683	1216.0
≥180 days (6 months)	212	135.7	387	251.8
≥270 days (9 months)	63	48.8	110	86.1
≥365 days (1 year)	–	–	3	3.7
≥547 days (1.5 years)	–	–	1	1.6
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
≥270 days (9 months)	62	48.1	56	42.9
Erectile Dysfunction (Once-a-Day)				
≥1 day	1561	462.0	2892	741.0
≥30 days (1 month)	1250	451.3	2245	715.0
≥90 days (3 months)	781	349.4	1251	492.6
≥180 days (6 months)	184	121.2	207	132.7
≥270 days (9 months)	63	48.8	54	43.2
≥365 days (1 year)	–	–	3	3.7
≥547 days (1.5 years)	–	–	1	1.6

Abbreviations: – = not applicable; BPH = benign prostatic hyperplasia; 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, LVJE.

Note: LVHR and LVJE are ED/BPH studies and are included in summaries for both populations.

Source: /lillyce/prd/ly450190/regulatory_Jun2021/output/smexph01_c2.rtf through smexph01_c4.rtf

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

Duration of Exposure (At Least)	Patients	Person-Time (Years)
≥1 day	4088	1634.3
≥30 days (1 month)	3877	1625.3
≥90 days (3 months)	1812	1180.8
≥180 days (6 months)	996	883.0
≥270 days (9 months)	678	717.5
≥365 days (1 year)	516	583.0

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

Studies included for this analysis: LVGC, LVHB, LVHG, LVHJ, LVHK, LVHR, LVHS, LVHT, LVIA, LVID, LVIR, LVIW, LVIY, LVJE, LVJF, LVJK
Note: Count a subject only once if the subject rolled over from 1 study to another.
Tadalafil exposure for the unique subject across studies will be added together.
Note: LVHR and LVJE are ED/BPH studies and are included in summaries for both populations.
Source: /lillyce/prd/ly450190/regulatory_Jun2021/output/smexph01_a5.rtf

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

Duration of Exposure (At Least)	Placebo		Tadalafil	
	Patients	Person-Time (Years)	Patients	Person-Time (Years)
≥1 day	2707	750.6	3841	1004.8
≥30 days (1 month)	2617	746.3	3669	997.0
≥90 days (3 months)	878	370.4	1113	437.1
≥180 days (6 months)	262	134.0	279	142.2
≥270 days (9 months)	1	0.8	1	0.8

Abbreviations: BPH = benign prostatic hyperplasia; ED = erectile dysfunction.
Studies included for this analysis: LVGC, LVHB, LVHG, LVHJ, LVHK, LVHR, LVHS, LVHT, LVIA, LVID, LVIR, LVIW, LVJE, LVJF, LVJK.
Note: LVHR and LVJE are ED/BPH studies and are included in summaries for both populations.
Source: /lillyce/prd/ly450190/regulatory_Jun2021/output/smexph01_c5.rtf

Table SIII.7. Duration of Exposure (All Pulmonary Arterial Hypertension Studies)

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

Studies included for the analysis: LVGX, LVGXE, LVGY.
Note: Count a subject only once if the subject rolled over from 1 study to another.
Tadalafil exposure for the unique subject across studies will be added together.
Source: /lillyce/prd/ly450190/regulatory_Jun2021/output/smexph01_a6.rtf

Table SIII.8. Duration of Exposure (Pulmonary Arterial Hypertension – Placebo-Controlled)

Duration of Exposure (At Least)	Placebo		Tadalafil	
	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

Study included for the analysis: LVGY.

Source: /lillyce/prd/ly450190/regulatory_Jun2021/output/smexph01_c6.rtf

Table SIII.9. Exposure by Dose and Indication (All Studies, Approved Indications)

Dose of Exposure	All Studies		Placebo-Controlled Studies	
	Persons	Person-Time (Years)	Persons	Person-Time (Years)
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	15,820	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	934	183.8	722	132.5
5 mg	3774	2353.0	1923	570.9
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	3251	1348.3	2616	717.8
10 mg	216	47.1	216	47.1
20 mg	433	81.7	433	81.7
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: – = not applicable; BPH = benign prostatic hyperplasia; ED = erectile dysfunction.

Studies included for the analysis: LVAC, LVBD, LVBE, LVBF, LVBK, LVBL, LVBN, LVBO, LVCE, LVCF, LVCG, LVCI, LVCK, LVCO, LVCQ, LVCR, LVCU, LVCY, LVDG, LVDI, LVDJ, LVDR, LVDU, LVDW, LVDX, LVDY, LVDZ, LVEB, LVEF, LVEG, LVEH, LVEI, LVEK, LVEL, LVEM, LVEQ, LVFD, LVFH, LVFL, LVFN, LVFR, LVFY, LVGD, LVIJ, LVIK, LVIZ, S002, S024, B022, GPEC, LVBG, LVBI, LVBJ, LVCV, LVFP, LVFZ, LVGH, LVHR, LVHX, LVHZ, LVIJ, LVIK, LVIP, LVJE, S024, LVGC, LVHB, LVHG, LVHJ, LVHK, LVHR, LVHS, LVHT, LVIA, LVID, LVIR, LVIW, LVIY, LVJE, LVJF, LVJK, LVGX, LVGXE, LVGY.

Note: Count a subject only once if the subject rolled over from 1 study to another.

Tadalafil exposure for the unique subject across studies will be added together.

Note: LVHR and LVJE are ED/BPH studies and are included in summaries for both populations.

Sources: /lillyce/prd/ly450190/regulatory_Jun2021/output/smexph02_a3.rtf through smexph02_a6.rtf; /lillyce/prd/ly450190/regulatory_Jun2021/output/smexph02_c3.rtf through smexph02_c6.rtf

Table SIII.10. 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)				
<18 years	1	N/A	0.1	N/A
≥18 to <65 years	14,468	N/A	5865.9	N/A
≥65 years	3049	N/A	1209.4	N/A
Missing	20	N/A	7.2	N/A
Total	17,538	N/A	7082.7	N/A
Erectile Dysfunction (Once-a-Day)				
≥18 to <65 years	3582	N/A	2241.0	N/A
≥65 years	925	N/A	396.3	N/A
Total	4507	N/A	2637.3	N/A
Benign Prostatic Hyperplasia				
≥18 to <65 years	2386	N/A	919.9	N/A
≥65 years	1702	N/A	714.4	N/A
Total	4088	N/A	1634.3	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: – = no data available; BPH = benign prostatic hyperplasia; ED = erectile dysfunction N/A = not applicable.

Studies included for the analysis: LVAC, LVBD, LVBE, LVBF, LVBK, LVBL, LVBN, LVBO, LVCE, LVCF, LVCG, LVCI, LVCK, LVCO, LVCQ, LVCR, LVCU, LVCY, LVDG, LVDI, LVDJ, LVDR, LVDU, LVDW, LVDX, LVDY, LVDZ, LVEB, LVEF, LVEG, LVEH, LVEI, LVEK, LVEL, LVEM, LVEQ, LVFD, LVFH, LVFL, LVFN, LVFR, LVFY, LVGD, LVIJ, LVIK, LVIZ, S002, S024, B022, GPEC, LVBG, LVBI, LVBJ, LVCV, LVFP, LVFZ, LVGH, LVHR, LVHX, LVHZ, LVIJ, LVIK, LVIP, LVJE, S024, LVGC, LVHB, LVHG, LVHJ, LVHK, LVHR, LVHS, LVHT, LVIA, LVID, LVIR, LVIW, LVIY, LVJE, LVJF, LVJK, LVGX, LVGXE, LVGY.

Note: Count a subject only once if the subject rolled over from 1 study to another.

Tadalafil exposure for the unique subject across studies will be added together.

Note: LVHR and LVJE are ED/BPH studies and are included in summaries for both populations.

Source: /lillyce/prd/ly450190/regulatory_Jun2021/output/smexph03_a3.rtf through smexph03_a6.rtf

Table SIII.11. Duration of Exposure (All Studies in Paediatric Patients)

Duration of Exposure (At Least)	Patients	Person-Time (Years)
≥1 day	377	499.4
≥30 days (1 month)	372	499.2
≥90 days (3 months)	355	495.9
≥180 days (6 months)	329	486.5
≥270 days (9 months)	300	468.8
≥365 days (1 year)	270	442.3
≥547 days (1.5 years)	161	309.4

Duration of Exposure (At Least)	Patients	Person-Time (Years)
≥730 days (2 years)	57	126.1

Studies included for the analysis: LVHV, LVIG, LVJJ.
Note: Count a subject only once if he/she rolled over from 1 study to another.
Tadalafil exposure for the unique subject across studies will be added together.
Source: /lillyce/prd/ly450190/regulatory_Jun2021/output/peds/smexph01_a1.rtf

Table SIII.12. Exposure by Dose Group (All Studies in Paediatric Patients)

Dose of Exposure*	All Studies		Placebo-Controlled Studies	
	Patients	Person-Time (Years)	Patients	Person-Time (Years)
0.3 mg	155	191.87	102	91.60
0.6 mg	170	204.12	112	100.49
2 mg	1	0.09	-	-
4 mg	5	0.47	-	-
5 mg	10	0.68	-	-
7 mg	1	1.98	-	-
7.5 mg	2	4.01	-	-
8 mg	1	2.15	-	-
10 mg	11	3.32	-	-
12 mg	1	0.00	-	-
14 mg	1	0.04	-	-
15 mg	6	7.38	-	-
16 mg	1	0.00	-	-
18 mg	1	0.00	-	-
20 mg	24	23.63	4	1.88
30 mg	1	0.48	-	-
40 mg	36	59.23	13	5.74

Abbreviation: - = no data available.
*Subjects maybe counted more than once if the subject's dose changed during the study.
Studies included for the analysis: LVHV, LVIG, LVJJ.
Note: Count a subject only once if he/she rolled over from 1 study to another.
Tadalafil exposure for the unique subject across studies will be added together.
Source: /lillyce/prd/ly450190/regulatory_Jun2021/output/peds/smexph02_a1 and smexph02_c1.rtf

Table SIII.13. Exposure by Age Group and Gender (All Studies in Paediatric Patients)

Age group	Male		Female		Total	
	Patients	Person-Time (Years)	Patients	Person-Time (Years)	Patients	Person-Time (Years)
Age ≥2 to <12 years	288	362.7	11	20.1	299	382.8
Age ≥12 to <18 years	58	76.6	20	40.2	78	116.8
Total	346	439.3	31	60.3	377	499.6

Studies included for the analysis: LVHV, LVIG, LVJJ.

Note: Count a subject only once if he/she rolled over from 1 study to another.

Tadalafil exposure for the unique subject across studies will be added together.

Source: /lillyce/qa/ly450190/regulatory_Jun2021/output/peds/smexph03_a1.rtf

Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

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. Given that tadalafil has been on the market since October 2002, the exclusion criteria used in the original clinical trial development programme are subsequently no longer considered applicable to determine potential safety concerns.

In the light of the extensive post-authorisation experience, with >84 million estimated post-marketing 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 that include patients with hepatic or renal impairment is regularly assessed and has been presented in the PSURs since the first tadalafil marketing authorisation. No new risks or specific issues relating to these populations have been observed.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

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

Ability to Detect Adverse Reactions	Limitations of Trial Programme	Discussion of Implications for Target Population
That are Rare	A total of 22,022 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 0.013% or less.
Due to Prolonged Exposure	In long-term ED studies, a total of 2172 patients were exposed for ≥365 days.	At this time, there are no known effects due to prolonged exposure from clinical trial data. However, the post-marketing experience with >84 million patients exposed to Cialis 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 post-marketing experience with >84 million patients exposed to Cialis does not suggest that there is specific organ toxicity due to cumulative effects.
That 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 post-marketing experience with >84 million patients exposed to Cialis 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	Limitations of Trial Programme	Discussion of Implications for Target Population
That are Rare	A total of 4088 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 0.07% 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 post-marketing experience with >84 million patients exposed to Cialis 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 post-marketing experience with >84 million patients exposed to Cialis 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.
That 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 post-marketing experience with >84 million patients exposed to Cialis 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	Limitations of Trial Programme	Discussion of Implications for Target Population
That are Rare	A total of 393 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 0.76% or less, which would allow detection of uncommon, but not rare ADRs that are specific to the PAH population.
Due to Prolonged Exposure	A total of 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 >2 years and no effects of prolonged exposure were identified. Additionally, the post-marketing experience with >84 million patients exposed to Cialis/Adcirca 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 >2 years and no evidence of cumulative effects was identified. Additionally, the post-marketing experience with >84 million patients exposed to Cialis/Adcirca does not suggest effects of specific organ toxicity due to cumulative effects.
That 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 post-marketing experience with >84 million patients exposed to Cialis/Adcirca does not suggest adverse effects due to long latency.

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

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

Table SIV.4. Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of Special Population	Exposure
Pregnant women or Breastfeeding women	*ED and BPH* ED 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 (e.g., barrier with spermicidal or hormonal contraception) until study completion. A cumulative review of pregnancy and lactation cases from tadalafil clinical trials, post-marketing studies, and spontaneous reports through 15 January 2016 did not reveal any new important safety concerns.
Patients with relevant co-morbidities:	
Patients with hepatic impairment	*ED and BPH* In clinical practice, patients with ED and BPH with severe hepatic impairment would not commonly be treated with tadalafil. Tadalafil data in patients with mild-to-moderate hepatic impairment are limited, but exposure in these patients is comparable 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). In patients with ED with mild-to-moderate hepatic impairment who are administered tadalafil on-demand, the recommended dose is 10 mg. 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 post-marketing experience has not revealed any new safety concerns for tadalafil use in patients with ED or BPH with hepatic impairment. *PAH* Patients with PAH may have comorbid hepatic impairment as part of their underlying disease. In patients with mild-to-moderate hepatic cirrhosis (Child-Pugh Class A and Class B), a starting dose of 20 mg once per day is recommended. 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 post-marketing experience has not revealed any new safety concerns for tadalafil use in patients with PAH having hepatic impairment.

Type of Special Population	Exposure
Patients with renal impairment	*All indications* As diabetes commonly coexists with ED and BPH, and renal dysfunction may coexist with BPH, the presence of some level of renal impairment in these patient populations is not unexpected. Patients with PAH may have some renal impairment as a sequela 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 mg to 20 mg), tadalafil exposure (area under the curve [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 patients on haemodialysis, maximum serum concentration (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. A starting dose of 20 mg once per day is recommended in patients with mild-to-moderate renal impairment. The dose may be increased to 40 mg once per day, based on individual efficacy and tolerability. The post-marketing experience has not revealed any new safety concerns for the use of tadalafil in patients with renal impairment.
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 post-marketing experience has not revealed any new safety concerns for tadalafil use in patients with ED and BPH having comorbid conditions. *PAH* The PAH clinical development programme included patients with comorbid connective tissue disease. The post-marketing experience has not revealed any new safety concerns for tadalafil use in patients with PAH having comorbid conditions.
Patients with a disease severity different from inclusion criteria in clinical trials	*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 post-marketing 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 Class 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 from these patients. Postmarketing data do not suggest significant use of Adcirca in patients with WHO Functional Class I and Class IV; however, information on WHO

Type of Special Population	Exposure
	functional class is generally not provided in post-marketing reports.
Population with relevant different 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 post-marketing experience with >84 million patients exposed to Cialis 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 was a limited number of patients enrolled in PAH clinical trials who were non-Caucasian, there are no known differences in efficacy or safety of tadalafil in these populations.
Subpopulations carrying relevant genetic polymorphisms	Not applicable
Children	*ED and BPH* ED and BPH disease states are not relevant in children and teenagers. *PAH* A total of 54 paediatric patients between 2.5 and 18 years of age with PAH were enrolled in tadalafil in clinical trials. A total of 391 paediatric patients with ages from newborn to 18 years were treated with tadalafil in an observational Japanese post-marketing study. In general, the adverse reaction profile of tadalafil in children and adolescents was similar to that observed in adults.

Type of Special Population	Exposure
Elderly	*ED and BPH* 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 reviews of post-marketing and clinical trial data, the Marketing Authorisation Holder 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 patients with ED and BPH. *PAH* Approximately 28% of the patients enrolled in the PAH trial LVGY were elderly (≥65 years). The clinical trial data do not suggest that there are clinically important differences in the safety profile of tadalafil in elderly patients with PAH compared with those who are non-elderly. In addition, the post-marketing experience has not revealed any safety concerns for the use of tadalafil in elderly patients with PAH.

Abbreviations: AUC = area under the curve; BPH = benign prostate hyperplasia; ED = erectile dysfunction; LVGY = H6D-MC-LVGY; PAH = pulmonary arterial hypertension; WHO = World Health Organization.

Module SV – Post-Authorisation Experience

SV.1 Post-Authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

The methodology uses internal bulk sales data, samples distributed, Intercontinental Medical Statistics (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, and 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 Eli Lilly and Company (Lilly) currently does not have sufficient data available to calculate an average length of therapy per patient or distribution of patients by age and gender for the Adcirca brand of tadalafil. As such, the Adcirca patient exposure estimate is provided in terms of PY and no age and gender distribution are included in this report.

SV.1.2 Exposure

Table SV.1. Post-marketing Exposure by Indication Age Group and Gender

	Gender			
Age Group	**Male**	**Female**	**Not Reported**	**Totals[a]**
Cialis PRN				
0 to 17 years	31,000	7000	0	39,000
18 to 65 years	44,087,000	240,000	23,000	41,351,000
>65 years	16,021,000	63,000	7000	16,092,000
Not reported	1,064,000	0	31,000	1,096,000
Total[a]	**61,205,000**	**310,000**	**63,000**	**61,580,000**
Cialis QD				
0 to 17 years	11,000	2000	0	14,000
18 to 65 years	16,533,000	90,000	8000	16,632,000
>65 years	6,008,000	23,000	2000	6,035,000
Not reported	399,000	0	11,000	411,000
Total[a]	**22,953,000**	**1,116,000**	**23,000**	**23,094,000**
Adcirca				
0 to 17 years	2000	4500	–	7000
18 to 65 years	47,000	91,000	–	138,000
>65 years	21,000	40,000	–	62,000
Total[a]	**72,000**	**136,000**	–	**208,000**

Abbreviations: – = no data available; PRN = as needed; QD = once daily.

A Totals may not sum due to independent rounding.

Table SV.2. Exposure Table by Indication

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

Abbreviation: N/A = not available.

Table SV.3. Exposure Table by Route of Administration

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

Abbreviation: N/A = not available.

Table SV.4. Exposure Table by Dose

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

Abbreviation: N/A = not available.

Table SV.5. Post-marketing Exposure by Country/Region

Country/Region	Cumulative Patients	Cumulative Patient-Years
Cialis PRN		
Europe	18,041,000	1,704,000
Japan	1,177,000	109,000
United States	17,456,000	1,792,000
Other countries	24,904,000	2,318,000
Worldwide[a]	**61,580,000**	**5,924,000**
Cialis/Zalutia® QD		
Europe	4,612,000	1,326,000
Japan[b]	2,915,000	838,000
United States	7,713,000	2,217,000
Other countries	7,852,000	2,257,000
Worldwide[a]	**23,094,000**	**6,638,000**
Adcirca		
Europe	40,000	37,000
Japan	38,000	35,000
United States	118,000	108,000
Other countries	10,000	9000
Worldwide[a]	**208,000**	**190,000**

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

A Worldwide total may not sum due to independent rounding.

B Trade name in Japan is Zalutia.

Module SVI - Additional EU Requirements for the Safety Specification

SVI.1 – Potential for Misuse for Illegal Purposes

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

Module SVII – Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

Not applicable, as this is not the initial RMP.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

No new safety concerns were identified since the last EU RMP (v 8.2).

The following safety concerns are removed from the tadalafil EU RMP based on current GVP Module V (Rev 2) guidance:

Important identified risks

- Hypotension/increased hypotensive effect and
- Priapism.

Important potential risks

- Nonarteritic anterior ischaemic optic neuropathy (NAION)
- Sudden hearing loss

Missing information

- Tadalafil Once-a-Day ED and BPH Indications: characterisation of adverse events in elderly patients (≥65 years of age)

The general considerations that support all the proposals for removal are discussed in the following sections. Additional considerations for each individual safety concern are presented thereafter.

General considerations supporting the proposed removals

- Extent of experience: tadalafil was first authorised in October 2002 and since then it has been authorised in 140 countries, for multiple indications, and has a cumulative exposure in excess of 84 million patients globally. In these circumstances, the safety profile of the active chemical substance has been subject to regular scrutiny in multiple global regulatory submissions including PSUR/PBRERs, RMP update submissions, and responses to regulatory requests. As such, the risk profile is considered to be well characterised.
- The benefit–risk profile of tadalafil continues to be assessed as positive by the European Medicines Agency and other global regulatory authorities, with the established risks appropriately managed for many years with routine PV and risk management activities.
- The list of safety concerns was determined at a time when the concepts of adverse reactions and risks as undesirable clinical outcomes of the ADRs were not fully clarified for RMP documents to the extent that they are today in GVP Module V (Rev 2). The

previously existing list of safety concerns is therefore not consistent with current standards and definitions.

- Similarly, lack of consistency with current GVP Module V (Rev 2) standards also applies to the concept of an important risk, that is, an undesirable outcome that is likely to have an adverse impact on benefit–risk usually warranting
    - further evaluation as part of the PV plan
    - risk minimisation activities advising on specific clinical actions to be taken to minimise the risk, and/or
    - additional risk minimisation activities.

This concept was not fully clarified in the original guidelines under which the current list of safety concerns was compiled.

Important Identified Risk Removed: Hypotension/increased hypotensive effect

Justification for removal

The risk of hypotension/increased hypotensive effect is considered a pharmacological class effect of PDE5 inhibitors known to have mild systemic vasodilatory properties that may result in transient minor decreases in BP. The hypotension/increased hypotensive effect was included in the EU RMP largely based on the results of DDI clinical pharmacology and Phase 1 studies. The BP decrease observed in healthy volunteers receiving tadalafil 20 mg was minimal (reduction of 0.2 to 1.6 mm Hg systolic and 0.8 to 4.6 mm Hg diastolic BP) (Reffelmann et al. 2008).

On 17 November 2004, based on a 2-year cumulative review of the safety database presented in the PSUR 4, hypotension/increased hypotensive effect was added to the CDS and summary of product characteristics (SmPC) as an ADR. In placebo-controlled clinical trials, the frequency of hypotension/increased hypotensive effect was 1.28% (135/10,568) in ED/BPH and 12.35% (40/324) in PAH, but the vast majority was not serious. There were no fatal outcomes due to hypotension/increased hypotensive effect in clinical trials.

When evaluating only serious cases of hypotension/increased hypotensive effects across a total of 72 placebo-controlled and open-label ED and BPH clinical trials involving 22,893 subjects who were exposed to tadalafil plus at least 1 concomitant non-alpha blocker antihypertensive medicine, only 2 serious hypotension-related events were observed (0.00007%). In a post-marketing setting, the events of hypotension/increased hypotensive effect in the tadalafil spontaneous database are very rarely reported based on the estimated patient exposure of 84,882,000.

The specific DDI between tadalafil and nitrates is the one of greater concern. The 5 clinical studies conducted to evaluate this DDI (LVAB, LVBY, LVCM, LVDN, and LVCP) confirmed that under both single- and multiple-dose conditions, tadalafil can augment the hypotensive effects of nitrates. The effectiveness of the risk minimisation measures for this specific DDI was evaluated in 2 observational studies that concluded that the labelling was effective in minimising codispensing. The nitrate codispensing proportion was 1.2% in the Study i3 and 1.02% to 3.31% in the Study IMS, lower than the rates reported for the other PDE5 inhibitors.

The current risk minimisation measure for hypotension/increased hypotensive effect relies on labelling as follows, and no further risk minimisation measures other than routine are conducted or planned at this time:

- *Specific label text in the SmPC under Section 4.3 (Contraindications) indicates that Tadalafil is contraindicated in patients using any form of organic nitrate, or who have hypotension (<90/50mmHg) or uncontrolled hypertension. Package leaflet states that Tadalafil 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, antihypertensives, 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.*

As such, the risk is well managed by routine risk minimisation measures that have been in place since 2002, including SmPC and package leaflet. Finally, the risk is considered to be well characterised after extensive experience in over 84 million patients across multiple indications and over the 19 years that the product has been on the market.

In the light of these considerations, and consistent with current GVP Module V (Rev 2) principles and definitions, hypotension/increased hypotensive effect no longer qualifies as an important risk for tadalafil for RMP purposes.

Important Identified Risk Removed: Priapism

Justification for removal

Priapism was included in the initial EU RMP as an important identified risk and in the initial CDS as an ADR based on its pharmacological properties and clinical trial data. In 2003, following a review on this topic presented in the PSUR 2, language from CDS and SmPC was revised and since then no modifications were made regarding this topic.

The overall risk for priapism is considered to be low. In tadalafil placebo-controlled clinical trials, the incidence of priapism was 0.01% (1/10,568) for ED and BPH and 1.41% (1/71) for PAH population. In the post-marketing setting, priapism was very rarely reported in the tadalafil spontaneous database based on the estimated patient exposure of 84,882,000 and most cases were non-serious.

The current risk minimisation measure for priapism relies on labelling as follows, and no further risk minimisation measures other than routine are conducted or planned at this time.

- *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 Tadalafil if they have any deformation of the penis.*

As such, the risk is well managed by routine risk minimisation measures that have been in place since 2002, including SmPC and package leaflet. Finally, the risk is considered to be well characterised after extensive experience in over 84 million patients across multiple indications and over the 19 years that the product has been on the market.

In the light of these considerations, and consistent with current GVP Module V (Rev 2) principles and definitions, priapism no longer qualifies as an important risk for tadalafil for RMP purposes.

Important Potential Risk Removed: Non-arteritic Anterior Ischaemic Optic Neuropathy

Justification for removal

The risk of NAION was included in the CDS on 17 May 2006 based on when post-marketing cases of patients receiving PDE5 inhibitors were first recorded. In addition, the Food and Drug Administration requested the sponsors of PDE5 inhibitors to conduct further evaluation of NAION to determine whether the use of a PDE5 inhibitor was an independent risk factor.

The Lilly Study H6D-MC-LVHQ evaluated the safety concern of NAION with PDE5 inhibitors. In the primary analysis, 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% CI: 0.99, 5.20). A secondary analysis using the person-time method showed that 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, 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.

Campbell et al. (2015), a Pfizer study, 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).

Based on the findings of these 2 studies, NAION was considered an ADR. However, as NAION occurs rarely and the impact on public health is low, this finding did not change the benefit–risk balance. Therefore, it is not considered to be “important” in the context of the RMP.

The current risk minimisation measure for NAION relies on labelling as follows, and no further risk minimisation measures other than routine is planned at this time.

- *Specific label text in the SmPC under Section 4.3 (Contraindications) indicates that Tadalafil 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 Tadalafil 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 Tadalafil 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.*

Finally, the risk is well managed by routine risk minimisation measures that have been in place, including SmPC and package leaflet. Based on the extensive experience in over 84 million patients across multiple indications and over the 19 years that the product has been on the market, this risk is considered to be well characterised. It is a rare ADR that does not change the benefit–risk of the product.

In the light of these considerations, and consistent with current GVP Module V (Rev 2) principles and definitions, NAION no longer qualifies as an important potential risk for tadalafil for RMP purposes.

Important Potential Risk Removed: Sudden hearing loss

Justification for removal

The risk of SHL was included as an important potential risk in the EU RMP on 01 July 2015 based on a cumulative review of data since tadalafil launch. Although a causal association was not established at that time, there was a suggestion of association based on some observational studies that showed a small increase in risk for patients using PDE5 inhibitors. Following this review, the CDS and SmPC were also updated and language on SHL was included in the Warnings and Precautions section as follows and no risk minimisation procedures were proposed at that time beyond labelling:

- *Specific label text in the SmPC under Special Warnings and Precautions (Section 4.4) states 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.*
- *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.*

This is the same language that remains in the CDS and labels worldwide currently, and no new risk minimisation measures were needed since that time.

The overall risk for SHL is considered to be low. In the tadalafil placebo-controlled studies, the incidence was 0.08% (8/10,568) for the ED/BPH population and 0.00% (0/324) for the PAH population. In the post-marketing setting, the event of SHL in the tadalafil spontaneous database is very rarely reported based on the estimated patient exposure of 84,882,000.

Based on the extensive experience in over 84 million patients across multiple indications and over the 19 years that the product has been on the market, this risk is considered to be well characterised. It is a very rare ADR and cumulative data no longer support this risk as impactful to the benefit–risk balance of the product. Finally, the risk is well managed by routine risk minimisation measures that have been in place since 2015, including appropriate CDS and subsequent worldwide labels.

In the light of these considerations, and consistent with current GVP Module V (Rev 2) principles and definitions, SHL no longer qualifies as an important potential risk for tadalafil for RMP purposes.

Missing Information Removed: Tadalafil Once-a-Day ED and BPH Indications – characterisation of adverse events in elderly patients (≥65 years of age)

Justification for removal

The EU RMP (Version 8.2) included as missing information "The characterisation of adverse events in elderly patients (≥65 years of age)" for the indications of ED (once-a-day) and BPH. Although information in the elderly population was limited when the indication of BPH was approved (2011), now, 10 years later, there are substantial data to evaluate the safety profile of tadalafil in this specific population.

As of 29 July 2021, cumulatively 5676 elderly patients (≥65 years) were enrolled in studies for ED and BPH indication. The analysis of the clinical trial data in these indications did not suggest that there were clinically important differences in the safety profile of tadalafil in elderly patients. When evaluating the SAEs, the majority of reported adverse events were the same in elderly (≥65 years) and non-elderly (18 to <65 years) populations; however, as expected and consistent with the advanced age, some SAEs were reported more frequently in this patient population. The SAEs in elderly varied from "uncommon" to "very rare" frequencies.
Table SVII.1 shows the comparison of the incidence of SAEs in elderly versus non-elderly from all clinical trials of ED and BPH that represented more than 1% of the SAEs reported.

Table SVII.1. Comparison between the Incidence of SAEs Cases for Elderly Patients and Non-elderly Patients Cumulatively in all Clinical Trials

Preferred Terms	Elderly (≥65 years) (Total n = 5676)	Nonelderly (18 to <65 years) (Total n = 20,436)
Myocardial infarction	12 (0.21%)	12 (0.06%)
Acute myocardial infarction	9 (0.16%)	9 (0.04%)
Prostate cancer	8 (0.14%)	5 (0.02%)
Colon cancer	8 (0.14%)	1 (0.00%)
Pneumonia	7 (0.12%)	13 (0.06%)
Urinary retention	7 (0.12%)	8 (0.04%)

Preferred Terms	Elderly (≥65 years) (Total n = 5676)	Nonelderly (18 to <65 years) (Total n = 20,436)
Cerebral infarction	7 (0.12%)	1 (0.00%)
Coronary artery disease	6 (0.11%)	12 (0.06%)
Inguinal hernia	6 (0.11%)	9 (0.04%)
Cerebrovascular accident	6 (0.11%)	8 (0.04%)
Chest pain	5 (0.09%)	8 (0.04%)
Fall	5 (0.09%)	6 (0.03%)
Osteoarthritis	5 (0.09%)	5 (0.02%)
Pulmonary embolism	5 (0.09%)	2 (0.01%)
Angina pectoris	5 (0.09%)	2 (0.01%)
Lung neoplasm malignant	5 (0.09%)	1 (0.00%)
Hip fracture	5 (0.09%)	1 (0.00%)
Arthritis	5 (0.09%)	0 (0.00%)
Benign prostatic hyperplasia	4 (0.07%)	3 (0.01%)
Large intestine polyp	4 (0.07%)	3 (0.01%)
Atrial fibrillation	4 (0.07%)	3 (0.01%)
Noncardiac chest pain	4 (0.07%)	2 (0.01%)
Cardiac failure congestive	4 (0.07%)	2 (0.01%)
Rheumatoid arthritis	4 (0.07%)	0 (0.00%)
Sudden hearing loss	4 (0.07%)	0 (0.00%)
Intervertebral disc protrusion	3 (0.05%)	8 (0.04%)
Cholelithiasis	3 (0.05%)	8 (0.04%)

Abbreviations: n = number of patients; SAE = serious adverse event.

The most frequent SAEs observed in clinical trials were myocardial infarction (0.21% in elderly versus 0.06% in non-elderly), acute myocardial infarction (0.16% in elderly versus 0.04% in non-elderly), and prostate cancer (0.14% in elderly versus 0.02% in non-elderly) - all events known to have its incidence impacted by age. In addition, the incidence rates observed for these events in Lilly trials were within the expected incidence range for the respective age group observed in the US (Mozaffarian et al. 2015; Choi et al. 2018).

As per post-marketing data, it is estimated that approximately 22,189,000 elderly (≥65 years) patients were exposed to tadalafil for ED and BPH since the marketing authorisation. Cumulatively, there were 4360 SAEs reported for the elderly population (an overall SAE reporting rate of 0.0196%). The same pattern from clinical trials was observed in the post-marketing setting: no difference in the type of reported SAEs, and again, as expected, the reporting rates of some SAEs were higher in elderly patients compared with the non-elderly. Frequencies from post-marketing are smaller than in clinical trials, as they are usually underreported. Table SVII.2 shows the comparison of the reporting rates of SAEs in elderly versus non-elderly cumulatively in the post-marketing setting that represented more than 1% of the SAEs reported.

Table SVII.2. Comparison between the Reporting Rates of SAEs for Elderly Patients and Non-elderly Patients Cumulatively in Post-marketing

Preferred Terms	Elderly (≥65 years)		Nonelderly (18 to <65 years)	
	N = 22,189,000	%	N = 58,121,000	%
Malignant melanoma	85	0.0004%	124	0.0002%
Myocardial infarction	53	0.0002%	82	0.0001%
Prostate cancer	43	0.0002%	50	0.0001%
Malignant melanoma in situ	37	0.0002%	63	0.0001%
Basal cell carcinoma	37	0.0002%	41	0.0001%
Cerebrovascular accident	34	0.0002%	38	0.0001%
Squamous cell carcinoma	31	0.0001%	39	0.0001%
Atrial fibrillation	31	0.0001%	21	0.0000%
Optic ischaemic neuropathy	28	0.0001%	53	0.0001%
Visual impairment	27	0.0001%	35	0.0001%
Syncope	24	0.0001%	28	0.0000%
Deafness	23	0.0001%	33	0.0001%
Neoplasm malignant	22	0.0001%	14	0.0000%
Malignant melanoma stage II	21	0.0001%	23	0.0000%
Hypotension	21	0.0001%	16	0.0000%
Death	20	0.0001%	22	0.0000%
Blindness	19	0.0001%	25	0.0000%
Transient ischaemic attack	19	0.0001%	10	0.0000%

Abbreviations: n = number of patients; SAE = serious adverse event.

Based on the extensive experience in over 22 million elderly patients across multiple indications and over the 10 years that the product has been on the market for BPH and over 19 years for ED, the safety profile in elderly (≥65 years) for ED (once-a-day) and BPH indications is no longer considered as missing information and will be removed from the list of missing information from this RMP. This update is also consistent with current GVP Module V (Rev 2) principles and definitions.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Important Identified/Potential Risk: None

SVII.3.2 Presentation of the Missing Information

Missing Information: None

Module SVIII - Summary of the Safety Concerns

Table SVIII.1. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risk[a]	None
Important potential risk[b]	None
Missing information[c]	None

[a] Hypotension/increased hypotensive effect and priapism are no longer considered important identified risks.

[B] Nonarteritic anterior ischaemic optic neuropathy and sudden hearing loss are no longer considered important potential risks in this RMP.

[C] Characterisation of adverse events in elderly patients (≥65 years of age) for once-a-day ED and BPH indications is no longer considered missing information in this RMP. See Module SVII for additional information.

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Routine follow-up will be conducted on events of special interest.

Other forms of routine pharmacovigilance activities:

None.

III.2 Additional Pharmacovigilance Activities

None.

III.3 Summary Table of Additional Pharmacovigilance Activities

None.

Part IV: Plans for Post-Authorisation Efficacy Studies

No post-authorisation efficacy studies are considered necessary by the MAH or have been imposed by Committee for Medicinal Products for Human Use or National Competent Authority.

Part V: Risk Minimisation Measures (Including Evaluation of the Effectiveness of Risk Minimisation Activities)

Risk Minimisation Plan

Aligned with GVP Module V (Rev 2), all safety concerns are now considered well characterised and they are properly communicated through labelling. There are no further risk minimisation measures conducted or planned at this time.

V.1 Routine Risk Minimisation Measures

All safety concerns are now considered well characterised and they are properly communicated through labelling.

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimisation Measures

Not applicable.

Part VI: Summary of the Risk Management Plan

Summary of Risk Management Plan for Cialis (tadalafil)

This is a summary of the RMP for Cialis®. The RMP details important risks of Cialis, how these risks can be minimised, and how more information will be obtained about Cialis's risks and uncertainties (missing information).

Cialis's SmPC and its package leaflet give essential information to healthcare professionals and patients on how Cialis should be used.

This summary of the RMP for Cialis should be read in the context of all this information, including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Cialis's RMP.

I - The Medicine and What It is Used for

Cialis is authorised for erectile dysfunction (ED), benign prostatic hyperplasia (BPH), ED and BPH (ED/BPH) (see SmPC for the full indication). It contains tadalafil as the active substance and it is given by oral administration.

Further information about the evaluation of Cialis's benefits can be found in Cialis's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:
https://www.ema.europa.eu/en/medicines/human/EPAR/cialis.

II - Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Cialis, together with measures to minimise such risks and the proposed studies for learning more about Cialis's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

Summary of Risk Management Plan for Adcirca (tadalafil)

This is a summary of the RMP for Adcirca®. The RMP details important risks of Adcirca, how these risks can be minimised, and how more information will be obtained about Adcirca's risks and uncertainties (missing information).

Adcirca's SmPC and its package leaflet give essential information to healthcare professionals and patients on how Adcirca should be used.

This summary of the RMP for Adcirca should be read in the context of all this information, including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Adcirca's RMP.

I - The Medicine and What It is Used for

Adcirca is authorised for PAH (see SmPC for the full indication). It contains tadalafil as the active substance and it is given by oral administration.

Further information about the evaluation of Adcirca's benefits can be found in Adcirca's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/adcirca

II - Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Adcirca, together with measures to minimise such risks and the proposed studies for learning more about Adcirca's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

Summary of Risk Management Plan for Tadalafil Lilly (tadalafil)

This is a summary of the RMP for Tadalafil Lilly®. The RMP details important risks of Tadalafil Lilly, how these risks can be minimised, and how more information will be obtained about Tadalafil Lilly's risks and uncertainties (missing information).

Tadalafil Lilly's SmPC and its package leaflet give essential information to healthcare professionals and patients on how Cialis should be used.

This summary of the RMP for Cialis should be read in the context of all this information, including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Cialis's RMP.

I - The Medicine and What It is Used for

Tadalafil Lilly is authorised for erectile dysfunction (ED) (see SmPC for the full indication). It contains tadalafil as the active substance and it is given by oral administration.

Further information about the evaluation of Tadalafil Lilly's benefits can be found in tadalafil Lilly's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/tadalafil-lilly.

II - Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Tadalafil Lilly, together with measures to minimise such risks and the proposed studies for learning more about Tadalafil Lilly's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of Important Risks and Missing Information

Important risks of Cialis/Adcirca/Tadalafil Lilly are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Cialis/Adcirca/Tadalafil Lilly. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation.

Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risk	None
Important potential risk	None
Missing information	None

II.B Summary of Important Risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

II.C Post-Authorisation Development Plan

II.C.1 Studies that are Conditions of the Marketing Authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation of Cialis, Adcirca, or Tadalafil Lilly.

II.C.2 Other Studies in Post-Authorisation Development Plan

Not applicable.

Part VII: Annexes

Annex **Page**

Annex 4 - Specific Adverse Drug Reaction Follow-up Forms

Not applicable.

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (if applicable)

Not applicable.