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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cialis

tadalafil

Procedure No. EMEA/H/C/000436/II/0060

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Scientific discussion

1.1. Introduction

Tadalafil is a selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP) - specific phosphodiesterase type 5 (PDE5). The PDE5 isoenzyme has been identified in the smooth muscle cells of corpus cavernosum, vascular and visceral smooth muscle, skeletal muscle, platelets, kidney, lung, and cerebellum, as well as in the prostate, urethra, and bladder.

Some of the available scientific data suggest that inhibition of PDE5 may improve signs and symptoms of BPH (including LUTS) through relaxation of smooth muscle in the prostate, bladder, and pelvic vasculature leading to increased perfusion of the lower urinary tract. Inhibition of PDE5 may also improve signs and symptoms of BPH through reduced smooth-muscle and endothelial-cell proliferation in the prostate and bladder, as well as modulation of afferent neural signalling from the lower urinary tract.

Tadalafil under the trade name of Cialis was approved 12 November 2002 in the European Union for on-demand dosing (10 and 20 mg) in the treatment of erectile dysfunction (ED) in adult men and was approved 20 June 2007 for once-a-day dosing (5 and 2.5 mg) in the treatment of ED in adult men.

It is also approved in once-a-day (40 mg) treatment of pulmonary arterial hypertension (PAH) under the trade name of Adcirca in EU. Furthermore, outside the EU the following indications were approved: once-a-day treatment of signs and symptoms of benign prostatic hypertrophy (BPH) (US approval 06 October 2011), and once-a-day treatment of ED and signs and symptoms of BPH (US approval 06 October 2011).

In September 2011, a new indication application was submitted for Cialis for the "treatment of the signs and symptoms of benign prostatic hyperplasia (BPH) in adult males including those with erectile dysfunction" (EMEA/H/C/436/II/060).

1.2. Non-clinical aspects

To support the use of Tadalafil on the treatment of low urinary tract symptoms of benign prostate hyperplasia, experimental work was conducted in rat model of genitourinary tract hypoxia, and in deferential arteries (animal and human). The safety pharmacology and the full toxicological evaluation performed to support the current indication at the dose of 5mg is fully supported by the studies previously conducted to support the use of Tadalafil for the treatment of erectile dysfunction. Since such studies were assessed already, the conclusions are considered valid and appropriate to support the current variation and no further studies or discussion is considered needed.

1.2.1. Methods – analysis of data submitted

Effect of PDE5 Inhibition with Tadalafil on Prostate Gland Oxygenation

The spontaneous hypertensive rat (SHR) is a species with an excessive neuroendocrine activity and is a rat strain commonly used as a model to study both lower urinary tract disease (such as BPH) and erectile dysfunction. The animal model is characterized by reduced pelvic blood flow to the genitourinary tract, ischemia/hypoxia leading to morphological/structural alterations, such as prostate and bladder fibrosis, increased prostate and bladder contractions, and an increase in urethral resistance (Tarcan et al. 1998; McVary et al. 2005; Yono et al. 2007). Fourteen-week-old SHR were treated with 2 mg/kg/daily tadalafil for 1 day, 7 days, and 4 weeks. Given the PK profile of tadalafil,

oral administration at 2 mg/kg/day would provide adequate exposure and coverage to explore the on target effects of inhibiting the PDE5A enzyme. These groups of treated SHR were compared with both untreated SHR and the normotensive counterpart Wistar Kyoto rats (WKY), used as reference for normal prostate oxygenation. Hypoxyprobe™ staining was used to study prostate oxygenation.

PDE5-Isoenzyme Expression in Human Lower Urinary Tract Tissues

In order to investigate the role of PDE5 inhibition in the vasculature supporting bladder and prostate, experiments were performed in tissue preparations of human vesicular-deferential artery, a branch of the main arterial supply to the seminal vesicles, vas deferens, bladder base, lower portion of ureter, and prostate gland. Samples of the vesicular-deferential artery, along with other LUT tissue, was collected during radical prostatectomy to assess the presence and activity of PDE5-isoenzymes and the impact of tadalafil in an in-vitro model (Report AMS42).

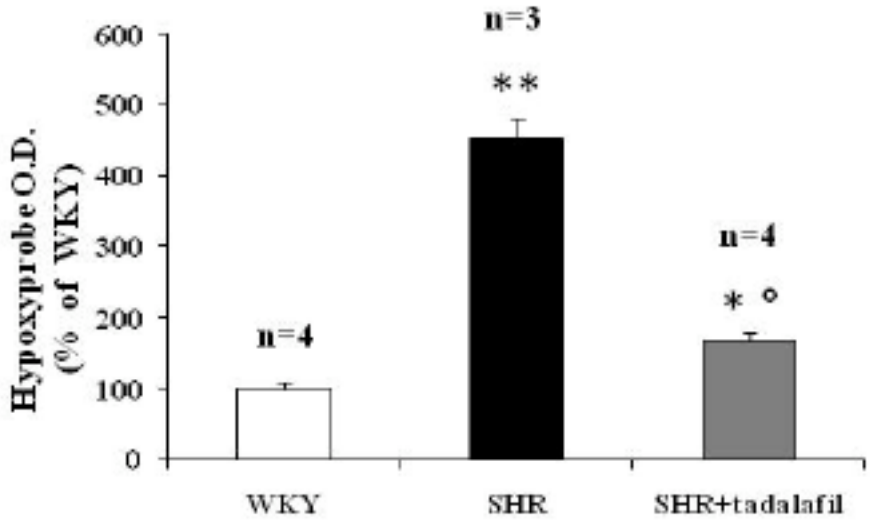
Vasorelaxant Effect of Tadalafil on Human Vesico-Deferential Artery

The ability of tadalafil to impact PDE5 activity was further confirmed in isolated rings of human vesico-deferential artery.

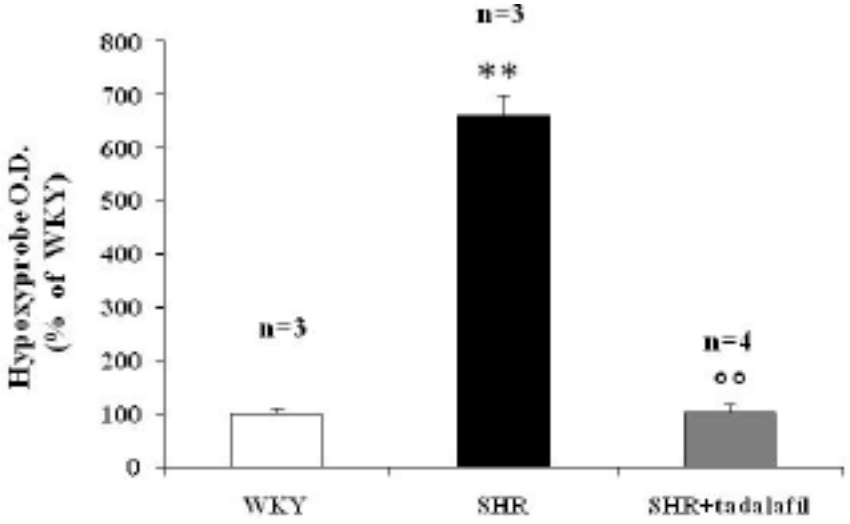
1.2.2. Results

Effect of PDE5 Inhibition with Tadalafil on Prostate Gland Oxygenation

Prostate sections from untreated SHR showed an intense immunopositivity for hypoxyprobe staining in the epithelial layers of prostatic ducts when compared with prostate sections from WKY rats, where the staining was almost undetectable. Quantitative statistical analysis of hypoxic areas was performed in prostate sections from 3 animals for each group and confirmed that SHR prostate is hypoxic in the epithelial compartment and that tadalafil treatment is able to restore hypoxiprobe immunopositivity to the level observed in WKY rats. Accordingly, the hypoxia-inducible factor 1 (HIF-1α) protein immunopositivity was significantly increased in SHR prostate sections when compared to WKY rats, and reduced by tadalafil treatment after 1 day, 7 days, and 4 weeks. Oxygenation was partially normalized after 1 day and completely restored to that of WKY after 7 days and 4 weeks. Similar results were obtained when rat prostate sections were analyzed for the immunopositivity of the endothelin-1 type B receptor (ETB), a protein known to be upregulated under hypoxic conditions (Davenport 2002). Moreover, by real time RT-PCR, it was determined that mRNA expression of BCL2/adenovirus E1B 19kDa interacting protein 3 (BNIP3), a HIF-1α target gene, was significantly increased in SHR prostate when compared to WKY rats. BNIP3 did not change after 1 day, while it was reduced and not significantly different than WKY after 7 days and 4 weeks of treatment with tadalafil.
Fig below: Tadalafil 2mg/Kg/day reduced the prostate levels of hypoxyprobe staining (measured by computer assisted densitometry) in spontaneously hypertensive rats (SHR) treated for 1 day (upper graph) and 7 days (lower graph). Levels approached those in WKY (normotensive rats)



In summary, tadalafil treatment improves prostate gland oxygenation and markers of hypoxia after 1 day, 7 days, and 4 weeks in the SHR animal model, which is characterized by ischemia/hypoxia of the genitourinary tract. These results support the hypothesis that stimulation of NO/cGMP-mediated relaxation in prostate vascular smooth muscle, increased blood perfusion and oxygenation of the prostatic tissue, and consequent restoration of tissue structure may be involved in the mechanism by which tadalafil treatment reduces LUTS in men with BPH.



PDE5-Isoenzyme Expression in Human Lower Urinary Tract Tissues

The vesicular-deferential artery was shown to express high levels of PDE5, similar to that observed in corpora cavernosa, and immunolocalized in the endothelial cells and smooth muscle layer. PDE5 immunopositivity also was confirmed in human corpora cavernosa and prostate sections, expressed mainly in endothelial and smooth muscle cells of blood vessels, with little positivity in the stromal component of the prostate. Human vesicular-deferential artery homogenate was shown to catabolyze cGMP, and tadalafil inhibited cGMP breakdown in these homogenates with an IC50 in the low nanomolar range. These results indicate that human vesiculo-deferential arteries and prostate vascular bed expresses the pharmacological target of tadalafil, and has the ability to respond to PDE5 inhibitors.

Vasorelaxant Effect of Tadalafil on Human Vesico-Deferential Artery

Human artery rings, precontracted with noradrenaline, were relaxed in a concentration-dependent manner by the NO donor sodium nitroprusside (SNP). Preincubation with tadalafil (100 nM) enhanced this SNP-induced relaxant effect, increasing both the potency and maximal relaxant effect of SNP. These results confirm that human vasculature supporting bladder and prostate perfusion is responsive to PDE5 inhibition with tadalafil.

1.2.3. Discussion

The use of tadalafil on the treatment of (Low urinary tract) symptoms associated to Benign Prostate Hyperplasia is proposed in the current variation. The basis for the proposal is the concept that

i) the urinary tract symptoms associated to BPH are related to the hypoxia and hypoxia-induced structural/morphological organ changes which promote increased contraction of eg the bladder, urethra and prostate,

ii) the Nitric Oxide Synthase / cGMP system are present in the tissues of the lower genitourinary tract as well as in the arteries responsible for the blood supply of bladder and prostate, and

iii) and the increased blood supply promoted by the increased levels of cGMP obtained by PDE5 inhibition in the concerned tissues (incuding vessels) will ameliorate tissues oxygenation and reverse the structural/morphological changes involved in the increased contaction of prostate/bladder/uretra.

The presence of PDE5 in the arteries which irrigate the lower genito-urinary tract tissues has been shown, in human and rodent tissues using rodent model of low urinary tract hypoxia.

The reduction of hypoxia by Tadalafil in the prostate of the animal model has also been shown, (the effects observed *in vivo* were dependent of the treatment duration when 1day-2weeks treatment were administered) as well as its ability to reduce the cGM break-down in animal and human arteries *in vitro.* Also, in human deferential artery, the potentiation by Tadalafil of the Nitroprussiate-induced vaso-relaxation has been shown.

Therefore, in qualitative terms, the Pharmacodynamic studies do support the concept behind the proposed indication in this variation.

1.3. Clinical Pharmacology aspects

To support this application for BPH indication and since the PK of tadalafil in healthy volunteers and other patient populations is well studied and established from both the original and the once daily applications, the MAH presented only one study comparing the PK of an elderly population (most likely to suffer from this disease condition) and a younger population (LVHN). A Phase 2 Study LVIA has also been conducted in Japanese men with BPH. This study is considered as supportive, and only relevant results from it will be presented.

1.3.1. Methods – analysis of data submitted

- Study to Evaluate the Pharmacokinetics of Tadalafil Administered Once Daily in Young and elderly BPH Subjects (LVHN).

A multicentre, parallel-group, open-label study was conducted to assess the single- and multiple-dose PK and cardiovascular dynamics of tadalafil in a more elderly population than the one included in the

previous clinical pharmacology or ED studies. This study included 12 elderly (70 to 76 years of age) and 12 young (48 to 59 years of age) subjects with lower urinary tract symptoms secondary to BPH and 3 younger subjects (45 to 60 years of age) with mild renal impairment, but without BPH. These 3 subjects were included to determine whether any age-related Pharmacokinetic (PK) differences might be attributable to altered renal function rather than age alone, but the primary analyses are based on PK and hemodynamic data from the BPH subjects only. Subjects received tadalafil 20 mg once daily for 10 consecutive days.

- Study to Evaluate the Efficacy and Safety of Tadalafil Administered Once Daily for 12 Weeks in Japanese Men with Signs and Symptoms of BPH (LVIA).

A Phase 2, multicentre, randomised, double-blind, placebo-controlled, parallel-design study was conducted to evaluate the efficacy, safety, and steady-state PK of tadalafil 2.5 (n=141) and 5 mg (n=134) once daily in Japanese male subjects with BPH and ≥45 years of age.

1.3.2. Results

- Study to Evaluate the Pharmacokinetics of Tadalafil Administered Once Daily in Young and elderly BPH Subjects (LVHN).

Mean tadalafil AUC and Cmax values were reduced by approximately 13% following single- and multiple-dose administration of tadalafil 20 mg in elderly BPH subjects compared to young BPH subjects, but these differences were not statistically significant.

Table 2.7.2.1. Statistical Analysis of the Effect of Age on the Pharmacokinetics of Tadalafil 20 mg in Subjects with BPH

Parameter of tadalafil	Day	Geometric LS mean (95% CI) Elderly	Geometric LS mean (95% CI) Young	Ratio of geometric LS means (elderly:young)	90% CI for the ratio (elderly:young)
AUC_{0-24} (ng.h/mL)	1	3899	4461	0.87	0.68, 1.13
	10	7359	8336	0.88	0.68, 1.14
C_{max} (ng/mL)	1	273	317	0.86	0.69, 1.07
	10	472	534	0.88	0.71, 1.10
t_{max}[a] (h)	1	4.00	4.00	0.00	-0.07, 0.00
	10	3.52	4.00	0.00	0.00, 0.03

Abbreviations: AUC_{0-24} = AUC from 0 to 24 hours; C_{max} = maximum observed plasma concentration; CI = confidence interval; t_{max} = time of C_{max}; LS = least squares.

Model: log(PK)= SUBJECT + DAY + GROUP + GROUP x DAY + RANDOM ERROR

[a] Median of differences (elderly-young) and associated 90% CI for median of differences for t_{max}.

Elderly subjects appeared to have higher levels of tadalafil's major metabolite (total methylcatechol,) AUC and Cmax after a single 20-mg dose of tadalafil, when compared to the younger subjects. No significant differences were observed following 10 days of once daily dosing as the confidence intervals for the AUC and Cmax comparisons on Day 10 included 1. Across dosing days, tmax for both tadalafil and total methylcatechol were similar in elderly and young BPH subjects.

The haemodynamic profile was comparable for elderly and young subjects with BPH. There appeared to be a larger decrease in systolic and diastolic blood pressure (BP) from baseline (Day 1, pre-dose) in supine and standing for elderly subjects compared to young subjects with BPH, over the first 4h post-dose on Days 1 and 10. This finding was attributed to a higher baseline BP (Day 1, pre-dose) in the elderly subjects and probable impaired baroreceptor function in this age group. None of the elderly subjects experienced adverse events (AE) associated with orthostatic changes in BP, whereas 2 young subjects experienced orthostatic hypotension.

Overall, tadalafil was tolerated when administered as single and multiple 20-mg daily doses for 10 days to elderly and young subjects with BPH, with no difference in the overall tolerability profile between age groups.

To compare the PK of tadalafil in healthy subjects and subjects with BPH, a historic comparison has been provided by the MAH between results from study LVHN and from study LVDK, study done in healthy subjects which was submitted in the original on-demand ED submission. Both studies dosed 20 mg once a day for 10 days. From a demographic point of view, study LVHN included a younger and an older subjects, whereas study LVDK included only young subjects. As might be expected, the mean weight of subjects in study LVHN was greater by <20% than that in healthy subjects; the magnitude of this difference was not deemed to unduly influence the comparison and interpretation of the results. The tadalafil plasma concentration time profiles during 20 mg once-daily doses of tadalafil were comparable between healthy subjects and subjects with BPH on Day 1 and Day 10.

When results were stratified by age, no clinically relevant differences in tadalafil exposure were found, irrespective of age.

Tadalafil exposures in subjects with BPH (Study LVHN) are comparable to those in healthy subjects (study LVDK). Overall, these results are consistent with expectations that the pathophysiology of BPH, like ED, does not alter the pharmacokinetics of tadalafil.

Table 2.7.2.7. Statistical Analyses of the Effect of BPH on the Pharmacokinetics of Tadalafil 20 mg in Healthy Subjects (LVDK) and Subjects with BPH (Study LVHN)

		Geometric LS Mean		Ratio (90% CI) of Geometric LS Means (Healthy:BPH)
Parameter	Day	Healthy	BPH	
AUC_{0-24} (ng*h/mL)	1	4949.75	4161.08	1.19 (1.01, 1.40)
	10	7388.59	7765.72	0.95 (0.76, 1.19)
C_{max} (ng/mL)	1	351.85	296.73	1.19(1.02, 1.38)
	10	480.96	500.11	0.96 (0.80, 1.16)

Abbreviations: AUC_{0-24} = area under the concentration/time curve from time zero to 24 hours; BPH = benign prostatic hyperplasia; C_{max} = maximal observed concentration; CI = confidence interval; LS = least squares.

- Study to Evaluate the Efficacy and Safety of Tadalafil Administered Once Daily for 12 Weeks in Japanese Men with Signs and Symptoms of BPH (LVIA).

Overall, mean tadalafil concentrations were similar across visits within the specified time intervals. Exposures in Japanese subjects in this study were significantly higher than exposures in historical studies in non-Japanese subjects. This is inconsistent with all other comparisons of Japanese and non-Japanese subjects within and between studies, which have consistently indicated comparable exposures between these groups.

1.3.3. Discussion

For the previous submission for the ED and PAH indications, over 60 clinical pharmacology studies were conducted. The pharmacokinetics of tadalafil at doses of 2.5mg to 20mg following single and multiple doses were characterised in the studies presented in these previous submissions. A summary of the studies and topics relevant to the present submission has been provided by the MAH. The MAH

argues that the clinical pharmacology package supporting these previous submissions for tadalafil is the same needed to support the current application to register tadalafil 5 mg for once-daily use for the treatment of benign prostatic hyperplasia (BPH). This is agreed upon.

In addition to the previously mentioned data, the MAH has presented a new clinical pharmacology study in subjects with BPH and additional supportive PK data from a Phase 2 study conducted in Japanese men with BPH.

Tadalafil AUC and Cmax values were reduced by approximately 13% following single- and multiple-dose administration of tadalafil 20 mg in elderly subjects compared to young BPH subjects. A higher exposure to tadalafil's major metabolite (total methylcatechol) was observed in elderly subjects. The data submitted shows a larger decrease in systolic and diastolic blood pressure (BP) from baseline (Day 1, pre-dose) in supine and standing for these elderly subjects compared to young subjects with BPH, over the first 4h post-dose.

The MAH was asked to clarify this issue. The MAH attributed these features to a higher baseline blood pressure and probable impaired baroreceptors in these subjects (≥65 years old). When changes in blood pressure recorded in the pivotal clinical trials (12 weeks) as well as on the open label extension (52 week) were reviewed these findings were not replicated.

The MAH claims that the mechanism of action resides in the inhibition of PDE5, which is thought to improve signs and symptoms of BPH through reduced smooth-muscle and endothelial-cell proliferation in the prostate and bladder, as well as modulation of afferent neural signalling from the lower urinary tract. The resulting vascular relaxation may increase blood perfusion, thus reducing BPH symptoms. The MAH has pointed out that with the evidence available, there are no indications that increased blood perfusion caused by PDE5 inhibitors could affect the prostate size and lead to worsening of the disease itself. Although no ultrasound examination of the prostates are available from patients treated with tadalafil the indirect signs (IPSS, PVR, Qmax and PSA levels) of patients that participated in the BHP pivotal studies do not suggest further concerns related to a potential enlargement of the prostate size.

1.4. Clinical Efficacy aspects

Table 2.7.3.1. Clinical Studies: LVHG, LVHJ, LVHR, and LVID

Identifier	Study Centers; Countries	Design	Treatment Period Duration	Population	Subjects Randomised to Each Treatment
LVHG	92; Australia, France, Canada, Germany, Greece, Italy, Mexico, Spain, Sweden, United States	Double-blind, placebo-controlled, parallel	12 weeks	Men with BPH-LUTS for at least 6 months prior to Visit 1	Total: N=1058[a] Tad 2.5 mg (N=209); Tad 5 mg (N=212); Tad 10 mg (N=216); Tad 20 mg (N=209); Placebo (N=212)
LVHJ	28; Argentina, Germany, Italy, Mexico, United States	Double-blind, placebo-controlled, parallel	12 weeks	Men with BPH-LUTS for at least 6 months prior to Visit 1	Total: N=325 Tad 5 mg (N=161); Placebo (N=164)
LVHR	54; Canada, France, Germany, Greece, Italy, Mexico, Portugal, Russian Federation, United States	Double-blind, placebo-controlled, parallel	12 weeks	Men with BPH-LUTS for at least 6 months and history of ED for at least 3 months prior to Visit 1	Total: N=606 Tad 2.5 mg (N=198); Tad 5 mg (N=208); Placebo (N=200)
LVID	44; Austria, Australia, Belgium, France, Germany, Greece, Italy, Mexico, Netherlands, Poland	Double-blind, placebo-controlled, active-controlled, parallel	12 weeks	Men with BPH-LUTS for at least 6 months prior to Visit 1	Total: N=511 Tad 5 mg: (N=171); Tamsulosin 0.4 mg (N=168)[b] Placebo (N=172);
Long-Term Open-Label Extension Study					
LVHG	44; Canada, United States	Open-label extension	52 weeks	Men who completed Study LVHG double-blind period and chose to continue	Total: N=428[c] Tad 5 mg (N=428)[d]

Dose response studies

The dose-response effect of tadalafil on total IPSS and BII was evaluated in 2 studies: Study LVHG where 4 doses ranging from 2.5 to 20 mg were examined in patients with BPHLUTS and in Study LVHR where the doses of 2.5 and 5 mg were examined in patients with BPH-LUTS and comorbid ED.

Study LVHG was a pivotal Phase 2b/3, randomised, double-blind, placebo-controlled, parallel design, dose-finding study to evaluate the efficacy, dose response, and safety of tadalafil 2.5, 5, 10, and 20 mg once a day for 12 weeks versus placebo in men with BPH-LUTS.

Inclusion criteria included subjects who: were ≥45 years old; had BPH-LUTS (as diagnosed by a qualified physician) for >6 months at screening; had total IPSS ≥13 at the start of the placebo lead-in period; had a peak urinary flow rate (Qmax) ≥4 and ≤15 mL/sec at the start of the placebo lead-in period.

Exclusion criteria excluded subjects who: had a prostate-specific antigen (PSA) value 10 ng/mL (men with a PSA of 4 to 10 ng/mL were required to have a prostate biopsy negative for malignancy within the preceding 12 months); had clinical evidence of a urinary tract infection/inflammation at screening; had a postvoid residual (PVR) volume ≥300 mL at screening; had clinical evidence of prostate cancer; received finasteride or dutasteride treatment within 3 and 12 months, respectively, before the start of the placebo lead-in period; had evidence of New York Heart Association (NYHA) ≥Class III cardiovascular disease (NYHA 1994) within 6 months of screening; had a history of significant renal insufficiency, defined as renal dialysis or having an estimated creatinine clearance <50 mL/min at screening as calculated by the Cockcroft- Gault formula.

After screening, subjects taking any prohibited BPH, overactive bladder, or ED treatment entered a 4-week wash-out period, followed by a 4-week single-blind, once-a-day placebo lead-in period to assess treatment compliance and establish baseline values of efficacy measures for the double-blind treatment period. Subjects not taking prohibited BPH, overactive bladder, or ED treatments could return to the study site to start the placebo lead-in period as soon as screening results were available. Randomization was stratified by baseline LUTS severity (total IPSS <20 or ≥20), geographic region (US/Canada, Latin America [Mexico], Europe [France, Germany, Greece, Italy, Spain, and Sweden], and Australia), and history of ED (yes/no).

The primary objective of Study LVHG was to evaluate the efficacy of tadalafil 5 mg once a day for 12 weeks compared to placebo in improving total IPSS in men with BPH-LUTS.

The secondary efficacy objectives included: Examining whether a dose-response relationship exists for placebo and tadalafil 2.5, 5, 10, and 20 mg once a day for 12 weeks in the treatment of BPH-LUTS. Evaluating the efficacy of tadalafil 2.5, 5, 10, and 20 mg once a day for 12 weeks compared to placebo in the treatment of BPH-LUTS as assessed by the following measures: total IPSS (for tadalafil 2.5-, 10-, and 20-mg doses); IPSS storage and voiding subscores and nocturia question; IPSS QoL Index; BII; LUTS-General Assessment Questions (GAQ); uroflowmetry parameters, including Qmax, mean flow rate (Qmean), and voided volume (Vcomp); and IIEF EF Domain score in sexually active men with ED.

While uroflowmetry measures were assessed as efficacy measures for Study LVHG, for consistency with the other BPH efficacy and safety studies, they were reported as safety measures for the purposes of this submission.

For the description of study LVHR see section "Main clinical studies".

Results

In Study LVHG, statistically significant improvements in total IPSS changes from baseline to endpoint were reported for all doses compared to placebo (range of mean differences: -3.8 to -5.2). Tadalafil 5 mg dosed once daily provided a 63% improvement in total IPSS compared to tadalafil 2.5 mg.

Table: Summary of Total IPSS Change Comparing Each Dose to Previous Dose - Study LVHG

		Tadalafil			
		2.5 mg	5 mg	10 mg	20 mg
Total IPSS	Mean difference in change with placebo	-1.6	-2.6	-2.9	-2.9
	Percentage decrease relative to next smallest tadalafil dose	n/a	63%	12%	0%

Abbreviations: IPSS = International Prostate Symptom Score.
Source: SCE Table 2.7.3.16.

Additional improvement in mean total IPSS change from baseline values for tadalafil 10 mg, relative to the tadalafil 5-mg treatment group, was minimal and there was no additional improvement of the tadalafil 20-mg group relative to the tadalafil 10-mg group, suggesting that the higher doses provided little additional benefit in improving total IPSS. For the secondary efficacy measure of BII, once-a-day dosing of tadalafil 5, 10, and 20 mg, but not 2.5 mg, resulted in statistically significant improvement in BII mean changes from baseline compared to placebo. All tadalafil doses were well tolerated; on the other hand, the incidence of patients with 1 or more treatment-emergent adverse event (TEAE) increased with increasing tadalafil dose. Based on the results of Study LVHG, 2.5 and 5 mg were selected as the appropriate doses for Study LVHR. In Study LVHR, a statistically significant improvement in total IPSS change from baseline to endpoint compared to placebo was reported for the tadalafil 5-mg dose (mean difference: -2.3, p<.001), but not the tadalafil 2.5-mg dose (-0.8, p=.181). Similarly, results for BII were significant for 5 mg but not 2.5 mg. These results support that treatment with tadalafil 5 mg, but not 2.5 mg, is effective in treating the symptoms of BPH in adult males with ED. The AEs reported for the tadalafil 5-mg treatment group were similar to those of the tadalafil 2.5-mg treatment group in this population of men and were consistent with the known AE profile of tadalafil.

Main clinical studies

The efficacy and safety of tadalafil once-a-day dosing in men with signs and symptoms of BPH has been evaluated in four pivotal randomised, double-blind, placebo-controlled, 12-week, parallel-design, multinational BPH studies (Studies LVHG, LVHJ, LVHR and LVID) and one open-label extension period (LVHG). Of the 4 pivotal studies, study LVHR included subject with both BHP and ED. Information about the dose-finding study LVHG is presented in the previous section.

These studies were conducted in Australia (LVHG, LVID), Europe and Mexico (LVHG, LVHJ, LVHR and LVID), Latin America (LVHJ), Canada (LVHG, LVHR and LVID), and US (LVHG, LVHJ, and LVHR).

1.4.1. Methods – analysis of data submitted

- **Efficacy measures**

The primary efficacy measure was total International Prostate Symptom Score (IPSS) in studies LVHJ, and LVID. In Study LVHR, total IPSS was a co-primary efficacy measure with the International Index of Erectile Function (IIEF EF) Domain.

The IPSS questionnaire is a validated, self-administered, 4-week recall questionnaire used to assess the severity of BPH-LUTS as well as the therapeutic efficacy of BPH therapy. This questionnaire consists of 7 questions regarding urinary storage, voiding, and nocturia symptoms. Each question response ranged from 0 (none/not at all) to 5 (almost always/5 or more times). Total IPSS ranged from a minimum of 0 to a maximum of 35.

The IPSS questionnaire has also been used for the assessment of BPH-LUTS severity. Total IPSS may be used to classify LUTS into the following severity categories: mild (total IPSS ≤7); moderate (total IPSS ≥8 to <20); and severe (total IPSS ≥20).

The IIEF is a validated, multidimensional, self-administered, 4-week recall, 15-question instrument commonly used to assess therapeutic efficacy of ED therapy. The IIEF has 5 domains: EF Domain, Orgasmic Domain, Sexual Desire Domain, Intercourse Satisfaction Domain, and the Overall Satisfaction Domain.

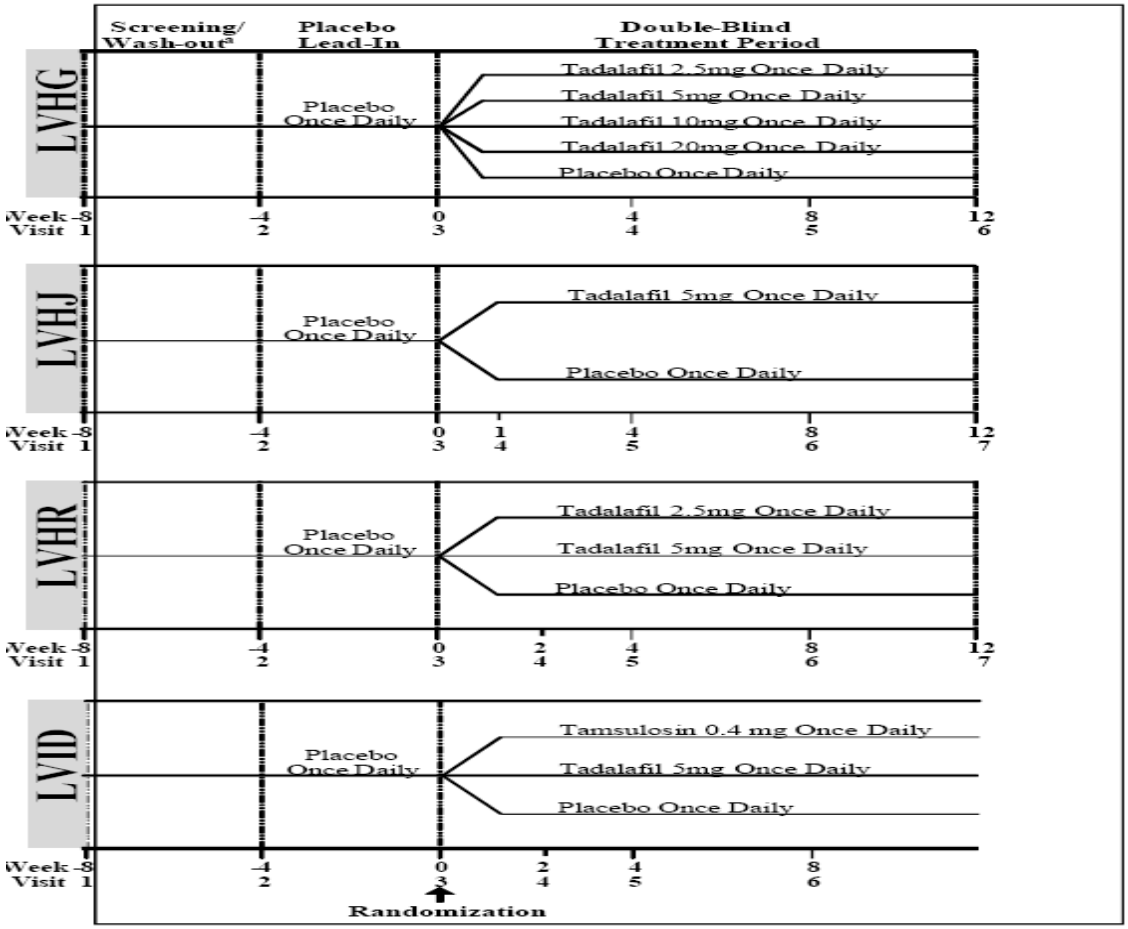
Secondary measures included Benign Prostatic Hyperplasia Impact Index (BII) and patient Sexual Encounter Profile (SEP) diary. The BII is a validated, self-administered, 4-week recall questionnaire evaluating the impact of urinary problems on overall health and activity, with 4 questions. The BII had a range from 0 to 13; higher scores on the BII represented an increased perceived adverse impact of BPHLUTS on overall health and activity.

The BII (in studies LVHJ and LVHR) and SEP question 3 (study LVHR), were key secondary efficacy variables assessed for significance as part of a gate-keeping procedure pre-specified in those study protocols. Additional secondary endpoints were IPSS Quality of Life (QoL), Patient Global Impression of Improvement (PGI-I, in Studies LVHJ, LVHR, and LVID), Clinician Global Impression of Improvement (CGI-I, in Studies LVHJ, LVHR, and LVID) the mIPSS (after 1 week of treatment in study LVHJ, after 2 weeks of treatment in studies LVHR and LVID), the LUTS-GAQ (Study LVHG), the EF-GAQ (Study LVHR), the TSS-BPH (Study LVID). All the studies assessed uroflowmetry variables of Qmax, Qmean, and Vcomp at the beginning of the placebo lead-in period, at baseline (after the placebo lead-in period), and at endpoint, but only in Study LVHG, a dose-finding study, they were considered as efficacy parameters, in the rest of the studies, they were considered as safety parameters.

- **Study designs**

Study periods were as follows: 4-week single-blind, once-a-day placebo lead-in period + 12 week placebo-controlled double-blind treatment period (LVHJ and LVHR) or 12 week placebo- and tamsulosin-controlled double-blind treatment period (LVID) + one-year open label extension period with tadalafil 5-mg once-a-day (LVHG). Patients taking prohibited BPH, overactive bladder, or ED treatment entered a 4-week wash-out period prior to the lead-in period.

2.7.3.6. Appendix



- **Statistical methods**

Primary and secondary outcomes were analysed on an intent-to-treat basis, using the last-observation-carried-forward (LOCF) and mixed model repeated measures (MMRM) methods for missing data. IPSS and BII responses were analyzed as changes from baseline to study endpoint. For sexually active subjects with ED within the integrated analysis set, the change in IIEF EF Domain scores were compared for the placebo and tadalafil treatment groups for the 12-week double-blind treatment period.

Efficacy data from the 1-year open-label extension are presented to support persistence of efficacy.

P-values associated with estimated treatment group differences are assessed for significance at a two-sided .05 level.

- **Study populations**

--General population studies

Key inclusion criteria for the pivotal studies included subjects ≥45 years old, who had BPH-LUTS (as diagnosed by a qualified physician) for >6 months at screening, who had total IPSS ≥13 at the start of the placebo lead-in period and had a peak urinary flow rate (Qmax) ≥4 and ≤15 mL/sec at the start of the placebo lead-in period.

Additional inclusion criteria in some of the studies included: subjects with PSA ≥4.0 to ≤10.0 ng/ml at screening had to have prostate cancer ruled out to the satisfaction of a urologist (Study LVHJ), subjects with PSA ≥4.0 to ≤10.0 ng/ml at screening had to have documentation of a histologic prostate biopsy negative for cancer within 12 months (Study LVHG).

Study treatments were as follows: Tadalafil 2.5 mg once a day (LVHG and LVHR), Tadalafil 5 mg once a day (all four pivotal studies), Tadalafil 10 mg once a day (LVHG), and Tadalafil 20mg once a day (LVHG). Placebo treatment groups were included in all four pivotal studies and tamsulosin 0,4md once a day was included as an active control in study LVID.

Subjects were stratified by baseline LUTS severity (total IPSS <20 or ≥20), geographic region, and history of ED (yes/no). Subjects were then randomly assigned to treatment groups in a 1:1 manner (placebo, and tadalafil 5 mg) for study LVHJ, and a 1:1:1 manner (placebo, tadalafil 5 mg, tamsulosin 0.4 mg) for Study LVID.

--Subjects with Erectile Dysfunction: Study LVHR

Inclusion and exclusion criteria used in Study LVHR were similar to those for the BPH Studies LVHG and LVHJ and for the once-a-day ED studies. Additional key inclusion criteria were: subjects who had a history of ED for ≥3 months, were required to be sexually active with an adult female partner and expected to remain sexually active with the same adult female partner for the duration of the study, and required to make at least 4 sexual intercourse attempts during the 4-week placebo lead-in period. In study LVHR, subjects were stratified by baseline LUTS severity (total IPSS <20 or ≥20), geographic region, and baseline ED severity (mild, moderate, or severe as defined by the IIEF EF Domain score). Patients were randomised to tadalafil 2.5 mg once a day, tadalafil 5 mg once a day, or placebo (1.1:1).

1.4.2. Results

Study LVHJ included 325 subjects (164 subjects in the placebo group and 161subjects in the 5 mg tadalafil treatment group) with an average age of 65 years. Most of the subjects completed the study (n=300, 92.3%).

For the primary endpoint, treatment with tadalafil 5 mg dosed once a day showed a statistically significant improvement in total IPSS change from baseline to endpoint as compared to placebo (mean difference: -1.9, p=.004), after 12 weeks of treatment.

In the assessment of key secondary efficacy measures, treatment with tadalafil 5 mg showed a statistically significant improvement in the IIEF EF Domain score change from baseline to endpoint compared to placebo in sexually active men with ED (p≤.001) and in total IPSS change from baseline after 4 weeks of treatment with tadalafil 5 mg compared to placebo (p=.003). Regarding mIPSS change from baseline after 1 week of treatment (compared to placebo) and BII change from baseline after 4 and 12 weeks of treatment (compared to placebo), the results were not statistically significant.

Results of other secondary measures such as IPSS storage and voiding subscores and QoL Index were statistically significant for the tadalafil treated group compared to the placebo group. However, there were no statistically significant improvements in the IPSS nocturia question in subjects treated with tadalafil 5 mg compared to placebo.

For the PGI-I and CGI-I, there was a statistically significant difference for the tadalafil 5-mg group compared to placebo for the 3 response categories (p=.003 and p=.009, respectively). More subjects in the tadalafil 5-mg group than in the placebo group reported that their symptoms were "better" at endpoint (74.2% versus 57.6%, respectively). Likewise, clinicians reported that more subjects in the

tadalafil 5mg group than in the placebo group had symptoms categorised as "better" at endpoint (71.0% versus 55.1%, respectively).

Study LVID included 511 subjects (172 subjects in the placebo group, 171 subjects in the 5mg tadalafil treatment group, and 168 subjects in the 0.4mg tamsulosin treatment group), with an average age of 63 years. A total of 454 subjects (88.9%) completed the study.

Treatment with tadalafil 5 mg showed a statistically significant improvement in total IPSS change from baseline to endpoint compared to placebo (mean difference: -2.1, p=.001) after 12 weeks of treatment.

The arm receiving the active comparator, tamsulosin 0.4 mg, also showed a statistically significant improvement in total IPSS change from baseline to endpoint compared to placebo (mean difference:

-1.5, p=.023). Both treatments (tadalafil 5 mg once a day and tamsulosin 0.4 mg once daily) also showed statistically significant improvements in mIPSS (total IPSS change from baseline to Week 1) (both -1.5; p=.003 and p=.005, respectively).

Treatment with tadalafil 5 mg once a day resulted in statistically significant improvements in total IPSS compared to placebo for Week 4 (-2.2, p<.001) and Week 8 (-1.8; p=.004). Additionally, using an MMRM (mixed model repeated measures) analysis, it also showed a statistically significant improvement in total IPSS compared to placebo overall (treatment effect p<.001) and at Weeks 4 (p<0.001), 8 (p=.005), and 12 (p=.005).

Treatment with tamsulosin 0.4 mg once daily also resulted in statistically significant improvements in total IPSS compared to placebo for Week 4 (-2.3, p<.001) and Week 8 (-1.3; p=.037). Additionally, using an MMRM analysis, treatment with tamsulosin 0.4 mg resulted in a statistically significant improvement in total IPSS compared to placebo overall (treatment effect p=.002) and at Weeks 4 (p<0.001), 8 (p=.029), and 12 (p=.026).

For the secondary efficacy measures, there was a statistically significant improvement in BII change from baseline to endpoint for the tadalafil 5-mg and tamsulosin 0.4-mg treatment groups compared to placebo (mean difference: -0.8, p=0.003 and -0.6, p=.026, respectively), for change from baseline to Week 4 (-0.8, and -0.9, respectively p<.001) and to week 8 (-0.6, p=0.023 and (-0.6, p=0.024, respectively). Additionally, using an MMRM analysis, both treatments showed a statistically significant improvement in BII compared to placebo overall (treatment effect: p<.001 and p=.003, respectively), at Weeks 4 (p<.001 both), week 8 (p=.026 and p=.022, respectively) and week 12 (p=.006, both).

For the additional secondary efficacy measures, statistically significant improvements in change from baseline to endpoint for IPSS voiding sub-score were observed in both the tadalafil 5-mg and tamsulosin.

0.4-mg treatment groups compared individually to placebo. Neither the tadalafil 5-mg nor the tamsulosin 0.4-mg treatment group had a statistically significant improvement in the IPSS storage sub-score or in the IPSS nocturia question by ANCOVA when compared individually to placebo.

The tadalafil 5-mg treatment group had a statistically significant improvement in change from baseline to endpoint for IPSS QoL, whereas Tamsulosin 0.4 mg did not have a statistically significant improvement compared to placebo for the same measure.

For the PGI-I and CGI-I 3-response category analysis, there was a statistically significant difference for the tadalafil 5-mg group compared to placebo (p=.005 and p=.013, respectively), but not for the tamsulosin 0.4-mg group compared to placebo (p=.116 and p=.216, respectively). More subjects in the tadalafil 5-mg group reported that their symptoms were "better" at endpoint compared to placebo (78.1% versus 62.9%, respectively) and more clinicians in the tadalafil 5-mg group reported that their

subjects' symptoms were "better" at endpoint compared to placebo (76.1% versus 62.5%, respectively).

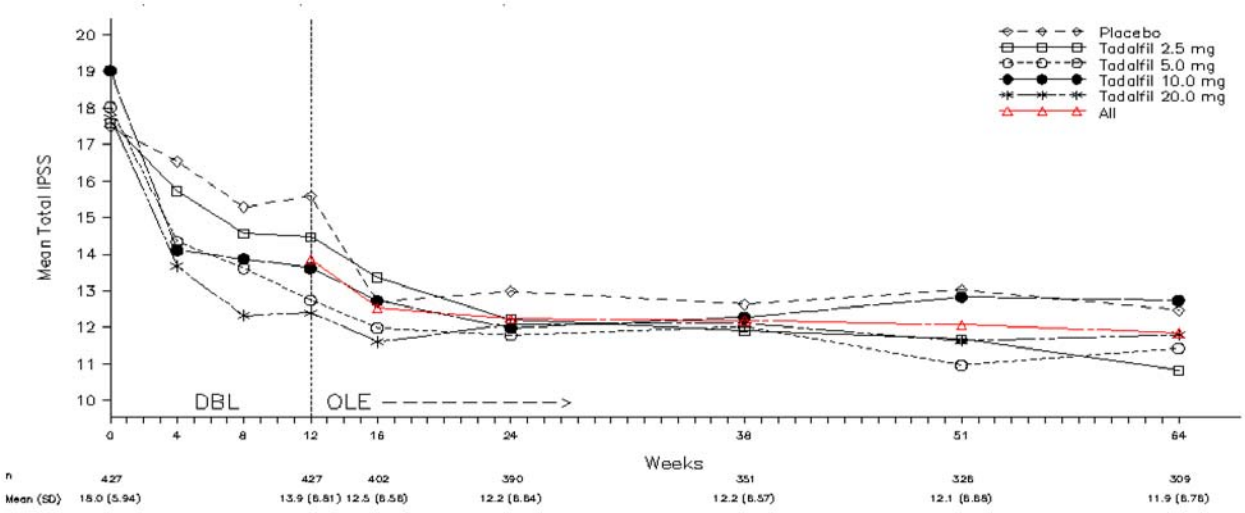
For the TSS-BPH, statistically significant differences were observed for the tadalafil 5-mg group compared to placebo for the overall score and the "satisfaction with efficacy" domain (p=.005 and p=.003, respectively) but not for the "satisfaction with dosing" or "satisfaction with side effects" domains. The tamsulosin 0.4-mg group was not statistically significantly different from placebo in TSS-BPH overall or in any of the subdomains.

- Persistence of the effect (Open-label extension study LVHG)

The long-term safety and persistence of efficacy of tadalafil in men with BPH-LUTS was evaluated in a 1-year (52-week), open-label extension (OLE) of Study LVHG. All subjects who elected to continue into the open-label extension were treated with tadalafil 5 mg once a day, regardless of their treatment assignment during the double-blind treatment period. The OLE included 428 subjects (from the US and Canada), with similar demographics and baseline characteristics to those of the entire population that participated in the double-blind treatment period of Study LVHG. A total of 299 subjects (69.9%) completed the Study LVHG open-label extension. The most common reason for discontinuation was subject decision (14%), followed by reported adverse events (5.1%). Approximately 3,5% of patients discontinued due to lack of efficacy. Discontinuations were similarly distributed over time, with the percentage of subjects discontinuing being <10% of those subjects remaining in the study at each open-label visit.

For those subjects assigned to placebo or tadalafil 2.5 mg during the placebo-controlled treatment period, improvements in total IPSS occurred during the first month of the open-label extension and persisted to the end of the open-label extension. For subjects who remained on tadalafil 5 mg or decreased from tadalafil 10 mg or tadalafil 20 mg to tadalafil 5 mg, the improvements obtained during the double-blind treatment period persisted through the open-label extension. For all subjects in the open-label extension, a similar pattern for persistence of efficacy was observed for BII over both treatment periods. During the open-label extension, the proportion of discontinuations reported as due to a perceived lack of efficacy was low (3.5%). The MAH concludes that these data support the persistence of efficacy (no tachyphylaxis or tolerance issues) of tadalafil 5 mg once a day in the treatment of symptoms of BPH.

Figure: Mean total International Prostate Symptom Score at baseline and each visit through the open-label extension of Study LVHG.



Abbreviations: BPH = benign prostatic hyperplasia; DBL = double-blind; n = number of randomized subjects with non-missing data; OLE = open-label extension; SD = standard deviation.

All subjects in the OLE period were administered tadalafil 5 mg; placebo and tadalafil dosage strengths in the legend refer to treatment assignment for the DBL treatment period.

Program Location: home/lillyce/prd/ly450190/integrations/bph_ise_2010/programs_stat/greffa1
Output Location: home/lillyce/prd/ly450190/integrations/bph_ise_2010/programs_stat/tfl_output/greffa11.rtf
Data Set Location: home/lillyce/prd/ly450190/integrations/idb_2010_july/data/ads
Source: SCE Figure 2.7.3.2.

- Study in subjects with ED (LVHR)

Study LVHR included 606 subjects (200 subjects in the placebo group, 208 subjects in the 5mg tadalafil treatment group, and 198 subjects in the 2.5mg tadalafil treatment group), with an average age of 63 years. A total of 526 subjects (86.8 %) completed the study.

Treatment with tadalafil 5 mg showed a statistically significant improvement in total IPSS change from baseline to endpoint compared to placebo (mean difference: -2.3, p<.001) and in IIEF EF Domain score change from baseline to endpoint compared to placebo (mean difference: 4.7, p<.001) after 12 weeks of treatment. For the 2.5 mg dose, the co-primary objectives were not met after 12 weeks of once-a-day dosing.

As the co-primary efficacy analyses were statistically significant only for tadalafil 5 mg, the key secondary efficacy measures, SEP Q3 and BII, were interpreted sequentially for statistical significance only for tadalafil 5 mg, and not for the tadalafil 2.5-mg group, compared to placebo (as pre-specified by the 3-step gatekeeping procedure). There was a statistically significant improvement in the percentage of "Yes" responses to SEP Q3 when tadalafil 5 mg was compared to placebo (mean difference of change: 19.7; p<.001). There was also a statistically significant improvement in BII change from baseline to endpoint compared to placebo (mean difference: -0.9; p<.001).

While the tadalafil 2.5-mg dose group did not achieve success under criteria established in the gatekeeping procedure for the co-primary endpoints, an increase in the percentage of "Yes" responses to SEP Q3 (mean difference: 12.5), and a decrease (mean difference: -0.4; Table 2.7.3.5) in BII compared to placebo was observed in this group.

Results of the additional secondary analyses were consistent with the primary analysis results; that is, tadalafil 5-mg dosing, but not tadalafil 2.5-mg dosing, statistically significantly improved measures related to assessment of BPH-LUTS, specifically the mIPSS at 2 weeks and IPSS storage and IPSS voiding subscores at 12 weeks. Both tadalafil doses statistically significantly improved measures

related to the assessment of ED (IIEF Intercourse Satisfaction Domain, the IIEF Overall Satisfaction Domain, IIEF Q3 and Q4, SEP Q2, Q4, and Q5 at 12 weeks). No statistically significant differences were observed between either tadalafil group versus the placebo group in the IPSS nocturia question or the IPSS QoL Index after 12 weeks of treatment.

For the PGI-I, there was a statistically significant difference between the tadalafil 5-mg group (p<.001) and the tadalafil 2.5-mg group (p=.009) compared to placebo for the 3 response categories. More subjects in the tadalafil 5-mg group (80.2%) and the tadalafil 2.5-mg group (73.5%) compared to the placebo group (57.3%) reported that their symptoms were "better" at endpoint.

For the CGI-I, there was a statistically significant difference between both the tadalafil 5-mg group (p<.001) and the tadalafil 2.5-mg group (p=.011) compared to placebo for the 3 response categories. More clinicians in the tadalafil 5-mg group (77.2%) and the tadalafil 2.5-mg group (71.8%) compared to the placebo group (57.6%) reported that their subjects' symptoms were "better" at endpoint (Table 2.7.3.5). Results for the 7 response categories of CGI-I are provided in the CSR.

For the EF-GAQ, a statistically significantly greater percentage of subjects in both the tadalafil 5-mg treatment group (79.1%; p<.001) and the tadalafil 2.5-mg treatment group (73.4%; p<.001) responded "Yes" to Q1 when compared to placebo (40.0%). Of those subjects who responded "Yes" to Q1, a statistically significantly greater percentage of subjects in both the tadalafil 5-mg (74.5%; p<.001) and tadalafil 2.5-mg (68.5%; p<.001) treatment groups responded "Yes" to Q2 when compared to placebo (36.2%;).

Analysis performed across trials (pooled analyses AND meta-analysis)

- Demographic and baseline characteristics

The integrated analysis set included 752 subjects randomised to treatment with tadalafil 5 mg and 748 subjects randomised to treatment with placebo. Demographics and baseline characteristics were similar between the placebo and tadalafil 5 mg treatment groups within the integrated analysis set, between the placebo and tadalafil 5 mg treatment groups within the 4 individual studies; and overall among the studies. The mean age of subjects was 63.1 years in both treatment groups, with 41.0% of subjects in both groups over age 65, and 11.2% of subjects in the taldalafil 5mg group and 12.4% in the placebo group over the age of 75. The majority of subjects (approximately 86-87%) were white and mean BMI was approximately 28 kg/m2. Mean PSA (1.9-2.0 ng/mL), mean PVR volume and Qmax categories were similar between the tadalafil 5mg and placebo groups. Approximately 13% subjects reported a history of diabetes mellitus, 39-40% reported hypertension, and 46% reported cardiovascular disease. At baseline, approximately 77-78% subjects had ED and the majority (approximately 65%) of subjects had mild to moderate LUTS severity (IPSS<20). The majority of subjects were classified as obstructed (Qmax<15mL/sec). Approximately 27% of subjects received prior alpha-blocker therapy and 23% received prior PDE5-inhibitor therapy.

A total of 428 subjects entered the Study LVHG open-label extension. Tadalafil 5 mg was the only dose administered in the Study LVHG open-label extension. The baseline characteristics of the subjects who chose to continue in the open-label extension and of those subjects who entered the double-blind treatment period in the integrated analysis set were generally similar.

Table below presents an overview of subject demographics and baseline characteristics for the integrated analysis set and the Study LVHG open-label extension:

	Integrated Placebo N=748	Integrated Tadalafil 5mg N=752	Study LVHG Open-Label Extension N=428
Mean Age at study entry	63.1	63.1	62.3
Subjects ≥ 65 years (%)	41.0	41.0	37.6
White (%)	87.0	86.3	91.6
Asian (%)	0.3	1.2	0.9
Black or African American (%)	2.1	2.3	3.5
Other race (%)	3.9	3.3	4.0
Mean BMI at Study entry kg/m^2	28.4	27.8	28.8
Subjects with Erectile Dysfunction at Study Entry (%)	77.0	77.8	69.6
Mild-moderate LUTS severity at baseline (IPSS <20) (%)	65.1	64.9	62.9
Severe LUTS severity at baseline (IPSS >=20) (%)	34.9	35.1	37.1
Peak Urine Flow Rate Categories (Qmax; mL/Sec)			
<10 mL/sec (%)	48.2	45.4	49.3
10-15 mL/sec (%)	40.1	45.0	40.2
>15 mL/sec (%)	11.6	9.6	10.5
Mean PSA (ng/mL) at study entry	1.9	2.0	1.6
Previous alpha-blocker therapy usage (%)	27.4	27.1	32.7
Previous PDE5-inhibitor therapy usage (%)	22.3	23.0	34.6

Abbreviations: BMI = body mass index; ED = erectile dysfunction; IPSS = International Prostate Symptom Score; LUTS = lower urinary tract symptoms; N = all subjects randomised (double-blind studies) or enrolled (Open-label extension Study LVHG); PDE5 = phosphodiesterase type 5; PSA = Prostate-Specific Antigen.

Note: Percentages are based on the total number of subjects with non-missing data for each treatment group (double-blind studies) or study (Study LVHG open-label extension).

Sources: Table APP.2.7.3.4 (smdema11); Table APP.2.7.3.5 (smbsca11); Table APP.2.7.3.6 (smbsca21); Table APP.2.7.3.7 (smbsca41); Table APP.2.7.3.8 (smbsca31); Table APP.2.7.3.9 (smluts11); Table APP.2.7.3.12 (smpsas11); Table APP.2.7.3.13 (smedfa11);Table APP.2.7.3.16 (smpmua11)

- Subject disposition

In the integrated analysis set, there were 752 subjects randomly assigned to tadalafil 5 mg once a day (n = 212, Study LVHG; n = 161, Study LVHJ; n = 208, Study LVHR; n = 171, Study LVID) and 748 subjects assigned to placebo (n= 212, Study LVHG; n= 164, Study LVHJ; n = 200, Study LVHR; n = 172, Study LVID.).

In the integrated analysis set, approximately 88% of subjects completed the double-blind treatment period of the studies. Among the 4 integrated studies and between treatment groups within the studies, the percentages of subjects who completed the studies were similar.

Among the 4 Studies LVHG, LVHJ, LVHR, and LVID, the percentages of subjects completing at each time point (Day 28, Day 56, or Day 84) were similar between the tadalafil 5-mg and placebo treatment groups within the integrated analysis set and within the individual Studies LVHG, LVHJ, LVHR and LVID.

For the Study LVHG open-label extension, the most common reason for discontinuation in the tadalafil 5-mg treatment group was adverse event and in the placebo treatment group was subject decision.

-- Comparison of Results in Subpopulations

The efficacy of tadalafil 5 mg was evaluated in subgroups of the integrated analysis set to assess the effect of the following characteristics or demographic factors at baseline on the change in total IPSS with tadalafil treatment: age ≤65 years and >65 years; age <75 years and ≥75 years; LUTS severity (IPSS ≥20 and IPSS <20); ED status (Yes/No); previous alpha-blocker therapy (Yes/No; defined as alpha-blocker therapy within 1 year prior to screening but not necessarily at screening); previous PDE5-inhibitor therapy (Yes/No); region (EU/non EU).

In addition, in a subgroup of patients with ED in the integrated analysis set, the efficacy of tadalafil 5 mg was assessed using the change in IIEF EF Domain. The 4 integrated Studies, LVHG, LVHJ, LVHR,

and LVID were designed to test their respective primary objectives and as such, the presented subpopulation analyses, which include smaller sample sizes, are exploratory.

			Placebo (N=746)			Tad 5 mg (N=752)			
	Parameter[a]		n	Mean	SD	n	Mean	SD	Interaction p-value [b]
Age									
Integrated	<=65 Years (N1=884)	Baseline	431	17.4	6.17	435	17.8	5.94	.666
		Endpoint	431	13.9	7.29	435	11.7	7.14	
		Change	431	-3.5	5.92	435	-6.1	6.58	
	>65 Years (N1=614)	Baseline	304	17.3	5.62	307	17.3	5.40	
		Endpoint	304	14.0	7.21	307	11.9	6.42	
		Change	304	-3.3	6.19	307	-5.4	6.02	
Integrated	<75 Years (N1=1321)	Baseline	642	17.3	5.98	658	17.6	5.79	.129
		Endpoint	642	14.0	7.37	658	11.7	6.83	
		Change	642	-3.3	6.12	658	-5.9	6.28	
	>=75 Years (N1=177)	Baseline	93	17.5	5.68	84	17.1	5.21	
		Endpoint	93	13.5	6.38	84	12.3	7.00	
		Change	93	-4.1	5.39	84	-4.8	6.87	
LUTS severity									
Integrated	IPSS < 20 (N1=975)	Baseline	483	14.0	3.79	479	14.3	3.60	.298
		Endpoint	483	11.4	5.91	479	9.6	5.36	
		Change	483	-2.6	5.47	479	-4.6	5.33	
	IPSS >= 20 (N1=523)	Baseline	252	23.8	3.42	263	23.6	3.52	
		Endpoint	252	18.7	7.16	263	15.7	7.49	
		Change	252	-5.1	6.68	263	-7.9	7.45	
ED status									
Integrated	Yes (N1=1158)	Baseline	566	17.5	5.80	579	17.7	5.54	0.865
		Endpoint	566	14.0	7.11	579	11.8	6.86	
		Change	566	-3.5	6.03	579	-5.9	6.48	
	No (N1=338) [c]	Baseline	167	16.8	6.41	163	17.1	6.33	
		Endpoint	167	13.6	7.69	163	11.7	6.81	
		Change	167	-3.3	6.08	163	-5.4	5.91	
Previous Alpha-Blocker Therapy									
Integrated	Yes (N1=409)	Baseline	204	17.5	5.80	203	18.2	5.73	.284
		Endpoint	204	14.9	7.74	203	12.5	6.80	
		Change	204	-2.6	6.34	203	-5.7	6.62	
	No (N1=1089)	Baseline	531	17.3	6.00	539	17.3	5.71	
		Endpoint	531	13.5	7.03	539	11.5	6.86	
		Change	531	-3.7	5.89	539	-5.8	6.26	
Previous PDE5 Inhibitor Use									
Integrated	Yes (N1=339)	Baseline	164	17.1	5.70	171	17.2	5.81	.947
		Endpoint	164	13.6	7.22	171	11.4	6.89	
		Change	164	-3.5	5.95	171	-5.8	6.30	
	No (N1=1159)	Baseline	571	17.4	6.01	571	17.7	5.70	
		Endpoint	571	14.0	7.26	571	11.9	6.84	
		Change	571	-3.4	6.06	571	-5.8	6.38	
IIEF EF Domain in Sexually Active Subjects with ED									
Integrated	Yes (N1=1158)	Baseline	566	17.5	5.80	579	17.7	5.54	0.865
		Endpoint	566	14.0	7.11	579	11.8	6.86	
		Change	566	-3.5	6.03	579	-5.9	6.48	
	No (N1=338) [c]	Baseline	167	16.8	6.41	163	17.1	6.33	
		Endpoint	167	13.6	7.69	163	11.7	6.81	
		Change	167	-3.3	6.08	163	-5.4	5.91	
Region (EU/Non-EU)									
Integrated	European Union (N1=641)	Baseline	319	17.3	5.48	318	17.2	4.82	.880
		Endpoint	319	13.4	7.24	318	11.1	6.48	
		Change	319	-3.8	6.30	318	-6.1	5.77	
	Non-European Union (N1=857)	Baseline	416	17.4	6.28	424	17.9	6.31	
		Endpoint	416	14.3	7.25	424	12.3	7.08	
		Change	416	-3.1	5.80	424	-5.5	6.76	

Supportive studies

--Asian studies

Study LVHT (pilot study), Study LVIA (dose-finding study), and Study LVHB (efficacy and safety study) were conducted to investigate tadalafil for the treatment of BPH in Asian men. The persistence of efficacy was assessed in the open-label extension of Study LVIA.

The primary objective of Study LVHT was to evaluate the change from baseline of tadalafil 5 mg compared to placebo in total IPSS after 12 weeks in Asian men with signs and symptoms of BPH, with Tamsulosin 0.2 mg was the active control. As a pilot study, it was not powered for the primary efficacy analysis. There was no statistically significant difference between tadalafil and placebo for total IPSS change from baseline to endpoint. Nevertheless, the magnitude of improvement in total IPSS for the tadalafil 5-mg group in Study LVHT was similar to that shown in the other Asian studies (Study LVHB and Study LVIA) and the integrated analysis set.

Study LVIA included 422 randomised subjects in the primary analysis population of Study LVIA (placebo, n=140; tadalafil 2.5 mg, n=142; tadalafil 5 mg, n=140). Baseline demographics and clinical characteristics were well balanced between treatment groups. The results showed that tadalafil 5 mg numerically improved total IPSS, but did not achieve statistical significance, which is not consitest with the integrated analysis set and other Asian studies. The MAH explains this due to differences in the statistical analysis methods (including statistical power and site effect), differences in baseline characteristics (for example, BPH severity), and a relatively large placebo effect in Study LVIA.

Study LVHB included were 612 randomised subjects in the primary analysis population (placebo, n=154; tadalafil 2.5 mg, n=151; tadalafil 5 mg, n=155; and tamsulosin 0.2 mg, n=152). Treatment with tadalafil 5 mg showed a statistically significant improvement in the mean total IPSS compared to placebo, which is consistent with the results of the integrated analysis set. The active control tamsulosin 0.2 mg also statistically significantly improved the mean total IPSS compared to placebo, which is consistent with the results of tamsulosin 0.4 mg in Study LVID.

Study LVIA Open-Label Extension assessed the long-term safety and persistence of efficacy of tadalafil 5-mg once-a-day dosing. When combined with the double-blind treatment period, subjects in the open-label extension (n=394) received 54 weeks of study drug treatment. Treatment with tadalafil 5 mg resulted in a mean total IPSS change from baseline of the doubleblind treatment period to the end of the open-label extension treatment period (-5.6±5.9), which was similar to the change observed from baseline of the double-blind treatment period in Study LVHG, in which the vast majority of men were Caucasian (non-Asian), to the end of the LVHG 52-week open-label extension.

1.4.3. Discussion

In support of this variation the MAH has provided four randomised, double-blind, placebo-controlled, 12-week, parallel-design, multinational studies performed to evaluate the efficacy and safety of tadalafil once-a-day dosing in men with signs and symptoms of BPH.

Studies LVHG (a dose finding study), LVHJ, and LVID were performed in the general BHP population, while study LVHR included subjects with both BHP and ED. Doses of 2,5mg, 5mg, 10 mg and 20 mg were tested in the treatment of BHP compared to placebo (study LVHG). Study LVID also included tamsulosin 0,4mg once a day as a comparator.

Results from study LVHG showed a statistically significant improvement in the primary endpoint, the International Prostate Symptom Score, for tadalafil 5 mg compared to placebo. Minimal additional improvements were observed for the higher dosing groups although statistically significant, they were not considered clinically meaningful by the MAH. That dose (5 mg) was the one selected for the three pivotal trials.

The population of subjects participating in the pivotal trials seems mostly adequate and representative for patients with BPH. The pivotal studies included male subjects (mean age at study entry 63 years old), with BPH-LUTS. Demographic and baseline characteristics were comparable across treatment groups and within each trial. Most of the subjects randomised were White (>86%), with mild-moderate LUTS at baseline (approximately 65% had IPSS<20), and reported a prior history of ED (77%). Approximately 27% of patients had a prior history of alpha-blocker therapy, indication that the large majority of patients were not previously treated for BPH.

Efficacy results of the general population studies showed a statistically significant improvement for the primary endpoint in patients treated with all doses of tadalafil compared to placebo. Across the studies, the results were mostly consistent, with the magnitude of the response (total IPSS change) for the 5 mg dose between these studies ranging from -4,8 to -6,3 and a treatment difference compared to placebo from -1,9 to -2,6. Some difference were noted between studies, such as a lower placebo effect in study LVHG and lower total IPSS change for the 5mg dose, when compared with the rest of the studies.

A change of >3 in IPSS was considered a clinical meaningful value by the MAH, reporting data from Barry et al, 1995. However, this value is adapted from 2 points in AUA Symptom index, and stands for patients with baseline of <20; for patients with baseline > 20 the significant improvement was a difference of 6 points. Addressing questions from the CHMP the MAH provided analysis of data that show that tadalafil demonstrate clinically meaningful efficacy as measured by percent change from baseline in total IPSS that is both statistically significant and of the same magnitude observed with silodosin.

With regards to BII and other secondary efficacy measures (IPSS storage, IPSS voiding, and IPSS QoL Index), tadalafil 5 mg showed a statistically significant improvement from baseline to endpoint compared to placebo in all 4 pivotal studies, with exception of IPSS QoL Index in study, which improved numerically, but was not statistically significant. However, for the IPSS nocturia question, only tadalafil 20mg showed a statistically significant improvement with a numerical difference compared to placebo that can be deemed not clinically relevant (-0,26). According to the MAH, tadalafil does not behave differently from other drugs currently approved in the EU to manage the BHP symptoms.

In study LVID, the efficacy of tadalafil compared to placebo was similar to that observed for tamsulosin compared to placebo although, a statistical comparison between the two treatment groups was not carried out. There are no data available comparing the efficacy of tadalafil with 5- α reductase inhibitors in this subpopulation of patients, nor is there any efficacy/safety data regarding the potential use in combination. In the clinical practice the use in combination of tadalafil and 5-ARIs may be considered as a therapeutic option for certain patients. The MAH's view drug-drug interactions are not expected to occur in theory, it is however encouraged that if PK and PD characterization become available on the combination of tadalafil and 5-ARIs they should be provided.

Study LVHR included subjects with BPH and ED and tested two doses of tadalafil (2,5 and 5 mg). Only treatment with tadalafil 5mg showed a statistically significant improvement in total IPSS change from baseline, compared to placebo. This is in line with the results observed in the other studies. In the assessment of ED, both doses tested (2,5 mg and 5mg) statistically significantly improved measures related to the assessment of ED (IIEF Intercourse Satisfaction Domain, the IIEF Overall Satisfaction Domain, IIEF Q3 and Q4, SEP Q2, Q4, and Q5 at 12 weeks), as expected.

The maintenance of the effect has been evaluated during the open label extension periods in Study LVHG (52 weeks) conducted in US. Data provided compare efficacy measures at the end of the open-label period to those at baseline (double-blind period). These data suggest that patients continuing on treatment during the open label period did not have a loss of efficacy, although the inherent limitations of these type of studies (lack of comparator, limited follow up time, and the large number of the

subjects (approximately 30%) in the open label extension period who did not complete the study) do not allow drawing sound conclusions on that. To address questions from the CHMP whether discontinuations might include patients with "self-perceived" lack of efficacy, the MAH has provided additional clarifications. One third of subjects (129/428) withdrew from the study, including all reasons. Half of those subjects (n=60, 14%) reported "subject's decision" as their reason to discontinue the study. Details are available only for 11 subjects (out of the 60 subjects) and the MAH agrees that their reasons for discontinuation could indicate lack of efficacy. In order to further investigate the lack of efficacy as a potential reason for discontinuation under "subject's decision" term, the MAH reviewed the results on the measures of efficacy (IPSS). A distinct behavior was observed according the reason of withdrawal of the study: IPSSs reduction from baseline to end of OLE period was greater in patients discontinuing due to subject decision (-3.2) than in those due to lack of efficacy (+ 1.3). These features although indirect, would not support in principle the hypothesis of the presumable self perceived lack of efficacy in this group, hence this point was resolved.

Regarding the long-term effect the CHMP raised that the non-controlled 1 year-treatment study is insufficient to demonstrate the maintenance of the effect of tadalafil.

Nevertheless, even though the maintanence of the effect has not formally been demonstrated, the CHMP accepted that data from these subjects from the 52-week open label study does not seem to indicate a loss of efficacy hence this issue was resolved.

The MAH proposes to maintain the current ED recommendations for the special populations. This is deemed acceptable, provided that the SPC adequately reflects the evidence available supporting these recommendations in elderly patients, renal and hepatic impairment.

When the analysis by subgroups was performed, no relevant differences were observed according the severity of the condition or the ED co-morbidity. A more marked placebo effect was shown among naïve patients, which may be responsible of the lower size effect of tadalafil with respect to placebo. The observations in the very elderly patients (>75 years), do not allow for sound conclusions since size of this subgroup of patients was very small.

1.5. Clinical Safety aspects

1.5.1. Methods – analysis of data submitted

The primary safety analysis set (integrated safety analysis set) is based on integrated data from the 4 phase III studies LVID, LVHG, LVHJ, and LVHR (n=1582, 752 of them received tadalafil 5mg once a day). These studies were conducted to assess the efficacy and safety of tadalafil in men with signs and symptoms of BPH, were placebo-controlled, 12 weeks in duration, included a tadalafil 5-mg treatment group, used similar entry criteria for enrollment, similar patient populations, and shared similar efficacy and safety outcomes. Study LVHR was conducted to assess the efficacy and safety of tadalafil in men with both BPH and ED, and study LVID included an active-control tamsulosin group, in addition to the tadalafil and placebo groups.

The long-term safety analysis set is based on the safety data from the 1-year open-label extension period of study LVHG (n= 428 subjects on tadalafil 5 mg once a day).

Other supportive studies provided by the MAH were not included in the primary safety analysis due to differences in study design or different study populations. These supportive studies include: safety studies LVHK, LVHS, proof-of-concept study LVGC, Clinical Pharmacology study LVHN and the Asian

studies previously mentioned in this AR. Only relevant results from these supportive studies are mentioned in this AR.

Two specific safety studies assessed tadalafil once-a-day use in subjects with BPH; firstly to evaluate tadalafil 5 mg once-a-day use in combination with alpha blockers (Study LVHS), and secondly, to evaluate tadalafil 20 mg once-a-day use in subjects with or without bladder outlet obstruction to assess the urodynamic effects of tadalafil (Study LVHK).

Additionally, a clinical pharmacology study assessed the pharmacokinetics and haemodynamics of tadalafil 20 mg once a day in elderly (between 70 and 85 years of age) and young (≤60 years of age) subjects with BPH (Study LVHN).

Study LVGC was a double-blind, placebo-controlled, randomised, parallel-arm, proof-of-concept study designed to explore the efficacy and safety of tadalafil administered once a day for 12 weeks (5 mg for 6 weeks followed by 20 mg for an additional 6 weeks) in men with BPH-LUTS. Because the duration of treatment was only 6 weeks at the 5-mg dose, Study LVGC was not integrated with the 4 pivotal trials included in the integrated analysis set.

Table 2.7.4.1. Overview of Studies Supporting the Safety Profile of Tadalafil in Men with BP

Study Type	Study ID	Design	Randomised Subjects	Population	Treatment Period	Treatment(s)
Placebo-controlled, clinical studies	LVID	Phase 3, double-blind, placebo-controlled, active-contolled, parallel	511	Men with BPH-LUTS for at least 6 months prior to Visit 1	12 weeks	Placebo Tadalafil 5 mg Tamsulosin 0.4 mg
	LVHG	Phase 2b/3, double-blind, placebo-controlled, parallel	1058	Men with BPH-LUTS for at least 6 months prior to Visit 1	12 weeks	Placebo Tadalafil 2.5 mg Tadalafil 5 mg Tadalafil 10 mg Tadalafil 20 mg
	LVHJ	Phase 3, double-blind, placebo-controlled, parallel	325	Men with BPH-LUTS for at least 6 months prior to Visit 1	12 weeks	Placebo Tadalafil 5 mg
	LVHR	Phase 3, double-blind, placebo-controlled, parallel	606	Men with BPH-LUTS for at least 6 months and ED for at least 3 months prior to Visit 1	12 weeks	Placebo Tadalafil 2.5 mg Tadalafil 5 mg
Long-term, open-label extension	LVHG OLE	Open-label extension	428[a]	Men who completed Study LVHG double-blind period	52 weeks	Tadalafil 5 mg
Placebo-controlled, clinical safety studies	LVHK	Phase 2, double-blind, placebo-controlled, parallel, urodynamic safety study	200	Men with BPH-LUTS (regardless of presence of bladder outlet obstruction) for at least 6 months prior to Visit 1	12 weeks	Placebo Tadalafil 20 mg
	LVHS	Phase 3, double-blind, placebo-controlled, parallel	318	Men with BPH-LUTS for at least 6 months prior to Visit 1 and on concomitant alpha-blocker therapy	12 weeks	Placebo Tadalafil 5 mg
Placebo-controlled, proof-of-concept study	LVGC	Phase 2, double-blind, placebo-controlled, parallel	281	Men with BPH-LUTS for at least 6 months prior to Visit 1	12 weeks	Placebo Tadalafil 5 mg and 20 mg (dose escalation at 6 weeks)
Clinical pharmacology study	LVHN	Clinical pharmacology, open-label, PK and haemodynamic study	27 subjects	12 elderly (70 to 85 years of age) men with BPH; 15 young (≤60 years of age) men with BPH; 3 young subjects did not have BPH; they had mild renal impairment and were included as an in-study reference group.	10 consecutive days	Tadalafil 20 mg
Studies conducted in Asian countries	LVIA	Phase 2, double-blind, placebo-controlled, 12-week, parallel study with a 1-year open-label extension	DBL period: 422 subjects OLE: 394 subjects[a]	Japanese men with BPH-LUTS for at least 6 months prior to Visit 1	DBL period: 12 weeks OLE: 52 weeks	DBL period: Placebo Tadalafil 2.5 mg Tadalafil 5 mg OLE: Tadalafil 5 mg
	LVHB	Phase 3, double-blind, placebo-controlled, parallel	612 subjects	Asian men with BPH-LUTS for at least 6 months prior to Visit 1	12 weeks	Placebo Tadalafil 2.5 mg Tadalafil 5 mg Tamsulosin 0.2 mg
	LVHT	Phase 2, double-blind, placebo-controlled, parallel	151 subjects	Asian men in Republic of Korea with BPH-LUTS for at least 6 months prior to Visit 1	12 weeks	Placebo Tadalafil 5 mg Tamsulosin 0.2 mg

Abbreviations: BPH = benign prostatic hyperplasia, DBL = double-blind, ED = erectile dysfunction, ID = identification, LUTS = lower urinary tract symptoms, OLE = open-label extension; PK = pharmacokinetics.

[a] Number of subjects enrolled in the OLE.

Patient exposure

As of 09 March 2011, the overall exposure to tadalafil included approximately 22,400 subjects, who had been exposed to tadalafil in completed clinical studies. The placebo-controlled BPH once-daily dosing studies included a total of 2500 subjects (n= 1058 in LVHG; n=325 in LVHJ; n=511 in LVID; n= 606 in LVHR). A total of 428 subjects enrolled in the open-label extension study. In the integrated analysis set (placebo-controlled periods of Studies LVID, LVHG, LVHJ, and LVHR) and the long-term analysis set (Study LVHG 1-year open-label extension) supporting the safety profile of tadalafil 5-mg once-daily dosing in men with BPH, 1096 subjects were exposed to tadalafil 5 mg; 357 subjects and 283 subjects have been exposed to tadalafil 5 mg for at least 6 months and at least 1 year,

respectively. In subjects >65 years of age, 440 subjects have been exposed to tadalafil 5 mg; 127 subjects and 104 subjects have been exposed to tadalafil 5 mg for at least 6 months and at least 1 year, respectively. In subjects ≥75 years of age, 117 subjects have been exposed to tadalafil 5 mg; 35 subjects and 28 subjects have been exposed to tadalafil 5 mg for at least 6 months and at least 1 year, respectively, in placebo-controlled and open-label extension periods combined.

Table 2.7.4.2 provides the number of subjects exposed and subject-year exposure to tadalafil for all doses in Studies LVID, LVHG, LVHJ, LVHK, LVHR, LVHS, and the open-label extension period of Study LVHG.

Table 2.7.4.3. Duration of Exposure to Tadalafil by Dosage
All Randomised Subjects
Placebo-Controlled Studies LVID, LVHG, LVHJ, LVHR, and Open-Label Extension of LVHG

	Tad 2.5 mg	Tad 5 mg	Tad 10 mg	Tad 20 mg	>=5 mg Tad
Duration	n	n	n	n	n
>= 1 day	405	1096	216	209	1365
>= 1 month	391	1058	205	197	1307
>= 3 months	355	969	174	165	1170
>= 6 months		357		1	363
>= 12 months		283			296

Most subjects (86.6%) completed the double-blind treatment period, whereas slightly over two thirds (69.9%) completed the 1-year open-label extension period.

During the placebo-controlled treatment periods, few subjects (n=32, 3.8%) discontinued study participation early due to an adverse event (2.8% in placebo vs 3-5.7% in tadalafil groups). Similarly, during the extension periods, few subjects (n=18, 3.8%) discontinued study participation early due to an adverse event.

1.5.2. Results

Adverse events

Overall, the percentage of patients with at least 1 TEAE was significantly greater in the tadalafil 5-mg group compared to the placebo group (27.4% versus 20.9%, p=.003). The incidence of common TEAEs (events occurring in ≥1% of the tadalafil group) was low in patients receiving tadalafil 5 mg and >90% of the events were mild or moderate in severity. The AE with the highest incidence in the tadalafil 5-mg treatment group was headache. Common TEAEs with a higher incidence in patients receiving tadalafil compared with placebo were headache, back pain, dyspepsia, hypertension, pain in extremity, diarrhoea, dizziness, myalgia, and gastrooesophageal reflux disease (GERD); headache, dyspepsia, pain in extremity, and GERD were statistically significantly higher compared with placebo. Among the TEAEs that were reported in >1% of tadalafil patients, dyspnoea was the only TEAE that was reported by a significantly greater percentage of patients in the tadalafil 5-mg group compared to the placebo group (4 patients [0.5%] versus 0 patients [0.0%], p=.045). Given that the patients had either pre-existing diseases and conditions or concomitant medications that are risk factors for dyspnoea, no causal association between the study drug and dyspnoea was suggested. One TEAE of priapism was reported in the integrated analysis set (a patient in the tadalafil 5-mg group for Study LVHR).

The overall profile of AEs was comparable between the integrated BPH studies and integrated ED studies, and there was considerable overlap in common TEAEs between the populations. With the exception of pain in the extremity, all of the common TEAEs in the integrated analysis set are already identified as adverse reactions in the current SPC for the treatment of ED. Pain in the extremity is also

already identified as an adverse reaction in the existing SPC for Cialis once a day for the treatment of PAH. This event is not unexpected given that AE related to myalgia are known to occur with tadalafil therapy. Thus, no new safety concerns were identified.

Table: Common Treatment-Emergent Adverse Events (≥1%) Reported in the BPH Integrated Analysis Set or ED Integrated Studies for Tadalafil 5-mg Once-Daily Dosing

	Integrated OAD BPH Studies[a]		Integrated OAD ED Studies[b]	
Common Treatment-Emergent Adverse Events[c]	**Placebo (N=748)**	**Tadalafil 5 mg (N=752)**	**Placebo (N=396)**	**Tadalafil 5 mg (N=715)**
Headache	2.0%	3.9%	4.0%	6.0%
Back pain	1.2%	2.4%	1.3%	2.5%
Dyspepsia	0.1%	2.4%	1.0%	4.2%
Nasopharyngitis	2.3%	2.3%	2.5%	2.2%
Hypertension	0.7%	1.6%	0.5%	0.4%
Pain in extremity	0.0%	1.5%	0.0%	1.5%
Diarrhoea	1.1%	1.3%	0.5%	1.4%
Dizziness	0.8%	1.3%	0.8%	0.7%
Myalgia	0.5%	1.2%	0.8%	2.1%
Gastrooesophageal reflux disease	0.0%	1.1%	0.0%	1.1%
Nasal congestion	0.3%	0.3%	0.0%	1.7%
Influenza	1.5%	0.8%	1.5%	1.3%
Flushing	0.1%	0.5%	0.5%	1.1%
Upper respiratory tract infection	0.4%	0.7%	0.8%	1.1%

Abbreviations: BPH = benign prostatic hyperplasia; ED = erectile dysfunction; N = number of randomised patients; OAD = once-a-day.

a Four integrated, placebo-controlled, 12-week BPH tadalafil once-daily Studies: LVID, LVHG, LVHJ, and LVHR

b Five integrated, placebo-controlled, 12-week ED tadalafil once-a-day Studies: LVCV, LVFP (12-week), LVFZ, LVGH, and LVHX

c MedDRA Preferred Terms shown for common treatment-emergent adverse events in the integrated analysis set for BPH or in the integrated ED studies, ordered by decreasing frequency in the tadalafil 5-mg group in the BPH studies.

Source: SCS Table 2.7.4.18.

Of the 427 enrolled patients who received at least 1 dose of tadalafil 5 mg in the long-term analysis set, a total of 47.5% reported ≥1 TEAE. Although the percentage of patients reporting at least 1 TEAE was numerically greater in the long-term analysis set compared to that of the integrated analysis set (47.5% versus 24.1%), this would be expected given that the patient exposure in the long-term analysis set is twice that of the integrated analysis set. The safety data from the long-term analysis set did not identify any new safety considerations for tadalafil 5-mg once-a-day when used in the treatment of men with BPH-LUTS, beyond what has previously been identified for tadalafil 5-mg once-a-day when used in the treatment of men with ED.

Table: Common Treatment-Emergent Adverse Events (≥1%) in the Long-Term Analysis Set by Decreasing Frequency in the Total Population Compared to Visit 7 (Baseline) Open-Label Extension Period Study LVHG

Preferred Term	Tadalafil 5 mg (N=427) n (%)
Patients with ≥1 TEAE	203 (47.5)
Sinusitis	11 (2.6)
Back pain	10 (2.3)
Dyspepsia	9 (2.1)
Gastrooesophageal reflux disease	8 (1.9)
Hypertension	8 (1.9)
Upper respiratory tract infection	8 (1.9)
Headache	7 (1.6)
Bronchitis	6 (1.4)
Cough	6 (1.4)
Insomnia	6 (1.4)
Myalgia	6 (1.4)
Tooth infection	6 (1.4)
Arthralgia	5 (1.2)
Blood creatine phosphokinase increased	5 (1.2)
Oedema peripheral	5 (1.2)
Osteoarthritis	5 (1.2)
Rash	5 (1.2)

Abbreviations: N = number of patients enrolled in the open-label extension and received at least one dose of Tadalafil; n = number of unique patients in each category; TEAE = treatment-emergent adverse event.
Source: SCS Table 2.7.4.7.

In Study LVID (tadalafil 5 mg or placebo, with tamsulosin 0.4 mg as an active control), the percentage of patients reporting at least 1 TEAE was not significantly different between either the tadalafil 5-mg group (23.4%) or tamsulosin 0.4-mg group (23.8%) and the placebo group (20.3%). There were also no statistically significant differences between either treatment group and the placebo group in the reporting of any individual TEAEs. Common TEAEs by decreasing frequency in the tadalafil treatment group in Study LVID are summarized below.

Common Treatment-Emergent Adverse Events by Decreasing Frequency in the Tadalafil Treatment Group Double-Blind Treatment Period Study H6D-MC-LVID

Preferred Term	Placebo (N=172) n (%)	Tad 5 mg (N=171) n(%)	Tam 0.4 mg (N=168) n(%)	Total (N=511) n(%)	p-value[a] (Tad 5 mg vs Placebo)	p-value[a] (Tam 0.4 mg vs Placebo)
Patients with ≥1 TEAE	35 (20.3)	40 (23.4)	40 (23.8)	115 (22.5)	.516	.513
Headache	2 (1.2)	5 (2.9)	7 (4.2)	14 (2.7)	.283	.101
Nasopharyngitis	8 (4.7)	5 (2.9)	3 (1.8)	16 (3.1)	.574	.219
Back pain	1 (0.6)	4 (2.3)	2 (1.2)	7 (1.4)	.215	.619
Dizziness	3 (1.7)	4 (2.3)	6 (3.6)	13 (2.5)	.723	.332
Dyspepsia	0 (0.0)	4 (2.3)	3 (1.8)	7 (1.4)	.061	.120
Flushing	0 (0.0)	3 (1.8)	2 (1.2)	5 (1.0)	.123	.243
Gastrooesophageal reflux disease	0 (0.0)	3 (1.8)	0 (0.0)	3 (0.6)	.123	-
Pain in extremity	0 (0.0)	3 (1.8)	1 (0.6)	4 (0.8)	.123	.494
Cough	1 (0.6)	2 (1.2)	3 (1.8)	6 (1.2)	.623	.367
Diarrhoea	2 (1.2)	2 (1.2)	1 (0.6)	5 (1.0)	1.00	1.00
Dyspnoea	0 (0.0)	2 (1.2)	0 (0.0)	2 (0.4)	.248	-
Gastritis	1 (0.6)	2 (1.2)	1 (0.6)	4 (0.8)	.623	1.00
Musculoskeletal pain	1 (0.6)	2 (1.2)	0 (0.0)	3 (0.6)	.623	1.00
Myalgia	2 (1.2)	2 (1.2)	2 (1.2)	6 (1.2)	1.00	1.00

Abbreviations: N = number of patients in the analysis population; n = number of patients with at least one treatment-emergent adverse event per category; TEAE = treatment-emergent adverse event; Tad = tadalafil; Tam = tamsulosin; vs = versus.

[a] The p-values are from Fisher's exact tests.

Source: CSR Table LVID.12.3 (smteaa11)

Common TEAEs in the tadalafil 5-mg group reported with a higher incidence than placebo were headache, back pain, dizziness, dyspepsia, flushing, GERD, pain in extremity, cough, dyspnoea, gastritis, and musculoskeletal pain. Common TEAEs in the tamsulosin 0.4 mg group reported with a higher incidence than placebo were headache, dizziness, dyspepsia, cough, back pain, flushing, and rash. Ejaculatory dysfunction, an AE known to be associated with some alpha blockers (Oelke et al. 2011), was reported by 1 patient in the tamsulosin group and no patients in the tadalafil group. Together these data suggest that the overall tolerability of tadalafil and tamsulosin relative to placebo appear similar with few differences in the overall AE profile, although the study was not designed for direct statistical comparisons between the active treatment groups. These findings support the conclusion that the TEAE profile of tadalafil 5 mg once a day in men with BPH-LUTS is consistent with that previously established for tadalafil once a day for treatment of ED, and no new safety concerns were identified. There were no new safety concerns with longer-term treatment relative to either the 12-week double-blind phases of the BPH studies or the long-term safety data in men with ED. Based on the overall frequency of TEAEs, the tolerability of tadalafil appears to be very similar to that of tamsulosin.

Labelling Considerations for the SPC

With regard to the SPC, adverse drug reactions (ADRs) from clinical trials to be included in Section 4.8 were identified using methodology and criteria consistent with that used in previous updates to the tadalafil label. Statistical criteria together with medical judgement based on biological plausibility were used to evaluate AEs for whether a causal relationship between tadalafil and the AE is a reasonable possibility. Similar evaluations were performed for laboratory and vital sign parameters. As a result of this latest analysis including BPH data, only 1 new ADR has been included in the SPC; namely, pain in the extremity. The frequencies of a number of existing adverse reaction terms have also been updated based on a large, combined database of ED and BPH placebo controlled trials as both the ED and BPH

populations are similar with a comparable safety profile between these 2 patient populations. Table underneath provides the reporting frequencies for the new term and those terms where the SPC frequency category changed. In addition, as 1 case of priapism has now been reported in clinical trials, the footnote previously indicating that this event was only seen in spontaneous reporting has been removed.

New and Updated Adverse Reaction Terms in the SPC

	Placebo N=3718	Tadalafil N=7116	Current frequency category of AR in SPC	New frequency category of AR in SPC
New AR Term(s)				
Pain in the extremity	9(0.24%)	110(1.55%)	-	Common
AR Term(s) Which Changed in Frequency				
Headache	116(3.12%)	614(8.63%)	Very Common	Common
Dizziness	29(0.78%)	68(0.96%)	Common	Uncommon
Epistaxis	5(0.13%)	10(0.14%)	Rare	Uncommon

Abbreviations: AR = adverse reaction; ED= erectile dysfunction; SPC = Summary of Product Characteristics.
Note: ED on-demand studies include: LVAC, LVBF, LVBG, LVBJ, LVBK, LVBN, LVCE, LVCI, LVCK, LVCO, LVCQ, LVCR, LVDG, LVDI, LVDJ, LVDU, LVDW, LVDX, LVDY, LVDZ, LVEF, LVEG, LVEH, LVEI, LVEK, LVEL, LVEQ, LVFD, and LVFY. ED once-a-day studies include: LVCV, LVFP, LVFZ, LVGH, LVHX, LVHZ. BPH studies include: LVGC LVHB LVHG LVHJ LVHR LVHT LVIA LVID.
Source: smaesa47; Cialis SPC

Severity Profile

The vast majority (93%) of AEs reported in the integrated analysis set were mild or moderate in severity, the overall incidence of AEs leading to discontinuation was low, and the incidence of SAEs was not significantly different between tadalafil and placebo groups (p=.318). The incidence of severe TEAEs reported in men with BPH-LUTS receiving tadalafil 5 mg once-a-day was low (2%) and comparable to that reported in men receiving tadalafil 5 mg once-a-day for ED (3.6%). Four TEAEs were reported as severe in the tadalafil 5 mg group in more than 1 patient (2 patients each): back pain, myalgia, pain, and pancreatitis. Back pain and myalgia are already identified as adverse reactions in the current SPC for the treatment of ED. The cases of pancreatitis occurred in patients with either pre-existing diseases and conditions or concomitant medications that are risk factors for pancreatitis. Therefore pancreatitis was not considered an adverse reaction. Data from the long-term analysis set indicated that the AEs continued to remain mild to moderate in severity with long-term use of tadalafil in patients with BPH-LUTS. Of the 203 patients reporting at least 1 TEAE in the long-term analysis set, 87.2% of these TEAEs were reported as being mild or moderate in intensity. In addition, data from Study LVID indicates that the severity profile for AEs reported was similar between patients treated with tadalafil and patients treated with tamsulosin. The percentage of patients reporting a severe TEAE was 1.8% in both the tadalafil and tamsulosin groups, compared with 0.6% in the placebo group. In summary, there were no notable differences in the severity profile of AEs with tadalafil 5 mg once a day in men with BPH-LUTS from the known safety profile of once-a-day tadalafil in men with ED.

Relation to Dose

All doses of tadalafil (2.5, 5, 10, and 20 mg) studied in men with BPH-LUTS were well tolerated in the dose range Study LVHG. The incidence of patients with 1 or more TEAEs increased with increasing tadalafil dose (placebo, 21.2%; tadalafil 2.5 mg, 26.8%; 5 mg, 30.7%; 10 mg, 34.7%; 20 mg, 39.7%). The difference in percent of patients who reported at least 1 TEAE was not significant between tadalafil 2.5 mg and placebo (p=.209), with the increase in TEAE rate seen for tadalafil 5 mg driven

primarily by increased reports of dyspepsia (1.0% for tadalafil 2.5 mg versus 4.7% for tadalafil 5 mg). There was a statistically significant increase compared to placebo in the number of patients in tadalafil 10 and 20 mg treatment groups who reported back pain, dyspepsia, and myalgia. Similarly, in Study LVHR (which included both tadalafil 2.5- and 5-mg dose groups), the incidence of TEAEs was numerically higher in the 5-mg group compared with the 2.5-mg group, with more reports of headache, back pain, and dyspepsia. Serious adverse events in the tadalafil treatment groups were rare and no dependence on dose in the reporting of SAEs was apparent in Study LVHG or Study LVHR. There was no relationship between dose and the incidence of severe TEAEs in either study. Together these data show that the overall frequency of TEAEs increase with increasing tadalafil dose in men with BPH-LUTS, as observed previously with tadalafil for the treatment of ED. The events primarily responsible for the increase in TEAEs by dose in men with BPH-LUTS are those known to be associated with tadalafil therapy (headache, dyspepsia, back pain, and myalgia) and are consistent with the AEs known to increase by tadalafil dose for treatment of ED (EU/1/02/237/001-004; EMEA/H/C/436/X/0026-0027). The frequency of headache, dyspepsia, back pain, and myalgia in men with BPH treated with tadalafil 5 mg once a day in the integrated analysis set was comparable if not slightly lower to the frequencies of these events reported for tadalafil 5 mg dosed once a day for ED, and the frequency of these same events are higher in men treated with tadalafil 10 or 20 mg as needed for ED (EU/1/02/237/001-004). Collectively, these data suggest that the frequency of the most common AEs associated with tadalafil use increase at higher doses. Given this, the MAH proposes adding the following statement to SPC Section 4.8 Undesirable Effects – Summary of the safety profile: The most commonly reported adverse reactions in patients taking tadalafil for the treatment of erectile function or BPH were headache, dyspepsia, back pain, and myalgia, in which the incidences increase with increasing dose of tadalafil.

Treatment-Emergent Adverse Events by Decreasing Frequency of Occurrence in Greater than 2% of Patients in Any Tadalafil Group Study LVHG

	Placebo (N=212) n (%)	Tadalafil 2.5 mg (N=209) n (%)	Tadalafil 5 mg (N=212) n (%)	Tadalafil 10 mg (N=216) n (%)	Tadalafil 20 mg (N=209) n (%)	All Tadalafil (N=846) n (%)	Overall p-value
Patients with ≥1 TEAE	45 (21.2)	56 (26.8)	65 (30.7)	75 (34.7)	83 (39.7)	279 (33.0)	<.001
Headache	6 (2.8)	5 (2.4)	6 (2.8)	11 (5.1)	7 (3.3)	29 (3.4)	.831
Dyspepsia	0 (0.0)	2 (1.0)	10 (4.7)	6 (2.8)	10 (4.8)	28 (3.3)	.003
Back pain	1 (0.5)	3 (1.4)	2 (0.9)	10 (4.6)	12 (5.7)	27 (3.2)	.028
Myalgia	0 (0.0)	3 (1.4)	3 (1.4)	6 (2.8)	6 (2.9)	18 (2.1)	.033
Nasopharyngitis	2 (0.9)	7 (3.3)	4 (1.9)	2 (0.9)	5 (2.4)	18 (2.1)	.397
Diarrhoea	3 (1.4)	2 (1.0)	6 (2.8)	1 (0.5)	5 (2.4)	14 (1.7)	1.00
Gastrooesophageal reflux disease	0 (0.0)	2 (1.0)	2 (0.9)	6 (2.8)	3 (1.4)	13 (1.2)	.083
Pain in extremity	0 (0.0)	3 (1.4)	5 (2.4)	2 (0.9)	3 (1.4)	13 (1.5)	.083
Influenza	1 (0.5)	4 (1.9)	4 (1.9)	1 (0.5)	2 (1.0)	11 (1.3)	.478
Bronchitis	1 (0.5)	3 (1.4)	1 (0.5)	5 (2.3)	0 (0.0)	9 (1.1)	.697
Muscle spasms	0 (0.0)	2 (1.0)	0 (0.0)	2 (0.9)	5 (2.4)	9 (1.1)	.218

Abbreviations: N = total number of patients; n = number of patients who reported a TEAE; TEAE = treatment-emergent adverse event.
Source: CSR Table LVHG.12.3

Four subjects died in BPH studies. One subject died during Study LVHJ (tadalafil 5 mg), approximately 2.5 months after receiving the first dose of study drug. The subject was hospitalised and diagnosed with an acute posterior myocardial infarction (MI) and third-degree atrioventricular heart block; his condition worsened and he died 3 days later. One subject in Study LVHR receiving tadalafil 2.5 mg, died approximately 1 day after his last dose of study drug; the death certificate indicated the cause of death as MI. One subject in Study LVHK receiving placebo (with pre-existing conditions of ED, type 2 diabetes mellitus, and GERD) died of an MI approximately 2 months after initially receiving study drug.

One death was reported during the open-label extension period of Study LVIA. One subject receiving tadalafil 5 mg died of a subarachnoid haemorrhage, approximately 5 months after he enrolled in the open-label extension period (Visit 7).

Only the death in study LVHJ was considered by the investigator as being possibly related to study drug. A review of individual subject data for the 3 deaths in tadalafil-treated subjects indicated all the subjects had preexisting risk factors for MI or subarachnoid haemorrhage.

-- Other Serious Adverse Events

Overall, 11 subjects reported 16 SAEs. The number of subjects reporting at least 1 SAE was not significantly different between treatment groups. Six subjects (0.8%) in the tadalafil 5-mg group reported 7 SAEs, and 5 subjects (0.7%) in the placebo group reported 9 SAEs. Serious adverse events that were considered by the investigator to be possibly related to study drug were reported in 2 subjects: 1 subject in the tadalafil 5-mg group in study LVHJ experienced an SAE of acute MI that resulted in death, and 1 subject in the placebo group in Study LVHG experienced an SAE of rheumatoid arthritis. In the tadalafil 5-mg group, 2 subjects reported an SAE of pancreatitis, and 1 subject reported an SAE of haemorrhagic pancreatitis. These 3 SAEs were considered unrelated to the study drug by the investigator. Additionally, the review of medical summaries of these 3 pancreatitis cases does not suggest any causal association with the study drug. The subjects had either preexisting diseases and conditions or concomitant medications that are risk factors for pancreatitis. Additionally, the cardiovascular SAEs reported in the tadalafil group in the integrated analysis set (acute MI, coronary artery disease, and endocarditis) were reported in elderly patients with preexisting cardiovascular diseases or risk factors (for example, coronary artery disease, arrhythmias, hypertension, or hyperlipidemia).

In the long-term analysis set, 20 subjects (4.7%) reported 23 SAEs. Serious adverse events that were considered by the investigator to be possibly related to study drug were transient global amnesia (one subject, previously on tadalafil 5 mg, reported transient global amnesia approximately 4 days after study completion, occurred while exercising and lasted for approximately 1 hour) and coronary artery disease (one subject with a history of hypercholesterolemia and previously on tadalafil 10 mg, reported worsening of coronary artery disease).

In Study LVID (tadalafil 5 mg or placebo, with tamsulosin 0.4 mg as an active control), 4 subjects reported an SAE: 2 subjects (1.2%) in the tadalafil 5-mg group reported 2 SAEs (coronary artery disease and pancreatitis) and 2 subjects (1.2%) in the tamsulosin 0.4-mg group reported 6 SAEs (dyspepsia in 1 subject, and dizziness, flushing, headache, hyperhidrosis, and tachycardia in another subject). One SAE (tachycardia) was considered by the investigator to be related to study drug (tamsulosin 0.4 mg).

In Study LVHK, 3 subjects reported 4 SAEs: 1 subject (1.0%) in the tadalafil 20-mg group reported 2 SAEs (pleurisy and pneumonia) and 2 subjects (2.0%) in the placebo group reported 2 SAEs (hypoasthesia and MI). The event of MI resulted in death (described previously). None of these SAEs were considered by the investigator to be related to study drug or protocol procedure.

In Study LVHS (tadalafil 5 mg or placebo coadministered with alpha-blocker therapy), 6 subjects reported 8 SAEs, with 3 subjects (1.9%) in the tadalafil 5-mg group reporting 4 SAEs of cellulitis, Mallory-Weiss syndrome, and fall and tendon rupture (both in 1 subject), and 3 subjects (1.9%) in the placebo group reporting 4 SAEs of non-cardiac chest pain, fall and hip fracture (both in 1 subject), and pacemaker lead dislodgement. None of these SAEs were considered by the investigator to be related to study drug or protocol procedure.

In the clinical pharmacology analysis set, few SAEs were reported in any treatment group: 3 SAEs in a total of 2080 subjects receiving tadalafil (tadalafil 5 mg: angina pectoris and spinal laminectomy; tadalafil 40 mg: spontaneous tension pneumothorax) versus 6 SAEs in a total of 1289 subjects

receiving placebo (adenocarcinoma, unstable angina, appendectomy, circulatory collapse, injury, and sinus arrest).

Special Safety Topics

Based on previous experience of tadalafil in the treatment of ED and PAH, a number of safety topics have been investigated. These special safety topics are bleeding events, cardiovascular events, ear disorders (including sudden hearing loss), eye disorders (including nonarteritic anterior ischemic optic neuropathy [NAION]), TEAEs possibly related to hypotension, myalgias and back pain, seizures, and transient global amnesia. For the special safety topics, incidence rates adjusted for time of exposure are presented for the tadalafil 5-mg groups of both analysis sets.

In the assessment of special safety topic TEAEs, no new safety concerns with tadalafil were identified. When adjusted for time of exposure, the incidence rates of the special safety topic TEAEs for the long-term analysis set were either lower than or generally similar to the incidence rates reported in the 12-week, double-blind periods of the integrated analysis set. Although special safety topics were not specifically analysed in the other individual studies, a review of individual TEAEs reported in Studies LVHS, LVHK, the clinical pharmacology analysis set, Study LVGC, and studies performed in Asian countries were consistent with the findings from the integrated analysis set with respect to these special safety topics, with no new or unique safety findings.

-- <u>Bleeding Events</u>

In the integrated analysis set, 8 subjects (1.1%) in the tadalafil 5-mg group reported a total of 8 bleeding TEAEs compared to none in the placebo group (p=.005). The bleeding TEAEs reported were epistaxis (3 subjects) and haematochezia, haematospermia, haemorrhoidal haemorrhage, haemorrhagic pancreatitis, and rectal haemorrhage (in 1 subject each). The TEAE of haemorrhagic pancreatitis was an SAE that led to study discontinuation (described previously). No other bleeding TEAEs were SAEs or led to study discontinuation.

In the long-term analysis set, 9 subjects (2.1%) reported at total of 9 bleeding TEAEs: haematuria (3 subjects) and contusion (2 subjects) and ecchymosis, eye haemorrhage, haematoma, and intra-abdominal haematoma (in 1 subject each). None of the bleeding events were SAEs or led to study discontinuation. When adjusted for time of exposure, the incidence rate for subjects with bleeding TEAEs in the in the long-term analysis set was 2.6 subjects per 100 person-years, which is numerically lower than the incidence rate observed in the integrated analysis set (4.8 subjects per 100 person-years). No new safety concerns relating to bleeding events were identified in subjects receiving tadalafil 5 mg once a day for BPH-LUTS compared to the known safety profile of tadalafil.

-- <u>Cardiovascular disorders and events possibly related to hypotension events</u>

There was no evidence suggestive of an adverse effect on the cardiovascular system, including events possibly related to hypotension, related to tadalafil treatment. No ischemic or haemorrhagic cerebrovascular events were reported for any patient assigned to tadalafil in the integrated analysis set. No significant differences were observed between the tadalafil 5-mg and placebo groups in the percentage of patients reporting at least 1 cardiovascular disorder TEAE or any individual cardiovascular disorder TEAE, including those possibly related to hypotension. The issue of cardiovascular events and specifically the risk of hypotension/increased hypotensive effect is therefore considered to be adequately addressed in the Contraindications, Special Warnings, and Precautions for Use, and Undesirable Effects sections of the current SPC for Cialis with no requirement for change. There will continue to be routine pharmacovigilance activities and targeted follow up supporting review of terms related to the risk of hypotension as detailed in the RMP.

-- Hypertension

In the integrated analysis set, 17 subjects reported a TEAE of hypertension: 12 (1.6%) in the tadalafil 5-mg group and 5 (0.7%) in the placebo group. Of these 17 subjects, 12 subjects had their highest systolic and/or diastolic blood pressure measurement during the study recorded prior to randomisation (4 in placebo and 8 in tadalafil), and 14 subjects (5 in placebo, 9 in tadalafil) had at least 1 blood pressure measurement prior to randomisation that already met the European Society of Hypertension (ESH)-European Society of Cardiology (ESC) criteria for Grade 1 or Grade 2 hypertension.

In Studies LVHG and LVID, blood pressure measurements were taken in the sitting position, and in Studies LVHJ and LVHR (which included orthostatic vital sign measurements), blood pressure measurements were taken in the supine position. As such, the sitting blood pressure measurements from Studies LVHG and LVID were combined with the supine blood pressure measurements from Studies LVHJ and LVHR.

The percentages of subjects with treatment-emergent systolic hypertension in all 3 categories (grade 1-3 hypertension according to ESH-ESC) were numerically lower in the tadalafil 5-mg group compared with placebo group, although these differences were not statistically significant. The percentages of subjects with treatment-emergent Grade 1 or higher and Grade 3 diastolic hypertension were numerically but not statistically significantly lower in the tadalafil 5-mg group compared with the placebo group, and the percentage of subjects with Grade 2 or higher hyptertension was statistically significantly lower in the tadalafil 5-mg group compared with the placebo group (p=.042).

In summary, although an increased incidence of the TEAE of hypertension was observed in the tadalafil subjects compared to placebo in the integrated analysis set, most of these subjects had either preexisting high blood pressure or risk factors for it. Review of subjects' pre- and post-randomisation serial blood pressure values finds no evidence for treatment-emergent increases in blood pressure in subjects with the TEAE of hypertension in the integrated analysis set.

The MAH argues that the discrepancy between the reported TEAE of hypertension in tadalafil subjects compared to placebo subjects and the objective serial blood pressure measurements in the integrated analysis set appears to be a chance finding refuted by objective blood pressure measures and the recognised mechanism of action (MOA) of tadalafil as a mild vasodilator.

-- Ear Disorders

In the integrated analysis set, no significant differences were observed between the tadalafil 5-mg and placebo groups in the percentage of subjects reporting ear disorder TEAEs. Seven subjects (0.5%) reported a total of 8 ear disorder TEAEs: 2 subjects (0.3%) in the tadalafil 5-mg group reported 2 events (deafness and vertigo), and 5 subjects (0.7%) in the placebo group reported 6 events (vertigo [3 subjects], balance disorder and labyrinthitis [1 subject], and vertigo positional [1 subject]). None of these events were SAEs or led to study discontinuation. The event of deafness was reported in an 82-year-old subject approximately 12 weeks after randomization and was reported as resolved at the final visit. The event was not considered by the investigator to be related to study drug, and the subject completed the study.

In the long-term analysis set, 5 subjects (1.2%) reported 8 ear disorder TEAEs: tinnitus (2 subjects); deafness unilateral, tinnitus, and vertigo positional (1 subject); tinnitus and vertigo (1 subject); and vertigo (1 subject). None of these events were SAEs, and only the event of unilateral deafness led to study discontinuation. This event was reported in a 73-year-old subject approximately 6 months after entering the long-term extension phase of Study LVHG, who had previously received tadalafil 2.5 mg in the double-blind phase. The investigator believed the event was possibly related to study drug, and the subject discontinued the study due to this event. When adjusted for time of exposure, the incidence rate for subjects with ear disorder TEAEs in the long-term analysis set was 1.4 subjects per 100

person-years, which is similar to observed rate in the integrated analysis set (1.2 subjects per 100 person-years).

No safety concerns relating to ear disorders were identified in subjects receiving tadalafil 5-mg once-daily dosing for BPH-LUTS.

-- Eye Disorders

In the integrated analysis set, no significant differences were observed between the tadalafil 5-mg and placebo groups in the percentages of subjects reporting eye disorder TEAEs. Seven subjects (0.5%) reported 9 eye disorder TEAEs: 5 subjects (0.7%) in the tadalafil 5-mg group reported 7 events (vision blurred [4 subjects] and photopsia, retinal tear, and vitreous floaters [1 subject]), and 2 subjects (0.3%) in the placebo group reported 2 events (vision blurred and photopsia). None of these events were SAEs. Two events in the tadalafil 5-mg group led to study discontinuation: vision blurred and retinal tear.

In the long-term analysis set, 6 subjects (1.4%) reported 6 eye disorder TEAEs: vision blurred (3 subjects) and Basedow's disease (reported as a SAE), eye haemorrhage, and visual impairment (1 subject each). When adjusted for time of exposure, the incidence rate for subjects with eye disorder TEAEs in the long-term analysis set was 1.7 subjects per 100 person-years, which is numerically lower than the incidence rate observed in the integrated analysis set (3.0 subjects per 100 person-years).

No TEAEs indicative of non-arteritic anterior ischemic optic neuropathy (NAION) were reported in either analysis set and no other safety concerns relating to eye disorders were identified in subjects receiving tadalafil 5-mg once-daily dosing for BPH-LUTS.

-- Myalgias and Back Pain

While the percentage of patients reporting at least 1 myalgia/back pain TEAE was significantly greater in the tadalafil 5-mg group compared with the placebo group (p=.002), 2 common TEAEs reported (back pain and myalgia) are known to be associated with tadalafil and are identified as adverse reactions in the existing SPC for Cialis. However pain in extremity was reported by a significantly greater percentage of patients in the tadalafil 5-mg group compared to the placebo group (1.5% versus 0.0%, p<.001) and hence it is proposed that this term be added to the SPC as a common adverse reaction.

-- Seizures

No seizure TEAEs were reported in either the integrated or long-term analyses sets.

-- Transient Global Amnesia

No safety concerns relating to transient global amnesia were identified in subjects receiving tadalafil 5-mg once-daily dosing for BPH-LUTS.

Laboratory findings

Clinical laboratory evaluations included chemistry, haematology, and urinalysis. In addition, treatment-emergent elevations in hepatic-related analytes (ALT ≥3 times ULN, AST ≥3 times ULN, and total bilirubin ≥2 times ULN) were evaluated.

--Chemistry

For the integrated analysis set, changes from baseline to last observation for chemistry laboratory values between the tadalafil 5-mg and placebo groups were not statistically significant, except for the mean change from baseline to last observation in alkaline phosphatase (tadalafil 5 mg: -3.24 U/L,

placebo: -1.26 U/L; p<.001) and chloride (tadalafil 5 mg: -0.19 mm/L, placebo: -0.60 mm/L; p=.010), which were not considered clinically meaningful.

In the long-term analysis set, changes in chemistry values from baseline to endpoint and from Visit 6 to endpoint were minimal and no clinically meaningful findings were observed. In the long-term analysis set, 3 subjects had elevated hepatic-related serum chemistry test results (ALT or AST ≥3 times ULN). No subjects had increased total bilirubin levels (≥2 times ULN).

-- Haematology

For the integrated analysis set, changes from baseline to last observation for haematology laboratory values between the tadalafil 5-mg and placebo groups were not statistically significant, except for the mean change from baseline to last observation in eosinophils (tadalafil 5 mg: -0.01 bill/L, placebo: -0.00 bill/L; p=.045), lymphocytes (tadalafil 5 mg: -0.04 bill/L, placebo: 0.04 bill/L; p=.001), and platelet count (tadalafil 5 mg: -9.00 bill/L, placebo: -4.41 bill/L; p=.030), which were not clinically meaningful.

In the long-term analysis set, changes in haematology values from baseline to endpoint and from Visit 6 to endpoint were minimal. Seven subjects reported a low platelet count (<130 x 109/L); however, none had a platelet count consistent with thrombocytopenia (<100 x109/L). One subject had a history of leukopenia, and was taking steroids. Two other subjects took steroids. One subject took clopidogrel, which has been associated with thrombocytopenia. One subject also had laboratory abnormalities of macrocytes and anisocytosis; his concomitant medications included colchicine for gout. The remaining subjects had platelet counts of 188 x 109/L and 179 x 109/L, respectively, at the last visit. For these subjects, baseline values ranged from 127 to 227 x 109/L. One subject taking tadalafil 2.5 mg per day, reported mild epistaxis throughout the treatment phase of the study (Visits 4 to 12). His lowest platelet count was 114 x 109/L at Visit 8; his platelet count was 156 x 109/L at baseline and 151 x 109/L at Visit 12. In summary, the finding of low platelet count appears to be coincidental to tadalafil use, and usually explainable by use of other concomitant drugs or conditions.

-- Urinalysis

No clinically adverse or statistically significant differences were observed between the tadalafil 5-mg and placebo groups in treatment-emergent abnormal results in urinalysis tests. In the long-term analysis set, no clinically meaningful findings were observed in treatment-emergent abnormal urinalysis results.

Vital signs

Vital sign data were not integrated for analysis of change over time due to the different methods used across studies. Based on results of vital sign data from the individual BPH studies, there is no evidence of an adverse impact of tadalafil therapy on blood pressure or heart rate. Categorical analysis of blood pressure data was performed on the integrated analysis set for the purpose of determining the occurrence of treatment-emergent hypertension based on objective criteria. The percentages of patients with treatment-emergent diastolic and systolic hypertension were numerically lower in the tadalafil 5-mg group compared with placebo group. These results are consistent with the pharmacological property of tadalafil as a mild vasodilator, and do not indicate an increase in the risk of hypertension in men with BPH-LUTS receiving tadalafil. Studies LVHJ, LVHR, and LVHS (tadalafil 5 mg or placebo co administered with alpha-blocker therapy) included measurement of orthostatic vital signs to assess for orthostatic hypotension and associated symptoms, as patients with BPH-LUTS are typically older than those with ED (McVary 2006), and thus potentially more susceptible to symptomatic hypotension due to vasodilation (Low et al. 2008). In these studies the percentage of patients with at least 1 treatment-emergent positive orthostatic test was similar, with no statistically

significant difference between the tadalafil 5 mg and placebo groups (p≥.418). No patients in LVHJ or LVHR reported a TEAE upon standing and simultaneously met any criteria for orthostatic hypotension. In Study LVHS, only 1 patient in each treatment arm reported a TEAE upon standing and simultaneously met any criteria for orthostatic hypotension. Similar results were observed when analyzed in subgroups defined by age (<65 and >65 years; <75 and ≥75 years). Thus, there was no evidence of an adverse impact of tadalafil therapy compared with placebo on orthostatic vital signs either overall or in elderly men with BPH-LUTS. There also was no evidence of an adverse impact of tadalafil added to alpha blocker therapy on orthostatic vital signs compared to placebo added to alpha blocker therapy.

Electrocardiograms

Electrocardiograms were undertaken in the double-blind and open-label periods of Study LVHG and in the pilot Study LVHT conducted in Asian subjects. No clinically adverse changes in ECGs related to tadalafil therapy were observed. No clinically relevant effects on cardiac electrophysiology were observed with tadalafil treatment.

During the double-blind period of Study, there were no statistically significant mean changes from baseline to endpoint in the tadalafil treatment groups in ECG parameters. For the long-term analysis set (open-label extension period of Study LVHG), no clinically adverse effects were observed on ECG changes that were associated with tadalafil. Additionally, in the pilot Study LVHT conducted in Asian subjects, no clinically adverse changes were observed in ECG evaluations (CSR LVHT Section 12.5.2).

A multi-centre, randomised, placebo-controlled, crossover study was performed to examine the effects of single oral doses of 100-mg tadalafil on ventricular repolarisation, as assessed by analysis of 12-lead ECG QTc intervals in 90 completing healthy male subjects. Ibutilide was administered as a positive control. The results of this study showed that tadalafil 100 mg had no clinically relevant effect on ventricular repolarisation, as assessed by the QTc interval.

-- Safety Assessments Related to Bladder Function

The safety of tadalafil on bladder function in men with BPH-LUTS was assessed by measurement of post-void residual urine (PVR) volume, uroflowmetry, and adverse events in the integrated analysis set, long-term analysis set. In addition, Study LVHK was a Phase 2 study with the primary objective of testing the urodynamic safety of tadalafil. Review of PVR, uroflowmetry, urinary retention adverse events, and specific urodynamic assessments provide no evidence for a clinically adverse effect of tadalafil on bladder emptying.

PVR volumes

In the integrated analysis set, there was no significant difference between the tadalafil 5 mg and placebo groups and in mean change from baseline to endpoint in PVR volume (tadalafil 5 mg: 0.4 mL, placebo: 0.2 mL). There were no TEAEs of urinary retention reported in the tadalafil group compared to 3 urinary retention TEAEs in the placebo group (p=0.085).

In the long-term analysis set, when evaluated by previous treatment group in the double-blind period, all previous treatment groups (except tadalafil 20 mg) showed small decreases in PVR volumes that were not considered clinically adverse. One urinary retention TEAE (0.2%) was reported in the long-term analysis set, which was not considered to be treatment-related.

In Study LVID (tadalafil 5 mg or placebo, with tamsulosin 0.4 mg as an active control), mean decreases were observed in all treatment groups; however, these changes were not statistically significantly different when comparing either the tadalafil 5-mg group (-4.6 mL) or the tamsulosin 0.4-mg group (-10.2 mL) to placebo (-1.2 mL). No TEAEs of urinary retention were reported in the tadalafil or tamsulosin groups, compared with 1 in the placebo group.

In Study LVHK, there were small decreases in PVR volume in both treatment groups (tadalafil 20 mg: -9.1 mL, placebo: -1.9 mL) from baseline to endpoint, but these changes were not statistically significant between treatment groups. No urinary retention TEAEs were reported (Table LVHK.12.3).

Similar results were observed in the other supportive studies (study LVHS, Study LVGC, proof-of-concept Study LVGC and in studies of Asian men with BPH-LUTS).

Uroflowmetry

Of the studies included in the integrated analysis set, uroflowmetry data was evaluated by a central reader in Studies LVHG, LVHR, and LVID. Therefore, an integrated analysis of peak urine flow (Qmax) was performed including only these studies. In all studies, uroflowmetry analyses were based only on valid assessments with prevoid total bladder volume (assessed by ultrasound) ≥150 to ≤550 mL and voided volume ≥125 mL.

For the integrated studies, the mean change in Qmax from baseline to endpoint was statistically significant for the tadalafil 5-mg group (1.8 mL/sec) compared to the placebo group (1.2 mL/sec) (p=.041). Numeric increases in mean change in Qmax were observed with tadalafil in each study, but was statistically significant compared with placebo only in Study LVID. Also in Study LVID, there was a statistically significant mean increase in Qmax in the tamsulosin active control group (2.2 mL/sec, p=.014). In each of these studies, numeric increases from baseline to endpoint were observed for both Qmean and Vcomp in the tadalafil 5-mg group compared with placebo, none of which were considered clinically adverse.

Safety in special populations

Subgroup analyses were performed only for the integrated analysis set. These subgroups included age (≤65 and >65 years of age; <75 and ≥75 years of age), various conditions reported at baseline (ED, cardiovascular disease, hypertension, diabetes, renal impairment, hepatic impairment, CYP3A4 inhibitor use, prior alpha-blocker therapy use, and prior PDE5 inhibitor use), and TEAEs possibly related to hypotension by concomitant antihypertensive medication use. No new safety concerns with tadalafil were identified based upon subgroup analyses for the integrated analysis set.

- Intrinsic Factors

-- Age

The safety profiles were generally similar between age subgroups (≤65 and >65 years of age; <75 and ≥75 years of age) in the integrated analysis set. No statistically significant or clinically meaningful differences were observed between treatment groups in the percentages and types of TEAEs (including those possibly related to hypotension) across age subgroups. Additionally, no statistically significant or clinically meaningful differences were observed between treatment groups in the percentages of subjects reporting SAEs and discontinuations due to AEs across subgroups. Overall, these data showed no evidence of age-related differences in the tolerability of tadalafil.

- Subjects ≤65 and >65 Years of Age

Of the 1500 randomised subjects in the integrated analysis set, 615 subjects (41%) were >65 years of age. A total of 308 subjects >65 years of age have been exposed to tadalafil 5 mg, with a total exposure of 68.7 subject-years. Baseline medical history was balanced between the tadalafil 5-mg and placebo groups. As expected, subjects >65 years of age had more baseline cardiovascular disorders,

primarily more ischemic heart disease, cardiac arrhythmias and hypertension, when compared to all subjects in the integrated analysis set.

The common TEAE profiles were similar between subjects ≤65 and >65 years of age. At the SOC level, no significant treatment-by-subgroup interactions were observed. However, at the individual preferred term level, a significant treatment interaction was observed for the uncommon TEAE of abdominal discomfort (HOR p=.025). The MAH argues that this finding is likely to be an artifact caused by the small number of events reported and the opposing treatment group differences within the subgroups and therefore does not appear to indicate a true treatment-by-subgroup interaction.

Overall, for subjects reporting at least 1 TEAE or any individual TEAEs possibly related to hypotension, no significant treatment-by-subgroup interactions or treatment-group differences were observed.

Overall, for subjects reporting at least 1 SAE or any individual SAEs, no significant treatment-by-subgroup interactions or treatment-group differences were observed. In regards to discontinuations due to AEs, overall, no significant treatment-by-subgroup interactions were observed.

Table APP.2.7.4.99. Common Treatment-Emergent Adverse Events by Age (<=65, >65) in the Integrated Analysis Set By Decreasing Frequency in the Overall Tadalafil 5-mg Group
All Randomized Subjects
Studies LVID, LVHG, LVHJ, and LVHR Double-Blind Treatment Period

Preferred Term	Age	Placebo N	Placebo n	Placebo (%)	Tad 5 mg N	Tad 5 mg n	Tad 5 mg (%)	Total N	Total n	Total (%)	Homogeneity of Odds Ratios p-value*a	Between Group Comparison p-value*b
Subjects with >= 1 TEAE	<=65	441	94	(21.3)	444	114	(25.7)	885	208	(23.5)	.261	.125
	>65	307	62	(20.2)	308	92	(29.9)	615	154	(25.0)		.006
Headache	<=65	441	10	(2.3)	444	19	(4.3)	885	29	(3.3)	.941	.094
	>65	307	5	(1.6)	308	10	(3.2)	615	15	(2.4)		.212
Back pain	<=65	441	7	(1.6)	444	9	(2.0)	885	16	(1.8)	.162	.623
	>65	307	2	(0.7)	308	9	(2.9)	615	11	(1.8)		.035
Dyspepsia	<=65	441	1	(0.2)	444	12	(2.7)	885	13	(1.5)	.486	.002
	>65	307	0	(0.0)	308	6	(1.9)	615	6	(1.0)		.014
Nasopharyngitis	<=65	441	12	(2.7)	444	10	(2.3)	885	22	(2.5)	.465	.653
	>65	307	5	(1.6)	308	7	(2.3)	615	12	(2.0)		.554
Hypertension	<=65	441	4	(0.9)	444	6	(1.4)	885	10	(1.1)	.249	.532
	>65	307	1	(0.3)	308	6	(1.9)	615	7	(1.1)		.055
Pain in extremity	<=65	441	0	(0.0)	444	6	(1.4)	885	6	(0.7)		.014
	>65	307	0	(0.0)	308	5	(1.6)	615	5	(0.8)		.023
Diarrhoea	<=65	441	4	(0.9)	444	4	(0.9)	885	8	(0.9)	.666	.998
	>65	307	4	(1.3)	308	6	(1.9)	615	10	(1.6)		.509
Dizziness	<=65	441	3	(0.7)	444	4	(0.9)	885	7	(0.8)	.690	.714
	>65	307	3	(1.0)	308	6	(1.9)	615	9	(1.5)		.312
Myalgia	<=65	441	2	(0.5)	444	7	(1.6)	885	9	(1.0)	.315	.096
	>65	307	2	(0.7)	308	2	(0.6)	615	4	(0.7)		.999
Gastrooesophageal reflux disease	<=65	441	0	(0.0)	444	4	(0.9)	885	4	(0.5)		.046
	>65	307	0	(0.0)	308	4	(1.3)	615	4	(0.7)		.046

- Subjects <75 and ≥75 Years of Age

Of the 1500 randomised subjects in the integrated analysis set, 177 subjects (11.8%) were ≥75 years of age. A total of 84 subjects ≥75 years of age have been exposed to tadalafil 5 mg, with a total exposure of 18.6 subject-years. Baseline medical history for subjects ≥75 years was balanced between the tadalafil 5-mg and placebo groups. As expected, subjects ≥75 years of age had more baseline cardiovascular disorders, primarily more ischemic heart disease, cardiac arrhythmias and hypertension, when compared to all subjects in the integrated analysis set.

In regards to common TEAEs for subjects <75 and ≥75 years of age in the integrated analysis set, overall, no significant treatment-by-subgroup interactions were observed. For individual common TEAEs, a significant treatment-by-subgroup interaction was observed for diarrhoea (HOR p=.027),

which was driven by a higher percentage of subjects ≥75 years of age in the tadalafil 5-mg group reporting diarrhoea compared with the placebo group (7.1% versus 1.1%, CMH p=.031) and no significant difference between the tadalafil 5-mg and placebo groups in subjects <75 years of age (0.6% versus 1.1%, CMH p=.375), but it was not considered clinically meaningful. There was no evidence from tadalafil once-a-day studies for the treatment of ED for an interaction with age and incidence of diarrhoea. Overall, regarding TEAEs possibly related to hypotension, no significant treatment-by-subgroup interactions or treatment group differences were observed. In subjects receiving tadalafil 5 mg compared with placebo, a numerically higher incidence of dizziness was observed in subjects ≥75 years of age (4.8% versus 1.1%) compared with subjects <75 years of age (0.9% versus 0.8%). These results observed in BPH subjects are similar to those in the tadalafil once-a-day submission for ED; in subjects receiving tadalafil 2.5-mg and 5-mg once-a day dosing in ED studies, a higher incidence of dizziness was observed in subjects older than 65years of age compared with younger subjects (>65 years, 2.3%; ≤65 years, 0.5%).

Table APP.2.7.4.105. Common Treatment-Emergent Adverse Events by Age (<75, >=75) in the Integrated Analysis Set By Decreasing Frequency in the Overall Tadalafil 5-mg Group
All Randomized Subjects
Studies LVID, LVHG, LVHJ, and LVHR Double-Blind Treatment Period

		Placebo			Tad 5 mg			Total			Homogeneity of Odds Ratios	Between Group Comparison
Preferred Term	Age	N	n	(%)	N	n	(%)	N	n	(%)	p-value*a	p-value*b
Subjects with >= 1 TEAE	<75	655	138	(21.1)	668	179	(26.8)	1323	317	(24.0)	.330	.013
	>=75	93	18	(19.4)	84	27	(32.1)	177	45	(25.4)		.043
Headache	<75	655	14	(2.1)	668	26	(3.9)	1323	40	(3.0)	.612	.063
	>=75	93	1	(1.1)	84	3	(3.6)	177	4	(2.3)		.259
Back pain	<75	655	9	(1.4)	668	17	(2.5)	1323	26	(2.0)	.445	.130
	>=75	93	0	(0.0)	84	1	(1.2)	177	1	(0.6)		.295
Dyspepsia	<75	655	1	(0.2)	668	17	(2.5)	1323	18	(1.4)	.798	<.001
	>=75	93	0	(0.0)	84	1	(1.2)	177	1	(0.6)		.439
Nasopharyngitis	<75	655	15	(2.3)	668	15	(2.2)	1323	30	(2.3)	.908	.930
	>=75	93	2	(2.2)	84	2	(2.4)	177	4	(2.3)		.714
Hypertension	<75	655	5	(0.8)	668	12	(1.8)	1323	17	(1.3)		.090
	>=75	93	0	(0.0)	84	0	(0.0)	177	0	(0.0)		
Pain in extremity	<75	655	0	(0.0)	668	10	(1.5)	1323	10	(0.8)		.002
	>=75	93	0	(0.0)	84	1	(1.2)	177	1	(0.6)		.280
Diarrhoea	<75	655	7	(1.1)	668	4	(0.6)	1323	11	(0.8)	.027	.375
	>=75	93	1	(1.1)	84	6	(7.1)	177	7	(4.0)		.031
Dizziness	<75	655	5	(0.8)	668	6	(0.9)	1323	11	(0.8)	.272	.803
	>=75	93	1	(1.1)	84	4	(4.8)	177	5	(2.8)		.087
Myalgia	<75	655	4	(0.6)	668	9	(1.3)	1323	13	(1.0)		.180
	>=75	93	0	(0.0)	84	0	(0.0)	177	0	(0.0)		
Gastrooesophageal reflux disease	<75	655	0	(0.0)	668	7	(1.0)	1323	7	(0.5)		.009
	>=75	93	0	(0.0)	84	1	(1.2)	177	1	(0.6)		.280

Overall, for subjects reporting at least 1 SAE or any individual SAEs, no significant treatment-by-subgroup interactions or treatment group differences were observed. Two tadalafil subjects ≥75 years of age reported SAEs: acute MI and coronary artery disease, both previously described.

Discontinuations due to AEs for subjects <75 and ≥75 years of age in the integrated analysis set, overall, did not show any significant treatment-by-subgroup interactions. A significantly greater percentage of subjects <75 years of age in the tadalafil 5-mg group discontinued due to AEs compared with the placebo group (3.3% versus 1.4%, CMH p=.018), whereas no significant treatment group difference was observed in subjects ≥75 years of age.

-- Erectile Dysfunction

In the integrated analysis set, 1159 (77.4%) reported ED at baseline and 338 (22.6%) reported no ED at baseline (ED status was unavailable for 3 subjects in the integrated analysis set). No significant

treatment-by-subgroup interaction was observed for subjects reporting at least 1 TEAE, and the profile of common TEAEs was generally similar between men with or without ED at baseline. A significant treatment-by-subgroup interaction was observed for hypertension (HOR p=.021), which was driven by a significantly greater percentage of subjects with ED reporting hypertension in the tadalafil 5-mg group compared with the placebo group (2.1% versus 0.5%, CMH p=.012) and no treatment group difference among subjects without ED. The MAH argues that this apparent increase in incidence of hypertension in subjects with ED compared to those subjects without ED appears to be a chance finding refuted by objective blood pressure measures, a lack of association between tadalafil treatment and development of hypertension in prior studies of men with ED and the recognised mechanism of action (MOA) of tadalafil as a mild vasodilator. These data show no evidence of reduced tolerability or unique safety issues with tadalafil 5 mg in subjects with BPH-LUTS who also have ED.

--Cardiovascular Disease

In the integrated analysis set, no significant treatment-by-subgroup interactions were observed for subjects reporting at least 1 TEAE or any individual TEAEs, and the profile of common TEAEs was generally similar between men with or without cardiovascular disease at baseline. These data show no evidence of reduced tolerability or unique safety issues with tadalafil 5 mg in subjects with cardiovascular disease at baseline.

-- Hypertension

In the integrated analysis set, a treatment-by-subgroup interaction was observed for subjects reporting nasopharyngitis (HOR p=.089); the MAH argues that this finding is likely an artifact caused by opposing treatment group differences within the subgroups (that is, more TEAEs of nasopharyngitis were reported in the tadalafil 5-mg group than in the placebo group [3.0% versus 1.4%] in subjects with baseline hypertension, and fewer TEAEs of nasopharyngitis were reported in the tadalafil 5-mg group than in the placebo group [1.8 % versus 2.8%] in subjects without baseline hypertension) and does not appear to indicate a true treatment-by-subgroup interaction. These data show no evidence of reduced tolerability or unique safety issues with tadalafil 5 mg in subjects with hypertension at baseline.

-- Diabetes

In the integrated analysis set, no significant treatment-by-subgroup interactions were observed for subjects reporting at least 1 TEAE or for any individual TEAEs. These data show no evidence of reduced tolerability or unique safety issues with tadalafil 5 mg in subjects with diabetes at baseline.

-- Renal Impairment

For the analysis of TEAEs by renal status, degree of renal impairment was defined as normal (CrCl >80 mL/min), mild (CrCl >50 to 80 mL/min), moderate (CrCl >30 to 50 mL/min), and severe (CrCl ≤30 mL/min) at baseline (Visit 3). Subjects with severe renal insufficiency as defined in the individual study protocols were excluded from study participation. In the integrated analysis set, no significant treatment-by subgroup interactions were observed for subjects reporting at least 1 TEAE or for any individual TEAEs. These data show no evidence of reduced tolerability or unique safety issues with tadalafil 5 mg in subjects with mild or moderate renal impairment at baseline. Consistent with existing label language, it is recommended that no dose adjustment is needed for subjects with mild or moderate renal impairment. However, in previous clinical pharmacology studies of 5- to 20-mg single tadalafil doses in subjects with mild renal insufficiency (creatinine clearance 51 to 80 mL/min), moderate insufficiency (creatinine clearance 31 to 50 mL/min), or end-stage renal disease (ESRD) on dialysis, exposure in subjects with renal insufficiency was approximately double that in healthy subjects. Across subjects with renal insufficiency, the mean t1/2 was prolonged (approximately 50

hours) and haemodialysis contributed negligibly to tadalafil elimination. As such, for subjects with severe renal impairment, as in the ED population, once-daily tadalafil is not recommended in the BPH population.

--Hepatic Impairment

Patients with clinical evidence of hepatic impairment were excluded from the BPH clinical studies, and once-a-day dosing has not been extensively evaluated in patients with hepatic impairment. Therefore, the current dosing recommendation for once-a-day treatment of ED remains scientifically appropriate for use in the treatment of BPH. Specifically, if tadalafil is prescribed to patients with hepatic impairment, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician.

- Extrinsic Factors

-- Prior Use of Alpha-Blocker Therapy

In the integrated analysis set, overall, a significant treatment-by-subgroup interaction was observed for subjects reporting at least 1 TEAE (HOR p=.058), which was driven by the significantly greater percentage of TEAEs reported by subjects who did receive prior alpha-blocker therapy in the tadalafil 5-mg group compared with the placebo group (35.8% versus 21.5%, respectively; CMH p=.001). For individual TEAEs, a significant treatment-by subgroup interaction was observed for nasopharyngitis (HOR p=.060), which the MAH argues that appears to be an artefact caused by the small number of events reported and opposing treatment-group differences within the subgroups (that is, more TEAEs of nasopharyngitis were reported in the tadalafil 5-mg group than in the placebo group [3.9% versus 1.5%] in subjects who did receive prior alpha-blocker therapy, and fewer TEAEs of nasopharyngitis were reported in the tadalafil 5-mg group than in the placebo group [1.6% versus 2.6%] in subjects who did not receive prior alpha-blocker therapy) and therefore does not appear to indicate a true treatment-by-subgroup interaction. The TEAE findings observed in subjects with prior alpha-blocker use are consistent with the known safety profile of tadalafil, with no clinically important findings relevant to prior alpha blocker use.

--Adverse Events Reported during Alpha-Blocker Washout Periods of the pivotal studies and study LVHK

Adverse events that occurred in screened subjects who discontinued alpha-blocker therapy during the screening/washout period were evaluated in order to assess the likelihood of symptomatic worsening and urinary retention during this timeframe.

In Study LVHK, of the 24 subjects requiring alpha-blocker washout, 3 subjects (12.5%) reported a total of 3 events: ecchymosis, skeletal injury, and 1 urinary event of urethral haemorrhage (this event was likely related to the invasive urodynamic procedure conducted at Visit 2).

In Study LVHG, of the 100 screened subjects requiring alpha-blocker washout during the screening/washout period, 8 subjects (8.0%) reported 14 events, including 1 urinary event of dysuria.

In Study LVHJ, no procedure-related AEs were reported during the screening/washout.

In Study LVHR, a total of 113 subjects who were screened required alpha-blocker washout; 4 of those subjects (3.5%) reported 5 procedure-related AEs: dysuria and nocturia (1 subject), micturition disorder (1 subject), residual urine (1 subject), and urinary retention (1 subject). Of the subjects reporting procedure-related AEs following alpha-blocker washout, all had discontinued tamsulosin.

In Study LVID, a total of 67 subjects who were screened required alpha-blocker washout; 1 of those subjects (1.5%) reported at least 1 procedure-related AE (pollakiuria); this subject had discontinued tamsulosin on his screening visit date.

--Prior Use of PDE5 Inhibitor Therapy

Overall, for subjects reporting at least 1 TEAE, no significant treatment-by-subgroup interaction was observed. Although a significant treatment-by-subgroup interaction was observed for myalgia (HOR p=.019), the MAH argues that this finding is likely due to the opposing treatment-group differences within the subgroups and therefore does not appear to indicate an actual treatment by-subgroup interaction. The common TEAEs observed in subjects with prior PDE5 inhibitor use are consistent with the known safety profile of tadalafil, with no clinically important findings relevant to prior PDE5 use identified.

Use in Pregnancy and Lactation

The transition of tadalafil or its metabolites to placenta and milk was observed in pregnant and lactating rats (previously submitted non-clinical reports). There were no reports of pregnancy in female partners of men associated with use of tadalafil in the BPH clinical trials.

In ED studies, 3 pregnancies were reported in female sexual partners of men who received tadalafil in once-a-day clinical studies. Two of these female partners gave birth to healthy babies, while no information about the outcome of the third pregnancy was made available to the MAH. In studies of patients with pulmonary artery hypertension (PAH), 2 pregnancies were reported. One subject became pregnant while receiving placebo, and continued into extension Study LVGX, where she received tadalafil 40 mg per day for 2 days during the first trimester, then discontinued therapy when a pregnancy test was found to be positive. She delivered a baby boy by caesarean section after 36 weeks' gestation. Another subject became pregnant during the study and due to the severity of PAH in this subject, a therapeutic abortion was performed without complications.

As of 15 April 2011, there have been 8 reports of pregnancy from spontaneous reports and literature involving the use of tadalafil. In only 1 of these was the patient taking tadalafil. This was a 26-year-old woman taking tadalafil 40-mg per day for PAH, starting at 16 weeks of gestation. The estimated due date was 9 October 2010, with follow-up information received 12 October 2010. There were no complications reported at the time of follow-up. The other 7 reports involved pregnancies where the male partner was taking tadalafil. In 1 case there was a spontaneous abortion at 5½ weeks' gestation. In another, the infant died due to a Bochdaleks hernia (diaphragmatic malformation resulting in abdominal organs invading the chest, causing lung malformation, often fatal). There were 2 reports of live births and 3 with no outcome reported.

No changes to the pregnancy and lactation section in the current SmPC are proposed.

Immunological events

N/A

Safety related to drug-drug interactions and other interactions

Only concomitant medications that are likely to present a PK interaction or those with an interaction already described in the SPC are summarized in this AR.

-- CYP3A4

Previously submitted clinical pharmacology studies evaluated the interactions of tadalafil with other drugs, and these studies are applicable to the once-a-day use of tadalafil for the treatment of BPH. The recommendations regarding CYP3A4 use and tadalafil present in the EU SPC for tadalafil for the treatment of ED are relevant for CIALIS for the treatment of BPH. Specifically, that caution should be exercised when prescribing CIALIS to patients using potent CYP3A4 inhibitors (ritonavir, saquinavir,

ketoconazole, itraconazole, and erythromycin) as increased tadalafil exposure (AUC) has been observed if the medicines are combined.

-- Alpha Blockers

As previously mentioned, studies were conducted with alpha-adrenergic receptor-blocking agents. In studies assessing the effect of co-administration of the alpha blockers tamsulosin (Study LVGN, Study LVAY) or alfuzosin (Study PDY5734), tadalafil had no clinically significant effects on blood pressure. In studies assessing the effect of co-administration of alpha blocker doxazosin (Study LVFG, Study LVGT, and Study LVFT), tadalafil augmented the blood pressure-lowering effect of doxazosin.

In Study LVGT, a clinical pharmacology study of once-daily tadalafil co-administered with doxazosin (previously submitted during procedure EMEA/H/C/436/X/0026-0027), the most frequently reported drug-related adverse events reported by subjects receiving tadalafil and doxazosin were myalgia and back pain. The majority of episodes of myalgia were described as pain in the legs, thighs or calves.

-- Co-administration of Alpha Blockers in Safety Study LVHS

Study LVHS assessed the safety of tadalafil once a day for 12 weeks in men with BPH on concomitant alpha-blocker therapy. In this study, 58.8% of subjects were over the age of 65, and 24.5% were 75 years or older. The primary objective was to evaluate the proportion of men with BPH-LUTS experiencing treatment-emergent dizziness when adding tadalafil 5 mg once daily to concomitant alpha-blocker therapy compared to adding placebo to alpha-blocker therapy. Similar proportions of subjects in each treatment arm, all of whom were taking a stable dose of alpha blocker, experienced treatment-emergent dizziness (tadalafil 7.0%, placebo 5.7%, p=.403). Secondary analyses of TEAEs possibly related to hypotension were conducted using both a focused list and an expanded list of MedDRA preferred terms in order to assess the incidence of clinical AEs related to orthostasis and hypotension. For both the focused and expanded analyses of TEAEs possibly related to hypotension, similar proportions of subjects in each treatment group reported at least 1 TEAE, with no statistically significant differences between treatment groups. There was a trend toward increased reporting of TEAEs possibly related to hypotension in men on non-selective alpha blockers (i.e. doxazosin).

In a subgroup analysis of TEAEs possibly related to hypotension by age (≥75 years, <75 years), results were similar between tadalafil and placebo within the younger subgroup and for tadalafil subjects between age subgroups. However, a smaller proportion of placebo subjects in the elderly subgroup reported these TEAEs than in the younger subgroup (5.3% and 10.7%, respectively), leading to a numerically greater proportion of elderly tadalafil subjects reporting events than elderly placebo subjects (12.5% and 5.3%, respectively). No statistically significant differences were observed between tadalafil and placebo in the percentage of subjects meeting at least 1 criterion for treatment-emergent orthostatic hypotension in subgroups of subjects ≥75 years of age. Overall, results of Study LVHS safety did not lead to identification of new safety concerns related to concomitant administration of tadalafil with alpha-blocker therapy. Results in this population of men with BPH were similar to past clinical pharmacology studies of tadalafil with concomitant alpha-blocker administration in healthy subjects, with a trend toward increased haemodynamic signs and symptoms in men on non-selective alpha blockers, most notably those subjects on concomitant doxazosin, as described in the existing CIALIS SmPC. Caution should therefore be exercised when prescribing tadalafil to patients who are taking alpha blockers, as simultaneous administration may lead to symptomatic hypotension in some patients, and the combination of tadalafil and doxazosin is not recommended.

--Antihypertensive Medications

No significant treatment-by-subgroup interactions were observed between the concomitant antihypertensive therapy subgroups. There was no evidence of an increase in TEAEs possibly related to

hypotension with tadalafil treatment compared to placebo in subjects receiving 1 class or 2 or more classes of antihypertensive agents.

Discontinuation due to AES

As previously discussed in the efficacy assessment, the percentage of subjects discontinuing due to an AE was significantly greater in the tadalafil 5-mg group compared to the placebo group (3.1% versus 1.5%, p=.039). Headache was the most frequently reported AE leading to discontinuation in the tadalafil 5-mg group (0.7%), and was the only event that was reported by a significantly greater percentage of subjects in the tadalafil group compared with placebo (p=.025).

In the tadalafil 5-mg group of the integrated analysis set, of the 23 AEs leading to discontinuation, 15 were considered by the investigator to be related to study drug: headache (5 subjects), myalgia (2 subjects), upper abdominal pain (2 subjects), back pain, muscle spasms, pain in extremity, dyspepsia, vision blurred, and acute MI. The acute MI was reported as an SAE that resulted in death, as previously mentioned. In the placebo group, of the 11 AEs leading to discontinuation, 8 were considered by the investigator to be related to study drug: anxiety, asthenia, dizziness, eye pain, upper abdominal pain (2 subjects), back pain, and blood creatine phosphokinase increased.

In the long-term analysis set, 22 subjects (5.2%) discontinued due to AEs. Eleven AEs leading to discontinuation were considered by the investigator to be related to study treatment: dyspepsia (2 subjects), visual impairment, muscle tightness, abdominal discomfort, unilateral deafness, hot flush, oesophagitis, hepatic enzyme increased (subject with known Hepatitis), coronary artery disease, and GERD.

In Study LVID (tadalafil 5 mg or placebo, with tamsulosin 0.4 mg as an active control), 5 subjects discontinued the study due to AEs: 2 subjects (1.2%) in the placebo group (anxiety and asthenia), 2 subjects (1.2%) in the tadalafil 5-mg group (pancreatitis and vision blurred), and 1 subject (0.6%) in the tamsulosin 0.4-mg group (headache). No statistically significant differences were observed between either the tadalafil or tamsulosin group compared with placebo. Among AEs leading to discontinuation that were considered by the investigator to be related to study treatment, 1 was in the tadalalfil 5-mg group (vision blurred), 1 was in the tamsulosin 0.4-mg group (headache), and 2 were in the placebo group (anxiety and asthenia).

In Study LVHK, few subjects discontinued the study due to AEs. Two subjects (2.0%) in the tadalafil 20-mg group reported AEs that led to study discontinuation: 1 subject discontinued due to headache, which was considered by the investigator to be related to study drug, and 1 subject reported an AE of Peyronie's disease 3 days after randomisation. In the opinion of the investigator, the Peyronie's disease was a preexisting condition that was undiagnosed prior to the subject's study participation. One subject (1.0%) in the placebo group discontinued the study due to MI, which resulted in death (previously mentioned).

In Study LVHS (tadalafil 5 mg or placebo co-administered with alpha-blocker therapy), 13 subjects discontinued the study due to AEs: 7 subjects (4.4%) in the tadalafil 5-mg group and 6 subjects (3.8%) in the placebo group. In the tadalafil 5-mg group, 4 AEs leading to discontinuation were considered by the investigator to be related to study treatment: headache (2 subjects), atrial fibrillation, and back pain. In the placebo group, 3 AEs leading to discontinuation were considered by the investigator to be related to study treatment (visual acuity reduced, vision blurred, and pollakiuria).

In the clinical pharmacology analysis set, the Asian studies (Studies LVIA, LVHB, and LVHT, and the open-label extension period of Study LVIA) and the proof-of-concept Study LVGC, few AEs leading to discontinuation were reported. These events were consistent with the known safety profile of tadalafil.

Post marketing experience

Cumulatively through 15 April 2011, there have been only 4 cases reporting off-label use for BPH or prostate disease in the Lilly safety system (LSS) database. The adverse events reported in these cases are myalgia (2), drug ineffective (1) and nausea (1).

1.5.3. Discussion

During the clinical development of tadalafil for BPH a total of 1582 patients have been exposed to tadalafil in the double blind, placebo-controlled BPH studies. Overall, 752 of them received tadalafil 5mg once a day. A total of 357 subjects were exposed to tadalafil 5mg for at least 6 months and 283 subjects were exposed to it for at least 1 year, for the BPH indication. The overall exposure to tadalafil 5 mg once-a-day for the proposed BPH indication fulfils ICH guideline recommendation with regard to exposure for chronically administered drugs for non-life-threatening conditions.

In relation to the elderly, 440 subjects >65 years and 117≥75 years of age, were exposed to tadalafil 5 mg in the clinical trials. Of them, 127 subjects >65 years of age and 35 subjects ≥75 years, were exposed for at least 6 months. A total of 104 subjects >65 years and 28 subjects ≥75 years had been exposed for at least 1 year. This exposure may be deemed as limited considering that the real use of tadalafil in BPH might include a larger proportion of elderly subjects.

The common TEAEs in the BPH population of headache, back pain, dyspepsia, hypertension, pain in extremity, diarrhea, dizziness, myalgia and GERD were reported in a greater percentage of patients in the tadalafil 5-mg group compared to placebo. The majority of AE were reported as mild or moderate in intensity. With the exception of pain in extremity, all were labelled in the current Cialis SPC as ADRs. Pain in extremity is not usually related to myalgia. Myalgia is a condition that preferably involves high bulk muscles, which are more proximal than distal. The cause may not be muscular per se, but may be vascular or neurological. The MAH was asked to comment on this newly reported AE. Apart from a potential relationship with the known vasodilatory activity proposed for myalgia/back pain, no other possible causal mechanism has been hypothesized. The MAH has included the term "pain in the extremity" in the product information (section 4.8).

Overall, no large differences between data by patient/ by event were observed. No new safety signals or safety profiles have been identified.

Four subjects died in BPH studies, 3 deaths in tadalafil-treated subjects (2 due to MI and one to subaracnoid haemorrhage). A review of individual subject data for the 3 deaths in tadalafil-treated subjects indicated all the subjects had preexisting cardiovascular risk factors. However, with respect to the case of the subaracnoid haemorrhage the fact that the patient was hypertensive and that this was considered the risk factor for SAH is not sufficient to discard this event. Moreover, the risk of SAH during sexual intercourse attempts is well known.

The uroflowmetry and post-void residual urine volume measures do not seem to suggest a clinically adverse effect of tadalafil on bladder function.

Several specific safety topics have been investigated by the MAH based on the previous experience of tadalafil in other therapeutic indications. This investigation was focused on bleeding events, cardiovascular events, ear and eye disorders as well TEAEs possibly related to hypotension, myalgias/back pain, seizures, and transient global amnesia.

Several cases of bleedings were reported. In general the risk of bleeding events does not seem to increase with the exposure. Among them, haematospermia, not previously described for tadalafil. A

type II variation for the safety signal to be listed in the SmPC is currently under evaluation. Few cases of hypertension, ear disorders and eye disorders were reported, as expected. Myalgias and back pain were reported in 64 subjects (4.3%).

The frequency of infections in the long term exposure was questioned by the CHMP. The MAH provided additional analyses with exposure-adjusted event rates for "infections and infestations" TEAEs. These new analyses adequately responded to the concern and the evidence did not show an increase in infection frequency, when adjusted for tadalafil patient exposure.

Hypotension was not especially frequent in patients on tadalafil although two cases of dizziness led to discontinuation of treatment. The MAH was asked to provide detailed information regarding changes in diastolic and systolic blood pressure. No relevant differences were observed in the blood pressure changes from baseline in the global BHP population. The review of the measures recorded in elderly patients as well as the potentially related to hypotension adverse events shows some numerical differences with respect to younger subjects. As similar figures are reported for the respective placebo groups they cannot be considered of clinical relevance.

With respect to laboratory data, vital signs and physical findings no relevant differences were observed in BPH patients treated with tadalafil with respect to those receiving placebo.

Attention was paid to the safety profile of patients > 75 years. Elderly patients under tadalafil treatment reported adverse events more often than adult patients. In general there were no important differences between patients older and younger than 75 years in the global safety profile except for diarrhoea and dizziness that were more frequent in older patients with respect to patients < 75 years (7,1% versus 0,6% and 4,8% versus 0,9% respectively). However, an additional integrated analyses using a larger sample size, including additional subjects from other BHP studies and the ED clinical program, seemed to suggest a more elevated incidence of AEs as well as discontinuations due to AEs was shown in elderly subjects, especially in the very elderly ones. Diarrhoea and dizziness were again more frequent in patients ≥75 years of age than in those < 75 years and with respect to placebo. Differences were also observed in the occurrence of CV events in tadalafil group between < 65 years (2.4%) and ≥ 65 years BPH patients (3.2% in 65-74 years, 3.6% in 75-84 year-patients) and with respect to placebo. Hypertension was the most reported CV event in 65-74 year group (2.4%) but not in the oldest one. The MAH stated that this effect is inconsistent with the recognized vasodilator action of tadalafil. It is acknowledged that the database is small to draw firm conclusions. Nevertheless, to address the limited size of the safety database (mainly the long-term one) in patients >65 years , safety data in elderly subjects has been added as missing information in the RMP and specific pharmacovigilance activities are identified.

A comparison of the safety profile between patients with ED and BPH showed a similar pattern for both populations, both in frequency and in type of events, except for pain in extremities that were reported in BPH population. Discontinuation due to AEs is slightly higher in the BPH studies than in the ED studies. Although no particular pattern was observed, the fact that BPH subjects were older than those in the ED studies cannot be rule out as a contributing factor, thus indication worse tolerance in this subgroup of patients.

With respect to the coadministration with other medicinal products relevant for this indication, the pharmacodynamic interaction between tadalafil and alpha blockers is already described in the SmPC. Caution is advised when they are coadministered specially for the elderly patients.

A formal PK/PD characterization of the combination of tadalafil and 5-ARIs has not been performed. In the MAH's opinion, in theory, drug-drug interactions are not expected to occur with concomitant treatment. In that sense, the data provided from a clinical trial that compared tadalafil 5 mg plus

finasteride 5 mg to placebo plus finasteride 5 mg in the relief of BPH symptoms seems to indicate that the safety profile of the combination treatment is not different from those of the separate drugs.

1.6. Risk management plan

Based on the safety conclusions, the CHMP requested the submission of an updated Risk Management Plan (version 5.2) which included a risk minimisation plan within this procedure.

Table 1. Summary of the risk management plan (including the changes related to the application presented highlighted)

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
Important Identified Risks For All Indications		
Identified Risk: Priapism	• routine pharmacovigilance activities • targeted follow-up investigations	• Specific label text in the SPC under Special Warnings and Precautions (Section 4.4) includes "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 SPC 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 patient to inform their doctor before taking CIALIS if they have any deformation of your penis.
Identified Risk: Hypotension/Increased Hypotensive Effect	• routine pharmacovigilance activities • targeted surveillance term	• Specific label text in the SPC under Section 4.3 (Contraindications) indicates that CIALIS is contraindicated in patients who using any form of organic nitrate, have, hypotension (<90/50mmHg), or uncontrolled hypertension • Specific label text in the SPC under Section 4.4 (Special warnings and precautions) describing the risk of hypotension with tadalafil. • Specific label text in the SPC Section 4.5 (Interaction with other medicinal products and other forms of interaction) for nitrates, anti-hypertensives,

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		and alcohol. • Hypotension has been listed as an adverse reaction under Section 4.8 (Undesirable effects). • The package leaflet, instructs patient not to take CIALIS if they are taking any form of organic nitrate or nitric oxide donors such as amyl nitrite or if they have low blood pressure or uncontrolled high blood pressure. • The package leaflet instructs patients to tell the doctor if they are taking nitrates, or alpha-blockers. • The package leaflet under Possible Side Effects (Section 4) includes low blood pressure
Important Potential Risks		
Important Potential Risks Identified for All Indications		
Potential Risk: Nonarteritic Anterior Ischemic Optic Neuropathy (NAION)	• routine pharmacovigilance activities • targeted follow-up investigations • Observational case crossover study (Study LVHQ) (per regulatory request from FDA)	• Specific label text in the SPC under Section 4.3 (Contraindications) indicates that CIALIS is contraindicated in patients who have loss of vision in one eye because of NAION • Specific label text in the SPC under Special Warnings and Precautions (Section 4.4) includes "Visual defects and cases of NAION have been reported in connection with the intake of CIALIS and other PDE5 inhibitors. The patient should be advised that in case of sudden visual defect he should stop taking CIALIS and consult a physician immediately." • NAION has been listed in the SPC as an adverse reaction under Section 4.8(Undesirable effects). • The package leaflet, instructs patient not to take CIALIS if they have ever had loss of vision because of NAION

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		• The package leaflet informs patients about NAION
Potential Risk: Sudden Hearing Loss	• routine pharmacovigilance activities • targeted follow-up investigations	• Sudden hearing loss has been listed in the SPC as an adverse reaction under Section 4.8(Undesirable effects) • The package leaflet includes this risk of sudden hearing loss.
Important Missing Information		
Important Missing Information Identified for Once-a-Day ED and BPH		
Important Missing Information: Characterization of adverse events in elderly patients (≥65 years)	Routine surveillance and targeted follow up: For ED and BPH indications only: o Comparative analysis of spontaneous ADR reports by SOC with once-a-day dosing data according to patient age: elderly (≥65 years) and patients <65 years to be completed annually in the PSUR that falls on the IBD. o Clinical trials: A cumulative comparison of adverse events reported in the elderly (≥65 years) and patients <65 years from completed placebo-controlled tadalafil studies using once-a-day dosing, to be completed annually in the PSUR that falls on the IBD. o Review cases of hypotension in the very elderly (≥75 years) to be completed annually in the PSUR that falls on the IBD.	• Not applicable

No new pharmacovigilance activities in addition to those already being performed were needed to monitor the safety of the product.

No additional risk minimisation activities were required beyond those included in the product information.

1.7. Changes to the Product Information

During the procedure, the CHMP approved the following amendments to the Product Information:

4.1 Therapeutic indications

In order for tadalafil to be effective for the treatment of erectile dysfunction, sexual stimulation is required.

Treatment of the signs and symptoms of benign prostatic hyperplasia in adult males.

4.2 Posology and method of administration

Posology
Erectile dysfunction in adult men

….

Benign prostatic hyperplasia in adult men
The recommended dose is 5 mg, taken at approximately the same time every day with or without food. For adult men being treated for both benign prostatic hyperplasia and erectile dysfunction the recommended dose is also 5 mg taken at approximately the same time every day. Patients who are unable to tolerate tadalafil 5 mg for the treatment of benign prostatic hyperplasia should consider an alternative therapy as the efficacy of tadalafil 2.5mg for the treatment of benign prostatic hyperplasia has not been demonstrated.

Special populations
Elderly men
Dose adjustments are not required in elderly patients.

Men with renal impairment
Dose adjustments are not required in patients with mild to moderate renal impairment. For patients with severe renal impairment 10 mg is the maximum recommended dose for on-demand treatment.

Once-a-day dosing of 2.5 or 5 mg tadalafil both for the treatment of erectile dysfunction or benign prostatic hyperplasia is not recommended in patients with severe renal impairment. (see sections 4. 4 and 5.2).

Men with hepatic impairment
For the treatment of erectile dysfunction using on-demand CIALIS the recommended dose of CIALIS is 10 mg taken prior to anticipated sexual activity and with or without food. There is limited clinical data on the safety of CIALIS in patients with severe hepatic impairment (Child-Pugh Class C); if prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician. There are no available data about the administration of doses higher than 10 mg of tadalafil to patients with hepatic impairment.

Once-a-day dosing of CIALIS both for the treatment of erectile dysfunction and benign prostatic hyperplasia has not been evaluated in patients with hepatic impairment; therefore, if prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician. (see sections 4.4 and 5.2).

4.4 Special warnings and precautions for use

Before treatment with CIALIS
A medical history and physical examination should be undertaken to diagnose erectile dysfunction or benign prostatic hyperplasia and determine potential underlying causes, before pharmacological treatment is considered.
….

Prior to initiating treatment with tadalafil for benign prostatic hyperplasia patients should be examined to rule out the presence of carcinoma of the prostate and carefully assessed for cardiovascular conditions (see section 4.3).

…

Renal and hepatic impairment

…

There are limited clinical data on the safety of single-dose administration of CIALIS in patients with severe hepatic insufficiency (Child-Pugh Class C). Once-a-day administration either for the treatment of erectile dysfunction or benign prostatic hyperplasia has not been evaluated in patients with hepatic insufficiency. If CIALIS is prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician.

4.5 Interaction with other medicinal products and other forms of interaction

5- alpha reductase inhibitors
In a clinical trial that compared tadalafil 5 mg coadministered with finasteride 5 mg to placebo plus finasteride 5 mg in the relief of BPH symptoms, no new adverse reactions were identified. However, as a formal drug-drug interaction study evaluating the effects of tadalafil and 5-alpha reductase inhibitors (5-ARIs) has not been performed, caution should be exercised when tadalafil is co-administered with 5-ARIs.

4.8 Undesirable effects

….

The most commonly reported adverse reactions in patients taking CIALIS for the treatment of erectile dysfunction or benign prostatic hyperplasia were headache, dyspepsia, back pain and myalgia, in which the incidences increase with increasing dose of CIALIS. The adverse reactions reported were transient, and generally mild or moderate. The majority of headaches reported with CIALIS once-a-day dosing are experienced within the first 10 to 30 days of starting treatment.

….

The table below lists the adverse reactions observed from spontaneous reporting and in placebo-controlled clinical trials (comprising a total of 7116 patients on CIALIS and 3718 patients on placebo) for on-demand and once-a-day treatment of erectile dysfunction and the once-a-day treatment of benign prostatic hyperplasia.

…

Very common	**Common**	**Uncommon**	**Rare**
Immune system disorders			
		Hypersensitivity reactions	Angioedema[3]
Nervous system disorders			
	Headache	Dizziness	Stroke[1] (including haemorrhagic events), Syncope, Transient ischaemic attacks[1], Migraine[3], Seizures, Transient amnesia
Eye disorders			
		Blurred vision, Sensations described as eye pain	Visual field defect, Swelling of eyelids, Conjunctival hyperaemia, Non-arteritic anterior ischemic optic neuropathy (NAION) [3], Retinal vascular occlusion[3]

Ear and labyrinth disorders			
			Sudden hearing loss[2]
Cardiac disorders[1]			
		Tachycardia, Palpitations	Myocardial infarction, Unstable angina pectoris[3], Ventricular arrhythmia[3]
Vascular disorders			
	Flushing	Hypotension[4], Hypertension	
Respiratory, thoracic and mediastinal disorders			
	Nasal congestion	Dyspnoea, Epistaxis	
Gastrointestinal disorders			
	Dyspepsia, Gastro-oesophageal reflux	Abdominal pain	
Skin and subcutaneous tissue disorders			
		Rash, Hyperhydrosis (sweating)	Urticaria, Stevens-Johnson syndrome[3], Exfoliative dermatitis[3],
Musculoskeletal, connective tissue and bone disorders			
	Back pain, Myalgia, Pain in extremity		
Reproductive system and breast disorders			
			Prolonged erections, Priapism[3]
General disorders and administration site conditions			
		Chest pain[1]	Facial oedema[3], Sudden cardiac death[1, 3]

(1) Most of the patients had pre-existing cardiovascular risk factors (see section 4.4).
(2) Sudden decrease or loss of hearing has been reported in a small number of postmarketing and clinical trial cases with the use of all PDE5 inhibitors, including tadalafil.
(3) Postmarketing surveillance reported adverse reactions not observed in placebo-controlled clinical trials.

Other special populations

Data in patients over 65 years of age receiving tadalafil in clinical trials, either for the treatment of erectile dysfunction or the treatment of benign prostatic hyperplasia, are limited. In clinical trials with tadalafil 5mg taken once a day for the treatment of benign prostatic hyperplasia, dizziness and diarrhoea were reported more frequently in patients over 75 years of age.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

…

Tadalafil has no effect in the treatment of erectile dysfunction in the absence of sexual stimulation.

The effect of PDE5 inhibition on cGMP concentration in the corpus cavernosum is also observed in the smooth muscle of the prostate, the bladder and their vascular supply. The resulting vascular relaxation increases blood perfusion which may be the mechanism by which symptoms of benign prostatic hyperplasia are reduced. These vascular effects may be complemented by inhibition of bladder afferent nerve activity and smooth muscle relaxation of the prostate and bladder.

…

Erectile dysfunction

For CIALIS on demand, three clinical studies were conducted in 1054 patients in an at-home setting to define the period of responsiveness. Tadalafil demonstrated statistically significant improvement in erectile function and the ability to have successful sexual intercourse up to 36 hours following dosing, as well as patients' ability to attain and maintain erections for successful intercourse compared to placebo as early as 16 minutes following dosing.

In a 12-week study performed in 186 patients (142 tadalafil, 44 placebo) with erectile dysfunction secondary to spinal cord injury, tadalafil significantly improved the erectile function leading to a mean per-subject proportion of successful attempts in patients treated with tadalafil 10 or 20 mg (flexible-dose, on demand) of 48% as compared to 17% with placebo.

For once-a-day evaluation of tadalafil at doses of 2.5, 5, and 10 mg 3 clinical studies were initially conducted involving 853 patients of various ages (range 21-82 years) and ethnicities, with erectile dysfunction of various severities (mild, moderate, severe) and etiologies.
….

Benign prostatic hyperplasia

CIALIS was studied in 4 clinical studies of 12 weeks duration enrolling over 1500 patients with signs and symptoms of benign prostatic hyperplasia. The improvement in the total international prostate symptom score with CIALIS 5mg in the four studies were -4.8, -5.6, -6.1 and -6.3 compared to -2.2, -3.6, -3.8 and -4.2 with placebo. The improvements in total international prostate symptom score occurred as early as 1 week. In one of the studies, which also included tamsulosin 0.4 mg as an active comparator, the improvement total international prostate symptom score with CIALIS 5mg, tamsulosin and placebo were -6.3, -5.7 and -4.2 respectively.

One of these studies assessed improvements in erectile dysfunction and signs and symptoms of benign prostatic hyperplasia in patients with both conditions. The improvements in the erectile function domain of the international index of erectile function and the total international prostate symptom score in this study were 6.5 and -6.1 with CIALIS 5 mg compared to 1.8 and -3.8 with placebo, respectively. The mean per-subject proportion of successful sexual intercourse attempts was 71.9% with CIALIS 5 mg compared to 48.3% with placebo.

The maintenance of the effect was evaluated in an open-label extension to one of the studies, which showed that the improvement in total international prostate symptom score seen at 12 weeks was maintained for up to 1 additional year of treatment with CIALIS 5mg.

2. Overall conclusion and impact on the benefit/risk balance

Benefits

- Beneficial effects

Tadalafil is a selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP) - specific phosphodiesterase type 5 (PDE5) for the treatment of erectile dysfunction (ED) in adult men.

In support of this variation the MAH has provided four randomised, double-blind, placebo-controlled, 12-week, parallel-design, multinational studies to evaluate the efficacy and safety of tadalafil once-a-day dosing in men with signs and symptoms of BPH. Three of those studies were performed in the general BHP population and one included subjects with both BHP and ED. Doses of 2,5mg, 5mg, 10 mg and 20 mg were tested in the treatment of BHP compared to placebo. One trial (Study LVID) also included tamsulosin 0,4mg once a day as an active control. The population of subjects participating in the pivotal trials seems mostly adequate and representative for patients with BPH.

Efficacy results of the general population studies showed a statistically significant improvement for the primary endpoint (IPSS) in patients treated with tadalafil compared to placebo. Across the studies, the

results were mostly consistent. The study population did have different absolute improvement values depending on whether they were < 20 IPSS vs. >= 20 IPSS values at baseline. On average, mild-moderate patients improved 2 points while severe patients improved 6 points. Overall the responder rates of the treatment effect were comparable (15%) across trials. The % improvement in the treatment arms were >25% and was comparable to other treatments.

A positive effect was also observed in the secondary efficacy outcomes of storage, voiding and most of subjective measures of impact in daily life. Nocturia was the less sensitive symptom to the tadalafil effect. This may negatively affect the quality of life of these patients.

Roughly, the efficacy of tadalafil seems to be similar to that observed for tamsulosin when both medicinal products (although without a statistically formal comparison) were compared. No data is available comparing the efficacy of tadalafil with 5-alpha reductase inhibitors in these patients and limited efficacy/safety data regarding the potential use of tadalafil in combination with 5-alpha reductase inhibitors, therefore the following wording has been included in the SmPC under section 4.5; caution should therefore be exercised when tadalafil is co-administered with 5-alpha reductase inhibitors.

The severity of the condition or the previous treatment, do not seem to systematically influence the response. For the very elderly patients (mainly those > 75 years) only limited clinical data has been obtained as results from limited number of subjects have been gathered this has hampered to reach sound conclusions for the very elderly, but yet no reason to believe there is no benefit.

The maintenance of the effect has only been evaluated during the open label extension periods in a study lasting 52 weeks. Despite the inherent limitations of these types of studies, the data suggest that patients continuing on treatment during the open label period did not have a loss of efficacy.

- Uncertainty in the knowledge about the beneficial effects

There are no new uncertainties in the knowledge about the beneficial effects.

Risks

- Unfavourable effects

The common TEAEs reported in the BPH population were headache, back pain, dyspepsia, hypertension, pain in extremity, diarrhoea, dizziness, myalgia and gastroesophagea reflux disease were reported. In general the safety profile can be considered as comparable to that one already described for the other approved indications. With the exception of pain in the extremities, all were already labelled in the current Cialis SPC. Pain in the extremity is now included in section 4.8.

- Uncertainty in the knowledge about the unfavourable effects

Data show that 32,1% of patients > 75 years versus 26,8% <75 years had at least one TAE. Although in general there were no important differences diarrhoea and dizziness were more frequent in older patients (7,1% versus 0,4% and 4,8% versus 0,9% respectively) than in adults. Acknowledging that the size of the sample is low, given that these patients constitute a relevant target population for the claimed indication the need to generate more data in this population has been added as missing

information in the RMP and specific pharmacovigilance activities are identified. These include a comparative analysis of spontaneous ADR reports by SOC with once-a-day dosing data according to patient age: elderly (≥65 years) and patients <65 years to be completed annually in the PSUR that falls on the IBD; a cumulative comparison of adverse events reported in the elderly (≥65 years) and patients <65 years from completed placebo-controlled tadalafil studies using once-a-day dosing, to be completed annually in the PSUR that falls on the IBD; and a review cases of hypotension in the very elderly (≥75 years) to be completed annually in the PSUR that falls on the IBD.

Benefit-risk balance

In summary, data provided show that tadalafil 5 mg given once daily is efficacious in the treatment of the signs and symptoms of benign prostatic hyperplasia in adult males, with or without erectile dysfunction. Safety does not seem to be significantly different from the already known safety profile except for pain in extremities that is now reported in the BPH population.

Based on the submitted data, the risk/benefit balance for Cialis for the signs and symptoms of benign prostatic hyperplasia in adult males, with or without erectile dysfunction is positive.

3. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Addition of a new indication "Treatment of the signs and symptoms of benign prostatic hyperplasia in adult males including those with erectile dysfunction" for the 5 mg formulation. Sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC and the package leaflet have been updated accordingly.

The requested variation proposed amendments to the Update of Summary of Product Characteristics, Labelling and Package Leaflet.

Conditions and requirements of the marketing authorisation

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 1 of the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

PSUR cycle for the product will follow a yearly cycle until otherwise agreed by the CHMP.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Not applicable.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.