Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for tadalafil

Proprietary Product Name: Cialis

Sponsor: Eli Lilly Australia Pty Ltd

July 2013

TGA Health Safety Regulation

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- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
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I. Introduction to product submission

Submission details

Type of Submission:	Extension of indications
Decision:	Approved
Date of Decision:	16 May 2013
Active ingredient:	Tadalafil
Product Name:	Cialis
Sponsor's Name and Address:	Eli Lilly Australia Pty Ltd 112 Wharf Road West Ryde NSW 2114
Dose form:	Film coated tablets
Strengths:	2.5 and 5 mg
Containers:	Tablet blister pack
Approved Therapeutic use:	Cialis is indicated for the treatment of: • erectile dysfunction (ED) in adult males • moderate to severe lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) in adult males.
Routes of administration:	Oral
Dosage:	5 mg once daily
ARTG Numbers:	128478 (2.5 mg), 128496 (5 mg)

Product background

This AusPAR describes an application by the sponsor, Eli Lilly Australia Pty Ltd, to extend the indications for tadalafil to include the treatment of patients with BPH. The current approved indication is:

> *"Cialis is indicated for the treatment of ED in adult males. Cialis is not indicated for use by women."*

The sponsor proposes to replace the approved indication with the following:

"Cialis is indicated for the treatment of:

- *ED in adult men*
- *the signs and symptoms of benign prostate hyperplasia(BPH) in adult men*
- *ED and the signs and symptoms of (ED/BPH) in adult men."*

Tadalafil is currently approved for on demand treatment of ED (10 and 20 mg) and once a day treatment of ED (5 and 2.5 mg) in adult males under the name Cialis and for the treatment of pulmonary arterial hypertension (40 mg) WHO functional class II and III under the name Adcirca. This submission concerns Cialis only.

Regulatory status

The application to extend the indications of Cialis (tadalafil) 5 mg has been submitted and approved in the following countries[1] shown in Table 1.

Table 1: Summary of the international regulatory status of Cialis for the proposed extended indications.

Country	Submission Date	Status (pending; approved; deferred; withdrawn; rejected)
US	03-Dec-2010	Approved 06 October 2011 Benign Prostatic Hyperplasia CIALIS is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH). Erectile Dysfunction and Benign Prostatic Hyperplasia CIALIS is indicated for the treatment of ED and the signs and symptoms of BPH (ED/BPH).
EU	07-Sep-2011	Approved 24 October 2012 Treatment of the signs and symptoms of benign prostatic hyperplasia in adult males.
Canada	03-Aug-2011	Approved 29 June 2012 CIALIS is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH). CIALIS is indicated for the treatment of ED and the signs and symptoms of benign prostatic hyperplasia (ED/BPH).
New Zealand	12 –Jan-2012	Pending

Product Information

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

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

[1] Sponsor comment: "This was correct at the time of pre ACPM; New Zealand has since received approval on 17 January 2013. Indication: 'Cialis is indicated for the treatment of:

- erectile dysfunction (ED) in adult men. In order for Cialis to be effective in treating ED, sexual stimulation is required.
- moderate to severe lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) in adult men.
- adult men with co-existing ED and LUTS associated with BPH.

III. Nonclinical findings

Introduction

The sponsor seeks an extension of indications for tadalafil to include the treatment of the signs and symptoms of BPH in adult males including those with ED. As the recommended dosage for BPH is 5 mg (considerably lower than the currently approved maximum dosages of 20 mg for ED and 40 mg for pulmonary arterial hypertension [PAH]), there are no outstanding safety issues that require addressing.

Benign prostatic hyperplasia is one of the most common diseases of aging men and can be associated with bothersome LUTS that affect quality of life by interfering with daily living activities. Lower urinary tract symptoms associated with BPH include both storage and voiding symptoms. A large proportion of men with BPH also have ED.

Nonclinical data previously submitted for the ED and PAH indications thoroughly characterised the pharmacology of tadalafil showing it to be a selective, reversible inhibitor of phosphodiesterase type 5 (PDE5), the enzyme responsible for the degradation of cyclic guanosine monophosphate (cGMP). For these indications, the elevation of intracellular cGMP leads to vascular relaxation of corpus cavernosum (ED) and PAH, respectively.

The rationale of this submission is that PDE5 inhibition by tadalafil could also help to alleviate the signs and symptoms of BPH by relaxing the smooth muscle of the prostate and the bladder and improving their vascular supply. Indeed, PDE5 has been identified in tissues throughout the LUT including prostate,[2] urethra,[3] bladder,[4] and the vasculature that supplies blood flow to these tissues.[5]

To support the new indication, the sponsor submitted over 30 literature references and a single original report consisting of three major studies:

- a primary pharmacology study investigating the effect of tadalafil on prostate gland oxygenation;
- a secondary pharmacology study quantifying PDE5 isoenzyme expression in human lower urinary tract tissues; and
- a secondary *in vitro* pharmacology study looking at the vasorelaxant effect of tadalafil on human vesico deferential artery rings.

Oral tadalafil (2 mg/kg/day) treatment for various time periods (1 day, 7 days, and 4 weeks) was shown to improve prostate gland oxygenation and markers of hypoxia (HIF-1α, ETB, BNIP3) in the Spontaneously Hypertensive Rat (SHR) animal model, which is characterised by ischaemia/hypoxia of the genitourinary tract. However, this occurred in the absence of significant changes in mean arterial pressure (a small reduction of 15% was

[2] Uckert S, *et al.* (2001) Characterisation and functional relevance of cyclic nucleotide phosphodiesterase isoenzymes of the human prostate. *J Urol.* 166: 2484-2490; Filippi S, *et al.* (2007) Characterisation and functional role of androgen-dependent PDE5 activity in the bladder. *Endocrinology* 148: 1019-1029; Waldkirch ES, *et al.* (2007) Immunohistochemical distribution of cyclic GMP-dependent protein kinase-1 in human prostate tissue. *Eur Urol.* 52: 495-502.
[3] Werkstrom V, *et al.* (2006) Phosphodiesterase 5 in the female pig and human urethra: morphological and functional aspects. *BJU Int.* 98: 414-423; Fibbi B, *et al.* (2010) Characterisation of phosphodiesterase type 5 expression and functional activity in the human male lower urinary tract. *J Sex Med.* 7: 59-69.
[4] Filippi S, *et al.* (2007) Characterisation and functional role of androgen-dependent PDE5 activity in the bladder. *Endocrinology* 148: 1019-1029; Fibbi B, et al. (2010) Characterisation of phosphodiesterase type 5 expression and functional activity in the human male lower urinary tract. *J Sex Med.* 7: 59-69.
[5] Morelli A, *et al.* (2011) Phosphodiesterase type 5 expression in human and rat lower urinary tract tissues and the effect of tadalafil on prostate gland oxygenation in spontaneously hypertensive rats. *J Sex Med.* 8: 2746-2760.

observed after 4 weeks only), suggesting that tadalafil induced local vasodilation of the prostate vasculature or feeding arteries to the prostate has the biggest impact on prostate oxygenation.

The direct relationship of these results to humans is difficult to assess. SHRs are characterised by reduced pelvic blood flow to the genitourinary tract, ischaemia/hypoxia leading to morphological/structural alterations, such as prostate and bladder fibrosis, increased prostate and bladder contractions, and an increase in urethral resistance.[6] Based on previous toxicokinetic data in rats and the lower recommended clinical dose of tadalafil for BPH, it can be roughly estimated that the 2 mg/kg/day dose given to rats in this study would yield a relative plasma exposure to unbound tadalafil of ~12 times that anticipated in humans at a daily dose of 5 mg.

Regardless of the direct applicability of the SHR model, the nonclinical results support the clinical hypothesis that stimulation of nitric oxide (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 through which tadalafil treatment reduces LUTS in men with BPH. This hypothesis is further supported by results from the secondary pharmacology studies obtained in human tissues – these studies showed that human prostate PDE5 is expressed mostly in the endothelial cells and smooth muscle layer of the vascular bed (particularly the vesicular deferential artery). Specific PDE5 inhibition by tadalafil in the deferential artery had an IC50 of 6.3 nM and was not different from that observed in the corpus cavernosum. Moreover, tadalafil induced a left shift of the concentration response curve to the NO donor, sodium nitroprusside, in human deferential artery rings.

Taken together, the results from the nonclinical pharmacology studies confirm that the human vasculature supporting bladder and prostate perfusion contains high expression and activity of PDE5 which is responsive to inhibition by tadalafil.

Overall, there are no novel safety concerns with the 5 mg once a day dose of tadalafil in adult males. The submitted nonclinical results and literature support the potential efficacy of tadalafil to reduce the signs and symptoms of BPH by a mechanism involving NO/cGMP induced vascular relaxation and increased blood perfusion and oxygenation in the LUT, smooth muscle relaxation of the prostate and bladder, and possibly inhibition of bladder afferent nerve activity.[7]

Nonclinical summary and conclusions

Summary

- The sponsor seeks an extension of indications for tadalafil to include the treatment of the signs and symptoms of BPH in adult males including those with ED. The recommended dosage for BPH is 5 mg, which is considerably lower than the currently approved maximum dosages of 20 mg for ED and 40 mg for PAH.

[6] Tarcan T, *et al.* (1998) Age-related erectile and voiding dysfunction: the role of arterial insufficiency. *Br J Urol.* 82 Suppl 1: 26-33; McVary KT. (2005) Erectile dysfunction and lower urinary tract symptoms secondary to BPH. *Eur Urol.* 47: 838-845; Yono M, *et al.* (2007) Effects of doxazosin on blood flow and mRNA expression of nitric oxide synthase in the spontaneously hypertensive rat genitourinary tract. *Life Sci.* 81: 218-222.
[7] Aizawa N, *et al.* (2011) Effects of nitric oxide on the primary bladder afferent activities of the rat with and without intravesical acrolein treatment. *Eur Urol.* 59: 264-271; Andersson KE, *et al.* (2011) Tadalafil for the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia: pathophysiology and mechanism(s) of action. *Neurourol Urodyn.* 30: 292-301; Yoshimura N, *et al.* (2001) Nitric oxide modulates Ca2+ channels in dorsal root ganglion neurons innervating rat urinary bladder. *J Neurophysiol.* 86: 304-311.

- The nonclinical information submitted consisted of over 30 literature references and a single original report containing one primary pharmacology and two secondary pharmacology studies.
- Oral tadalafil treatment (2 mg/kg/day) improved prostate gland oxygenation and markers of hypoxia after 1 day, 7 days, and 4 weeks in the SHR animal model, which is characterised by ischemia/hypoxia of the genitourinary tract.
- Secondary pharmacology studies in human tissues showed that human prostate PDE5 is expressed mostly in the endothelial cells and smooth muscle layer of the vascular bed (particularly the vesicular deferential artery). Specific PDE5 inhibition by tadalafil in the deferential artery had an IC50 of 6.3 nM, and was not different from that observed in the corpus cavernosum. Moreover, tadalafil induced a left shift of the concentration response curve to the NO donor, sodium nitroprusside, in human deferential artery rings.

Conclusions and recommendation

- Results from the nonclinical pharmacology studies confirmed that the human vasculature supporting bladder and prostate perfusion contains high expression and activity of PDE5 which is responsive to inhibition by tadalafil. The submitted nonclinical data and literature support the potential efficacy of tadalafil to reduce the signs and symptoms of BPH by a mechanism involving NO/cGMP induced vascular relaxation, increased blood perfusion and oxygenation in the LUT, and smooth muscle relaxation of the prostate and bladder.
- As the recommended dosage for BPH is 5 mg (considerably lower than the currently approved maximum dosages of 20 mg for ED and 40 mg for PAH) there are no outstanding nonclinical safety issues that require addressing.
- There are no nonclinical objections to registration of Cialis for the proposed extension of indications.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

The clinical dossier documented a development program of pharmacology, efficacy and safety studies relating to the proposed extension of indications.

The clinical submission contained the following information:

- Ten clinical pharmacology studies, including six that provided pharmacokinetic (PK) data and six that provided pharmacodynamic (PD) data
- Four pivotal efficacy studies, one of which was a dose finding study
- Three pivotal safety studies
- Six other efficacy/safety studies
- Integrated analysis set (LVHG, LVHJ, LVHR, LVID)
- Literature references

Comment: Four pivotal efficacy studies relate to the proposed indication of the treatment of the signs and symptoms of BPH in adult men, namely studies LVHG, LVHJ, LVHR and LVID. Study LVHR also relates to the proposed indication of treatment of ED and the signs and symptoms of BPH (ED/BPH) in adult men. One of the ten clinical pharmacology studies (LVHN) evaluated the PK and cardiovascular dynamics of tadalafil in young and elderly men with BPH-LUTS. One safety and efficacy study (LVDI) relates to the use of tadalafil in men with ED only. A number of the non pivotal clinical efficacy and safety studies and clinical pharmacology studies were in Asian study populations.

The clinical evaluation includes reports of bioanalytical and analytical methods for human studies and other nonclinical information relating to method validation and sample testing.

Pharmacokinetics

Studies providing PK data

Only one PK study was submitted to specifically support the proposed BPH indication (Study LVHN). Other conventional PK studies were submitted in this application as they were included in the integrated clinical pharmacology analysis set.

Of all the studies conducted, Studies H6D-FW-LVFU, H6D-EW-LVCT, H6D-EW-LVGG, H6D-EW-LVHN and H6D-EW-LVFV had a PK primary objective.

None of the PK studies had deficiencies that excluded their results from consideration.

Evaluator's overall conclusions on PK

Study H6D-EW-LVHN was the only PK study submitted to specifically support the proposed use of tadalafil in the treatment of the signs and symptoms of BPH in adult men. This study compared the PK of tadalafil following a single 20 mg oral dose and multiple doses between men with BPH-LUTS aged 70 to 85 years and men with BPH-LUTS aged 60 years and younger. The effect of age on the PK of tadalafil in subjects with BPH-LUTS showed no statistically significant difference at Day 1 or Day 10 between the elderly and young groups for $AUC_{0\text{-}24h}$ (amount of unchanged drug excreted into the urine within first 24 h), Cmax (maximum plasma drug concentration) and tmax (time to reach maximum plasma concentration following drug administration). Exposure ($AUC_{0\text{-}24h}$) to the metabolite of tadalafil, total hydrolysed methyl cathecol glucaronide metabolite, was higher in the elderly subjects compared to the younger subjects at Day 1 and the difference between the groups was statistically significant. At Day 10 the exposure to the metabolite of tadalafil was comparable in subjects in both age groups. As the proportion of men with BPH-LUTS increases with age it is anticipated that a significant proportion of subjects who may use tadalafil for the treatment of BPH will be 70 years and older. This study indicates that the PK of tadalafil in men of such an age are comparable to the PK in younger men.

It is recommended that the results of Study H6D-EW-LVFV, which assessed the effects of ritonavir 500 mg or 600 mg twice daily on the PK of tadalafil following a single 20 mg oral dose in healthy men, are added to the Australian PI for Cialis as they are potentially clinically relevant. The results of the other PK studies submitted do not appear to warrant any changes to the Australian PI for Cialis.

Pharmacodynamics

Studies providing PD data

Of all the studies conducted, Studies H6D-EW-LVFB, H6D-EW-LVFF, H6D-EW-LVFS and H6D-EW-LVFT had a primary PD objective.

There were no PD studies submitted in relation to the effect of tadalafil in the proposed indications. The studies submitted relate to secondary PD effects. The results of these studies contribute to the adverse effects profile of tadalafil.

Evaluator's overall conclusions on PD

Study H6D-EW-LVFB was a PD study with the primary objective of demonstrating that tadalafil had no adverse effect on ventricular repolarisation as assessed by QTc when tadalafil was given as a single 100 mg dose. As the upper limit of the 90% CI (Confidence Interval) for the difference in change in QTc interval in the comparison of 100 mg tadalafil and placebo was below the pre defined limit of +10 ms, the effect of 100 mg tadalafil on the change in QTc interval was declared to be equivalent to that of placebo.

Efficacy

Study LVHR was a single Phase III, randomised double blind, placebo controlled study submitted to support the use of tadalafil in the treatment of ED and the signs and symptoms of BPH in adult men. There was a significantly greater improvement from baseline to endpoint for tadalafil 5 mg, compared with placebo, for both of the co primary efficacy outcomes, total IPSS (International Prostate Symptom Score) and IIEF-EF (International Index of Erectile Function - Erectile Function) Domain. For the comparison between tadalafil 2.5 mg and placebo, the change from baseline to endpoint was statistically significant only for the IIEF-EF Domain score. It is unclear if the clinically meaningful improvements in total IPSS and IIEF-EF Domain in the tadalafil 5 mg treatment group of Study LVHR were assessed based on the mean change from baseline to Week 12 in the tadalafil 5 mg group, the placebo adjusted change in the tadalafil 5 mg group, or the limits of the 95% CI for the placebo adjusted change.

The results of Study LVHR support the proposed indication at the proposed dosage of 5 mg once daily. These results are supported by relevant secondary and exploratory analyses undertaken in the other three pivotal efficacy studies. Change from baseline to endpoint in IIEF-EF Domain was a secondary efficacy outcome in the in pivotal Studies LVHG, LVHJ, and LVID. In these studies, subjects with BPH-LUTS who had ED and were sexually active in the tadalafil 5 mg group had a greater mean improvement in IIEF-EF Domain from baseline to endpoint compared with the placebo group. Although not confirmatory, these results support the proposed indication. IPSS total was evaluated in men with BPH-LUTS, who had a history of ED at study entry, in the primary analysis populations of pivotal Studies LVHG, LVHJ, and LVID. The mean change from baseline to endpoint was greater in the tadalafil 5 mg group compared with the placebo group in both subjects who had a history of ED, and those who did not, across all three studies. Although these subgroup analyses were exploratory, the results are also supportive of the proposed indication.

Study LVHR, the single study submitted to support this indication, was of 12 weeks duration. No long term efficacy data were provided in relation to the study subjects. However, for men with BPH-LUTS, long term efficacy of tadalafil 5 mg once daily was evaluated as a secondary objective of Study LVHG OLE. The results of this study support the efficacy of tadalafil 5 mg once daily for the treatment of BPH-LUTS over 64 weeks. IIEF-EF Domain was also a secondary efficacy measure in this study. Fifty-five per cent of

subjects (n=235) had ED and were sexually active. Based on descriptive statistics, mean IIEF-EF Domain score increased in subjects from baseline to the end of the randomised treatment period and the improvement was still present at the end of the OLE period. These results were seen regardless of the dose of tadalafil received during the double blind treatment period. This suggests that the improvement in IIEF-EF Domain score is maintained with long term use. The current PI for Cialis states that there is insufficient evidence on the maximum duration of once a day dosing treatment for ED and that the appropriateness of continued use of the once a day regimen should be reassessed periodically. As the IIEF-EF Domain score was a secondary efficacy measure in Study LVHG OLE, and subjects with ED who were sexually active were only a subset of all study subjects, it would be appropriate to include a similar statement in relation to the results of once daily doing of tadalafil 5 mg on IIEF-EF Domain in this study.

Of note, the number of subjects aged over 65 years in the tadalafil 5 mg group in Study LVHR was 83, fewer than the number recommended in the guideline "Clinical investigation of medicinal products in geriatrics" (26) to allow detection of a clinically important difference in this subgroup versus younger subjects. Only 21 randomised subjects were aged 75 years or older. There were no detectable differences in treatment effects between the age subgroups (≤ 65 and > 65 years and < 75 and ≥ 75 years) for each of the co primary endpoints. Across all the pivotal BPH studies, however, more than 100 subjects aged over 65 were treated with tadalafil 5mg and, including subjects from the non pivotal efficacy studies, more than 100 subjects aged 75 years or older were treated with tadalafil 5 mg. This number of subjects would appear adequate to support the proposed indication in relation to the treatment of BPH. In relation to the treatment of ED, tadalafil 5 mg once daily dosing for the treatment of ED is already approved in Australia without restriction on the age of the patient who can use tadalafil in this indication.

Study LVHR had a large number of exclusion criteria. The efficacy of tadalafil 5 mg once daily in the proposed indication has, therefore, not been evaluated in the subgroups of the potential target population who have these medical conditions.

No objective measures of the signs of BPH were included as primary or key secondary efficacy variables in the pivotal efficacy studies. It is unclear to the evaluator why the proposed indication includes the treatment of the signs of BPH. The sponsor is requested to clarify the wording of the proposed indication in this regard.

Safety

Studies providing evaluable safety data

The evaluable safety data included data from pivotal efficacy studies, pivotal studies that assessed safety as a primary efficacy, non pivotal efficacy studies, a study relating to the ED indication, and clinical pharmacology studies. An integrated analysis of safety data from the four pivotal efficacy studies was undertaken by the sponsor.

> *Comment: The pivotal efficacy and safety studies had a large number of exclusion criteria. The safety of the use of tadalafil in the proposed indications has, therefore, not been assessed for patients with excluded medical conditions.*
>
> *Exclusion criteria of particular importance include renal impairment, hepatic impairment and certain cardiac and coronary conditions. As BPH-LUTS affects ageing men, it is anticipated that a proportion of men will have such conditions. The existing precautions in relation to hepatic impairment and renal impairment that are included in the currently approved PI appear to be adequate for the proposed indication. The current PI includes contraindications to the use of tadalafil in groups of patients with cardiovascular disease that were not included in the ED trials. These*

contraindications are applicable to the proposed indications also. There are a number of cardiovascular conditions that were exclusion criteria in the pivotal studies in the proposed indications that are not proposed as contraindications or precautions in the draft PI. It is recommended cardiovascular conditions that were exclusion criteria in the pivotal studies are included in the PI as contraindications or precautions in relation to the use of tadalafil in the treatment of BPH-LUTS and the treatment of ED and BPH-LUTS. The sponsor is requested to summarise the important exclusion criteria in the introductory paragraph describing the four pivotal studies in the Clinical Trials section of the PI.

Pivotal efficacy studies

Comment: Safety data from the four pivotal efficacy studies (LVHG, LVHJ, LVHR and LVID) relate to both of the proposed indications as all men had BPH-LUTS. The demographics and baseline characteristics of the subjects in Study LVHR, the study supporting the indication treatment of ED and the signs and symptoms of BPH in adult, were similar to those of the other three studies. The only difference was all the men in Study LVHR had ED compared with a proportion of men in the other three pivotal efficacy studies.

In the pivotal efficacy studies, the following safety data were collected: adverse events (AEs), post void residual volume (PVR), clinical chemistry, haematology and urinalysis.

Additional safety data were collected in one or more of the pivotal studies as follows:

- Vital signs: LVHG, LVID
- Uroflowmetry: LVHJ, LVHR and LVID
- Orthostatic vital signs: LVHR, LVHJ
- Electrocardiogram (ECG): LVHG
- Prostate specific antigen (PSA): LVHG

General AEs

General AEs were collected at each visit and included AEs reported since informed consent was given (including protocol related AEs in Studies LVHJ, LVHR, and LVID). Study subjects were to report AEs to the investigator. AEs were assessed to determine if they were treatment emergent and if they were related to the study drug (or protocol).

Comment: The method by which AEs were collected does not appear to have been described.

AEs of particular interest

In Study LVHG, AEs of particular interest, based on previous regulatory concerns or relevance to BPH-LUTS disease state, were Treatment Emergent Adverse Events (TEAEs) related to the cardiovascular system, vision/eyes, hepatic system, PSA and urinary tract invasive procedures. Terms were chosen from the MedDRA dictionary to reflect these AEs of interest. Cases in the safety database matching the list of MedDRA terms were evaluated further to gain additional knowledge about any correlation with tadalafil.

Orthostatic signs were of particular interest in Studies LVHJ and LVHR. Blood pressure and heart rate were measured at Visits 2 to 7 according to a protocol. A subject was reported to have had a positive orthostatic test if they met one of the following criteria at any time as assessed from supine to standing position: SBP decrease ≥ 20 mm Hg, DBP decrease ≥ 10 mm Hg, heart rate increase ≥ 20 beats/minute or unable to remain standing during the orthostatic assessment. A treatment emergent positive orthostatic test was defined as one in which one of the four criteria was present at any post baseline visit but was not present at baseline (Visit 3). Subjects were to report AEs upon standing during the orthostatic vital

sign assessment. TEAEs were events first reported or worsened in severity during the assessment. The Visit 3 assessment was used as the baseline severity for a specific AE preferred term.

Adverse events possibly related to hypotension were of particular interest in Study LVID. TEAEs possibly related to hypotension were assessed using a list of predefined MedDRA preferred terms. HR, SBP and DBP in the sitting position were measured at each visit. Potentially significant vital signs occurring during the double blind treatment period were summarised using the criteria:

- Heart rate: Low if <50 beat per minute (bpm) and the decrease from baseline was ≥15 bpm, High if >120 bpm and the increase from baseline was ≥15 bpm.
- Systolic blood pressure: Low if ≤90 mm Hg and the decrease from baseline was ≥20 mm Hg, High if ≥160 mm Hg and the increase from baseline was ≥20 mm Hg.
- Diastolic blood pressure: Low if ≤50 mm Hg and the decrease from baseline was ≥10 mm Hg, High if ≥100 mm Hg and the increase from baseline was ≥10 mm Hg.

Laboratory tests

Clinical haematology and chemistry and urinalysis were undertaken in each of the pivotal studies. In Study LVHG, clinical haematology and chemistry, and urinalysis were performed at Visits 1, 3, 6 (Weeks -8 to -5, 0, 6). In the other three pivotal studies, standard laboratory tests including chemistry, haematology and urinalysis were collected at Visit 1 (Week -8 to -5), Visit 3 (Week 0) and Visit 7 (Week 12) or the final visit for subjects who discontinued the study early. A central laboratory performed all the clinical laboratory assessments.

PSA testing was done in study LVHG at Visit 1 (Week -8 to -5), Visit 3 (Week 0) and Visit 6 (Week 12). Blood samples for the PSA were to be collected at least 48 h after the subject's most recent ejaculation. To monitor the possible effect of time and frequency of ejaculation on serum PSA subjects were asked to record the date and time of each ejaculation in ejaculation diaries given to them at Visits 2, 3, 4 and 5. The completed diary for the period between the visits was returned to the study sites. PSA was only measured once in the other three studies, during the screening/wash out period.

Other safety variables assessed

Post-void residual volume (PVR)

Post void residual volumes were determined by ultrasound at all six study visits in Study LVHG. In Studies LVHJ, LVHR and LVID, PVR was determined by ultrasound at Visits 1, 3 and 7. There was a specific protocol for the PVR determination.

ECG

In Study LVHG, ECGs were done at Visit 1 (screening) and Visit 6 (final study visit). ECGs were to be electronically obtained and sent to an interpreted by a specific central cardiologist who was to compare each tracing sequentially to evaluate if there were treatment emergent ECG wave abnormalities. Standardised codes for wave form changes were used.

Uroflowmetry

In Studies LVHJ, LVHR and LVID, uroflowmetry measurements were performed at Visits 2 (Week -4), 3 (Week 0) and 7 (Week 12). Parameters assessed were Qmax (peak urine flow rate), Qmean (mean urine flow rate) and Vcomp (volume of voided urine). Results were considered valid only if the pre void bladder volume was ≥ 150 to ≤ 550 mL on ultrasound and the voided volume was ≥ 125 mL. In Study LVHJ, the uroflowmetry data were read by the principal investigator. In Studies LVHR and LVID, at Visit 2 uroflowmetry data were

recorded on the case report form by a central reader for those subjects randomised. Data from Visits 3 and 7 were recorded by the blinded principal investigator and central reader.

Pivotal studies that assessed safety as a primary outcome

Studies H6D-MC-LVHS (LVHS), H6D-MC-LVHK (LVHK) and the open label extension period of Study LVHG (LVHG OLE) were pivotal studies that assessed safety as a primary outcome.

Dose response and non pivotal efficacy studies

Dose response and non pivotal efficacy studies provided safety data as follows.

Study LVGC provided data on AEs, vital signs, clinical chemistry and haematology, PSA, urinalysis, and PVR.

Studies in Asian populations:

- Study LVHT provided data on AEs, concomitant medications, vital signs, ECG, clinical chemistry and haematology, urinalysis, and PVR
- Study LVIA provided data on AEs, vital signs, clinical chemistry and haematology, urinalysis, PSA, and PVR
- Study LVIA OLE provided data on AEs, vital signs, clinical chemistry and haematology, urinalysis, PSA, and PVR
- Study LVHB provided data on AEs, concomitant medications, vital signs, clinical chemistry and haematology, urinalysis, PSA, and PVR.

Study LVDI, a study related to the currently approved ED indication, provided data on AEs, vital signs, ECG, clinical chemistry and haematology, and urinalysis.

Other studies evaluable for safety only

There were no other studies evaluable for safety only.

Clinical pharmacology studies

All the clinical pharmacology studies provided AE data. A number of the studies also provided data on ECG parameters, clinical chemistry and haematology, vital signs and physical examination.

Study LVFB was a QT study. Study LVHN provided hemodynamic data.

Evaluator's overall conclusions on clinical safety

Overall, the safety profile of tadalafil in the studies submitted to support the proposed indications, treatment of the signs and symptoms of BPH in adult men and treatment of ED and the signs and symptoms of BPH in adult men, was similar to the known safety profile for tadalafil in the treatment of ED. There were few potential safety issues arising from the submitted studies.

Of clinical relevance to the use of tadalafil in the proposed indications, a higher proportion of subjects aged 75 years or older had at least one treatment emergent positive orthostatic test, compared with younger subjects, in Study LVHS, a pivotal safety study. This finding was seen in both the placebo and tadalafil 5 mg treatment groups but only in subjects aged aged 75 years or older was the proportion of subjects who had at least one treatment emergent positive orthostatic test higher in the tadalafil 5 mg group compared with the placebo group. As the target population for the use of tadalafil in the treatment of BPH-LUTS is anticipated to be older than the target population for the use of tadalafil for the treatment of ED, this is of concern. If the decrease in blood pressure is associated with

hypotension related symptoms, such as dizziness, this may in turn result in morbidity for older men, such as falls and their potential clinical sequelae.

The effect of 100 mg tadalafil on the change in QTc interval was found to be equivalent to that of placebo in one thorough QT/QTc study, Study LVFB. However, QTc prolongation has been reported with vardenafil, another PDE5 inhibitor. There were no reports of torsade de pointes in any of the submitted studies, although other clinical events which may be evidence of an effect on the QT interval, such as ventricular tachycardia and syncope, were reported. QT/QTc prolongation is considered a potential safety concern with tadalafil and should be added as a potential risk to the Risk Management Plan.

The concomitant administration of a single dose of tadalafil 20 mg and ritonavir 500 mg and 600 mg twice daily affected the PK of tadalafil. This is of particular clinical relevance in relation to men who are receiving treatment for HIV with ritonavir 600 mg twice daily and who may wish to take tadalafil 20 mg in an on demand dosing regimen for the treatment of ED. It is possible that this drug interaction may affect the PD effect of tadalafil in the treatment of ED.

The pivotal studies had a large number of exclusion criteria. The safety of tadalafil 5 mg once daily in the proposed indications has, therefore, not been evaluated in patients who have the excluded medical conditions.

There appeared to be no new safety issues arising from the studies in Asian study populations with BPH-LUTS.

First round benefit-risk assessment

First round assessment of benefits

The benefits of tadalafil in the proposed usage "treatment of the signs and symptom of BPH in adult men" are:

- Tadalafil is in a different drug class than the currently approved medicines for use in the management of the symptoms of BPH. It has a different mechanism of action and a different adverse effect profile. The addition of tadalafil to the suite of pharmacological management options for BPH-LUTS would be beneficial as patients who cannot use other treatment options may be able to use tadalafil. The contraindications to the use of tadalafil, tamsulosin and dutasteride are not identical potentially enabling a greater proportion of men with BPH-LUTS to receive pharmacological treatment. Of note, tadalafil is indicated for the treatment of ED and does not have the same sexual function adverse effect profile as tamsulosin and dutasteride.
- The results of the pivotal and other efficacy studies submitted to support this indication showed a consistent improvement from baseline in BPH-LUTS, as measured by the total IPSS score.

The benefits of tadalafil in the proposed usage "treatment of ED and the signs and symptom of BPH in adult men" are:

- For men who have both BPH-LUTS and ED, the approval of tadalafil for the treatment of both conditions removes the need for the patient to take separate medications for each condition which in turn reduces the possibility of adverse effects and drug interactions.
- As outlined above, tadalafil is in a different drug class than the currently approved medicines for use in the treatment of BPH-LUTS. Tadalafil is indicated for the treatment of ED and does not have the same sexual function adverse effect profile as tamsulosin, finasteride and dutasteride.

- The single supporting pivotal study for this proposed indication showed a greater improvement in total IPSS score and IIEF-EF score from baseline for tadalafil 5 mg, compared with placebo, and a statistically significant result for both total IPSS score and IIEF-EF score for the comparison between tadalafil 5 mg and placebo.

First round assessment of risks

The risks of tadalafil in the proposed usages "treatment of the signs and symptom of BPH in adult men" and "treatment of ED and the signs and symptom of BPH in adult men" are:

- Although the effect of 100 mg tadalafil on the change in QTc interval was declared to be equivalent to that of placebo based on the results of a thorough QT/QTc study, an association between tadalafil and QT interval prolongation may still exist as vardenafil, another PDE5 inhibitor, produced increases in QTc interval at therapeutic and supratherapeutic doses in a study to elucidate the effect of vardenafil on QT interval in healthy males.
- The pivotal studies had a large number of exclusion criteria. The efficacy and safety of tadalafil 5 mg once daily in the proposed indications has, therefore, not been evaluated in patients who have these excluded medical conditions.
- The effect of tadalafil 5 mg in the improvement in total IPSS and IIEF-EF Domain in the pivotal efficacy studies may not be considered clinically meaningful.
- Although an adequate number of subjects aged over 65 years were exposed to tadalafil 5 mg once daily for at least 12 months in the pivotal efficacy and safety studies, only 28 subjects aged 75 years or older had such exposure, a number unlikely to be sufficient to detect safety signals in this population subgroup with the ongoing use of tadalafil 5 mg once daily.
- In two Studies LVHN and LVHS, there was evidence that tadalafil had a greater negative effect on the blood pressure of older subjects compared with younger subjects. In Study LVHN, a PK study, the mean maximum drop in standing and supine systolic and diastolic blood pressure at both Day 1, following a single dose of tadalafil 20 mg, and Day 10, following once daily dosing with tadalafil 20mg, were higher in the elderly subjects compared with the young subjects. In Study LVHS, a pivotal safety study, a higher proportion of subjects in the tadalafil 5 mg group aged 75 years or older reported TEAEs possibly related to hypotension compared with subjects in the tadalafil 5 mg group aged less than 75 years. In addition, a greater proportion of subjects in the tadalafil 5 mg group aged 75 years or older had at least one treatment emergent positive orthostatic test compared with subjects aged under 75 years. It is anticipated that a proportion of the target population for the proposed indication will be men aged 75 years or older as the proportion of men with BPH-LUTS increases with age. These effects on blood pressure are of potential clinical concern as they may be associated with hypotension related adverse events and possibly falls and the complications of falls.
- Ritonavir 500 mg and 600 mg twice daily affected the PK of tadalafil following a single 20 mg oral dose. This drug interaction may affect the PD effect of tadalafil in the treatment of ED.

In relation to the proposed usage "treatment of ED and the signs and symptom of BPH in adult men", additional risks are:

- The efficacy and safety of use of tadalafil in this specific indication has not been demonstrated beyond 12 weeks although the safety of tadalafil 5 mg once daily in the treatment of BPH-LUTS has been demonstrated over 52 weeks. It is indicated in the currently approved PI for Cialis that there is insufficient evidence of the maximum

duration of treatment with tadalafil 5 mg once daily for the treatment of ED. This limitation would also apply to the proposed usage treatment of ED and the signs and symptom of BPH in adult men.

First round assessment of benefit-risk balance

The benefit-risk balance of tadalafil, given the proposed usage, is favourable.

First round recommendation regarding authorisation

It is recommended that the use of tadalafil 5 mg once daily in the proposed indications is approved if:

- the indications are amended to the treatment of "the lower urinary tract symptoms associated with benign prostatic hyperplasia in adult men" and the treatment of the "ED and the lower urinary tract symptoms associated with benign prostatic hyperplasia in adult men", respectively;
- the product documentation is amended as recommended; and
- the sponsor provides satisfactory answers to the questions.

List of questions

Pharmacokinetics

No questions.

Pharmacodynamics

No questions.

Efficacy

1. With regard to Study LVHG, the sponsor is requested to clarify why the results of the analysis of covariance (ANCOVA) analysis are included in the draft PI given the non parametric permutation test was used for the primary comparison of the primary efficacy outcome.
2. With regard to Study LVHJ, the sponsor is requested to clarify why the amended study report and protocol H6D-MC-LVHJ (a) differ in relation to the testing of secondary endpoints and at what point in the study the order of testing the key secondary endpoints, as described in the amended study report, was determined.
3. With regard to the integrated analysis set, the sponsor is requested to clarify if the integrated analyses were pre specified and to confirm if the data from the four pivotal efficacy studies were integrated using simple pooling.
4. Regarding the two proposed indications, no objective measures of the signs of BPH were included as primary or key secondary efficacy variables in the pivotal efficacy studies. It is unclear to the evaluator why the proposed indications include the treatment of the signs of BPH. The sponsor is requested to clarify the wording of the proposed indications in this regard.

Safety

5. For the two subjects with raised liver transaminases more than three times the upper limit of normal reported in the open label extension period of Study LVHG, there appears to be no information regarding the results of liver function tests after the tadalafil 5 mg was ceased so it is unclear if there was a positive dechallenge. It is requested that the sponsor provide this information.
6. In Study LVGC, a subject randomised to tadalafil who had normal liver function test results at screening and raised alanine aminotransferase (ALT) and aspartate aminotransferase (AST) at Week 12 appears to have had a positive dechallenge after the study ended. From the subject narrative his concomitant medications had been started at least four months prior to the subject commencing tadalafil and they were not ceased. Please clarify if this subject had a positive dechallenge and whether the raised ALT and AST were considered related to tadalafil.
7. With regard to exposure to tadalafil by duration of treatment, it appears that the information on exposure for at least 12 weeks was not available for a number of the studies. The sponsor is requested to provide the number of subjects exposed for 12 weeks or more to tadalafil 2.5 mg in Study LVHR, and tadalafil 5 mg in Studies LVHJ, LVHR and LVGC, and to tadalafil 20 mg in Study LVGC, or indicate where this information can be found in the submission.
8. The TEAEs reported in the pivotal efficacy studies are presented as the proportions of subjects who have had at least one TEAE in the preferred term category. This information does not indicate how many times the subjects reported the individual AEs during the course of the study and when the adverse events occurred in relation to the commencement of the study drug. The sponsor is requested to describe any specific patterns in the AEs reported over the course of the respective pivotal efficacy studies, specifically if there were certain adverse events reported on multiple occasions and, if so, the time between the study commencement and the reporting of the AE, and whether there were any changes in the severity of the AE over the study period.
9. In the clinical pharmacology analysis set, nausea and vomiting led to the discontinuation of a number of study subjects receiving tadalafil (nausea [n=9], vomiting [n=5]). The sponsor is requested to advise if these AEs were considered to be related to tadalafil.
10. Nausea and arthralgia are listed in the US PI for Cialis as adverse reactions reported in less than 1% of subjects in the controlled clinical trials of Cialis for BPH or ED and BPH. These adverse reactions are not included in the proposed Australian PI for Cialis. The sponsor is requested to clarify why these adverse reactions are not included in the proposed PI.

Second round evaluation of clinical data

Question 1: With regard to Study LVHG, please clarify why the results of the ANCOVA analysis are included in the draft PI given the non parametric permutation test was used for the primary comparison of the primary efficacy outcome.

Evaluation of sponsor's response to Question 1:

The sponsor has confirmed that the primary analysis for Study LVHG was a non parametric permutation test and indicates that this test of the differences in the distributions of the change from baseline in total IPSS between tadalafil 5 mg and placebo does not rely on an easily interpretable test statistic. The sponsor indicates that the least squares means from the ANCOVA were used in the proposed PI to allow Study LVHG to be

compared to the other BPH studies. The sponsor reports that this had been deemed an appropriate characterisation of the results based on the observed normality of total IPSS data and based on the fact that there were no noteworthy differences in inference using the least squares means relative to the unadjusted means or the medians. The sponsor's response seems reasonable.

Question 2: With regard to Study LVHJ, please clarify why the amended study report and protocol H6D-MC-LVHJ (a) differ in relation to the testing of secondary endpoints and at what point in the study the order of testing the key secondary endpoints, as described in the amended study report, was determined.

Evaluation of sponsor's response to Question 2:

The sponsor has clarified that the analyses of the secondary endpoints presented in the clinical study report for Study LVHJ are different from those stated in protocol LVHJ (a) as, after protocol LVHJ (a) was approved, the US Food and Drug Administration (FDA) requested that a procedure was pre specified for controlling the overall type I error rate for secondary endpoints that followed the BPH Impact Index. With the agreement of the FDA, a fixed sequence testing procedure to control the family wise type I error in the primary and secondary endpoints was pre specified in the statistical analysis plan. The sponsor has clarified that this change was made prior to the completion of the study. The sponsor's response is accepted.

Question 3: With regard to the integrated analysis set, please clarify if the integrated analyses were pre specified and to confirm if the data from the four pivotal efficacy studies were integrated using simple pooling.

Evaluation of sponsor's response to Question 3:

The sponsor has clarified that the analysis plan for the integrated summaries reported in the submission was completed prior to the last patient visit of Study LVID, the final study, but after the sponsor was unblinded to the results of the other three pivotal efficacy studies. The sponsor has highlighted that, in the analyses of the integrated data, the efficacy parameters were generally consistent with those of the individual studies, that the ANCOVA models used were the same as those used in individual studies with the exception of the addition of an effect for study, and that the analyses used the intent to treat population. The sponsor has confirmed that the analyses of the integrated data from the four pivotal efficacy studies used a simple pooling technique. It is unclear to the evaluator whether using simple pooling to integrate the efficacy results of the pivotal efficacy studies for statistical analysis yields valid results. The comments provided with regard to the inclusion of results from the integrated data analyses remain unchanged.

Question 4: Regarding the two proposed indications, no objective measures of the signs of BPH were included as primary or key secondary efficacy variables in the pivotal efficacy studies. It is unclear to the evaluator why the proposed indications include the treatment of the signs of BPH. Please clarify the wording of the proposed indications in this regard.

Evaluation of sponsor's response to Question 4:

The sponsor has not provided clarification of the wording of the proposed indications but has proposed to remove reference to the signs of BPH from the proposed indications as follows:

"Cialis is indicated for the treatment of:

- *erectile dysfunction (ED) in adult men*
- ~~*the signs and*~~ *lower urinary tract symptoms (LUTS) associated with* ~~*of*~~ *benign prostatic hyperplasia (BPH) in adult men*

- *ED and ~~the signs and symptoms~~ LUTS associated with ~~of~~ BPH (~~ED/BPH~~) in adult men"*

This is acceptable.

Question 5: For the two subjects with raised liver transaminases more than three times the upper limit of normal reported in the open label extension period of Study LVHG, there appears to be no information regarding the results of liver function tests after the tadalafil 5 mg was ceased so it is unclear if there was a positive dechallenge. Please provide this information.

Evaluation of sponsor's response to Question 5:

The sponsor has provided further information on two subjects, denoted as subjects "A" and "B" for the purposes of this AusPAR. Although not stated, the question was in regard to two other subjects, denoted as subjects "C" and "D" for the purposes of this AusPAR. The sponsor has not provided further information in relation to these two subjects.

On further review by the evaluator of the information provided in relation to these subjects, for subject C it is acknowledged that the ALT level was three times the upper limit of normal at the end of the double blind period in which the subject received placebo and it is noted that the investigator did not believe that the increase in hepatic enzymes was due to the study drug. It is also noted that after the subject entered the open label extension period, and was receiving tadalafil 5 mg once daily, the ALT decreased from Visit 6 (111 International Units (IU)/L)to Visit 8 (88 IU/L). The subject discontinued the study at Visit 9 due to subject decision. No further information is required in relation to this subject.

With regard to subject D, information regarding whether the subject had a positive dechallenge after study discontinuation would have been pertinent as the investigator had assessed the adverse event of "hepatic enzyme increased" as possibly related to the study drug and this adverse event led to study discontinuation. It is noted that this subject had been randomised to tadalafil 5 mg during the double blind period and that the AST and ALT were raised more than three times the upper limit of normal at the end of the double blind period. The sponsor is requested to clarify if this patient had a positive dechallenge.

The information provided by the sponsor in relation to subjects LVHG-107-1752 and LVHG-117-2713 does not suggest a safety signal. Subject LVHG-107-1752 had an AST level of 119 IU/L (Upper limit of normal 36 IU/L) at study Visit 8. At this visit, ALT was also elevated (72 IU/L; upper limit of normal 43 IU/L) and the total bilirubin level was normal. The subject also had elevated creatine phosphokinase levels at Visits 1, 3, 8 and 12; the highest value was recorded at Visit 8. The subject was not discontinued from the study. At Visit 10 the AST had decreased to 27 IU/L and the ALT and total bilirubin levels were within the normal range. Subject LVHG-117-2713 had an AST level greater than three times the upper limit of normal (144 IU/L; upper limit of normal 36 IU/L) at Visit 12 only. ALT was also increased (127 IU/L; upper limit of normal 43 IU/L) at this visit only. This subject also had elevated creatine phosphokinase levels at Visits 1, 3, 8, 10 and 12; the highest value was recorded at Visit 8. Total bilirubin was normal at study Visits 1, 3, 8, 10 and 12. The subject completed the study but the sponsor indicates that there are no laboratory data available for this patient after he completed the study and ceased tadalafil.

The sponsor has highlighted that, based on the integrated data from the double blind periods of studies LVID, LVHG, LVHJ and LVHR, the proportions of subjects randomised to placebo and tadalafil 5 mg who had treatment emergent ALT levels of more than three times the upper limit of normal, AST levels of more than three times the upper limit of normal, and total bilirubin of more than two times the upper limit of normal were similar. Based on these integrated data there were no treatment emergent reports of ALT or AST

more than three times the upper limit of normal with a total bilirubin of more than two times the upper limit of normal. This is acknowledged.

Question 6: In Study LVGC, a subject randomised to tadalafil who had normal liver function test results at screening and raised ALT and AST at Week 12 appears to have had a positive dechallenge after the study ended. From the subject narrative his concomitant medications had been started at least four months prior to the subject commencing tadalafil and they were not ceased. Please clarify if this subject had a positive dechallenge and whether the raised ALT and AST were considered related to tadalafil.

Evaluation of sponsor's response to Question 6:

The sponsor has clarified that the patient does appear to have had a positive dechallenge but indicates that, based on analysis of integrated data from the double blind period of Studies LVID, LVHG, LVHJ and LVHR, it is not likely that the increases in AST and ALT in this patient are related to treatment with tadalafil. This is accepted.

Question 7: With regard to exposure to tadalafil by duration of treatment, it appears that the information on exposure for at least 12 weeks was not available for a number of the studies. Please provide the number of subjects exposed for 12 weeks or more to tadalafil 2.5 mg in Study LVHR, and tadalafil 5 mg in Studies LVHJ, LVHR and LVGC, and to tadalafil 20 mg in Study LVGC, or indicate where this information can be found in the submission.

Evaluation of sponsor's response to Question 7:

The sponsor has provided the number of subjects exposed to tadalafil 2.5 mg in Study LVHR (n=172) and to tadalafil 5 mg in Studies LVHR (n=184) and LVHJ (n=148), respectively, for 12 weeks, and has clarified the location of this information in the respective clinical study reports. With regard to Study LVGC, the sponsor has clarified that no subjects were exposed to a single dose of tadalafil for 12 weeks as subjects were randomised to tadalafil 5 mg daily for six weeks and those subjects who completed six weeks of tadalafil 5 mg daily were dose escalated to receive tadalafil 20 mg daily for six weeks. The information provided by the sponsor is accepted. The information on exposure to tadalafil in clinical studies according to dose and duration in Table 2 is updated below to incorporate the numbers of subjects exposed for 12 weeks to tadalafil 2.5 mg in study LVHR and to tadalafil 5 mg in Studies LVHR and LVHJ, and to indicate that exposure of ≥ 12 weeks was not applicable for tadalafil 5 mg and tadalafil 20 mg in Study LVGC.

Table 2: (Updated) exposure to tadalafil in clinical studies according to dose and duration.

Study type/ Indication	Tadalafil 2.5mg				Tadalafil 5mg				Tadalafil 10mg				Tadalafil 20mg			
	≥ 12 weeks	≥ 6 mo.	≥ 12 mo.	Any dur'n	≥ 12 weeks	≥ 6 mo (≥ 182 days)	≥ 12 months (≥ 365 days)	Any dur'n	≥ 3 mo.	≥ 6 mo.	≥ 12 mo.	Any dur'n	≥ 12 weeks	≥ 6 mo.	≥ 12 mo.	Any dur'n
Clinical pharmacology																
LVHN																27
LVFU												24				24
LVCT																18
LVFV																16
LVFB*																
LVFF**																
LVFS																37
LVFT																72
LVGG																18
LVFA***																9
Indication 1																
Placebo-controlled																
LVHG	156			204	161			207	154			212	148			202
LVHJ					148			161								
LVHR	172			197	184			208								
LVHS (safety)								158								
LVHK (safety)													86			96
LVGC					Not applicable			137					Not applicable			129
LVID (also active controlled)								171								
LVIA	114			142	106			140								
LVHB (also active controlled)				151				155								
LVHT (also active controlled)					31			51								
Uncontrolled																
LVHG OLE					372	349	233	427								
LVIA OLE					362	342		394								
Subtotal Indication 1	**442**			**694**	**1364**	**691**	**233**	**2209**	**154**			**212**	**234**			**427**
Indication 2																
Placebo-controlled																
LVHR	172			197	184			208								
Subtotal Indication 2	**172**			**197**	**184**			**208**								
TOTAL	**442**			**694**	**1364**	**691**	**233**	**2209**	**154**			**236**	**234**			**648**

* 92 subjects were exposed to tadalafil 100 mg in study LVFB
** 59 subjects were exposed to tadalafil 40 mg in study LVFF
*** 8 subjects were exposed to tadalafil 80 mg in study LVFA

Question 8: The TEAEs reported in the pivotal efficacy studies are presented as the proportions of subjects who have had at least one TEAE in the preferred term category. This information does not indicate how many times the subjects reported the individual AEs during the course of the study and when the AEs occurred in relation to the commencement of the study drug. Please describe any specific patterns in the AEs reported over the course of the respective pivotal efficacy studies, specifically if there were certain AEs reported on multiple occasions and, if so, the time between the study commencement and the reporting of the AE, and whether there were any changes in the severity of the adverse event over the study period.

Evaluation of sponsor's response to Question 8:

In response to this question, the sponsor has provided:

- an analysis of TEAEs, and episodes of TEAEs, reported in at least 1% of tadalafil patients in the integrated analysis set.
- an analysis of the mean and median time of first occurrence, in days from randomisation, for TEAEs reported in at least 1% of tadalafil patients in the integrated analysis set.
- analyses of the incidence of all, and clinically relevant, TEAEs, by visit and treatment group in the placebo controlled double blind period, reported by all randomised subjects in the integrated placebo controlled once a day studies for ED.

The sponsor indicates the analysis of multiple occurrences of the same TEAE is limited by patient recall and how the investigators reported multiple occurrences of an AE in the individual studies. These limitations are acknowledged.

The results of this analysis indicate that, for TEAEs reported in at least 1% of tadalafil patients in the integrated analysis set, only a small number of subjects had more than one episode of the AE and multiple episodes of an AE were more common in subjects randomised to tadalafil 5 mg than to placebo. The sponsor reports that, of subjects randomised to placebo, one subject reported two episodes of nasopharyngitis. Of subjects randomised to tadalafil 5 mg, one subject reported two episodes of headache, one subject reported three episodes of nasopharyngitis, one subject reported two episodes of back pain, one subject reported two episodes of dyspepsia and another subject four episodes of dyspepsia, one subject reported two episodes of diarrhoea and another six episodes, and one patient reported two episodes of pain in extremity.

The median and mean numbers of days from randomisation to the first occurrence of TEAEs reported in at least 1% of tadalafil patients in the integrated analysis set were, respectively, less than 30 days except for hypertension and diarrhoea (median time to first occurrence 55 days and 54 days, respectively). The sponsor indicates that, overall, these findings are consistent with previously undertaken analyses of integrated data from placebo controlled once a day studies for the treatment of erectile dysfunction. These analyses were provided by the sponsor and show that the incidences of first reporting of any TEAE, and the most common TEAE, were generally highest at the four week study visit for subjects randomised to tadalafil.

The sponsor does not indicate in the response if the severity of the TEAE changed for those subjects who had multiple episodes of the one event.

The information provided by the sponsor does not raise new safety concerns.

Question 9: In the clinical pharmacology analysis set, nausea and vomiting led to the discontinuation of a number of study subjects receiving tadalafil (nausea [n=9], vomiting [n=5]). Please advise if these AEs were considered to be related to tadalafil.

Evaluation of sponsor's response to Question 9:

The sponsor has provided a summary of the AEs reported as the reason for study discontinuation in the clinical pharmacology analysis set and information on the individual study subjects who discontinued due to nausea or vomiting. Of the nine subjects who discontinued due to nausea, and the five who discontinued due to vomiting, the information provided suggests that tadalafil was the sole study drug implicated in the discontinuation of three subjects due to nausea or vomiting.

The sponsor highlights that, based on the integrated analysis set of Studies LVID, LVHG, LVHJ and LVHR, the proportion of subjects who had treatment emergent nausea was higher in subjects randomised to placebo than tadalafil 5 mg and the proportions of subjects who had treatment emergent vomiting were identical in the two treatment groups. The sponsor also indicates that in these four studies no subjects discontinued from the study due to nausea or vomiting.

The sponsor indicates that nausea and vomiting are not considered to be adverse drug reactions in the treatment of men with BPH-LUTS. This seems reasonable. The proportions of subjects who had treatment emergent nausea and vomiting based on the integrated analysis set of Studies LVID, LVHG, LVHJ and LVHR, do not suggest that these AEs are adverse drug reactions. In addition, as there were 2080 subjects who received tadalafil in the clinical pharmacology analysis set, the proportion who discontinued due to nausea or vomiting, where tadalafil was the sole study drug implicated, was small (0.14%).

However, it is noted that the US label for Cialis includes nausea and vomiting as adverse reactions reported in less than 1% of subjects in the controlled clinical trials for BPH or ED and BPH. The sponsor's response to Question 10 below suggests that in relation to the Australian and US PI documents, the criteria used to determine if TEAEs are adverse reactions are different.

Question 10: Nausea and arthralgia are listed in the US PI for Cialis as adverse reactions reported in less than 1% of subjects in the controlled clinical trials of Cialis for BPH or ED and BPH. These adverse reactions are not included in the proposed Australian PI for Cialis. Please clarify why these adverse reactions are not included in the proposed PI.

Evaluation of sponsor's response to Question 10:

The sponsor has outlined the process used for determining adverse drug reactions. The sponsor indicates that, as per guidance from the Council for International Organisations of Medical Sciences (CIOMS), a set of criteria was applied in the review and analysis of TEAEs in the integrated database of the Phase III studies to determine if a specific TEAE could have a potential causal association with tadalafil use. The criteria in the determination of a possible causal association include a higher incidence of a given TEAE in the tadalafil treatment group compared with the placebo treatment group that is statistically significant ($p < 0.05$), a numerical imbalance in the incidences between the two treatment groups, even if the difference is not statistically significant, and a significant positive dose-response. The sponsor indicates that medical personnel review all TEAEs and use clinical judgement to determine if there is a potential causal association.

The sponsor indicates that the TEAEs nausea and arthralgia, respectively, do not fulfil any of these criteria. Based on the integrated analysis set of Studies LVID, LVHG, LVHJ and LVHR, the proportion of subjects who had treatment emergent nausea was higher in subjects randomised to placebo than tadalafil 5 mg. Based on the integrated analysis set of Studies LVID, LVHG, LVHJ and LVHR, the proportion of subjects who had treatment emergent arthralgia was higher in subjects randomised to tadalafil 5 mg than placebo (tadalafil 5 mg 0.8%; placebo 0.3%) but the difference between the groups was not statistically significant (p=0.159). The sponsor reports that, after review, arthralgia was not considered an adverse drug reaction.

The sponsor has acknowledged that nausea and arthralgia are listed in the US PI for Cialis with a frequency of less than 1%. The sponsor indicates that nausea and arthralgia are included in the US PI as TEAEs based on their frequency and not because they were considered to be adverse drug reactions. The sponsor also indicates that in the US PI TEAEs are listed based on their frequency and a numerical imbalance (higher than placebo), and not necessarily following the CIOMS criteria for considering if a TEAE could be an adverse drug reaction.

The sponsor's response seems reasonable and is accepted. However, it is still not clear why nausea is included in the US PI as an adverse reaction reported by < 1% subjects in the controlled clinical trials of Cialis for BPH or ED and BPH, as treatment-emergent nausea was reported by a higher proportion of subjects randomised to placebo than tadalafil 5 mg based on the integrated analysis set.

Question 11: In relation to the AEs identified from BPH clinical studies:

- It is noted that the term "treatment emergent adverse reactions" is used in the proposed PI. However, it is indicated in the clinical study reports for Studies LVHG, LVHR and LVID that adverse reactions may not have been treatment emergent. The reference in the draft PI for the proposed information on treatment emergent adverse reactions reported by <2% of subjects treated with tadalafil 5 mg in Phase III studies is a table of common treatment emergent **adverse events** in the integrated analysis set (Table 2.7.4.6). As the proposed subheading relates to treatment emergent **adverse reactions**, it is unclear if this Table is referenced in error. Please clarify the reference for the treatment emergent adverse reactions and whether the adverse reactions were treatment emergent.

Evaluation of sponsor's response to Question 11:

The sponsor has clarified that the reference for the treatment emergent adverse reactions reported by <2% of patients treated with tadalafil 5 mg in the BPH Phase III studies is Table 2.7.4.27 in the Summary of Clinical Safety. Table 2.7.4.27 includes all TEAEs in the integrated analysis set by decreasing frequency in the tadalafil 5 mg group (all randomised subjects in Studies LVID, LVHG, LVHJ and LVHR, double blind treatment period), whereas Table 2.7.4.6 includes common TEAEs in the integrated analysis set by decreasing frequency in the tadalafil 5 mg group (all randomised subjects in Studies LVID, LVHG, LVHJ and LVHR, double blind treatment period). Dyspnoea is included in Table 2.7.4.27 but not Table 2.7.4.6. The sponsor has clarified that all adverse drug reactions are TEAEs but not all TEAEs are adverse drug reactions. To determine if a specific TEAE could have a potential causal association with tadalafil use, and therefore be an adverse drug reaction, a set of criteria was applied in the review and analysis of the TEAEs in the integrated database of the Phase III studies, as per CIOMS guidance. This explanation is accepted.

On further review of the clinical study reports for Studies LVHG, LVHR and LVID, it is noted that it is stated that treatment related adverse events may not have been treatment emergent, rather than adverse reactions may not have been treatment emergent as indicated in Question 11. The evaluator had assumed that the terms "treatment related adverse event" and "adverse (drug) reaction" had the same meaning. It is noted that in the response to Question 12, the sponsor clarifies the meanings of the terms "treatment related adverse events" and "adverse drug reactions". The sponsor indicates that treatment related adverse events are determined to be related to the study drug by the investigator but the relatedness, as determined by the investigator, is not considered as part of the medical evaluation to determine if a TEAE is an adverse drug reaction.

To avoid confusion, the sponsor proposes to revise the text as follows:

> "~~Treatment-Emergent~~ Adverse <u>drug</u> reactions reported by <2% of patients treated with Tadalafil 5 mg in Phase III studies"

The sponsor also proposes similar changes to the related text in relation to the on demand and once a day ED sections of the ADVERSE EFFECTS section of the draft PI.

The proposed change to the text, and to the text in relation to the on demand and once a day ED sections to be consistent, seems reasonable.

To provide clarification for the reader of the PI, it is recommended that the terms "adverse events" and "adverse drug reactions" are defined in the PI.

Question 12: In Table 2.7.4.8, treatment related AEs in the integrated analysis set are presented. With regard to the treatment related AEs reported by <2% of subjects treated with tadalafil 5 mg, only some of the treatment related AEs reported in the integrated analysis set are listed in the PI and others are not. Please clarify how the treatment related adverse reactions were determined.

Evaluation of sponsor's response to Question 12:

The sponsor has clarified that treatment related AEs were not used as the basis for determining adverse drug reactions. The sponsor indicates that as per CIOMS guidance, a set of criteria was applied in the review and analysis of TEAEs in the integrated database of the Phase III studies to determine if a specific TEAE could have a potential causal association with tadalafil use, and, therefore, be considered an adverse drug reaction. The sponsor states that relatedness, as determined by the investigator, is not considered as part of the medical evaluation undertaken to consider if a TEAE is an adverse drug reaction. The evaluator had assumed that the terms "treatment related AE" and "adverse (drug) reaction" had the same meaning. The sponsor has clarified that a "treatment related AE" is an AE determined to be related to the study drug by the investigator, and which may or may not be treatment emergent, and an "adverse drug reaction" is determined by the application of a set of criteria based on CIOMS guidance.

It is now understood how the list of adverse drug reactions, reported with a frequency <2% of patients treated with tadalafil 5 mg in the Phase III BPH studies, was determined. The explanation is accepted.

The sponsor has also provided background information in relation to the proposed addition of dyspnoea to the PI as an adverse drug reaction. Dyspnoea was reported by four subjects (0.5%) randomised to tadalafil 5 mg during the double blind treatment period based on the integrated analysis set of Studies LVID, LVHG, LVHJ and LVHR. No subjects randomised to placebo reported dyspnoea. The sponsor has provided summaries of these four cases with the response to this question. The sponsor indicates that based on the clinical trial cases in the ED (as needed and once a day) and BPH placebo controlled studies, a potential contribution of tadalafil to dyspnoea could not be ruled out in the respective patient populations. It is reported that the review of rarely reported spontaneous cases in the spontaneous AE database suggested that there may be a possible causal association between dyspnoea and tadalafil use in the ED patient population.

The proposed addition of dyspnoea as an uncommon adverse drug reaction reported by <2% of patients treated with tadalafil 10-20 mg in Phase III ED studies and by <2% of patients treated with tadalafil 5 mg in Phase III BPH studies, to be consistent with the CCDS, is acceptable.

The sponsor has also provided background information in relation to the addition of transient amnesia to the PI as an adverse drug reaction reported by <2% of patients treated with tadalafil 5 mg in Phase III BPH studies. Although there were no cases of transient amnesia in the integrated analysis set of Studies LVID, LVHG, LVHJ and LVHR, the proposed inclusion, for consistency, of transient amnesia as an adverse drug reaction reported by <2% of patients treated with tadalafil 5 mg in Phase III BPH studies is acceptable. The sponsor has included an explanatory note under this adverse drug reaction indicating that the frequency category is based on events reported in ED placebo

controlled trials in patients who were treated with tadalafil on demand and daily at doses within the currently approved dosing range. The proposed dosage for the proposed indications, 5 mg once daily, is the same as that recommended for once a day dosing for ED, so this safety related information is applicable to the proposed indications.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of tadalafil in the proposed usage are unchanged from those identified in the first round assessment.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of tadalafil in the proposed usage are unchanged from those identified in the first round assessment.

Second round assessment of benefit-risk balance

The benefit-risk balance of tadalafil, given the proposed usage, is favourable.

Second round recommendation regarding authorisation

It is recommended that the use of tadalafil 5 mg once daily in the proposed indications is approved if:

- The product documentation is amended as recommended or the sponsor justifies why the recommended changes should not be made;
- The sponsor provides an analysis of outlier QT/QTc interval results for the open-label extension period of study LVHG, study LVDI and study LVHT, or clarifies the location of such information in the submission;
- The sponsor clarifies if use of the term “clinically meaningful improvement”, in relation to total IPSS and IIEF EF Domain in the draft PI, is referring to the absolute change from baseline in the tadalafil 5 mg group, or the placebo subtracted change from baseline in the tadalafil 5 mg group, or the 95% CI for the LS mean difference in the change from baseline for the two treatments;
- The sponsor clarifies if there have been important changes in the analytical methods used in the studies submitted in the dossier and specifies any such changes and their impact on the interpretation of the data;
- The sponsor clarifies if subject “D” had a positive dechallenge;
- The sponsor further clarifies why nausea is included in the US PI as an adverse reaction reported by < 1% subjects in the controlled clinical trials of Cialis for BPH or ED and BPH in view of the fact that treatment emergent nausea was reported by a higher proportion of subjects randomised to placebo than tadalafil 5 mg, based on the integrated analysis set.

V. Pharmacovigilance findings

Risk management plan

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

Safety specification

The sponsor provided a summary of Ongoing Safety Concerns (Table 3).

Table 3: Ongoing Safety Concerns for Cialis.

Important Identified Risks	All indications: • Increased hypotensive effects from coadministration of tadalafil with nitrates • Hypotension/Increased hypotensive effect • Priapism
Important Potential Risks	All indications: • Sudden hearing loss • Non-arterial anterior ischemic optic neuropathy PAH Indication: • Increased uterine bleeding
Important Missing Information	PAH Indication: Patient populations • Women who were nursing or pregnant • Paediatric patients <12 years of age • Patients with severe renal impairment • Patients with severe hepatic cirrhosis (Child-Pugh class C)

OPR reviewer's comment:

The clinical evaluator has recommended that 'QT/QTc prolongation' is added as an important potential risk and 'Safety in patients aged 75 years and over' is added as important missing information. The RMP evaluator supports the addition of these safety concerns.

Otherwise, the above summary of the Ongoing Safety Concerns is considered acceptable.

Pharmacovigilance plan

Proposed pharmacovigilance activities

Proposed pharmacovigilance activities are shown in Table 4.

Table 4: Proposed pharmacovigilance activities for Cialis.

Important identified risks	
• Priapism	• Routine surveillance activities • Targeted follow-up investigations
• Hypotension/Increased hypotensive effect (including effects from coadministration of nitrates)	• Routine surveillance activities • Targeted follow-up investigations
Important potential risks	
• Nonarteritic anterior ischemic optic neuropathy (NAION)	• Routine surveillance activities • Targeted follow-up investigations • Observational prospective case-crossover study (Study LVHQ) to evaluate the possible association between the use of PDE5 inhibitors and the acute risk of NAION
• Sudden hearing loss	• Routine surveillance activities • Targeted follow-up investigations

Note: The pharmacovigilance plan specific to the approved PAH indication has not been included in this summary for clarity.

OPR reviewer's comments in regard to the pharmacovigilance plan and the appropriateness of milestones:

The clinical evaluator recommended that 'QT/QTc prolongation' is added as an important potential risk and 'safety in patients aged 75 years and over' is added as important missing information. The inclusion of these as safety concerns should include consideration of the pharmacovigilance plan related to each and this should be detailed in an update to the RMP.

Routine pharmacovigilance activities described by the sponsor in the RMP are consistent with published guidelines[8] and this is acceptable.

Targeted questionnaires (as part of follow up investigations of adverse event reports) are proposed for the important identified and potential risks. The evaluator has no objection to this proposal however the questionnaires have not been provided. Presumably they are already in use and it is recommended that the questionnaires are included as an annex to the RMP for completeness.

The FDA has requested that the sponsor conduct an observational prospective case crossover study (Study LVHQ) to evaluate the possible association between the use of PDE5 inhibitors and the acute risk of nonarteritic anterior ischemic optic neuropathy (NAION). As this study is ongoing, the protocol has not been evaluated in detail for the purposes of this report. The sponsor commits to providing updates on the results of this study in future Periodic Safety Update Reports (PSURs) and this is acceptable.

There are no other additional activities as part of the pharmacovigilance plan.

Evaluation of the need for risk minimisation activities

Sponsor's conclusion in regard to the need for risk minimisation activities

The sponsor provided the following justification for routine risk minimisation for the Ongoing Safety Concerns:

> *A comprehensive review of data from nonclinical and clinical trials and from postmarketing surveillance demonstrates that tadalafil is safe for treatment of ED*

[8] European Medicines Agency, "ICH Topic E 2 E Pharmacovigilance Planning (Pvp) Step 5: Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03)", 24 June 2005, Web, accessed 1 July 2013 <www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/ 2009/09/WC500002818.pdf>.

and BPH at the approved and proposed doses respectively. No new important risk was identified in the analysis of BPH studies. In general, the safety profile of patients with BPH in clinical trials was consistent with the known safety profile of tadalafil. A comprehensive review of data from nonclinical and clinical trials demonstrate that tadalafil at the approved doses for the treatment of PAH is safe and well tolerated.

The safety profile of tadalafil is well described and consistent with the information presented in the current labelling. The contraindication of tadalafil with nitrates and the AEs of priapism and hypotension/increased hypotensive effect have been identified as risks for all tadalafil use. NAION and hearing loss have been identified as potential risks, regardless of indication. Increased uterine bleeding (including menorrhagia and/or vaginal bleeding) have been identified as potential risks for the populations studied in the PAH clinical trials.

Nonarteritic Anterior Ischemic Optic Neuropathy (NAION)

Since the market introduction of tadalafil, reports of NAION and other visual disturbances have been received, and publications concerning the occurrence of NAION with other PDE5 inhibitors have appeared.[9] *Although the relationship between these events and PDE5 inhibitors (including tadalafil) is not clear,*[10] *blurred vision, NAION, retinal vein occlusion, and visual field defect have been added to the Australian PI.*

The benefits and risks of tadalafil were discussed in detail in the original Marketing Authorisation Holder (MAH) submitted in each region for tadalafil on demand dosing in ED. Further, no new important risks were identified in large, placebo controlled studies evaluating once a day dosing of tadalafil in patients with ED or in the clinical program for BPH. Reports of vision related events with tadalafil are rare, and a clear plausible mechanism linking tadalafil to the events is absent. Data review and analysis do not indicate that the overall benefit-risk balance for tadalafil has markedly changed from the time of initial marketing.

At the present time, the steps already taken to communicate the potential relationship between tadalafil use and the occurrence of NAION in the exposed population are sufficient to alert prescribers and consumers to this potential risk and to provide them with the information needed to make drug use decisions. The MAH does not have any additional information on this topic at this time that would have a significant effect on public health.

Sudden Hearing Loss

In November 2007, Lilly completed an extensive analysis of hearing loss/hearing impairment that included cases from clinical trial and postmarketing databases. This analysis also included a causality assessment of the cases to evaluate the likelihood of their association to the use of tadalafil. Additionally, Lilly conducted an analysis of the FDA AERS database, which showed similar reporting rates across all PDE5 inhibitors and that did not meet the established or representative threshold for a possible signal. However, for other drugs with known ototoxic effects (gentamycin, cisplatin, and furosemide) investigated in the AERS database, a threshold for a possible signal was met.

Sudden hearing loss has been added as a surveillance term for postmarketing cases and the sponsor has developed a surveillance questionnaire to be used by case managers for follow up of hearing loss events to enhance the sponsor's ability to evaluate future reports.

[9] Pomeranz HD, Bhavsar AR. (2005) Nonarteritic ischemic optic neuropathy developing soon after use of sildenafil (viagra): a report of seven new cases. *J Neuroophthalmol.* 25: 9-13.
[10] Hellstrom WJG, Kendirci M. (2005) PDE-5 inhibitors and NAION. *Medscape Urology* 6(2).

> *As of the data lock date of PSUR 15, 15 October 2011, a review of sudden hearing loss casesreceived during the PSUR period interval revealed there was a slight increase in the number of cases with hearing loss and hearing impairment for the reporting period (16 October 2010 to 15 October 2011) in comparison to the last review completed for PSUR 13 (16 October 2009 to 15 October 2010), but a decrease from the previous year (PSUR 11, 16 October 2008 to 15 October 2009). In light of the review of cases in the reporting period of PSUR 15, no changes to the CCDS were warranted. The MAH will continue to monitor newly reported cases of hearing loss and hearing impairment through routine pharmacovigilance activities.*

OPR reviewer's comment:

The sponsor's justification for routine risk minimisation is acceptable.

Potential for medication errors

The sponsor has provided the following comment in the RMP:

> *Compared to Cialis 20 mg tablets, the distinguishing features of Adcirca 20 mg tablets include a unique colour, unique tablet printing, and unique package graphics. The Adcirca 20 mg tablet is orange, compared to the light yellow Cialis 20 mg tablet. The Adcirca tablets are debossed with the 4 digit Identicode, whereas the Cialis tablets are debossed with "C20." In addition to the different trade name, the package includes different branding, artwork, and colours compared to those of the Cialis tablets.*
>
> *Should tadalafil receive approval for the treatment of signs and symptoms of BPH in adult males including those with ED, Cialis 5 mg tablets will be used in Australia for this treatment.*

OPR reviewer's comment:

This is acceptable.

Toxicity in overdose

The sponsor has provided the following comment in the RMP:

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

OPR reviewer's comment:

The information provided in the PI and CMI regarding overdose is acceptable.

Summary of recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application; the implementation of the tadalafil AU-RMP (Revision 2, Approval Date 8 December 2011) is imposed as a condition of registration; and the submitted RMP is applicable without modification in Australia unless so qualified:

Ongoing safety concerns

- The clinical evaluator has recommended that 'QT/QTc prolongation' is added as an important potential risk and 'Safety in patients aged 75 years and over' is added as important missing information.

Pharmacovigilance plan

- The clinical evaluator recommended that 'QT/QTc prolongation' is added as an important potential risk and 'Safety in patients aged 75 years and over' is added as important missing information. The inclusion of these as safety concerns should include consideration of the pharmacovigilance plan related to each and this should be detailed in an update to the RMP to be provided to OPR within 3 months post approval if this application is successful.
- Targeted questionnaires (as part of follow up investigations of AE reports) are proposed for the important identified and potential risks. The evaluator has no objection to this proposal however the questionnaires have not been provided. Presumably they are already in use and it is recommended that the questionnaires are included as an annex to the RMP for completeness.

Risk minimisation plan

- The clinical evaluator recommended that 'QT/QTc prolongation' is added as an important potential risk and 'safety in patients aged 75 years and over' is added as important missing information. The inclusion of these as safety concerns should include consideration of the risk minimisation plan related to each and this should be detailed in an update to the RMP to be provided to OPR within 3 months post approval if this application is successful.
- In regard to the proposed routine risk minimisation activities, the draft PI document is considered satisfactory.
- In regard to the proposed routine risk minimisation activities, the draft CMI is considered satisfactory.

VI. Overall conclusion and risk/benefit assessment

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

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

The nonclinical evaluator has no objections to the registration of tadalafil for the proposed indication. The evaluator notes that the proposed dose of 5 mg daily is considerably less than the currently approved maximum doses of 20 mg for ED and 40 mg for pulmonary arterial hypertension and therefore there were no outstanding nonclinical safety issues. The human vasculature supporting the bladder and prostate contains high expression and activity of PDE5 and the submitted data support the efficacy of tadalafil by a mechanism involving NO/cGMP induced vascular relaxation, increased perfusion and oxygenation in the lower urinary tract and smooth muscle relaxation of the prostate and bladder.

Clinical

The clinical evaluator has reviewed the submitted data, which included:

- 10 pharmacology studies: single and multiple dose PK studies, bioequivalence, hepatic impairment, renal impairment, elderly, Asian population, ritonavir drug interaction and a population PK analysis.
- 4 pivotal efficacy studies
- 3 pivotal safety studies
- 6 other efficacy/safety studies
- Integrated analyses and literature

The clinical evaluator recommended approval in the evaluation report. This recommendation was based on satisfactory responses to a number of outstanding items which the sponsor must address in the pre ACPM (Advisory Committee on Prescription Medicines) response.

Some of the benefits (edited) noted by the evaluator in BPH ± ED include:

- Tadalafil is in a different drug class than the currently approved medicines and has a different mechanism of action, adverse effect profile and contraindications. This may be beneficial to patients who cannot use other treatment options.
- The results of the pivotal and other efficacy studies submitted to support this indication showed a consistent improvement from baseline in BPH-LUTS, as measured by the total IPSS score.
- For patients with BPH and ED, the single supporting pivotal study for this proposed indication showed a greater improvement in total IPSS score and IIEF-ED score from baseline for tadalafil 5 mg, compared with placebo, and a statistically significant result for both total IPSS score and IIEF-ED score for the comparison between tadalafil 5 mg and placebo.

Some of the risks (edited) noted by the evaluator in BPH ± ED include:

- Although the effect of 100 mg tadalafil on the change in QTc interval was declared to be equivalent to that of placebo based on the results of a thorough QT/QTc study, an association between tadalafil and QT interval prolongation may still exist because vardenafil, another PDE5 inhibitor, produced increases in QTc interval at therapeutic and supratherapeutic doses.
- The pivotal studies had a large number of exclusion criteria and therefore efficacy and safety has not been evaluated in these patients.
- The effect of tadalafil 5 mg in the improvement in total IPSS and IIEF-ED in the pivotal efficacy studies may not be considered clinically meaningful.
- Although an adequate number of subjects aged over 65 years were exposed to tadalafil 5 mg once daily for at least 12 months, only 28 subjects aged 75 years or older had such exposure, a number unlikely to be sufficient to detect safety signals in this population subgroup.
- In two Studies LVHN and LVHS, there was evidence that tadalafil had a greater negative effect on blood pressure and a higher proportion of TEAEs possibly related to hypotension in older subjects compared with younger subjects. These effects on blood pressure are of potential clinical concern as they may be associated with falls.
- Ritonavir affected the PK of tadalafil following a single 20 mg oral dose. This drug interaction may affect the PD effect of tadalafil in the treatment of ED.

- The efficacy and safety of use of tadalafil in the treatment of both ED and BPH has not been demonstrated beyond 12 weeks although the safety of tadalafil 5 mg once daily in the treatment of BPH-LUTS has been demonstrated over 52 weeks.

Pharmacology

Six studies examined the PK of tadalafil and six studies examined the PD.

Some of the findings noted by the evaluator include:

- The PK of tadalafil in men with BPH-LUTS aged 70-85 years is similar to men aged <60 years.
- Tadalafil AUC was increased by 48% with ritonavir 500mg BD and 18% with ritonavir 600mg BD and Cmax was decreased by 30% in either dose.
- Higher exposure in Japanese subjects however this appeared inconsistent with previous data and may be due to a lack of adherence to assigned treatment.
- Exposure to tadalafil in elderly and younger subjects was comparable with or without mild renal impairment.
- A thorough QTc study indicated that the change in QTc interval from 100 mg tadalafil was similar to placebo (ANCOVA mean difference 3.3 msec, 95% CI 1.7, 5.0), (QTcF mean difference 3.5 msec, 95% CI 1.9, 5.1). No QTc intervals of >450 msec. The proportion of subjects with QTcF interval increases of >30 msec was similar to ibutilide (positive control) but double that of placebo (15 versus 16 versus 8%).
- Tadalafil did not appear to effect colour vision.
- Mean maximum drop in blood pressure was higher in elderly subjects with BPH-LUTS than younger subjects (mean difference was about 8.7/2.7 mmHg).
- Similar changes in blood pressure with and without alcohol.
- Blood pressure lower when tadalafil and doxazosin are administered concomitantly.

Efficacy

The efficacy data submitted were large and comprised 4 pivotal studies in BPH patients, 8 other studies in BPH patients, 1 study in patients with ED and BPH and 1 study in ED only. Summaries of the studies are shown below. The primary efficacy endpoint for the pivotal studies in BPH was the change from baseline in the internationally validated instrument called IPSS that is a self administered questionnaire of seven questions with each question valued at 0-5, for a total score range of 0-35 (higher score means greater severity of symptoms; mild IPSS <7, moderate IPSS 8-19, and severe IPSS 20-35). The Clinical Evaluation Report has the questionnaire. The sponsor has indicated that a change in IPSS score of at least 3 is clinically meaningful. All subjects had at least BPH-LUTS and bladder outlet obstruction. Some of the secondary measure included subscores of the IPSS examining storage, voiding and nocturia, the validated BPH Impact Index (BII, overall health and activity), uroflowmetry and the validated IIEF that is commonly used for erectile dysfunction assessment. IIEF-ED domain difference of 4 points is considered clinically meaningful and the scale is 0-30 with a higher result being better. ANCOVA analysis was used in the studies; however, the first study below also used a permutation test which gave similar results.

BPH studies

LVHG: Phase IIb/III, multinational, randomised, double blind, placebo controlled, parallel study assessing dose response of tadalafil 2.5, 5, 10 and 20mg daily for 12 weeks in 1058

men (mean 62 years, >6 months of BPH-LUTS, IPSS ≥13, 34% severe IPSS, 65-69% had ED) with BPH-LUTS. The primary efficacy endpoint using the ANCOVA was statistically significant with a mean placebo subtracted difference in IPSS of -2.6 (tadalafil 5 mg -4.83 versus placebo -2.23), 95% CI -3.69, -1.51. Subgroup analysis indicated a larger reduction in subjects who had not used BPH therapies before. Results for other strengths are in the Clinical Evaluation Report and show the mean placebo subtracted difference from baseline of -1.58 on 2.5 mg, -2.90 on 10 mg, and -2.94 on 20 mg. IPSS subscores were consistent with the primary result. BII using ANCOVA was significant for the 5 mg, 10 mg and 20 mg doses only whereas IIEF-ED domain was significant for all doses (tadalafil 5 mg placebo subtracted difference of 4.75). Changes in peak flow rate were not statistically significant.

LVHJ: Phase III, multinational, randomised, double blind, placebo controlled, parallel study assessing tadalafil 5mg daily for 12 weeks in 325 men (mean 65 years, 20%>75 years, >6 months of BPH-LUTS, IPSS≥13, 35% severe IPSS, 69% had ED) with BPH-LUTS. The primary efficacy endpoint was statistically significant with a mean placebo subtracted difference in IPSS of -1.9 (tadalafil 5 mg -5.6 versus placebo -3.6), 95%CI -3.2, -0.6. BII was not significantly different from placebo. IIEF-ED domain was significant with a placebo subtracted mean difference of 4.7.

LVID: Phase III, multinational, randomised, double blind, placebo and active controlled, parallel study assessing tadalafil 5 mg daily and tamsulosin 0.4 mg daily for 12 weeks in 511 men (mean 64 years, 10%>75 years, >6 months of BPH-LUTS, IPSS≥13, 71% moderate IPSS, 70% had ED) with BPH-LUTS. The primary efficacy endpoint was statistically significant with a mean placebo subtracted difference in IPSS of -2.1 (tadalafil 5 mg -6.3 versus placebo -4.2), 95% CI -3.3, -0.8. The result for the primary endpoint with tamsulosin was -1.5 (tamsulosin 0.4 mg -5.7 versus placebo -4.2), 95% CI -2.8, -0.2. BII was significantly different from placebo. IIEF-ED domain was significant with a placebo subtracted mean difference of 3.9.

LVHR: This study was submitted to support the BPH-LUTS indication and the BPH-LUTS and ED indication and is discussed below.

Eight other studies discussed by the evaluator in BPH men are briefly noted below.

LVGC: A proof of concept study in 281 subjects for 12 weeks escalating from 5 mg to 20 mg tadalafil that was consistent with the pivotal studies for IPSS and IIEF-ED.

LVHG extension: This open label extension of Study LVHG showed a maintenance of effect of tadalafil 5 mg for 12 months in IPSS. 55% of patients also had ED in this study and the improvement seen in the double blind phase was maintained in the extension.

LVHS: This primarily safety study showed the change in IPSS was not significantly different to placebo when tadalafil was added to alpha blocker therapy. A small increase in urine flow rate was seen on placebo and tadalafil 5 mg.

LVHK: This primarily safety study showed the change in IPSS was greater on tadalafil 20 mg than placebo but this study was not powered for efficacy.

LVHT: This underpowered study was conducted in 151 Korean men and compared tadalafil 5 mg with placebo for 12 weeks but did not demonstrate a significant difference in IPSS.

LVIA: This study was conducted in 422 Japanese men and compared tadalafil 5 mg with placebo for 12 weeks and demonstrated a non significant difference of -1.1 (95% CI -2.2, +0.1) in IPSS.

LVIA extension: This open label extension of Study LVIA showed a maintenance of effect of tadalafil 5mg for 12 months in IPSS.

LVHB: This study in 612 Japanese, Korean and Taiwanese men for 12 weeks showed a significant difference of -1.7 (95% CI -2.9, -0.6) in IPSS.

An integrated analysis of the four pivotal studies showed a statistically significant mean placebo subtracted difference in IPSS of -2.3 (tadalafil 5 mg -5.0 versus placebo -2.7), 95% CI -2.9, -1.7.

ED and BPH studies

LVHR: This was a Phase III, multinational, randomised, double blind, placebo controlled, parallel study assessing tadalafil 2.5 and 5 mg daily for 12 weeks in 606 men (mean 63 years, 6-10% >75 years, >6 months of BPH-LUTS, IPSS ≥13, 39% severe IPSS, 92% had ED) with BPH-LUTS and ED. The primary efficacy endpoint was statistically significant with a mean placebo subtracted difference in IPSS of -2.3 (tadalafil 5 mg -6.1 versus placebo -3.8), 95% CI -3.5, -1.2. The result for 2.5 mg tadalafil was not statistically significant at -0.8 (tadalafil 2.5 mg -4.6 versus placebo -3.8), 95% CI -2.0, +0.4. IIEF-ED domain was significant with a placebo subtracted mean difference of 4.7 for tadalafil 5mg and 3.4 for tadalafil 2.5 mg. The Sexual Encounter Profile Question 3 showed a significant change in the "yes" result of 19.7% for tadalafil 5 mg whilst the tadalafil 2.5 mg result was 12.7%. BII was significantly different from placebo for tadalafil 5 mg.

LVHG, LVHJ and LVID: These studies discussed above all had IIEF-ED change as secondary endpoints and all three demonstrated a significant improvement in this domain with placebo subtracted changes for the tadalafil 5 mg dose of 4.75, 4.7 and 3.9, respectively.

An integrated analysis of the pivotal studies showed a statistically significant mean placebo subtracted difference in IIEF-ED of 4.8 (tadalafil 5 mg 6.3 versus placebo 1.5), 95% CI 3.9, 5.6.

ED studies

LVDI: This was a Phase II study in ED patients only from Japan. As it did not include patients with BPH, it is not relevant to the proposed indications. The analysis of this study can be found in the Clinical Evaluation Report.

Safety

Overall patient exposure was 2618 men to any dose of tadalafil with 752 exposed to the 5 mg in the four pivotal studies and 283 exposed for at least one year (104 men >65 years). The TEAE were similar in the four pivotal studies to the known safety profile of tadalafil. The integrated analysis of these studies showed TEAEs occurred more frequently on tadalafil 5mg than placebo (27 versus 21%) and included headache, back pain, dyspepsia, nasopharyngitis, hypertension (1.6 versus 0.7%), myalgia/pain (5.9 versus 2.7%), diarrhoea, dizziness, myalgia and gastro oesophageal reflux. Three subjects reported urinary retention on placebo but there were no reports for patients on tadalafil 5 mg. There were eight bleeding events (3 epistaxis) on tadalafil 5 mg compared with none on placebo. Four dyspnoea on tadalafil compared with none on placebo. One subject reported deafness that resolved and five subjects reported eye disorders (4 blurred vision) compared to 2 on placebo. There were no reports of NAION, seizures or transient global amnesia. Adverse drug reactions were slightly higher on tadalafil at 13 versus 7% with headache being the most common. One subject randomised to tadalafil died from a myocardial infarction (no deaths on placebo) and SAE numbers were similar to placebo. Discontinuation due to adverse events was double on tadalafil (3.1 versus 1.5%) with headache being the most common reason. Changes in hepatic and renal function, chemistry and haematology parameters were small and similar to placebo. Changes in prostate specific antigen were small and mixed. Vital sign changes, positive orthostatic tests and QTc interval changes were similar amongst the groups. Changes in post void residual volume overall were less than 1 mL on placebo and tadalafil 5 mg.

Two studies were conducted that had safety as a primary endpoint:

LVHS: Phase III, randomised, double blind, placebo controlled, parallel study assessing tadalafil 5 mg daily on top of alpha blocker therapy (67% selective alpha blocker) for 12 weeks in 318 men (mean 67 years, 25% >75 years, >6 months of BPH-LUTS, 58% moderate IPSS, 62% had ED) with BPH-LUTS. The primary safety endpoint of treatment emergent dizziness was not significantly different from the placebo group (5.7% placebo, 7% tadalafil 5 mg, p=0.403). TEAE were higher at 42 versus 33% on placebo but TEAEs related to hypotension were similar (7 versus 6.3%) and slightly higher in those >75 years. No deaths were reported.

LVHK: Randomised, double blind, placebo controlled, parallel study assessing tadalafil 20 mg daily for 12 weeks in 200 men (mean 59 years, >6 months of BPH-LUTS, IPSS ≥13, 64% severe IPSS, 59% had ED) with BPH-LUTS. The primary safety endpoint of change in detrusor pressure at peak urinary flow rate was not significantly different from the placebo group (-2.95 cmH_2O for tadalafil 20mg versus +1.92 cmH_20 for placebo, p=0.068). A decrease of 15 cmH_2O or more is considered potentially clinically adverse. TEAEs were higher on tadalafil 20mg than placebo (56 versus 28%). One subject on placebo died from myocardial infarction.

The **LVHG extension** included 428 North American men for 12 months (70% completion) and demonstrated 4.7% with SAEs. TEAEs were reported by 58% and were similar to the double blind period with no new safety signals. Cardiovascular disorders were reported in 25 subjects with five being hypotension and some QTc changes of >60 ms from baseline and overall QTc time of >500 ms.

The individual studies are discussed by the evaluator in the Clinical Evaluation Report but there did not appear to be any new safety signals. Arthralgia was noted to be higher on tadalafil in the pharmacology studies (3.4 versus 0.2%) but not the integrated analysis of pivotal studies (0.8 versus 0.3%).

Risk management plan

The Office of Product Review has accepted the AU-RMP, Version 2 (8 Dec 2011) for tadalafil and recommended further changes as outlined in their report:

- Ongoing Safety Concerns: QT/QTc added as an important potential risk and safety in patients aged 75 years and older is added as important missing information.
- Pharmacovigilance Plan: The inclusion of the above two matters requires consideration of the pharmacovigilance plan for each and an updated RMP within 3 months post approval. The targeted questionaries for follow up of adverse event reports should be included as an annex to the RMP.
- Risk Minimisation Plan: The inclusion of the above two matters requires consideration of the risk minimisation plan for each and an updated RMP within 3 months post approval.

The sponsor should address these in the pre ACPM response. The clinical data included very limited exposure in males >75 years and there appeared to be a greater risk of orthostatic hypotension in this group, therefore the inclusion of patients aged >75 years as important missing information is reasonable.

Risk-benefit analysis

Delegate considerations

Efficacy

The efficacy results are statistically significant for tadalafil 5mg in patients with BPH-LUTS with or without ED and a maintenance of effect was demonstrated for 12 months in two studies for BPH-LUTS. The efficacy beyond 12 weeks was not specifically studied for patients with both ED and BPH-LUTS; however, Study LVHG extension did have half of their patients with ED and these patients demonstrated a maintenance of effect. However, according to the sponsor, a difference of at least 3 points is required to be considered clinically meaningful. The results in the pivotal studies of a placebo subtracted difference showed improvements of -2.6, -1.9, -2.3 and -2.1 in IPSS score; however, these remain small differences on a scale of 0-35 and there is a significant placebo effect occurring with the placebo result being about half the tadalafil results. When compared, the data indicate a statistically significant result that is consistently observed across multiple studies and the CIs do include 3 for each study. It is likely that in these studies of moderate to severe BPH-LUTS patients, some will observe a clinically meaningful difference in symptomatology while others will not. The IPSS result for tamsulosin from Study LVID was less with a difference from placebo of -1.5. It is noted that tamsulosin is registered for the treatment of LUTS in patients with BPH and that the two pivotal studies reported in the PI for tamsulosin showed mean differences from placebo in total IPSS of -1.6 and -1.7. The sponsor and ACPM have been requested to comment on this matter. The number of subjects older than 75 years was limited in each study and given the use in an older population, a greater inclusion should have been considered.

The change in IIEF-ED score was considered clinically meaningful if a score of 4 or more was demonstrated. In the pivotal studies, the placebo subtracted results for tadalafil 5 mg were greater than 4 or close to it: LVHG (4.75), LVHJ (4.7), LVID (3.9) and LVHR (4.7), thus indicating clinically meaningful results.

Safety and RMP

The safety profile of tadalafil 5 mg in BPH patients was similar to the ED patients in the currently approved PI. The safety profile from one year of treatment was also similar to the profile for patients exposed during the four pivotal double blind trials. Patient exposure for men over 65 years was adequate but limited for those over 75 years. AEs of hypertension, back pain, myalgia, epistaxis, hypotension, dizziness, hearing loss, blurred vision and dyspnoea are included in the PI. Patients >75 years appeared to be at higher risk of orthostatic hypotension than younger men.

Indication

Although statistically significant results have been seen in patients with both ED and BPH, it is unclear why a specific indication is needed that covers both conditions, given that the individual indications are listed as separate entries. The separate entries do not necessarily imply they are mutually exclusive.

QT interval

A thorough QT study did not indicate a significant increase in QTc interval for tadalafil 100mg compared to placebo and there were no QTc intervals of >450 msec. The number of subjects with an increase in QTc of >30 msec was double that of placebo but the same as the positive control. No cases of torsades de pointes were reported in the trials. It is noted that vardenafil has reported increases in QTc interval at therapeutic doses. The clinical evaluator has recommended that results of the study be included in the PI which is supported.

Data deficiencies

There was a lack of data in BPH men with renal and hepatic impairment and a limited number of men over 75 years with BPH-LUTS were exposed to tadalafil 5 mg (n=28). The maintenance of efficacy for men with ED and BPH-LUTS over 12 months was also not formally assessed. There was a lack of objective assessment of BPH in the dataset but this is not inconsistent with the data for tamsulosin.

Conditions of registration

The following are proposed as conditions of registration:

1. An update to the pharmacovigilance plan and risk minimisation plan regarding QT/QTc and safety in patients aged 75 years and older is to be provided to the Office of Product Review within 3 months post approval.
2. The implementation in Australia of the tadalafil RMP version 2, dated 8 December 2011, and the changes agreed to in the sponsor's pre ACPM response, included with the submission, and any subsequent revisions, as agreed with the TGA and its Office of Product Review.

Summary

Overall, the present submission appears approvable with demonstrated efficacy and an acceptable safety profile.

Recommendation

The Delegate proposes to **approve** this submission by Eli Lilly Australia Pty Ltd to register Cialis (tadalafil) based on the quality, safety and efficacy of the product being satisfactorily established for the indication below and for the reasons stated above in the Risk/Benefit Discussion:

Cialis is indicated for the treatment of:

- *Erectile dysfunction (ED) in adult males*
- *Lower urinary tract symptoms (LUTS) associated with being prostatic hyperplasia (BPH) in adult males*
- *ED and LUTS associated with BPH in adult males*

The sponsor should address the following issues in the pre ACPM response:

a. The changes to the RMP, Ongoing Safety Concerns, regarding QT/QTc being added as an important potential risk and safety in patients aged 75 years and older being added as important missing information. The inclusion of an annex on the targeted questionnaires should also be added.

b. The outstanding items the clinical evaluator has requested further information on in the Clinical Evaluation Report.

c. The statistically significant results for IPSS score difference from placebo in the pivotal studies were less than -3 (for example -2.6, -1.9, -2.1, -2.3). In the sponsor’s submission, the sponsor indicated that a difference in IPSS score of at least 3 is required to be considered clinically meaningful. Please discuss why these results should be considered clinically meaningful.

d. Why is a separate indication that combines ED and BPH required given that the individual indications are included?

e. Please justify why the dosing in renally impaired patients in the US for tadalafil is different to the dosing proposed in Australia?

Response from sponsor to questions from the Delegate's overview

Question 1

The changes to the RMP, Ongoing Safety Concerns, regarding QT/QTc being added as an important potential risk and safety in patients aged 75 years and older being added as important missing information. The inclusion of an annex on the targeted questionnaires should also be added.

Question 1 response

The sponsor acknowledges the limitation of data on patients aged 75 years and older in the clinical trial (CT) program, and therefore, patients aged 75 years and older will be added as important missing information in the RMP. The relevant targeted questionnaires will be added as an annex to the RMP. However, the sponsor does not agree that QT/QTc should be considered as an important potential risk for tadalafil for the following reasons:

- A thorough QT (TQT) study, Study LVFB, to investigate this risk has already been performed for tadalafil. The TQT study was negative, demonstrating that tadalafil had no significant QT/QTc effect across a wide concentration range, including high tadalafil concentrations that may be present due to a 3A4 inhibitor or renal disease. In this regard, tadalafil differs from vardenafil, which demonstrated a significant relationship with QT in a TQT study. Consistent with International Conference on Harmonisation (ICH) guidance, the results of the TQT study represent the most important findings for determining whether a compound has a potential impact on QT.
- The results of the requested outlier QT/QTc interval analyses of the tadalafil studies (Study LVHG, LVDI and LVHT) are consistent with the results of the outlier analysis of the TQT Study LVFB (Question 2 Response). These findings do not suggest a safety concern for tadalafil with respect to prolongation of the QT interval.
- Postmarketing data also support the sponsor's position. As of March 2012, over 36 million patients have been exposed to tadalafil worldwide. Cumulatively, torsade de pointes/QT prolongation (MedDRA SMQ) was very rarely reported in the sponsor's postmarketing spontaneous AEs database.

In conclusion, QT/QTc should not be identified as an important potential risk. A tadalafil TQT study was found to be negative in healthy volunteers, at approximately 10 times the expected therapeutic exposure for BPH. This conclusion is further supported by the results from tadalafil studies submitted in this new indication application (see Question 2 Response) as well as post marketing data.

Question 2

The sponsor provides an analysis of outlier QT/QTc interval results for the open label extension period of Study LVHG, Study LVDI, and Study LVHT, or clarifies the location of such information in the submission.

Question 2 response

The statistical outputs of the outlier analysis for QT/QTc interval results for the open label extension period of Studies LVHG, LVDI and LVHT are presented in the appendix to this response. In Study LVHT, a study of tadalafil administered once a day compared with placebo, no subjects assigned in either treatment group had an absolute QTc value >480 msec or >500 msec at baseline or at the end of treatment. No subjects had increases in QTc interval of >30 msec or 60 msec from baseline. In Study LVDI, an ED study of tadalafil administered "on demand" prior to expected sexual activity, no subjects in any treatment group had an absolute QTc value >480 msec or 500 msec at baseline or at the end of treatment. No subjects had an increase from baseline of >60 msec.

Numerically more subjects in the tadalafil groups had absolute values of QTc >450 at end of treatment compared with baseline and compared to placebo, but there was no clear dose dependence. In the Study LVHG 1-year open label extension (OLE), during which time all subjects received tadalafil 5 mg once daily, the number of subjects with QTc values >480 msec or >500 msec was similar at baseline and at the end of treatment, and the number of subjects with increases from baseline in QTc of >30 msec or >60 msec did not suggest a safety concern.

In preparing for this response, the sponsor reviewed the results of the original outlier analysis performed for the Study LVHG double blind phase. Outlier analysis was not performed in the other pivotal BPH studies (LVHR, LVHJ, and LVID) because post baseline electrocardiograms (ECGs) were not collected. During that review, we discovered programming and table labelling errors pertaining to the cut offs used for the absolute QT/QTc values at baseline and the end of treatment. Additionally, there was an error in the denominator used to calculate subject percentages. The upper threshold of QT/QTc interval was mislabelled as 580 msec when it should have been 500 msec, and the output was programmed incorrectly to the >480 msec threshold rather than the >500 msec threshold for this row. The most substantial difference is in Study LVHG.

In the revised Study LVHG double blind phase analysis conducted for this submission, the thresholds used for absolute QT/QTc interval outliers are consistent with those recommended in FDA and European Union Committee for Medicinal Products for Human Use (EU CHMP) guidelines (absolute values >450, 480, or 500 msec, and increases from baseline of >30 msec or >60 msec). The results of the revised analysis from the Study LVHG double blind phase remains largely the same as the results originally reported in the clinical study report and included in the submission. Using the corrected upper threshold of >500 msec, there was 1 subject on tadalafil with a QTc interval >500 msec at the end of treatment, unlike the original analyses which suggested that 4 subjects on tadalafil had a QTc interval >580 msec.

The conclusions of the outlier analyses of Studies LVHG, LVDI and LVHT are consistent with the results of the TQT/QTc Study LVFB (Question 1 Response) and do not indicate a safety concern for tadalafil with respect to prolongation of the QT interval.

Question 3

The sponsor clarifies if use of the term “clinically meaningful improvement”, in relation to total IPSS and IIEF-EF Domain in the draft PI, is referring to the absolute change from baseline in the tadalafil 5 mg group, or the placebo subtracted change from baseline in the tadalafil 5 mg group, or the 95% CI for the LS mean difference in the change from baseline for the two treatments

Question 3 response

For both total IPSS and IIEF-EF domain, the term “clinically meaningful improvement” is referring to the absolute change from baseline in the tadalafil 5 mg group. Barry and colleagues[11] identified a 3 point change in IPSS scores from baseline as a clinically meaningful threshold. For the IIEF-EF, an absolute change from baseline of 4 or more points is defined as clinically meaningful, as determined by Rosen and colleagues.[12] The term clinically meaningful as it pertains to total IPSS and IIEF-EF is now defined in the proposed PI.

[11] Barry MJ, *et al.* (1995) Benign prostatic hyperplasia specific health status measures in clinical research: how much change in the American Urological Association symptom index and the benign prostatic hyperplasia impact index is perceptible to patients? *J Urol.* 154: 1770-1774.
[12] Rosen RC, et al. (2011) Minimal clinically important differences in the erectile function domain of the International Index of Erectile Function scale. *Eur Urol.* 60: 1010-1016.

Question 4

The sponsor to clarify if there have been important changes in the analytical methods used in the studies submitted in the dossier and specifies any such changes and their impact on the interpretation of the data.

Question 4 response

Since the time of submission (December 2011), there have been no significant changes in analytic methods, including bioanalytical methods. Any significant changes in analytical methods outlined in the protocols made prior to submission would have been described in the methods section of the respective study reports.

Question 5

The sponsor should clarify if subject D had a positive dechallenge.

Question 5 response

No additional information was received or laboratory assessments were performed on this subject after completion of the study, so it cannot be determined if the patient had a positive dechallenge.

Question 6

The sponsor further clarifies why nausea is included in the US PI as an adverse reaction reported by <1% subjects in the controlled clinical trials of Cialis for BPH or ED and BPH in view of the fact that treatment emergent nausea was reported by a higher proportion of subjects randomised to placebo than tadalafil 5 mg, based on the integrated analysis set.

Question 6 response

The inclusion of nausea as an "adverse reaction" (<1%) in the United States Package Insert (USPI) was based on the FDA's decision after its review of the proposed label. However, as described in our previous response, the sponsor does not consider nausea an adverse drug reaction for tadalafil for the treatment of ED and BPH. Nausea did not meet the threshold of an adverse drug reaction per the CIOMS guidance,[13] which the sponsor uses as the basis for defining adverse drug reactions.

Question 7

The statistically significant results for IPSS score difference from placebo in the pivotal studies were less than -3 (for example -2.6, - 1.9, -2.1, -2.3). In the sponsor's submission, the sponsor indicated that a difference in IPSS score of at least three is required to be considered clinically meaningful. Please discuss why these results should be considered clinically meaningful.

Question 7 response

It is correct the sponsor defined "clinically meaningful" in our submission, but please note that this definition was based on a change from baseline, not mean difference from placebo, since there is no consensus on the definition of a clinically meaningful change in IPSS scores compared with placebo. Specifically, the sponsor stated: "An improvement of at least three in total IPSS compared to baseline is considered a clinically meaningful improvement in BPH symptoms[14]." This is the definition we applied to the BPH CT results

[13] Council for International Organisations of Medical Sciences (CIOMS), Guidelines for preparing core clinical-safety information on drugs: report of CIOMS Working Groups III and V, including new proposals for investigator's brochures. Geneva, Council for International Organisations of Medical Sciences, 1999.
[14] Barry MJ, *et al.* (1995) Benign prostatic hyperplasia specific health status measures in clinical research: how much change in the American Urological Association symptom index and the benign prostatic hyperplasia impact index is perceptible to patients? *J Urol.* 154: 1770-1774; American Urological Association, "American Urological Association Guideline: Management of Benign Prostatic Hyperplasia (BPH)", 2003, updated 2010, Web, accessed 11 June 2012 <www.auanet.org/ common/pdf/education/clinical-guidance/Benign-Prostatic-Hyperplasia.pdf>.

reported in the proposed PI. Using this definition, changes from baseline in the tadalafil 5 mg group exceeded the 3 point threshold in all four studies.

The majority of patients across the four global studies (Studies LVHG, LVHJ, LVHR and LVID), achieved a clinically meaningful improvement (using the Barry and colleagues[15] criteria) which was statistically significantly different than placebo. In the integrated studies, 69% of all patients in the tadalafil 5 mg group achieved at least a minus 3 point total IPSS change (improvement) compared to 55% of placebo patients ($p<0.001$), corresponding to a 26% increased likelihood that tadalafil patients achieved at least a 3 point total IPSS improvement compared to placebo. Similar results were observed in each of the four individual studies. In Study LVID (which included a tamsulosin 0.4 mg active control group), the percentage of patients in the tadalafil 5 mg group achieving clinically meaningful improvements in their BPH symptoms (73.1%) was numerically greater than in the tamsulosin group (65.5%).

To further investigate the clinically meaningful improvement of tadalafil compared to placebo, an alternative threshold approach was used, defining a ≥25% decrease in IPSS from baseline to endpoint as clinically meaningful. This standard was used in previous trials of the alpha blocker, tamsulosin.[16] In the integrated efficacy data, 59.8% of patients treated with tadalafil 5 mg and 43.7% treated with placebo achieved at least a 25% decrease in total IPSS, corresponding to a 37% increased likelihood that tadalafil treated patients achieved a 25% reduction in total IPSS compared to placebo ($p<0.05$). This is comparable to tamsulosin registration studies, where the percentage of patients achieving at least a 25% decrease in total IPSS ranged from 55% to 70% for those receiving tamsulosin 0.4 mg, from 52% to 74% for those receiving tamsulosin 0.8 mg, and from 40% to 51% for those receiving placebo.[17]

In conclusion, using the definition from Barry and colleagues[18] changes from baseline in the tadalafil 5 mg group exceeded the 3 point threshold in all four studies. Therefore, these changes can be classified as clinically meaningful improvement. In addition, across the four global studies, using the clinically meaningful criteria described by Barry and colleagues[19] or using an alternative threshold approach, significantly more tadalafil treated patients compared with placebo achieved a clinically meaningful improvement in their BPH symptoms as measured by the IPSS. Finally, the clinically meaningful improvement in the BPH symptoms observed with tadalafil in Study LVID was comparable to the improvement observed with tamsulosin.

Question 8

Why is a separate indication that combines ED and BPH required, given that the individual indications are included?

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[15] Barry MJ, *et al.* (1995) Benign prostatic hyperplasia specific health status measures in clinical research: how much change in the American Urological Association symptom index and the benign prostatic hyperplasia impact index is perceptible to patients? *J Urol.* 154: 1770-1774.

[16] Lepor H. (1998) Phase III multicenter placebo-controlled study of tamsulosin in benign prostatic hyperplasia. Tamsulosin Investigator Group. *Urology* 51: 892-900; Narayan P, Tewari A. (1998) A second phase III multicenter placebo controlled study of 2 dosages of modified release tamsulosin in patients with symptoms of benign prostatic hyperplasia. United States 93-01 Study Group. *J Urol.* 160: 1701-1706; Chapple CR, *et al.* (2011) European Silodosin Study Group. Silodosin therapy for lower urinary tract symptoms in men with suspected benign prostatic hyperplasia: results of an international, randomized, double-blind, placebo- and activecontrolled clinical trial performed in Europe. *Eur Urol.* 59: 342-352.

[17] Lepor H. (1998) Phase III multicenter placebo-controlled study of tamsulosin in benign prostatic hyperplasia. Tamsulosin Investigator Group. *Urology* 51: 892-900; Food and Drug Administration. US Center for Drug Evaluation and Research (CDER). Approval Package for: NDA 20-579. 1997.

[18] Barry MJ, *et al.* (1995) Benign prostatic hyperplasia specific health status measures in clinical research: how much change in the American Urological Association symptom index and the benign prostatic hyperplasia impact index is perceptible to patients? *J Urol.* 154: 1770-1774.

[19] Barry MJ, *et al.* (1995) Benign prostatic hyperplasia specific health status measures in clinical research: how much change in the American Urological Association symptom index and the benign prostatic hyperplasia impact index is perceptible to patients? *J Urol.* 154: 1770-1774.

Question 8 response

The sponsor considers the value in this statement lies with provision of explicit information to the prescriber as it relates to the co morbid patient group. It is acknowledged that a deduction can be made given the inclusion of the individual indications. However, the inherent value of the PI document is to provide maximum clarity to the prescriber wherever possible. This position was informed by a discussion with a small group of practicing clinicians who provide advice to the sponsor.

It is not a typical scenario to have a treatment option with established safety and efficacy for potential co morbid conditions. It is indeed possible that presenting patients may already be receiving alternative treatment for one or other of the indications. On this basis, providing explicit information to prescribers will assist in optimising the management plan for a given patient, particularly as it relates to potentially reducing the number of concurrent medications. Therefore, the sponsor recommends maintaining a separate indication statement for the co morbid use.

Question 9

Please justify why the dosing in renally impaired patients in the US for tadalafil is different to the dosing proposed in Australia?

Question 9 response

The current USPI (October 2011) recommends a starting dose of 2.5 mg, increasing to 5 mg based on individual response, in patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min). This recommendation was based on prior regulatory mandate pertaining to once a day tadalafil dosing for ED (where 2.5 mg is an approved dose for this indication), which was then also requested by the FDA for the BPH indication. However, the sponsor does not consider dose adjustments necessary for BPH patients with moderate renal impairment based on the following rationale.

The current recommendations in the Australian PI on dosing in renally impaired patients ("Dosage adjustments are not required in patients with mild or moderate renal impairment. Once a day dosing of tadalafil is not recommended in patients with severe renal impairment.") are based primarily on the results of Study LVAJ. Although this study showed an approximately 2 fold increase in exposure in patients that was comparable between patients with mild or moderate renal impairment, no new significant safety concerns were identified with the use of tadalafil in these patients.

Specifically regarding BPH patients, no significant safety concerns were identified in the renally impaired patients enrolled in the pivotal BPH studies (Summary of Clinical Safety). The incidence of TEAEs among tadalafil patients with mild or moderate renal impairment (49/199, 24.6%) was numerically lower than that in tadalafil patients with normal renal function (157/547, 28.7%), and there was no significant treatment by subgroup interactions observed for subjects reporting at least 1 TEAE or for any individual TEAE. These data show no evidence of reduced tolerability or unique safety issues with tadalafil 5 mg in patients with BPHLUTS with mild or moderate renal impairment at baseline.

In summary, there is no new safety information from clinical trials in men with BPH or postmarketing experience with BPH or ED that would necessitate a change in the existing once a day tadalafil dosing regimen for those with moderate renal impairment.

Advisory committee considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

The submission seeks to register an extension of indications for currently registered products.

The ACPM taking into account the submitted evidence of efficacy, safety and quality considered these products to have an overall uncertain benefit-risk profile to extend the approved indication to include use in adult men:

- With LUTS associated with BPH; and
- With ED and LUTS associated with BPH.

In making this recommendation, the ACPM advised that:

- The effect of the improvement in total IPSS and IIEF-ED domain score in the pivotal efficacy studies is not considered clinically meaningful.
- The deficiencies relating to clinical meaningfulness and relative efficacy in BPH compared with ED are magnified by the pivotal trials' exclusion criteria with regard to appropriate match with the target clinical population and the high placebo response rate.
- Efficacy has not been demonstrated for use in mild BPH.
- Efficacy and safety for the proposed new indication in adult males aged over 75 years have not been demonstrated beyond 12 weeks. This duration is considered inadequate to detect safety signals particularly in regards to hypotensive toxicity in this age group.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Cialis (tadalafil) 2.5 mg and 5 mg tablet for the **new indication**:

> *Cialis is indicated for the treatment of moderate to severe lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) in adult males.*

The **full indications** are now:

> *Cialis is indicated for the treatment of:*
>
> - *erectile dysfunction (ED) in adult males*
> - *moderate to severe lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) in adult males.*

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
http://www.tga.gov.au